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Review

The efficacy of inspiratory muscle training in improving clinical outcomes in heart failure patients: An updated systematic review and meta-analysis

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SUMMARY

Background: Inspiratory muscle training (IMT) has shown improvements in clinical variables for heart failure (HF) patients. We conducted a meta-analysis to investigate if IMT can enhance respiratory muscle strength, quality of life (QoL), and reduce cardiac biomarker levels in HF patients.
Methods: PubMed, Cochrane Library, and Google Scholar databases were systematically searched up to July 8, 2024. Randomized controlled trials of IMT in HF patients were included. A random effects model was used to calculate weighted mean differences (WMDs) and 95 % confidence intervals. Outcomes analyzed included minute ventilation to carbon dioxide output slope (VE/VCO2), QoL, six-minute walk distance (6MWD), maximum expiratory pressure, maximum inspiratory pressure (MIP), N-terminal pro B-type natriuretic peptide (NT-pro-BNP), forced vital capacity, forced expiratory volume in one second, and metabolic equivalents.
Results: Seventeen studies involving 510 patients (252 in IMT group, 258 in control) were included. IMT significantly improved 6MWD [WMD: 72.72; 95 % CI: (16.65 to 128.78); $p = 0.01$], QoL [WMD: -15.27; 95 % CI: (−21.01 to −9.53); $p < 0.00001$], VE/VCO2 [WMD: -5.09; 95 % CI: (−7.36 to −2.83); $p < 0.0001$], MIP [WMD: 13.77; 95 % CI: (7.51 to 20.03); $p < 0.0001$], and NT-pro-BNP levels [WMD: -659.66; 95 % CI: (−1212.87 to −106.46); $p = 0.02$].
Conclusion: IMT significantly improved respiratory muscle strength, QoL, and reduced cardiac biomarker levels in patients with both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. These findings suggest that IMT may be a promising exercise-based strategy for treating HF.

Introduction

Heart failure (HF) is a significant public health issue, affecting 56.19 million people worldwide in 2019 [1]. Projections for the USA indicate a 46 % increase in HF prevalence from 2012 to 2030, with a 127 % rise in associated healthcare costs [2]. HF is clinically characterized by exercise intolerance, respiratory muscle weakness, and diminished quality of life (QoL) [3,4]. It also carries a significant rate of mortality. Respiratory muscle dysfunction, including inspiratory muscle weakness, exacerbates symptoms such as dyspnea and fatigue, thereby limiting exercise capacity in patients with both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) significantly impairing activities of daily living and QoL [5,6].

The interaction between risk factors in patients with HF (e.g. obesity, hypertension, metabolic syndrome, and diabetes) and the pathophysiology of HF attributable to HF symptoms with a resultant increase in intracardiac pressures and overall volume overload status, further enhances and aggravates respiratory muscle dysfunction. This dysfunction is linked to a poor prognosis and worse long-term outcomes and mortality [7,8]. Inspiratory muscle training (IMT) is a promising intervention for HF patients, enhancing peripheral and respiratory muscle function, endurance,

Abbreviations: IMT, inspiratory muscle training; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; QoL, quality of life; VE/VCO_2, minute ventilation to carbon dioxide output slope; 6MWD, six-minute walk distance; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; NT-pro-BNP, n-terminal pro b-type natriuretic peptide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; METs, metabolic equivalents of training; LVEF, left ventricular ejection fraction; RCTs, randomized controlled trials.

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and cardiopulmonary function [9–11]. IMT improves exercise performance and respiratory function by reducing oscillatory ventilation, enhancing inspiratory muscle strength, and attenuating the exaggerated peripheral chemoreflex in HF patients [6]. IMT increases exercise duration and reduces lactate levels in active individuals, while also attenuating the inspiratory metaboreflex, which improves hemodynamic function, respiratory mechanics, and cardiovascular autonomic control [6].

A recent meta-analysis showed IMT significantly improves QoL and respiratory muscle strength as well as exercise capacity in patients with HF [12]. However, the meta-analysis was constrained by the thorough inclusion of all available randomized controlled trials (RCTs), and it only analyzed a restricted set of variables. To address this gap and include the latest RCT data on IMT [13–18], we performed an updated meta-analysis evaluating the impact of IMT on patients with HFpEF and HFrEF, comparing multiple outcomes across various IMT implementation programs.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. Permission from an ethical review board was not required as the data were publicly available.

Data sources and search strategy

Two reviewers (A.K. and S.S.J.) separately performed a comprehensive literature search of multiple electronic databases, including PubMed, Google Scholar, and Cochrane Library, covering the period from inception up to July 8, 2024. The search strategies employed for each database are detailed in Online Table S1. All the selected articles were imported into Endnote X7 (Clarivate Analytics, Philadelphia, PA, USA) to identify and delete duplicates. The remaining studies were examined by two reviewers, (A.K. and S.S.J.), based on their titles and abstracts. The entire material was rigorously examined against the inclusion and exclusion criteria before articles were selected. No language restriction was applied during the literature search. Additional studies were also retrieved by manually screening the reference list of already included studies to ensure that all possible relevant studies were included. Any discrepancies were resolved by a third reviewer (A.K.S.).

Study selection

Studies were considered eligible to be included in our systematic review and meta-analysis if they met the following inclusion criteria: 1) included patients with HF aged ≥18 years; (2) included IMT in the active arm of the trial (3) implementation of sham IMT treatment, a blank control, traditional training, or educational intervention in the control group; (4) were RCTs; (5) reported outcomes of interest and (6) provided raw data to allow estimation of weighted mean difference (WMD) with 95 % confidence intervals (CIs). Exclusion criteria were: (1) experimental studies; (2) conference articles, case reports, systematic reviews, and meta-analysis; (3) insufficient outcome data provided (4) duplicate reports of literature research (5) animal studies.

Data extraction and quality assessment

The studies were initially screened and shortlisted by two independent researchers (A.K. and S.S.J.) based on their title and abstract that complied with our inclusion criteria. The full text of studies that met our inclusion criteria was carefully reviewed. The results were compared simultaneously, and any differences were addressed by consensus with a third researcher (A.K.S.). The baseline characteristics included study duration, sample size, type of intervention assigned, and etiology of HF (Table 1). The following outcomes of interest were extracted from each individual study: 1) Minute ventilation to carbon dioxide output slope (VE/VCO2); 2) QoL; 3) Six-minute walk distance (6MWD); 4) Maximum expiratory pressure (MEP); 5) Maximum inspiratory pressure (MIP); 6) Levels of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP); 7) Left ventricular ejection fraction (LVEF); 8) Forced vital capacity (FVC); 9) Forced expiratory volume in one second (FEV1); and 10) Metabolic equivalents of training (METs).

The risk of bias in the included RCTs was evaluated by two independent authors (A.K. and M.S.) using Cochrane's Collaboration tool for assessing the risk of bias in randomized trials (RoB 2) [20]. Any disagreements were resolved through mutual consensus.

Statistical analysis

All statistical analysis was performed using RevMan, version 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). The data were pooled using a random effects model according to the (Mantel–Haenszel model). Fixed effects models were not tested and therefore not reported. The effect size of the measurement data was expressed by weighted mean difference (WMD), and 95 % confidence intervals (CI) were used to estimate the interval range of the effect size [21]. Forest plots were created to visualize the results. This study evaluated heterogeneity among studies using Cochran's Q statistic and the I^2 index. I^2 values below 25 %, between 25 % and 50 %, or above 50 % indicated low, moderate, or high heterogeneity, respectively [22]. A p-value of <0.05 was always considered significant. We also conducted a subgroup analysis based on the type of HF, dividing patients into three subgroups: those with HFpEF, those with HFrEF, and those in studies that included patients with HF of any etiology. Additionally, a leave-one-out (LOO) sensitivity analysis was also performed for outcomes with high heterogeneity ($I^2 \geq 50$ %).

Results

Search results

The initial search yielded 17,908 potential articles, of which 17 RCTs met the inclusion criteria for this meta-analysis. Fig. 1 presents the PRISMA flowchart summarizing the study selection process. This study included a total of 510 patients with HF, with 252 receiving IMT as the intervention. The mean age of the individuals was 63.1 years, and there were 288 male participants. Fourteen studies utilized IMT as the sole intervention [10,11,13,15–18,23–29], while two studies combined IMT with aerobic exercise [30,31] and one study combined IMT with an autonomous walking program [14]. The intervention period ranged from 4 to 24 weeks, with an average duration of 12 weeks across 10 studies. The included studies were geographically diverse with 2 studies from the USA, 4 from Brazil, 4 from Spain, 2 from Turkey, and 1 each from Japan, Egypt, Poland, Lebanon, and Greece (Fig. 2) (Table 1).

Results of quality assessment

The risk of bias was assessed using the Cochrane Risk of Bias tool across the 17 included RCTs (Online Fig. S1a, b). Overall, the majority of the studies demonstrated a low risk of bias. However, three studies were identified as having a high risk of bias due to issues with allocation concealment; these studies either did not mention participant blinding or the participants were aware of the intervention they received [15,27,29]. Additionally, two studies exhibited a moderate level of bias, primarily because participant blinding was not reported [13,26,28,31].

Results of meta-analyses

A central illustration summarizing the findings of this study is provided in the Graphical abstract (Fig. 2). Detailed forest plots showing the results of this meta-analysis are provided in Figs. 3–12.

Table 1
Baseline characteristics of the included studies.

Studies	Location	Intervention		Duration (weeks)	LVEF (%)	NYHA functional class	Sample size		Age (years)		Male (%)	
		Experimental group	Control group				Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Farghaly et al. [16]	Egypt	Patients underwent IMT, initial workload was measured as 30 % and increased gradually to 60 % of MIP, 6 times per week.	Breathing calisthenics, 6 times per week.	12	≤40 %	II and III	20	20	55.55 ± 8.36	55.90 ± 6.54	NR	NR
Piotrowska et al. [15]	Poland	IMT was conducted at 30 % of MIP during the first week, progressively increased to 60 % by the sixth week, and maintained at this level until the eighth week. The sessions consisted of two 5-minute sessions per day, which were gradually increased to 15 min per session by the eighth week.	Cardiac rehabilitation, 45 min per session, 5 times per week.	8	NR	I and II	30	30	63.67 ± 7.59	63.60 ± 5.1	60	60
Trevizan et al. [13]	Brazil	IMT at 60 % MIP, 5 times per week.	No training	16	≤40 %	II and III	11	10	55 ± 3[a]	57 ± 3[a]	27.27	60
Sadek et al. [17]	Lebanon	IMT at 60 % of MIP, 3 times per week.	No training	12	≤45 %	II and III	10	10	52.5 ± 13.7	52.6 ± 11.2	50	50
Tanriverdi et al. [18]	Turkey	Patients underwent H-IMT. 3 sessions per week for 8 weeks. Training load started at 30 % of MIP and increased progressively to 70 % by the third session, reaching maximum tolerated load thereafter.	Sham H-IMT at MIP of 0 cmhg	8	≤40 %	II and III	17	17	63.7 ± 7.6	62.5 ± 8.1	76.5	76.5
Lin et al. [14]	USA	Autonomous walking program + H-IMT at 60 % of MIP	Autonomous walking program with a weekly step goal measured via pedometer + Sham IMT at 15 % of MIP	6	NR	II and III	5	3	51–64	49–76	80	100
Padula et al. [10]	USA	IMT at 30 % of MIP, 10–20 min each time, 6 times a week	Standard Education Program	12	<45 %	II and III	15	17	76 (51–89)	73 (32–95)	33.3	41.2
Bosnak-Guclu et al. [23]	Turkey	IMT at 40 % of MIP, 30 min each time, once a day	Sham IMT at 15 % of MIP, 30 min each time, once a day	6	<40 %	II and III	16	14	69.5 ± 7.96	65.71 ± 10.52	75	85.71
Marco et al. [24]	Spain	IMT, breathing rate 15–20 breaths/min	Sham IMT at 10 % of MIP	4	NR	II and III	11	11	68.5 ± 8.88	70.1 ± 10.75	63.6	90.9
Dall'Ago et al. [25]	Brazil	IMT at 30 % of MIP, 30 min each time, 7 times a week	Sham IMT, 30 min each time, 7 times a week	12	<45 %	II and III	16	16	58 ± 2	54 ± 3	62.5	68.8
Mello et al. [11]	Brazil	IMT at 30 % of MIP	Sham IMT	12	<45 %	II	15	12	54.3 ± 2	53.3 ± 2	64	91
Winkelmann et al. [30]	Brazil	IMT 30 % MIP, 30 min each time, 7 times a week; aerobic exercise, 20–45 min each time, 3 times a week	Aerobic exercise, 20–45 min each time, 3 times a week	12	<45 %	NR	12	12	54 ± 12	59 ± 9	33.3	58.3
Adamopoulos et al. [31]	Greece	IMT at 60 % of MIP, 30 min each time, 3 times a week; aerobic exercise, 30 min each time, 3 times a week	Sham IMT, 30 min each time, 3 times a week; aerobic exercise, 30 min each time, 3 times a week	12	≤35 %	II and III	21	22	57.8 ± 11.7	58.3 ± 13.2	90.5	77.3
Palau et al. [26]	Spain	IMT 20 min per session, twice a day	Blank control	12	>50 %	≥ II	14	12	68 (60–76)	74 (73–77)	50	50
Palau et al. [28]	Spain	IMT 20 min per session, twice a day	Blank control	12	>50 %	≥ II	18	27	76 (68–80)	72 (66–76)	72	41
Palau et al. [27]	Spain	IMT 20 min per session, twice a day	Blank control	12	>50 %	≥ II	13	13	75 ± 10	75 ± 9	46.7	30.8
Kinugasa et al. [29]	Japan	IMT 30 % of MIP, 20 min per session, once a day	Blank control	24	>50 %	NR	8	12	NR	NR	NR	NR

NYHA, New York Heart Association functional classification; NR, not reported; IMT, inspiratory muscle training; LVEF, left ventricular ejection fraction; MIP, maximum inspiratory pressure.
[a] The values are reported as mean ± SE.

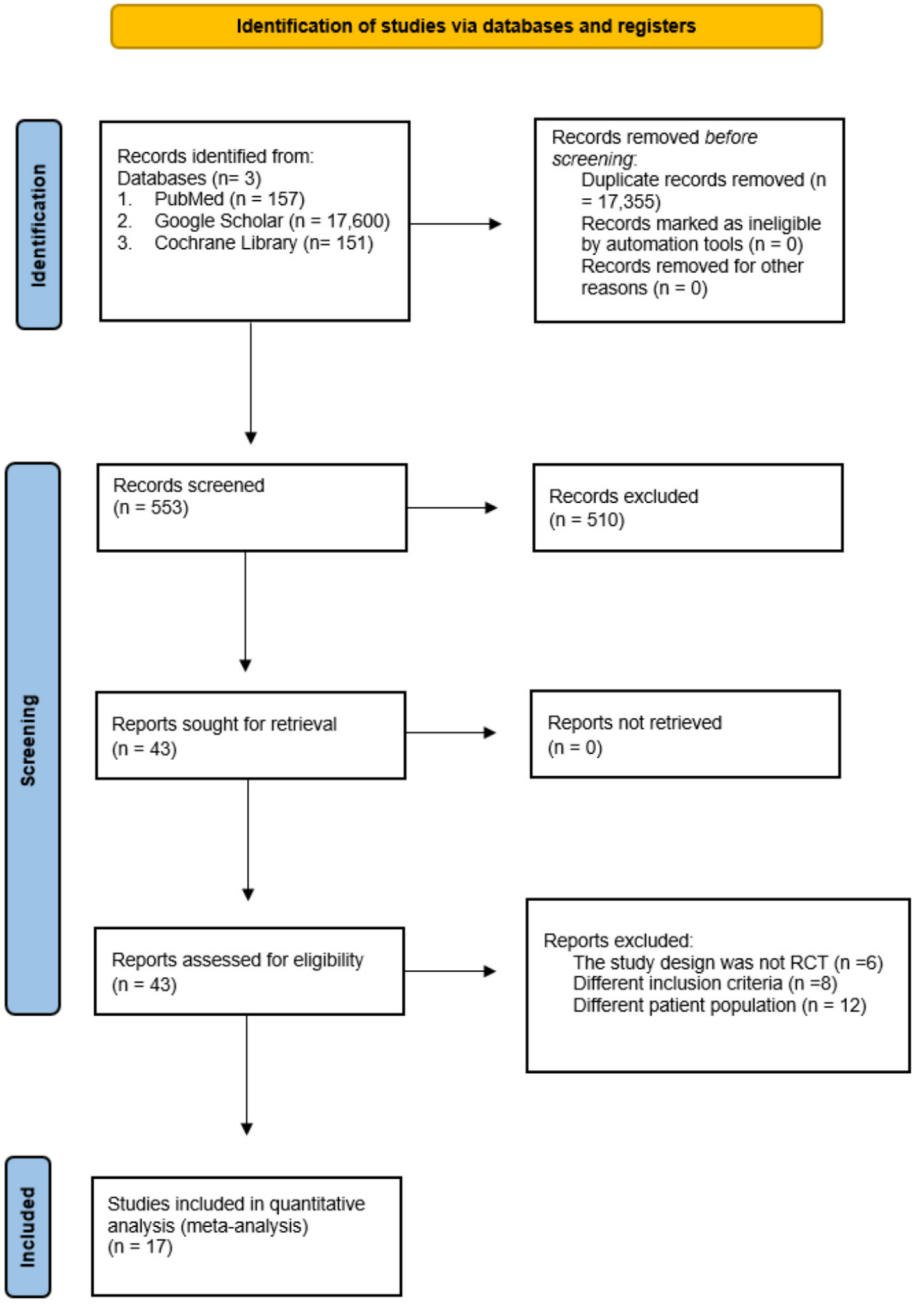

Fig. 1. PRISMA flowchart. This figure presents the PRISMA flowchart, detailing the selection process of studies included in the meta-analysis.

Minute ventilation carbon dioxide output slope

The outcome VE/VCO2 was reported by 9 out of 17 selected studies with a total of 215 patients (IMT group: 110; Control group: 105). Our pooled analysis demonstrated that IMT showed significant reductions in VE/VCO2 ratio, in comparison to the control in patients with HF [WMD: -5.09; 95 % CI: (−7.36 to −2.83); p-value <0.0001; Fig. 2]. These results were consistent in the subgroup of patients with HFpEF (WMD: -4.76; 95 % CI: −10.44 to 0.92; p-value = 0.005; Fig. 3).

Quality of life

The QoL outcome, assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), was reported in 8 out of 17 selected studies with a total of 198 patients (IMT group: 101; Control group: 97). Our pooled analysis demonstrated that IMT was associated with significant improvements in QoL compared to the control in patients with HF [WMD: -15.27; 95 % CI: (−21.01 to −9.53); p-value <0.00001; Fig. 4]. These results were consistent in patients with HFpEF, with IMT leading to a significantly improved quality of life [WMD: -14.52; 95 % CI: (−18.53 to −10.52); p-value <0.00001; Fig. 4].

Six-minute walking distance

The outcome of 6MWD was reported by 6 out of 17 selected studies with a total of 166 patients (IMT group: 85; Control group: 81). Our pooled analysis demonstrates that IMT was associated with significant improvements in 6MWD as compared to control in patients with HF [WMD: 72.72; 95 % CI: (16.65 to 128.78); p-value = 0.01; Fig. 5].

Maximum expiratory pressure

The outcome of MEP was reported by 2 out of 17 selected studies with a total of 64 patients (IMT group: 33; Control group: 31). Our pooled analysis demonstrated that IMT was not associated with any

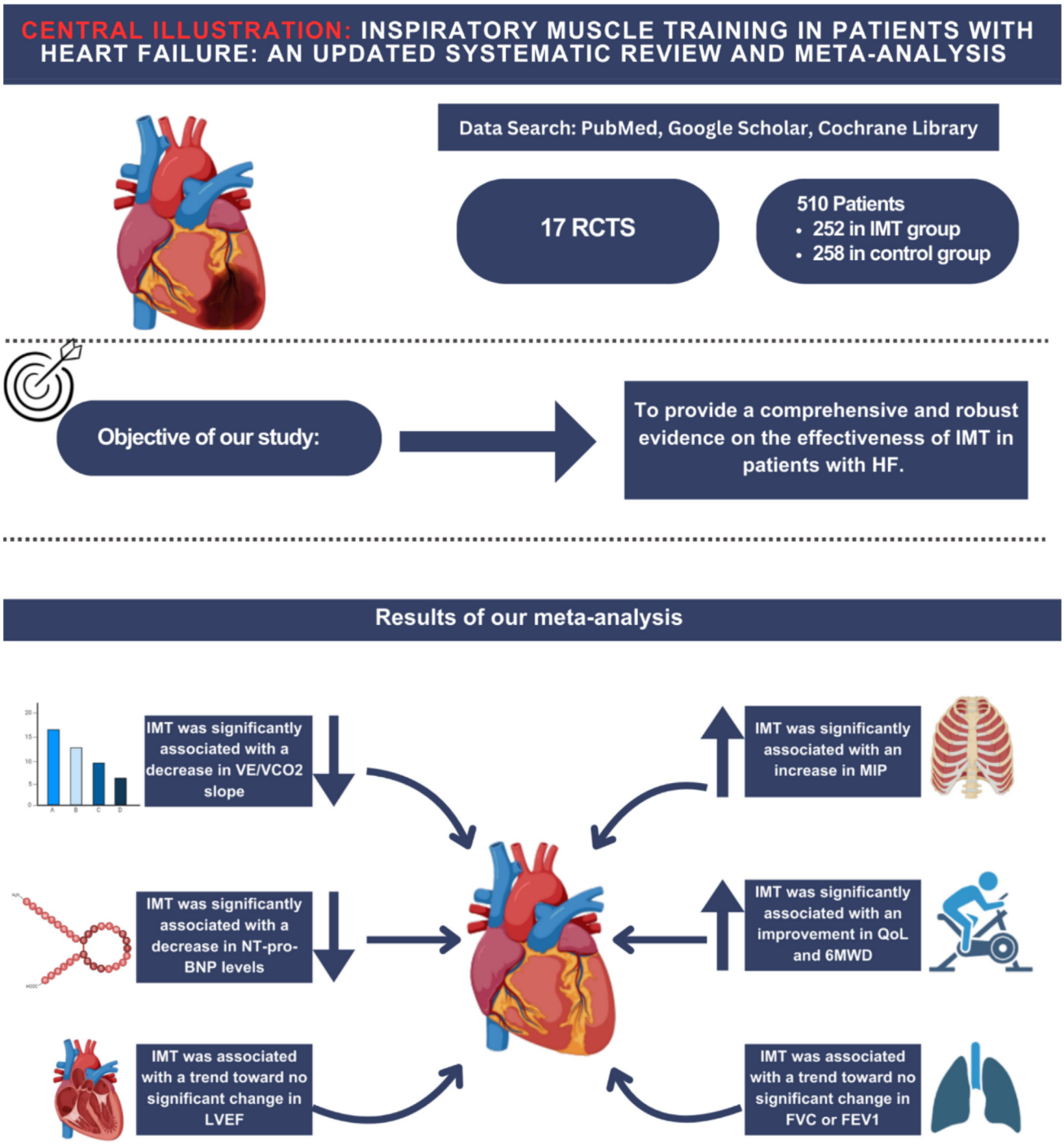

Fig. 2. Central illustration summarizing the results of this meta-analysis. Overview of the pooled effects of IMT across various outcomes including VE/VCO2, QoL, 6WMD, MEP, MIP, NT-pro-BNP, FVC, FEV1, LVEF, and METs, demonstrating its impact on heart failure parameters.

significant changes in MEP in patients with HF [WMD: 11.11; 95 % CI: (−6.44 to 28.66); p-value = 0.21; Fig. 6].

Maximum inspiratory pressure

The outcome MIP was reported by 9 out of 17 selected studies with a total of 268 patients (IMT group: 136; Control group: 132). Our pooled analysis demonstrated that IMT showed significant improvements in MIP, in comparison to the control in patients with HF [WMD: 13.77; 95 % CI: (7.51 to 20.03); p-value <0.0001; I^2: 75 %; Fig. 7]. These results were consistent in the subgroup of patients with HFrHF [WMD: 10.86; 95 % CI: (3.42 to 18.31); p-value = 0.004; Fig. 7].

N-terminal pro-B-type natriuretic peptide

The levels of NT-pro-BNP were reported by 4 out of 17 selected studies with a total of 117 patients (IMT group: 59; Control group: 58). Our pooled analysis demonstrates that IMT was associated with a significant reduction in the levels of NT-pro-BNP [WMD: -659.66; 95 % CI: (−1212.87 to −106.46); p-value = 0.02; Fig. 8].

Forced vital capacity

The outcome of FVC was reported by 4 out of the 17 selected studies with a total of 108 patients (IMT group: 56; Control group: 52). Our pooled analysis demonstrates that IMT was not associated with

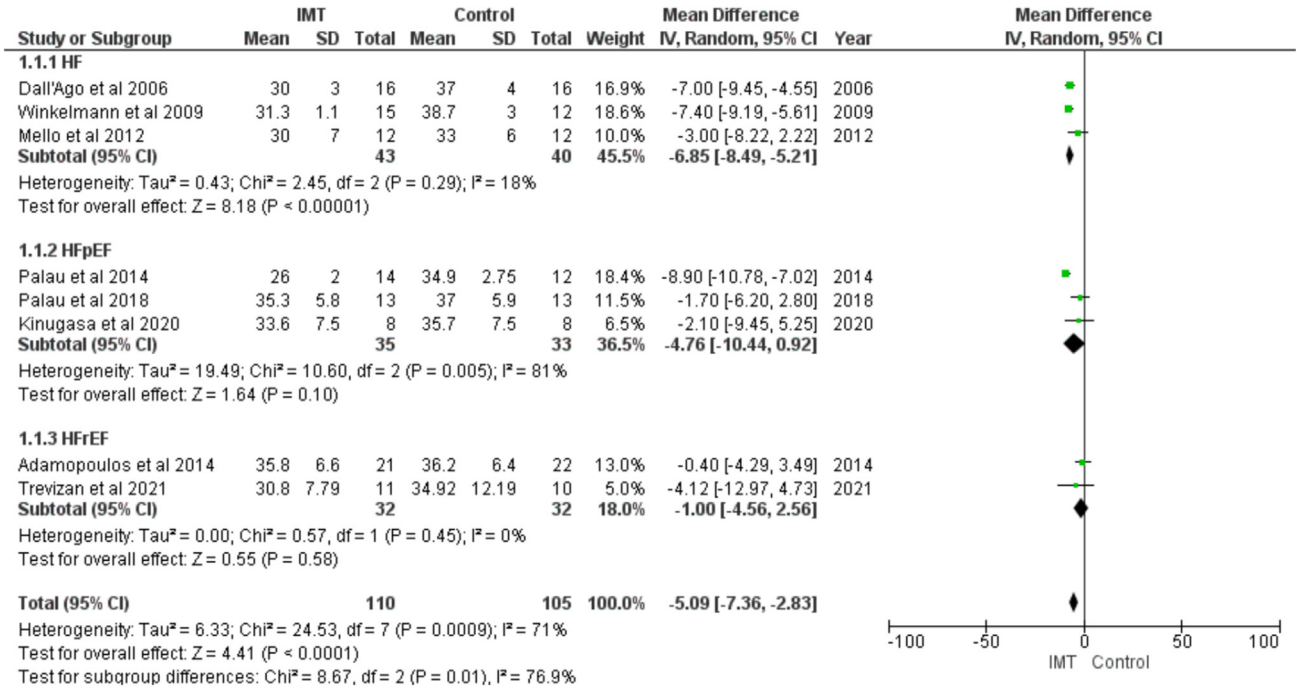

Fig. 3. Forest plot for the outcome of VE/VCO2. This figure shows a significant reduction in the VE/VCO2 with IMT compared to controls in patients with heart failure.
CI, confidence interval; VE/VCO2, minute ventilation/carbon dioxide output slope.

any significant changes in FVC [WMD: -0.16; 95 % CI: (−1.79 to 1.48); p-value = 0.70; Fig. 9].

Forced expiratory volume in one second

The outcome of FEV1 was reported by 5 out of the 17 selected studies with a total of 185 patients (IMT group: 94; Control group: 91). Our pooled analysis demonstrates that IMT was not associated with any significant changes in FEV1 [WMD: -3.43; 95 % CI: (−8.29 to 1.43); p-value = 0.17; Fig. 10].

Left ventricular ejection fraction

The outcome of LVEF was reported by 3 out of 17 selected studies with a total of 90 patients (IMT group: 46; Control group: 44). Our pooled analysis demonstrates that IMT was not associated with any

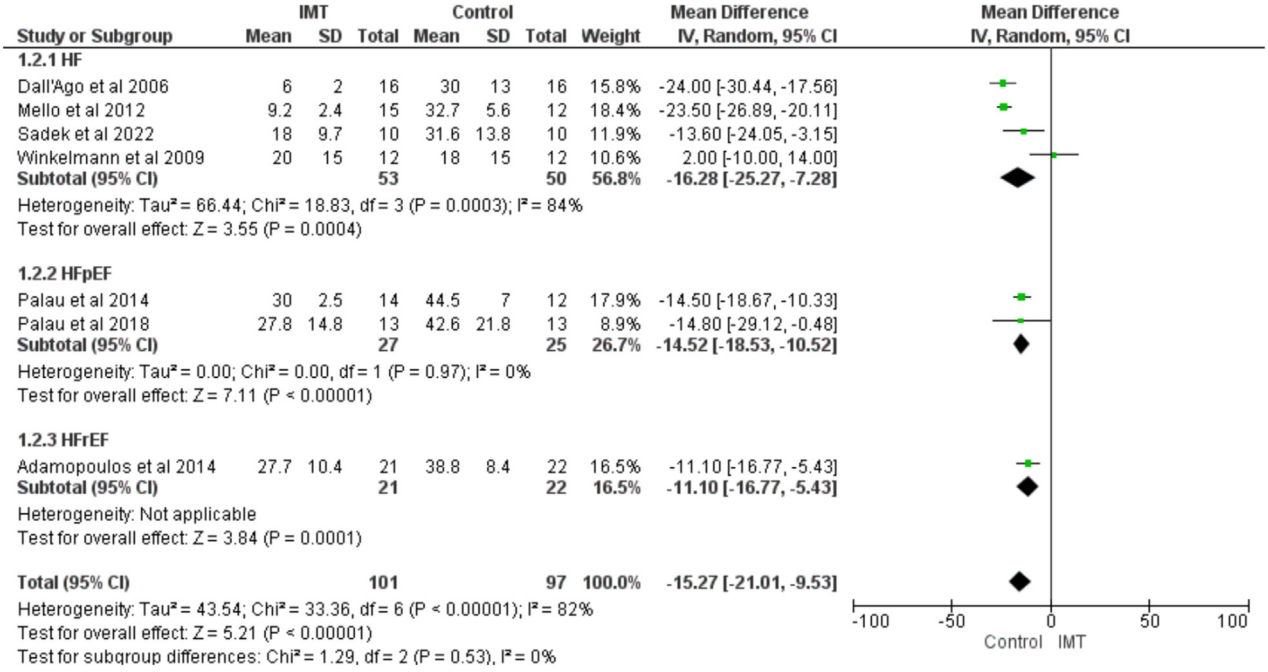

Fig. 4. Forest plot for the outcome of QoL. This figure illustrates significant improvements in QoL as measured by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) with IMT compared to controls.
CI, confidence interval; QoL, quality of life.

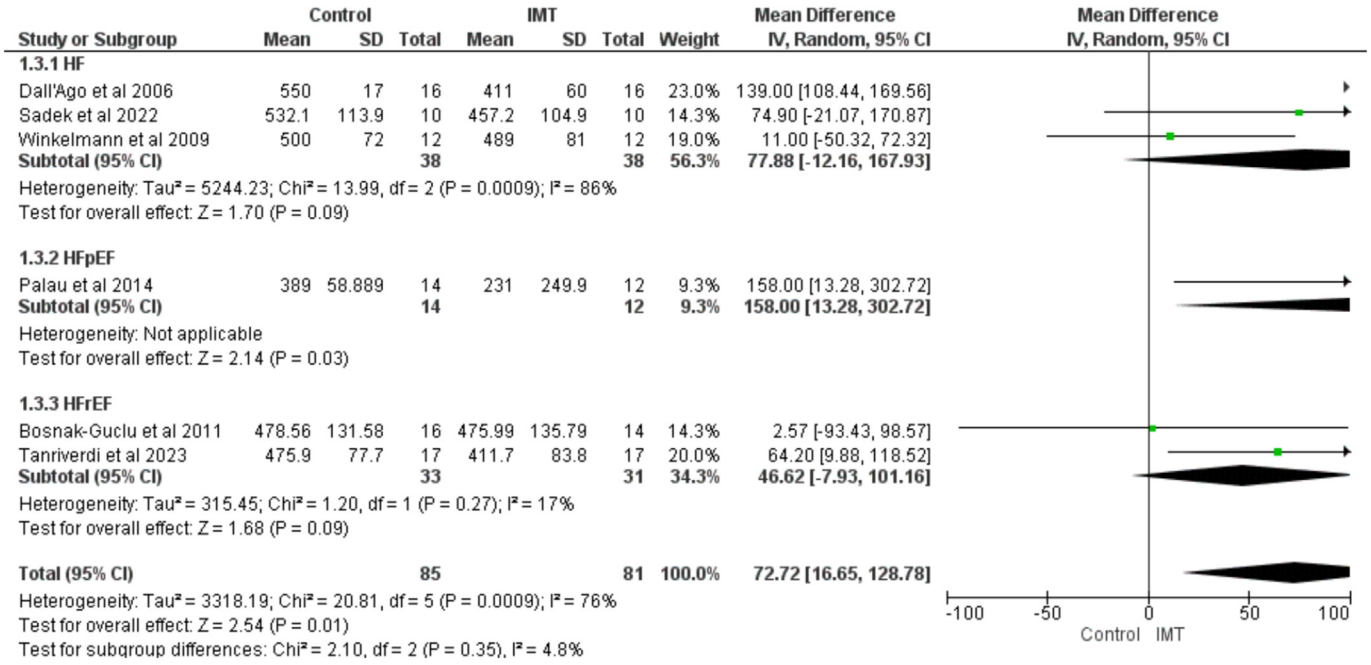

Fig. 5. Forest plot for the outcome of 6MWD. This figure depicts the significant increase in 6WMD with IMT compared to control groups in patients with heart failure. CI, confidence interval; 6MWD, six-minute walking distance.

significant change in the LVEF [WMD: -1.73; 95 % CI: (−9.56 to 6.10); p-value = 0.67; Fig. 11].

Metabolic equivalent of training

The outcome of METs was reported by 3 out of 17 selected studies with a total of 108 patients (IMT group: 56; Control group: 52). Our analysis demonstrates that IMT was not associated with any significant change in METs [MD: -0.16; 95 % CI: (−1.79 to 1.48); p-value = 0.85; Fig. 12].

Leave-one-out analysis

We conducted a LOO sensitivity analysis for outcomes with high heterogeneity ($I^2 \geq 50$ %). For VE/VCO2, excluding Adamopoulos et al. reduced heterogeneity to $I^2 = 56$ %, and the pooled estimates showed a significant decrease in the IMT group compared to the control group [MD = −6.16; 95 % CI: (−8.10 to −4.23), p < 0.00001; Online Fig. S2a] [30]. For MIP, excluding Farghaly et al. reduced heterogeneity to $I^2 = 3$ %, and the pooled estimates indicated a significant increase in MIP in the IMT group compared to the control group [MD: 16.89; 95 % CI: (13.13 to 20.65); p < 0.00001; Online Fig. S2b] [16]. For 6WMD, excluding Dall'Ago et al. reduced heterogeneity to $I^2 = 22$ %, with pooled estimates showing a significant increase in the distance covered in the IMT group as compared to the control group [MD: 72.72 95 % CI: (16.65 to 128.78); p = 0.02; Online Fig. S2c] [24]. For LVEF, removing Palau et al. reduced heterogeneity to $I^2 = 0$ %, but no significant change associated with IMT was observed [MD: 1.73; 95 % CI: (−3.05 to 6.51); p = 0.48; Online Fig. S2d] [25]. For QoL, excluding Mello et al. reduced heterogeneity to $I^2 = 71$ %, with pooled estimates showing a significant increase associated with IMT as compared to the control group [MD: -13.55; 95 % CI: (−19.29 to −7.82); p < 0.00001; Online Fig. S2e] [11]. For FVC, excluding Sadek et al. reduced heterogeneity to $I^2 = 21$ %, with pooled estimates showing a significant increase associated with IMT as compared to the control group [MD: 0.73; 95 % CI: (−0.09 to −1.55); p < 0.00001; Online Fig. S2f] [17]. Lastly, for METs, excluding Sadek et al. reduced heterogeneity to $I^2 = 21$ %, but no significant change associated with IMT was observed [MD: 0.73; 95 % CI: (−0.09 to 1.55); p = 0.08; Online Fig. S2g] [17].

Discussion

This meta-analysis, comprising 17 RCTs with 510 patients, assessed the effectiveness of IMT in patients with HF. Our pooled results showed significant improvements in VE/VCO2, QoL, 6WMD, MIP, and NT-pro-BNP levels compared to the control group.

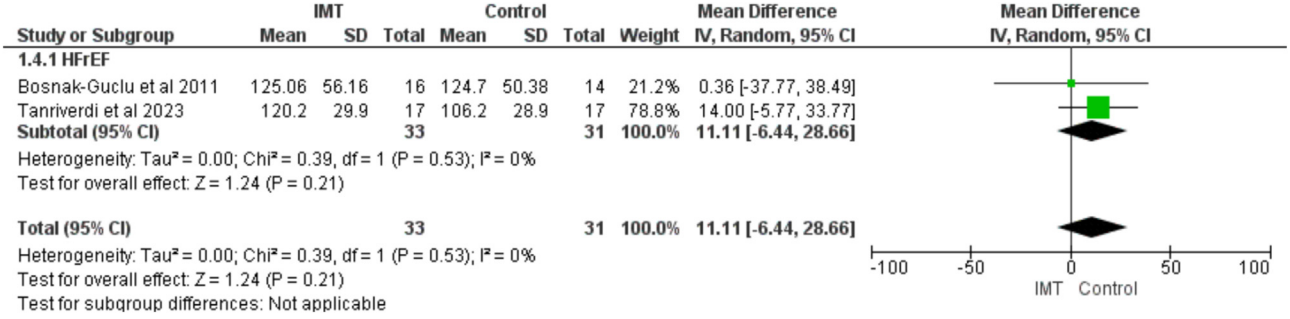

Fig. 6. Forest plot for the outcome of MEP. This figure depicts no significant change in MEP with IMT in patients with heart failure. CI, confidence interval; MEP, maximum expiratory pressure.

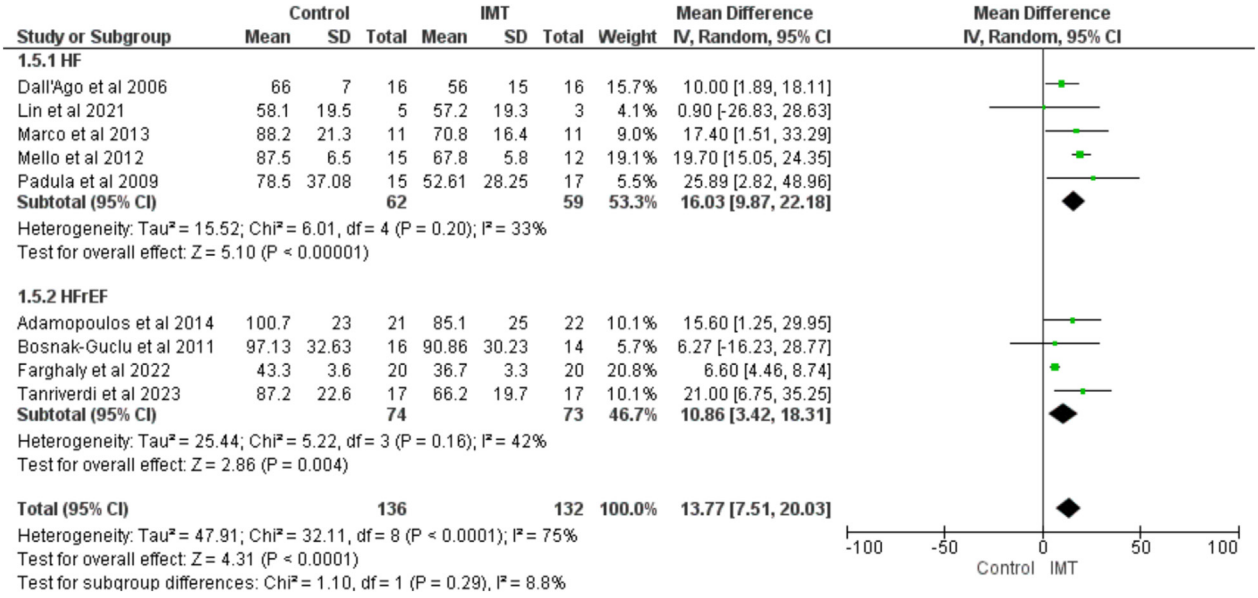

Fig. 7. Forest plot for the outcome of MIP. This figure demonstrates a significant improvement in MIP with IMT, indicating enhanced inspiratory muscle strength. CI, confidence interval; MIP, maximum inspiratory pressure.

Similar to the previous meta-analysis, our findings demonstrate that IMT significantly decreased the VE/VCO2 and increased MIP in patients with HF. An elevated VE/VCO2 slope and reduced MIP are associated with worsening outcomes in patients with HF. It indicates poor exercise tolerance, diminished ventilatory drive, and inspiratory muscle weakness, potentially due to peripheral chemoreceptor hypersensitivity, an enhanced peripheral ergo-receptor response, increased ventilatory dead space, and decreased respiratory muscle endurance [32–36]. Our findings demonstrate that IMT improves ventilatory and respiratory muscle weakness in HF patients by improving systemic myopathy, enhancing inspiratory muscle endurance, strengthening the inspiratory muscles, and increasing diaphragm thickness [18,36–38]. Increasing the strength of inspiratory muscles by IMT reduces the oxygen requirement during exercise, resulting in enhancement of the delivery of oxygen to other muscles thereby improving exercise tolerance in patients with HF [17]. Although significant improvements were noted in MIP, the lack of notable improvements in MEP may be due to the fact that IMT primarily focuses on inspiratory muscles rather than expiratory muscles [18]. Despite these improvements, IMT did not significantly improve FVC or FEV1. Possible reasons for these findings include that very few studies reported FVC and FEV1 as outcomes, along with variability in IMT protocols and differences in the duration, frequency, and intensity of IMT intervention across studies.

Second, our findings reveal that implementing IMT in patients with HF significantly decreased NT-pro-BNP levels, suggesting a potential reduction in cardiac stress and HF severity, an aspect not assessed by previous meta-analysis. NT-pro-BNP is a crucial biomarker for evaluating HF severity and long-term prognosis. Higher NT-pro-BNP levels are linked to increased risks of recurrent hospitalizations and death, highlighting the importance of our findings in improving patient outcomes

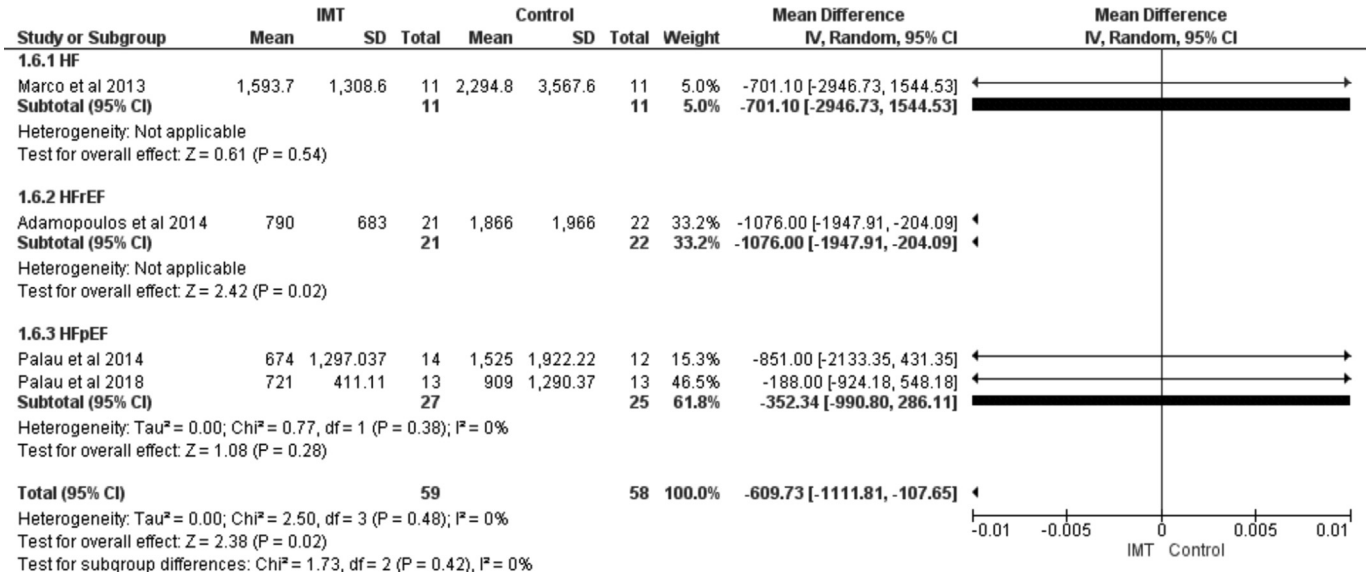

Fig. 8. Forest plot for the outcome of NT-pro-BNP levels. This figure depicts a significant reduction in NT-pro-BNP levels with IMT, reflecting improved cardiac stress. CI, confidence interval; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

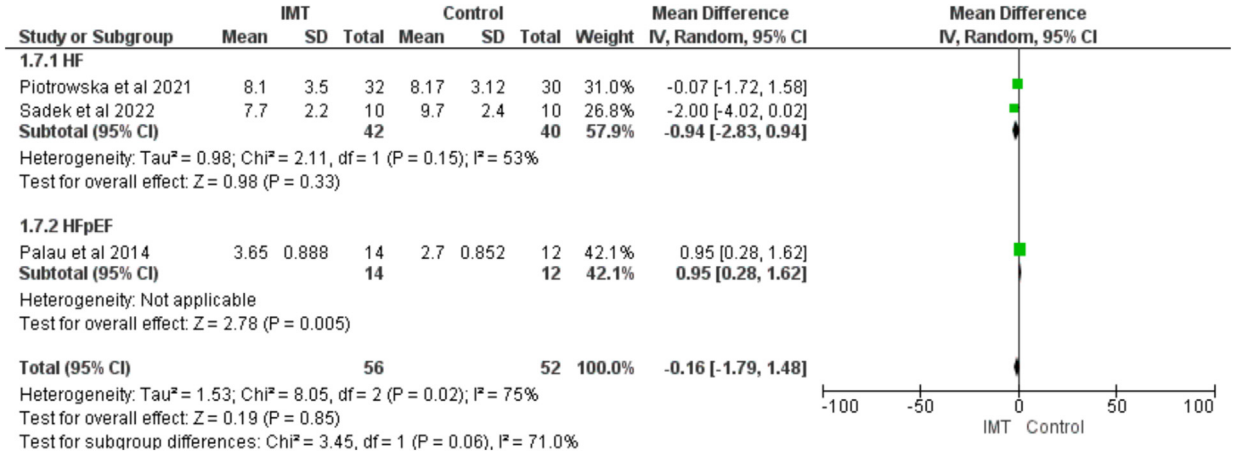

Fig. 9. Forest plot for the outcome of FVC. This figure depicts no significant change in FVC with IMT.
CI, confidence interval; FVC, forced vital capacity.

[39]. The main determinant of NT-pro-BNP release is myocardial diastolic wall stress. The decreased levels observed in our study suggest substantial left ventricular (LV) reverse remodeling and improvements in LV function thereby reducing the risk of adverse events and improving the overall cardiac function in patients with HF [40–43]. Our meta-analysis also evaluated changes in LVEF, which had not been analyzed previously. The absence of improvements in LVEF may be because IMT primarily targets respiratory muscles, strengthening them, rather than directly influencing cardiac contractility. While the reduction in NT-pro-BNP suggests a possible trend toward improvements in LV function, the lack of significant change in LVEF does not fully support this trend.

Third, our results demonstrated that IMT significantly improves both QoL and 6MWD. The 6MWD is a measure of functional capacity, and a significant increase was observed when IMT was implemented in HF patients, contrary to the previous meta-analysis [12]. As per prior clinical reports, reduced performance in the six-minute walk test (6MWT) is associated with higher rates of mortality, nonfatal cardiovascular events, and HF hospitalizations, particularly in populations with mild-to-moderate HF (New York Heart Association functional class II–III) [44,45]. Thus, the observed improvements in 6WMD with IMT in our study may be attributed to increased peripheral muscle mass, better regulation of the muscle reflex system, enhanced cardiovascular and respiratory responses, and reduced perception of dyspnea thereby leading to an improved QoL [25,46]. An improved 6MWD is indicative of better QoL, symptomatic relief, and enhanced ability to perform daily activities. Furthermore, maintaining a stable 6MWD over one year in HF patients suggests higher survival rates [11,31]. Our study shows a statistically significant improvement in 6MWD, likely due to the inclusion of more studies and a larger sample size. This increased sample size likely enhanced the statistical power of our analysis, leading to the observed significant effects.

Our meta-analysis examined the effects of IMT both as a standalone intervention and in combination with other exercise modalities, such as aerobic exercise (AE) and cardiac rehabilitation (CR). The evidence highlights the synergistic benefits of combining IMT with AE and CR resistance training (RT) to improve cardiorespiratory fitness and functional capacity. First, Winkelmann et al. found that combining AE with IMT led to significant improvements in maximal inspiratory muscle pressure (PImax), peak oxygen uptake (VO2peak), circulatory power, oxygen uptake efficiency slope, and ventilatory efficiency compared to AE alone [30]. Second, Adampoulos et al. demonstrated that combining AE with IMT resulted in greater improvements in QoL, dyspnoea, NT-proBNP, PImax, VO2, and LVEF [31]. Third, Piotrowska et al. observed that the combination of CR and IMT led to significant improvements in

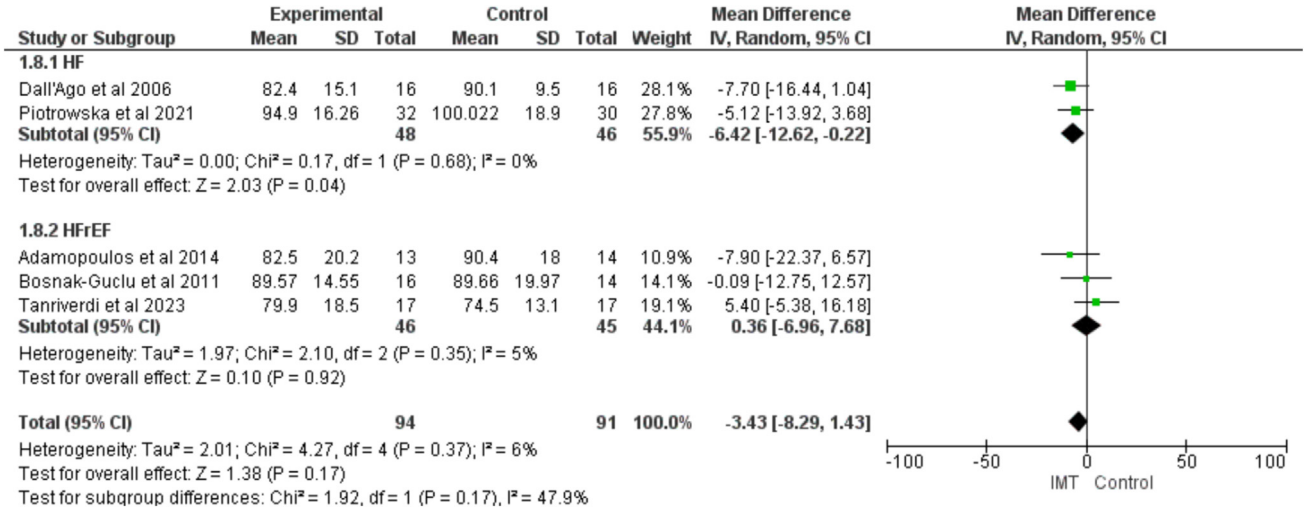

Fig. 10. Forest plot for the outcome of FEV1. This figure depicts no significant change in FEV1 with IMT.
CI, confidence interval; FEV1, forced expiratory volume in 1 s.

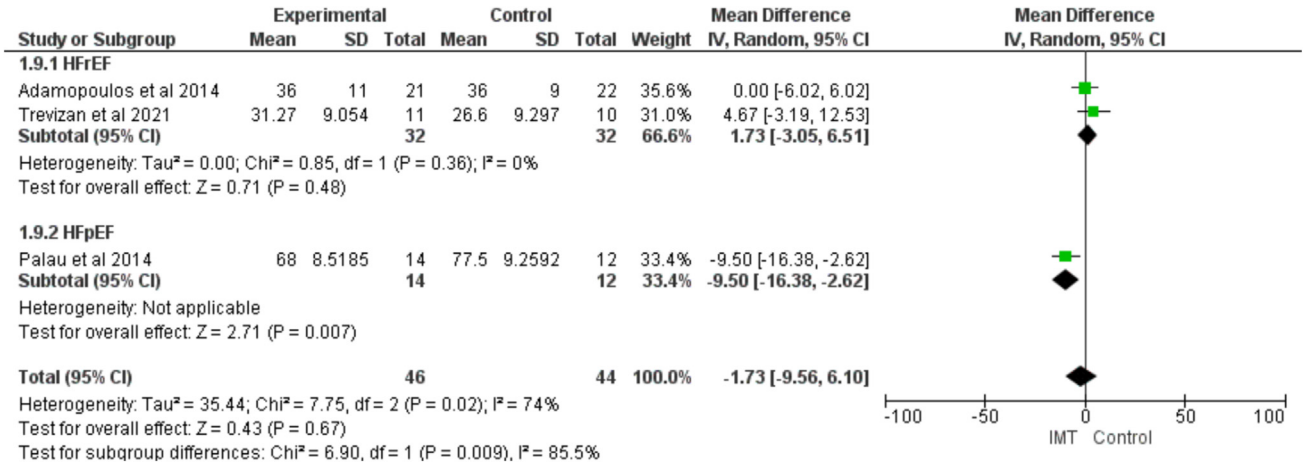

Fig. 11. Forest plot for the outcome of LVEF. This figure depicts no significant change in LVEF with IMT.
CI, confidence interval; LVEF, left ventricular ejection fraction.

PImax and METs, although it also caused a decrease in vital capacity and FEV1, likely due to increased respiratory muscle fatigue and the added load on the respiratory system during intensive exercise [15]. In contrast, IMT alone was associated with significant increases in vital capacity and FEV1 [15]. Lastly, Lin et al. assessed the combination of IMT with an autonomous walking program, showing notable improvements in the MLHFQ for participants in the combined program [14]. Regarding RT and IMT, Laoutaris et al. demonstrated that combining RT, AE, and IMT resulted in the greatest improvements in circulatory power, 6MWT performance, QoL, limb muscle indices, inspiratory muscle function, and dyspnea [47]. These findings suggest that combining IMT with AE and RT may enhance inspiratory muscle performance, alleviate exertional dyspnea, and improve limb muscle strength, which collectively reduce fatigue and improve endurance during daily activities [47].

Previous studies have highlighted the benefits of combining IMT with AE, CR, and RT. This combined regimen offers a comprehensive rehabilitation strategy for patients with HF. We have also included additional references [47] to support this discussion and strengthen our analysis. Moreover, previous studies have reported varying approaches to the frequency, duration, intensity, and respiratory rate control in IMT. Most studies included in our analysis employed a training regimen of at least 30 min per day with 6–7 sessions per week [10,16,23,25,29]. Regarding the training cycle, the longest duration reported was 24 weeks, as described by Kinugasa et al. [29], while the shortest was 4 weeks, as demonstrated by Marco et al. [24]. Ramirez-Sarmiento et al. [48] observed that a minimum of 5 weeks of IMT is required to induce structural and functional changes in respiratory muscles in patients with chronic obstructive pulmonary disease. Similarly, McConnell demonstrated that a minimum of 3 weeks of IMT benefits patients with asthma [49]. These findings suggest that an IMT intervention lasting between 3 and 5 weeks may significantly benefit patients with HF. Furthermore, although the studies varied in factors such as sample sizes, training duration, control group treatment, frequency, and load of IMT, the consistent outcome across studies was that higher intensity training yielded greater gains. Based on these findings, it can potentially be concluded that an intensity of 60 % is optimal for IMT [13,17,31]. Additionally, a progression from an initial load of 30 % to 60 %–70 % or higher may potentially further enhance the effectiveness of the intervention [15,18].

IMT offers a range of benefits across outcomes for both HFrEF and HFpEF patients. Our results demonstrated that IMT significantly improved ventilatory efficiency (VE/VCO2 slope), QoL, and functional and exercise capacity (6MWD) in both groups. Additionally, IMT led to a notable reduction in NT-proBNP levels, particularly in the HFpEF subgroup, indicating a decrease in cardiac stress. The greater reduction in NT-proBNP in the HFpEF group may be partially due to the larger number of studies assessing NT-proBNP in this subgroup, compared to only one study in HFrEF. Thus, further research is needed to confirm

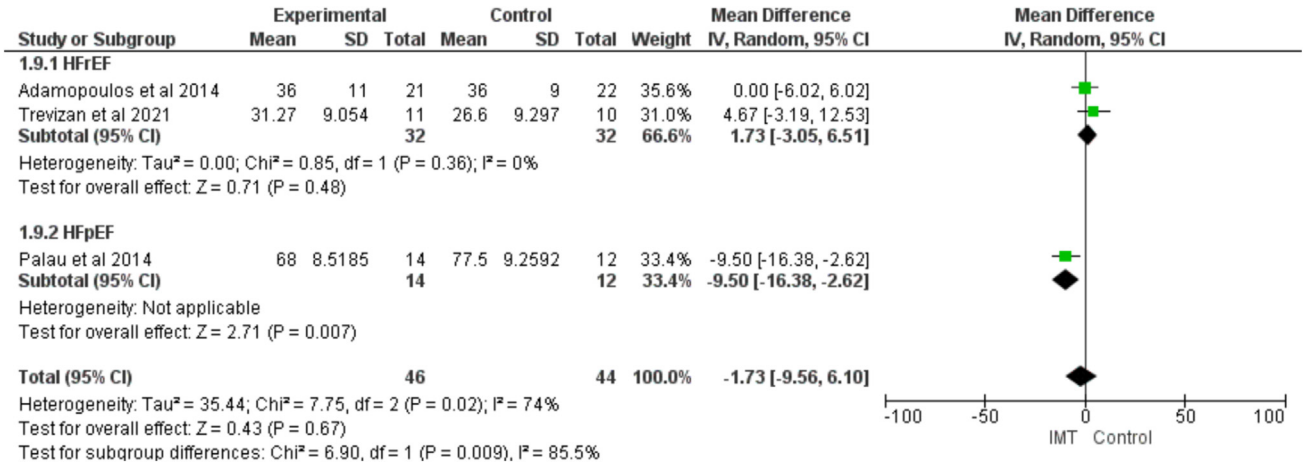

Fig. 12. Forest plot for the outcome of METs. This figure depicts no significant change in METs with IMT.
CI, confidence interval; METs, metabolic equivalent of training.

the impact of IMT on NT-proBNP levels in HFrEF and to clarify trends across both HF phenotypes.

We observed substantial heterogeneity in several outcomes, which led us to perform an LOO sensitivity analysis. Excluding Dall'Ago et al. [25] from the 6MWD analysis significantly reduced heterogeneity. This study involved a younger cohort with severe inspiratory muscle weakness (MIP ≤70 % predicted) and lower mean LVEF (≤45 %), using a more intensive IMT regimen (7 sessions per week). This differed from the broader meta-analysis baseline, which included a wider age range, moderate IMT intensity (typically 3–5 sessions per week), and varied degrees of inspiratory muscle strength. For VE/VCO2, removing Adamopoulos et al. [31] decreased heterogeneity, likely due to this study's inclusion of patients with diverse ages and baseline physical exercises, contrasting with the generally narrower age range and focused IMT interventions in the meta-analysis baseline. Finally, for the QoL outcome, excluding Mello et al. [11] resulted in a slight reduction in heterogeneity. This study specifically targeted patients with systolic HF and atrial hypertension, which differed from the overall meta-analysis baseline that included patients with stable HF. These findings highlight the need for future research to ensure more homogeneous patient selection in studies.

Strengths and limitations

The strengths of our study include the larger number of RCTs, and a greater sample size compared to a previous meta-analysis. While the previous analysis included data from 354 patients, our study examined data from a total of 510 patients, demonstrating stronger analytical power. The increased sample size and broader range of RCTs provide a more comprehensive evaluation of the effects of IMT on HF, leading to more reliable conclusions. The strengths of this meta-analysis lie in the inclusion of a larger number of RCTs, and a significantly greater sample size compared to previous studies, thereby increasing the analytical power of the analysis. The expanded sample size and broader range of RCTs enable a more comprehensive evaluation of the impact of IMT on HF, leading to more reliable and generalizable conclusions.

Additionally, we conducted an exhaustive literature search, ensuring no relevant studies were left out. We applied strict inclusion and exclusion criteria, used a random effects model meta-analysis to minimize bias, and performed a sensitivity analysis to identify and address sources of heterogeneity. However, this study has some limitations. First, the sample sizes of the included studies were generally small, and only four studies focused on patients with HFpEF, potentially limiting the generalizability of our findings. This small representation restricts the statistical power and generalizability of findings specific to this subgroup, which is inherently heterogeneous and characterized by distinct pathophysiological mechanisms compared with HFrEF. The underrepresentation of HFpEF studies may also reflect a broader gap in clinical research, as patients with HFpEF have historically been less studied. While our subgroup analysis cautiously suggests potential benefits of IMT in HFpEF patients, the limited sample size and heterogeneity of these studies warrant careful interpretation. To establish the efficacy of IMT in this subgroup, future research should focus on larger, HFpEF-specific cohorts and explore tailored IMT protocols that address the unique clinical and physiological characteristics of these patients. Second, only a limited number of studies with small sample sizes reported data on changes in LVEF due to the implementation of IMT, making it challenging to accurately assess the effects of IMT on LVEF. Future RCTs with larger sample sizes are necessary to better evaluate the impact of IMT on LVEF. Lastly, the included studies exhibit variability in study design, patient populations, and IMT protocols, contributing to heterogeneity in the results. Variability in IMT protocols across the included studies, including differences in intensity, duration, frequency, and adherence to intervention could be the explanation for this observed heterogeneity. Additionally, variability in patients' clinical characteristics, such as baseline functional capacity, severity of HF, and the presence of comorbid conditions, likely also contributed to the observed heterogeneity. These factors underscore the need for standardization in future trials. Future studies should adopt uniform IMT protocols, specifying clear thresholds for session intensity, frequency and exercise duration and also stratify results based on consistent baseline patient characteristics. Although we performed subgroup analyses and sensitivity tests to account for these differences, residual confounding cannot be entirely excluded.

Conclusion

In summary, implementation of IMT in patients with HF can significantly enhance ventilation efficacy, address inspiratory muscle weakness, improve exercise capacity, and support cardiac function. Hence, based on our results IMT should be considered as an adjunct to both pharmacological and non-pharmacological treatments to further improve symptoms in patients with HF. However, due to existing limitations, further large-scale, multicenter-controlled trials are necessary to validate these findings, investigate IMT's effects specifically on the HFpEF population, and identify the optimal IMT intervention protocols.

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CRediT authorship contribution statement

Ahmed Kamal Siddiqi: Conceptualization, Writing – original draft, Investigation, Writing – review & editing, Methodology, Data curation. **Maryam Shahzad:** Data curation, Investigation, Visualization, Writing – original draft, Formal analysis. **Akash Kumar:** Visualization, Writing – original draft, Data curation, Formal analysis. **Manahil Ahmed:** Supervision, Validation, Writing – review & editing. **Lakshmi Sridharan:** Writing – review & editing, Supervision, Project administration. **Mahmoud H. Abdou:** Writing – review & editing, Supervision, Project administration. **Muhammad Naeem:** Writing – review & editing, Visualization.

Declaration of competing interest

The authors state that they do not have any known conflicting financial interests or personal relationships that could have influenced the work documented in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2025.01.016

Data availability

All data sources utilized are available in the result and supplementary section and cited in the references.

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