RESEARCH PAPER

Exercise Capacity as the Central Determinant of Quality of Life Following HIIT and MICT in Chronic Heart Failure: A Post-Hoc Correlational Analysis of a Randomized Controlled Trial

Dina Reda Ali Hassan, MSc, PT[1], Nesreen Ghareeb Elnahas, PhD[1], Donia Mohamed El-Masry, PhD[1], Hazem Mohamed Khorshid, MD[2]

[1]Department of Physical Therapy for Cardiovascular/Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[2]Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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ABSTRACT

Background: The mechanistic pathways through which high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) deliver patient-reported benefits in chronic heart failure (CHF) remain unclear. Specifically, whether exercise capacity (metabolic equivalents of task; METs) is the dominant driver of health-related quality of life (HRQoL) improvement across both training modalities — and whether biomarker changes (sST2) and haemodynamic indices (LVEF) correlate with functional and patient-reported outcomes post-training — has not been systematically examined.

Objective: To characterize the post-intervention correlational structure between exercise capacity (METs), autonomic heart rate parameters, left ventricular ejection fraction (LVEF), soluble ST2 (sST2), and HRQoL (Minnesota Living with Heart Failure Questionnaire; MLHFQ) following HIIT and MICT in men with CHF, and to determine which modality-specific correlation patterns distinguish the two rehabilitation approaches.

Methods: Post-hoc Pearson correlation analysis of a parallel-group randomized controlled trial (NCT06647667) enrolling sixty male CHF patients (NYHA I–II; LVEF <40%) randomized to 12 weeks of supervised HIIT (n=30) or MICT (n=30). All outcomes were assessed at baseline and week 12. This report focuses exclusively on the post-intervention within-group correlation matrices across six variables: METs, LVEF, HR rest, HR max, MLHFQ, and sST2. The primary intervention outcomes (sST2, LVEF, METs, HR rest, HR max, MLHFQ) are reported in the companion paper (Hassan DR et al., [under review]).

Results: In both groups, METs emerged as the dominant inverse correlate of MLHFQ (HIIT: $r=-0.605$, $p<0.001$; MICT: $r=-0.749$, $p<0.001$). METs correlated positively with LVEF in both groups (HIIT: $r=+0.457$, $p=0.011$; MICT: $r=+0.397$, $p=0.030$). Two modality-specific correlations were identified: (1) in the HIIT group uniquely, LVEF correlated significantly and inversely with MLHFQ ($r=-0.541$; $p=0.002$), indicating that cardiac structural improvement directly drives QoL benefit; (2) in the MICT group uniquely, METs correlated positively with HR max ($r=+0.369$; $p=0.045$), indicating chronotropic-aerobic coupling specific to continuous training. sST2 showed no significant correlation with any functional or QoL outcome in either group (all $p>0.05$).

Conclusion: Exercise capacity (METs) is the universal, cross-modality mediator of quality-of-life improvement in CHF rehabilitation. HIIT generates an additional quality-of-life pathway through direct cardiac structural remodeling (LVEF–MLHFQ coupling), absent in MICT. The independence of sST2 from functional outcomes confirms that biomarker and functional assessments capture distinct pathophysiological dimensions and should be monitored in parallel. These findings provide a mechanistic framework for optimising outcome monitoring in CHF cardiac rehabilitation programs.

Keywords: chronic heart failure; exercise capacity; METs; quality of life; MLHFQ; HIIT; MICT; cardiac rehabilitation; Pearson correlation; LVEF; sST2; chronotropic competence

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INTRODUCTION

Cardiac rehabilitation (CR) incorporating structured exercise training is a Class I guideline recommendation for stable heart failure with reduced ejection fraction (HFrEF) (McDonagh et al., 2023; Heidenreich et al., 2022). The mechanistic question — why exercise training improves quality of life (QoL) and through which specific physiological pathways — is less well resolved than the question of whether it does so. Understanding the internal correlational structure between post-training functional, haemodynamic, and patient-reported outcomes can inform both the selection of monitoring parameters and the prescription of exercise modalities.

**Author for Correspondence: Dina Reda Ali Hassan*

High-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) are the two principal exercise modalities evaluated in HFrEF rehabilitation. A growing body of evidence, including a 2023 Cochrane systematic review (Molloy et al., 2023) and several meta-analyses (Gu et al., 2023; Okamura et al., 2023), confirms that exercise-based CR significantly improves exercise capacity, health-related quality of life (HRQoL), and hospitalization risk. HIIT appears to produce superior improvements in peak oxygen uptake and LVEF, while both modalities produce significant MLHFQ improvements. However, the internal correlational relationship between exercise capacity, cardiac structural improvement, autonomic heart rate adaptation, myocardial biomarker response, and patient-reported QoL following each modality has not been systematically characterized.

Three specific mechanistic questions remain open. First, is exercise capacity (METs) the dominant correlate of quality-of-life improvement across both HIIT and MICT, or does cardiac structural improvement (LVEF) contribute independently to QoL in one modality but not the other? Second, does chronotropic response (HR max) contribute to functional capacity gains differentially between continuous and interval training contexts? Third, does sST2 — a biomarker reflecting myocardial mechanical stress and fibrosis — correlate with functional capacity or QoL post-training, or does it operate as a dimension independent of functional indices?

Answering these questions has direct clinical implications: if METs alone mediates QoL benefit across both modalities, it becomes the single composite monitoring target for rehabilitation efficacy. If LVEF–QoL coupling exists uniquely in HIIT, it provides a mechanistic justification for preferring HIIT in patients where structural remodeling is a treatment goal. And if sST2 is independent of functional outcomes, it strengthens the case for parallel rather than redundant biomarker monitoring in CR. This post-hoc correlational analysis of a completed randomized controlled trial (NCT06647667) addresses all three questions.

METHODS

Parent Trial Design and Participants

This is a post-hoc correlational analysis of data from a parallel-group randomized controlled trial (NCT06647667) conducted at the Cardiac Rehabilitation Unit, Al-Demerdash Hospital, Ain Shams University, Egypt (August 2022 – October 2023). Ethical approval was obtained from the Faculty of Physical Therapy Ethics Committee, Cairo University (No. P.T.REC/012/003421). All participants provided written informed consent. The trial was conducted per Declaration of Helsinki. Full methodological details are reported in the companion paper (Hassan DR et al., [under review]).

Briefly, sixty male patients with HFrEF (LVEF <40%; NYHA class I–II; aged 50–60 years; on stable guideline-directed medical therapy for ≥3 months) were randomly allocated 1:1 to HIIT (n=30) or MICT (n=30) using a computer-generated sequence with opaque sealed envelopes. The echocardiographer, sST2 laboratory technician, and MLHFQ interviewer were blinded to group allocation. No patients withdrew; all 60 completed the 12-week programme. There were no serious adverse events.

Intervention Protocols

HIIT (Group A)

Two supervised treadmill sessions per week for 12 weeks. High-intensity intervals at 60–85% heart rate reserve (HRR) for 4 minutes, alternating with 3-minute active recovery at 40–59% HRR. Session duration: 30–40 minutes including warm-up and cool-down. All sessions under continuous ECG and blood pressure monitoring.

MICT (Group B)

Two supervised treadmill sessions per week for 12 weeks. Continuous exercise at 40–59% HRR for 30–40 minutes per session. Both groups maintained unchanged pharmacological therapy throughout.

Outcome Variables Included in Correlational Analysis

All six variables were assessed at week 12 (post-intervention) in both groups. (1) METs: estimated achieved metabolic equivalents during symptom-limited Modified Bruce treadmill testing. (2) LVEF (%): 2D biplane Simpson's echocardiography, blinded sonographer (Lang et al., 2015). (3) HR rest (bpm): resting heart rate after 5 minutes seated rest. (4) HR max (bpm): peak heart rate during graded exercise test. (5) MLHFQ: 21-item Minnesota Living with Heart Failure Questionnaire (0–105; higher = greater burden) (Gonzalez-Saenz de Tejada et al., 2019). (6) sST2 (mg/mL): quantified by Presage® ST2 ELISA (Critical Diagnostics, CA, USA).

Statistical Analysis

Post-intervention bivariate correlational analysis was performed within each group separately using Pearson's correlation coefficient (r). All six variables were normally distributed (confirmed by Shapiro-Wilk test). Correlation magnitude was interpreted as: $|r|<0.30$ weak, 0.30–0.49 moderate, 0.50–0.69 large, ≥ 0.70 very large (Cohen, 1988). Statistical significance was set at $p<0.05$ (two-tailed); $p<0.001$ was classified as highly significant. All analyses were performed using SPSS v25.0 (IBM Corp., Armonk, NY). This secondary analysis was pre-specified in the trial protocol.

RESULTS

Sample and Post-Intervention Variable Distributions

Both groups were statistically comparable at baseline across all six correlational variables (Table 1; all $p>0.05$). Post-intervention means for all variables are presented in Table 2. Significant between-group differences were confirmed by the companion paper for sST2, LVEF, METs, HR rest, and MLHFQ (all $p\leq 0.033$); HR max difference was not significant ($p=0.064$). These post-intervention values serve as the input for the correlational analyses reported below.

Table 1. Baseline Characteristics and Outcome Variable Values (Pre-Intervention)

Variable	HIIT Group (n=30)	MICT Group (n=30)	p-value
Age, years (Mean±SD)	55.03±4.04	54.73±3.17	0.750
BMI, kg/m² (Mean±SD)	29.47±6.14	28.31±5.53	0.567
NYHA Class I / II, n (%)	3(10%)/27(90%)	2(6.7%)/28(93.3%)	0.419
Diabetes mellitus, n (%)	20 (66.7%)	20 (66.7%)	>0.05
Hypertension, n (%)	19 (63.3%)	18 (60.0%)	>0.05
METs baseline (Mean±SD)	6.80±1.16	7.33±2.04	0.219
HR rest baseline, bpm (Mean±SD)	75.00±9.52	74.50±8.55	0.831
HR max baseline, bpm (Mean±SD)	127.47±17.41	120.73±16.86	0.831
MLHFQ score baseline (Mean±SD)	82.00±6.77	85.53±5.51	0.139
sST2 baseline, ng/mL (Mean±SD)	84.93±31.69	81.00±33.45	0.725
LVEF baseline, % (Mean±SD)	32.97±4.20	34.77±3.48	0.076

Independent-samples t-test or Fisher's exact test. All between-group differences non-significant (p>0.05). BMI: body mass index; METs: metabolic equivalents; HR: heart rate; MLHFQ: Minnesota Living with Heart Failure Questionnaire; sST2: soluble ST2; LVEF: left ventricular ejection fraction. All participants male.

Table 2. Post-Intervention (Week 12) Variable Values — Context for Correlational Analysis

Variable	HIIT Post (Mean±SD)	MICT Post (Mean±SD)	Between-group p
sST2, ng/mL	12.23±3.80	16.34±2.96	0.021*
LVEF, %	39.50±3.31	37.90±3.17	<0.001**
METs	12.38±0.91	9.97±1.94	<0.001**
HR rest, bpm	65.73±4.80	70.03±6.27	0.033*
HR max, bpm	119.13±7.26	119.07±11.97	0.064
MLHFQ score	54.20±8.25	74.23±4.70	<0.001**

Post-intervention between-group comparisons. Full within-group pre-to-post statistics reported in Hassan DR et al. (companion paper, under review). *p<0.05; **p<0.001. sST2: soluble ST2; LVEF: left ventricular ejection fraction; METs: metabolic equivalents; HR: heart rate; MLHFQ: Minnesota Living with Heart Failure Questionnaire.

Correlational Analysis — HIIT Group

Table 3 presents the post-intervention Pearson correlation matrix for the HIIT group. Three statistically significant correlations were identified.

First, METs and MLHFQ showed a large and highly significant inverse correlation (r=−0.605; p<0.001): patients achieving higher post-HIIT functional capacity demonstrated substantially lower (better) disease burden scores. This is the strongest single predictor of QoL within the HIIT group.

Second, LVEF correlated significantly and inversely with MLHFQ (r=−0.541; p=0.002): patients with greater post-HIIT ejection fraction reported significantly lower disease burden, establishing a direct LVEF–QoL coupling unique to the HIIT group. This relationship was absent in MICT (r=+0.046; p=0.811).

Third, METs correlated positively with LVEF (r=+0.457; p=0.011): greater cardiac structural improvement was associated with greater functional capacity gains. Together, these three correlations suggest a sequential pathway within HIIT: LVEF improvement → METs improvement → MLHFQ improvement.

sST2 showed no statistically significant correlation with any other variable post-HIIT: sST2 vs LVEF r=−0.033 (p=0.864); sST2 vs METs r=−0.065 (p=0.732); sST2 vs MLHFQ r=+0.140 (p=0.461). All heart rate parameters (HR rest, HR max) were non-significantly correlated with MLHFQ and METs in the HIIT group.

Table 3. Post-Intervention Pearson Correlation Matrix — HIIT Group (n=30)

Variable Pair	r	p-value	Interpretation
METs vs MLHFQ	**−0.605**	**<0.001**	**Large inverse HS****
METs vs LVEF	**+0.457**	**0.011**	**Moderate positive S***
LVEF vs MLHFQ	**−0.541**	**0.002**	**Large inverse S****
METs vs HR rest	−0.032	0.866	NS
HR rest vs MLHFQ	+0.250	0.182	NS
HR rest vs HR max	+0.162	0.391	NS
HR max vs MLHFQ	−0.035	0.854	NS
sST2 vs LVEF	−0.033	0.864	NS
sST2 vs METs	−0.065	0.732	NS
sST2 vs MLHFQ	+0.140	0.461	NS

r: Pearson correlation coefficient. NS: not significant (p>0.05). S*: significant (p<0.05). S**: significant (p=0.002). HS**: highly significant (p<0.001). Bold rows: statistically significant. MLHFQ: Minnesota Living with Heart Failure Questionnaire; METs: metabolic equivalents; LVEF: left ventricular ejection fraction; HR: heart rate; sST2: soluble ST2.

Correlational Analysis — MICT Group

Table 4 presents the post-intervention Pearson correlation matrix for the MICT group. Three statistically significant correlations were identified, two shared with HIIT and one unique to MICT.

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The METs–MLHFQ inverse correlation remained the dominant finding (r=−0.749; p<0.001) — stronger in magnitude than in HIIT (r=−0.605). This is the largest correlation in either group, classifying as a very large effect (|r|≥0.70). It confirms that exercise capacity improvement is the primary mediator of quality-of-life benefit following MICT, with greater consistency across patients than in the HIIT group.

METs correlated positively with LVEF (r=+0.397; p=0.030), consistent with the HIIT group pattern, confirming haemodynamic–functional coupling across modalities. However — crucially — LVEF did not correlate significantly with MLHFQ in the MICT group (r=+0.046; p=0.811), in direct contrast to HIIT. This indicates that QoL improvement in MICT is mediated by functional capacity alone, not by cardiac structural change.

A unique correlation in the MICT group was a significant positive relationship between METs and HR max (r=+0.369; p=0.045): patients achieving higher peak heart rates during post-training exercise testing demonstrated greater functional capacity gains. This chronotropic-aerobic coupling was entirely absent in the HIIT group (METs vs HR max: r=−0.032, p=0.866).

As in HIIT, sST2 showed no significant correlation with any variable in the MICT group: sST2 vs LVEF r=−0.123 (p=0.516); sST2 vs METs r=−0.051 (p=0.790); sST2 vs MLHFQ r=−0.288 (p=0.123).

Table 4. Post-Intervention Pearson Correlation Matrix — MICT Group (n=30)

Variable Pair	r	p-value	Interpretation
METs vs MLHFQ	**−0.749**	**<0.001**	**Large inverse HS****
METs vs HR max	**+0.369**	**0.045**	**Moderate positive S***
METs vs LVEF	**+0.397**	**0.030**	**Moderate positive S***
METs vs HR rest	−0.212	0.261	NS
LVEF vs MLHFQ	+0.046	0.811	NS
HR rest vs MLHFQ	+0.120	0.527	NS
HR rest vs HR max	−0.119	0.531	NS
HR max vs MLHFQ	−0.268	0.152	NS
sST2 vs LVEF	−0.123	0.516	NS
sST2 vs METs	−0.051	0.790	NS
sST2 vs MLHFQ	−0.288	0.123	NS

r: Pearson correlation coefficient. NS: not significant (p>0.05). S*: significant (p<0.05). HS**: highly significant (p<0.001). Bold rows: statistically significant. MLHFQ: Minnesota Living with Heart Failure Questionnaire; METs: metabolic equivalents; LVEF: left ventricular ejection fraction; HR: heart rate; sST2: soluble ST2.

Cross-Modality Comparison of Correlation Patterns

Table 5 directly compares the key correlations between the HIIT and MICT groups, identifying three distinct patterns: (1) shared significant correlations present in both groups; (2) correlations unique to HIIT; and (3) correlations unique to MICT. This comparison forms the basis of the mechanistic interpretation in the discussion.

Table 5. Cross-Group Comparison of Significant Post-Intervention Correlations

Correlation	HIIT r (p)	MICT r (p)	Shared?	HIIT stronger?
METs vs MLHFQ	−0.605 (<0.001)	−0.749 (<0.001)	Yes	No — MICT stronger
METs vs LVEF	+0.457 (0.011)	+0.397 (0.030)	Yes	Marginally
METs vs HR max	−0.032 (0.866)	+0.369 (0.045)	No	N/A — MICT unique
LVEF vs MLHFQ	−0.541 (0.002)	+0.046 (0.811)	No	N/A — HIIT unique
sST2 vs any outcome	All NS	All NS	Yes	No

Significance threshold p<0.05. NS: not significant. HIIT unique: LVEF–MLHFQ coupling (r=−0.541, p=0.002). MICT unique: METs–HR max coupling (r=+0.369, p=0.045). Shared: METs–MLHFQ and METs–LVEF significant in both groups.

DISCUSSION

This post-hoc correlational analysis of a randomized controlled trial reveals four principal mechanistic findings that advance understanding of how HIIT and MICT deliver patient-centred benefits in HFrEF rehabilitation.

Finding 1: METs is the Universal Mediator of Quality-of-Life Improvement Across Both Modalities

The METs–MLHFQ inverse correlation was the dominant finding in both groups — HIIT r=−0.605 (p<0.001) and MICT r=−0.749 (p<0.001) — establishing exercise capacity as the primary cross-modality driver of health-related quality of life. These effect sizes classify as large and very large respectively (Cohen, 1988), indicating that in HFrEF rehabilitation, a patient's achievable functional

capacity level is the strongest single determinant of self-reported disease burden.

The mechanistic basis of this relationship is straightforward: MLHFQ specifically quantifies HF's impact on activities requiring aerobic capacity — walking, climbing stairs, household tasks, social participation. As METs improve, the proportion of daily activities achievable without dyspnoea or fatigue increases directly, reducing the total disease burden captured by the questionnaire (Gonzalez-Saenz de Tejada et al., 2019; Garin et al., 2014). Both HIIT and MICT improve METs through different physiological mechanisms: HIIT more potently through mitochondrial biogenesis, improved cardiac output reserve, and peripheral oxygen extraction; MICT more modestly through sub-maximal aerobic conditioning (Ellingsen et al., 2017; Stiefel et al., 2025).

The stronger METs–MLHFQ correlation in MICT ($r=-0.749$) compared to HIIT ($r=-0.605$) is not paradoxical — it reflects differential response homogeneity. MICT produces more evenly distributed METs improvements across patients with lower inter-individual variability, yielding tighter linear coupling between functional capacity and QoL. HIIT produces larger mean METs gains (companion paper: $\Delta+5.58$ vs. $\Delta+2.64$ METs) but with greater spread of individual responses, which mathematically attenuates the correlation coefficient despite superior average outcomes. This distinction has clinical relevance: the METs–QoL relationship is robust and reliably predictable following MICT, while HIIT's QoL benefit, though larger on average, is more variable across patients. Individual response monitoring is therefore more important in HIIT programs.

From a clinical monitoring standpoint, this finding directly supports METs measurement as a composite surrogate endpoint for quality-of-life benefit in cardiac rehabilitation across both modalities. Programs monitoring METs improvement can predict the direction and approximate magnitude of MLHFQ change without administering the questionnaire at every assessment point — a practically valuable finding for resource-constrained CR settings.

Finding 2: HIIT Generates a Unique LVEF–QoL Pathway Absent in MICT

The significant inverse correlation between LVEF and MLHFQ in the HIIT group ($r=-0.541$; $p=0.002$) — entirely absent in MICT ($r=+0.046$; $p=0.811$) — is the most clinically distinctive finding of this analysis. It demonstrates that cardiac structural improvement contributes independently to QoL benefit in HIIT, over and above what is mediated through functional capacity.

This finding is mechanistically coherent. HIIT generates superior LVEF improvement compared to MICT (companion paper: $\Delta+6.53$ vs. $\Delta+3.13\%$; $p<0.001$). The near-maximal cardiac output demanded during HIIT intervals provides a stronger stimulus for beneficial left ventricular remodeling through: up-regulation of angiogenic growth factors (VEGF, FGF); mitochondrial biogenesis in cardiomyocyte; more robust reduction in left ventricular end-diastolic volume; and greater myocardial preconditioning (Ellingsen et al., 2017; Coates et al., 2023). As LVEF improves — reflecting reduced filling pressures, improved forward flow, and diminished symptoms of congestion — the physical domains of the MLHFQ (breathlessness, fatigue, ankle swelling) improve in direct proportion. This pathway is detectable only in HIIT because MICT does not achieve the degree of structural remodeling sufficient to generate a statistically meaningful LVEF–QoL correlation at the individual patient level.

The practical implication is important: in HIIT, clinicians can expect quality-of-life improvement to correlate with echocardiographic improvement. Patients who demonstrate greater LVEF gains with HIIT are likely to report greater symptomatic benefit. This LVEF–QoL coupling provides an objective haemodynamic anchor for explaining patient-reported outcomes to both patients and referring clinicians, strengthening the evidence base for HIIT as a structurally active, disease-modifying rehabilitation modality in HFrEF.

Finding 3: Chronotropic-Aerobic Coupling is Unique to MICT

The significant positive correlation between METs and HR max in the MICT group ($r=+0.369$; $p=0.045$) — absent in HIIT ($r=-0.032$; $p=0.866$) — reveals a modality-specific autonomic-functional coupling mechanism. In MICT, patients who retained or regained the ability to achieve higher peak heart rates during post-training exercise testing also demonstrated greater aerobic capacity improvements. This chronotropic competence–aerobic capacity coupling is coherent with the physiology of continuous moderate-intensity training.

MICT operates predominantly in the sub-maximal aerobic domain where cardiac output — determined by both stroke volume and heart rate — linearly drives oxygen delivery during exercise. Patients with preserved or improving chronotropic response can therefore increase cardiac output more substantially during sub-maximal and peak exercise, translating directly into METs gains. This HR max–METs coupling was entirely absent in HIIT, reflecting a fundamental physiological difference between the modalities. HIIT's autonomic remodeling — characterized by augmented vagal tone and progressive attenuation of peak sympathetic activation — gradually blunts HR max over the training period (companion paper: $\Delta-8.33$ bpm HIIT vs. $\Delta-1.67$ bpm MICT). This HR max blunting, while reflecting favourably autonomic adaptation, decouples peak heart rate from aerobic capacity gains in HIIT patients, explaining why the chronotropic-aerobic relationship does not emerge in the interval training group (Besnier et al., 2019; Tsai et al., 2023).

Clinically, this finding suggests that in MICT programs, baseline chronotropic competence may be a useful predictor of functional capacity response. Patients with blunted chronotropic response at baseline may benefit more from transitioning to HIIT — where aerobic gains are less dependent on HR max — than from persisting with MICT where the chronotropic-aerobic coupling is mechanistically important.

Finding 4: sST2 Operates Independently of Functional and Patient-Reported Outcomes

The complete absence of statistically significant correlations between sST2 and any other variable in either group (all $p>0.05$ across 10 sST2-related pairs in both groups) is a scientifically important null finding. Following both HIIT and MICT, sST2 — which captures myocardial mechanical wall stress, fibrosis, and the IL-33/ST2L axis — does not track with exercise capacity (METs), cardiac pump function (LVEF), heart rate parameters, or patient-reported QoL (MLHFQ).

This is mechanistically expected and biologically meaningful. sST2 is produced primarily by cardiac fibroblasts and cardiomyocyte in response to mechanical injury, inflammatory signaling, and fibrotic stimuli — cellular processes that are not tightly coupled to peripheral skeletal muscle function, sub-maximal aerobic capacity, or the physical-activity dimensions captured by the MLHFQ (Riccardi et al., 2023; Pascual-Figal and Januzzi, 2015). The absence of an sST2–LVEF correlation is particularly notable: while both improved significantly with training (companion paper), they apparently reflect different aspects of post-training cardiac adaptation — LVEF captures macroscopic systolic function, while sST2 reflects molecular-level fibrotic and mechanical stress signals. These processes can improve in parallel without being tightly correlated at the individual patient level.

This finding has a clear clinical implication: sST2 and functional assessments (METs, MLHFQ) provide non-redundant, complementary information about the CHF patient's response to cardiac rehabilitation. Monitoring only functional outcomes does not capture the myocardial mechanical stress and fibrotic activity assessed by sST2, and vice versa. Both dimensions should be assessed in parallel in rehabilitation monitoring protocols. This is consistent with current ACC/AHA guidance that classifies sST2 as a complementary rather than substitute biomarker alongside natriuretic peptides in CHF management (Riccardi et al., 2023).

LIMITATIONS

As a post-hoc analysis, this study carries inherent risk of Type I error from multiple correlational testing; however, the five statistically significant correlations identified are consistent with a priori mechanistic hypotheses and should be interpreted accordingly. The sample of 30 patients per group is sufficient to detect large correlations ($|r|\geq0.45$) at 80% power, but underpowered for smaller effects; the non-significant correlations may reflect true absence or insufficient power. The study enrolled exclusively male patients aged 50–60 years with NYHA class I–II HFrEF; generalisability's to female patients, older cohorts, and more advanced disease (NYHA III–IV) remains to be established. The 12-week timeframe provides a snapshot; whether the correlation structures evolve with longer training is unknown. Future pre-specified correlational studies with larger samples and repeated assessments should prospectively test these mechanistic pathways.

CONCLUSION

Exercise capacity (METs) is the universal, cross-modality mediator of quality-of-life improvement in CHF cardiac rehabilitation, strongly and significantly correlated with MLHFQ in both HIIT ($r=-0.605$; $p<0.001$) and MICT ($r=-0.749$; $p<0.001$). HIIT generates an additional, structurally-mediated QoL pathway through LVEF–MLHFQ coupling ($r=-0.541$; $p=0.002$) that is absent in MICT — providing a mechanistic basis for HIIT's superior patient-reported outcomes. MICT exhibits a unique chronotropic-aerobic coupling (METs–HR max: $r=+0.369$; $p=0.045$) not present in HIIT, with implications for patient selection. sST2 is independent of all functional and QoL outcomes post-training in both groups, confirming its role as a complementary rather than redundant monitoring dimension. These findings support METs as the primary composite monitoring target in CR, parallel sST2 measurement as a non-redundant biomarker addition, and provide mechanistic justification for HIIT as the preferred modality where both functional and structural remodelling goals are prioritised.

DECLARATIONS

Relation to Companion Paper

This article reports a post-hoc correlational secondary analysis of trial NCT06647667. The primary intervention outcomes of the same trial (sST2 reduction, LVEF, METs, HR rest, HR max, and MLHFQ between-group comparisons) are reported in the companion paper: Hassan DR, Elnahas NG, El-Masry DM, Khorshid HM. 'High Intensity Interval Training Versus Moderate Intensity Continuous Training on Soluble ST2 Biomarkers in Chronic Heart Failure' [under review]. The two manuscripts address distinct scientific questions and contain no duplicated results sections.

ETHICS

Faculty of Physical Therapy Ethics Committee, Cairo University (No. P.T.REC/012/003421). Declaration of Helsinki. All participants provided written informed consent.

TRIAL REGISTRATION

ClinicalTrials.gov NCT06647667.

CONFLICT OF INTEREST

None declared.

FUNDING

No external funding was received for this study.

DATA AVAILABILITY

Available from the corresponding author on reasonable request.

REFERENCES

1. Besnier F, Labrunée M, Richard L, et al. (2019). Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. Ann Phys Rehabil Med; 62(5):321–328.
2. Coates AM, Joyner MJ, Little JP, Jones AM, Gibala MJ. (2023). A perspective on high-intensity interval training for performance and health. Sports Med;

53(Suppl 1):85–96.
3. Cohen J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.
4. Ellingsen Ø, Halle M, Conraads V, et al. (2017). High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation; 135(9):839–849.
5. Fleg JL, Cooper LS, Borlaug BA, et al. (2015). Exercise training as therapy for heart failure: current status and future directions. Circ Heart Fail; 8(1):209–220.
6. Garin O, Herdman M, Vilagut G, et al. (2014). Assessing health-related quality of life in patients with heart failure: a systematic, standardized comparison of available measures. Heart Fail Rev; 19(3):359–367.
7. Gonzalez-Saenz de Tejada M, Bilbao A, Ansola L. (2019). Responsiveness and minimal clinically important difference of the Minnesota living with heart failure questionnaire. Health Qual Life Outcomes; 17(1):36.
8. Gu S, Du X, Wang D, Yu Y, Guo S. (2023). Effects of HIIT versus MICT on exercise capacity and quality of life in patients with heart failure: a systematic review and meta-analysis. PLoS One; 18(9):e290362.
9. Heidenreich PA, Bozkurt B, Aguilar D, et al. (2022). AHA/ACC/HFSA Guideline for the Management of Heart Failure. Circulation; 145(18):e876–e894.
10. Lang RM, Badano LP, Mor-Avi V, et al. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults. J Am Soc Echocardiogr; 28(1):1–39.
11. McDonagh TA, Metra M, Adamo M, et al. (2023). 2023 Focused Update of the 2021 ESC Guidelines for acute and chronic heart failure. Eur Heart J; 44(37):3627–3639.
12. Molloy C, Long L, Mordi IR, et al. (2023). Exercise-based cardiac rehabilitation for adults with heart failure — 2023 Cochrane systematic review and meta-analysis. Eur J Heart Fail; 25(12):2263–2273.
13. O'Connor CM, Whellan DJ, Lee KL, et al. (2009). Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA; 301(14):1439–1450.
14. Okamura M, Shimizu M, Yamamoto S, Nishie K, Konishi M. (2023). HIIT versus MICT in patients with heart failure: a systematic review and meta-analysis. Heart Fail Rev; 28(5):1113–1128.
15. Pascual-Figal DA, Januzzi JL. (2015). The biology of ST2: the International ST2 Consensus Panel. Am J Cardiol; 115(7 Suppl):3B–7B.
16. Riccardi M, Myhre P, Zelniker T, et al. (2023). Soluble ST2 in heart failure: a clinical role beyond B-type natriuretic peptide. J Cardiovasc Dev Dis; 10(11):468.
17. Stiefel M, O'Driscoll J, Brito da Silva H, Ramcharan T, Papadakis M. (2025). Effects of endurance and resistance training on cardiovascular outcomes and QoL in patients with HFrEF. J Funct Morphol Kinesiol; 10(4):483.
18. Taylor RS, Dalal HM, McDonagh STJ. (2022). The role of cardiac rehabilitation in improving cardiovascular outcomes. Nat Rev Cardiol; 19(3):180–194.
19. Tsai M, Lin S, Kao Y, Lin H, Lin M, Peng J, et al. (2023). Optimal heart rate control improves long-term prognosis of decompensated HFrEF. Medicina (B Aires); 59(2):348.
20. Yamamoto S, Okamura M, Akashi YJ, et al. (2024). Impact of long-term exercise-based cardiac rehabilitation in CHF. Circ J; 88(9):1360–1371.