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CASE REPORT

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Effect of a multimodal exercise program combined with inspiratory muscle training on cardiovascular recovery, functional capacity, and quality of life in CKD patients with Type 4 cardiorenal syndrome

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ABSTRACT

Background: Chronic Kidney Disease (CKD)-associated Type 4 cardiorenal syndrome is marked by progressive cardiac dysfunction, reduced functional capacity, and impaired Quality of Life (QOL).

Objective: To determine whether a multimodal exercise programme combining flexibility, aerobic, and resistance training with Inspiratory Muscle Training (IMT) produces greater improvement in cardiovascular recovery, functional capacity, and QOL than IMT alone in patients with CKD-associated Type 4 cardiorenal syndrome.

Methods: Fifty-two participants were randomly allocated to an experimental group (multimodal exercise plus IMT, n=26) or a control group (IMT alone, n=26). Left Ventricular Ejection Fraction (LVEF), Heart Rate Recovery (HRR), Six-Minute Walk Distance (6MWD), Kidney Disease Quality of Life (KDQOL), and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were assessed pre- and post-intervention.

Results: Both groups improved significantly from baseline ($p<0.001$), but improvement was consistently and substantially greater in the experimental group across all five outcomes, with large-to-very-large effect sizes that remained significant after Bonferroni correction and ANCOVA adjustment for baseline scores.

Conclusion: Adding multimodal exercise training to IMT yields superior cardiovascular, functional and quality-of-life outcomes than respiratory training alone in Type 4 cardiorenal syndrome.

KEYWORDS

Cardiorenal syndrome; Chronic kidney disease; Exercise training; Inspiratory muscle training; Left ventricular ejection fraction; Functional capacity

ARTICLE HISTORY

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Introduction

CKD has emerged as one of the most pressing public health challenges of the present era. Globally, an estimated 788 million adults were living with CKD in 2023, corresponding to an age-standardized prevalence of 14.2% and a relative rise of more than three and a half percent since 1990. CKD is now the ninth leading cause of death worldwide, and impaired kidney function alone is estimated to account for over one-tenth of all cardiovascular deaths globally [1]. This tight coupling between a failing kidney and a failing heart is not incidental; it reflects a bidirectional pathophysiological relationship in which chronic dysfunction of one organ drives progressive injury to the other [2].

To capture this interdependence, Ronco and colleagues proposed a five-part classification of the Cardiorenal Syndromes (CRS), differentiating each subtype by the organ of primary insult and by the acuity of onset [2,3]. Within this framework, Type 4 CRS, also termed chronic renocardiac syndrome, describes the clinical situation in which a primary, chronic reduction in kidney function drives structural and functional deterioration of the heart, manifesting as ventricular hypertrophy, diastolic dysfunction, and heightened vulnerability to adverse cardiovascular events [4]. The mechanisms underlying this process are considered multifactorial, involving neurohormonal activation, chronic volume overload, accumulation of uraemic toxins, vascular calcification, and a persistent low-grade inflammatory state [4]. Together, these processes place patients with Type 4 CRS among the highest-risk cardiovascular populations encountered in clinical nephrology practice [2,4].

Two clinical hallmarks of this cardiac decline are of particular relevance to rehabilitation research: a reduction in LVEF, and impairment of the autonomic reflexes that govern cardiac recovery after exertion. HRR in the first minute after peak exercise, a marker of post-exercise vagal reactivation, has been shown to decline progressively across the stages of non-dialysis CKD, and is independently predicted by both age and estimated glomerular filtration rate [5]. This blunted autonomic response is one expression of a broader pattern of sympathovagal imbalance that develops early in the course of kidney disease and worsens with declining renal function, driven by mechanisms that include baroreflex impairment, renal afferent activation, and chronic stimulation of the renin-angiotensin-aldosterone system [6]. Because both LVEF and HRR are responsive to modifiable physiological stressors, they are frequently used as objective outcome markers in cardiac rehabilitation research, including in the present study [5,6].

Beyond the cardiovascular axis, CKD imposes a broader physical and functional toll. Skeletal and respiratory muscle wasting, sedentary behavior, chronic low-grade inflammation, and anaemia converge to reduce exercise tolerance, an impairment commonly quantified using the 6MWD, a simple and reproducible field measure of submaximal functional capacity. Reduced walking distance in CKD populations has been consistently associated with greater morbidity, more frequent hospitalization, and diminished independence in activities of daily living and is accompanied by a marked erosion of health-related QOL spanning both generic and disease-specific domains of functioning [7,8].

Two complementary patient-reported outcome instruments were used in the present study to capture this burden. The KDQOL instrument, developed by Hays and colleagues, was designed specifically to capture the symptom burden, daily-life disruption, and psychosocial impact unique to individuals living with kidney disease [9]. The KCCQ, originally developed by Green, Spertus and colleagues for the heart failure population, offers a disease-specific, clinically responsive measure of the symptomatic and functional consequences

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of cardiac impairment, and is equally relevant to the cardiac phenotype that characterizes Type 4 CRS [10]. Used together, these two instruments provide complementary windows into the lived experience of a condition that is, at its core, a combined cardiac and renal disorder [9,10].

Structured exercise has accumulated a substantial evidence base as a means of interrupting this cycle of decline. A systematic review of randomized controlled trials incorporating aerobic, resistance, and respiratory exercise modalities in CKD populations found consistent improvements in both functional capacity and QOL across a pooled sample of 619 participants. More recent meta-analytic work in dialysis-dependent populations confirmed statistically significant gains in both the physical and mental component summary scores of quality-of-life instruments following structured exercise, with the largest effects seen for moderate-intensity, supervised programs lasting 12 to 26 weeks [8]. Exercise prescription specifically for patients with overt cardiorenal involvement, however, remains comparatively under-studied, and few trials to date have evaluated multimodal programs combining flexibility, aerobic, and resistance components within a single protocol [7,8].

A further, frequently overlooked component of physical decline in CKD is respiratory muscle weakness, arising from the same uraemic myopathic processes that erode peripheral skeletal muscle [11]. IMT has therefore been investigated as a targeted countermeasure. A randomized controlled trial of five weeks of high-intensity IMT, progressing to 70% of maximal inspiratory pressure, in haemodialysis patients demonstrated significant gains in inspiratory muscle strength relative to a control group, and a subsequent systematic review confirmed that IMT reliably improves maximal inspiratory and expiratory pressures, forced expiratory volume, and forced vital capacity across multiple randomized trials in CKD, although its effect on 6MWD in isolation has been less consistent [12,13]. This inconsistency raises the possibility that IMT delivers its greatest functional benefit when combined with, rather than substituted for, whole-body exercise training [11,13].

Taken together, the literature supports two complementary rehabilitation strategies for CKD-related cardiac impairment: whole-body multimodal exercise, targeting peripheral muscular and cardiovascular deconditioning, and IMT, targeting the respiratory muscle weakness characteristic of the uraemic state [7,8,11-13]. No study identified in the current literature, however, appears to have evaluated the combined, simultaneous application of both strategies specifically in patients with Type 4 Cardiorenal Syndrome, or examined its comparative effect against IMT delivered alone, a meaningful gap, given that these patients are simultaneously exposed to the cardiovascular, muscular, and respiratory consequences of CKD and may be expected to benefit disproportionately from an intervention addressing more than one of these systems concurrently [4,11,13].

The present study was therefore designed to evaluate the effect of a multimodal exercise programme comprising flexibility, aerobic, and resistance training, combined with IMT, against IMT delivered alone, on cardiovascular recovery (LVEF, HRR), functional capacity (6MWD), and KDQOL and KCCQ in patients with CKD-associated Type 4 Cardiorenal Syndrome. It was hypothesized that the addition of a multimodal exercise programme to IMT would produce significantly greater improvement across all measured domains than IMT alone, reflecting the combined benefit of addressing cardiovascular, musculoskeletal, and respiratory impairment simultaneously in this high-risk patient population.

Materials and Methods

Study design

This study employed a prospective, two-group pre- and post-intervention comparative design to evaluate the effects of a multimodal exercise programme combined with inspiratory muscle training (IMT) compared with IMT alone in patients with CKD-associated Type 4 Cardiorenal Syndrome. Cardiovascular function, functional capacity, and health-related quality of life were assessed before and after the 12-week intervention period.

Study duration

The intervention was conducted over a period of 12 weeks. Baseline assessments were performed before commencement of the intervention, and the same outcome measures were reassessed following completion of the 12-week intervention programme.

Sample size

A total of 52 clinically diagnosed patients with CKD-associated Type 4 Cardiorenal Syndrome were included in the study. The participants were divided equally into two groups, with 26 participants in the experimental group receiving multimodal exercise combined with IMT and 26 participants in the control group receiving IMT alone.

Sampling technique

Participants who fulfilled the predefined eligibility criteria were recruited using convenience sampling from the study setting. Eligible participants who were medically stable and willing to participate were enrolled after obtaining written informed consent, and the participants were allocated to the respective study groups.

Study setting

The study was conducted in the Department of Cardiovascular and Respiratory Physiotherapy in collaboration with the Department of Nephrology. Written informed consent was obtained from all participants before enrollment.

Participants

A total of 52 clinically diagnosed CKD patients with type 4 cardiorenal syndrome were recruited using convenient sampling and were allocated into two equal groups (n = 26 each).

Group A

Multimodal exercise program with IMT

Flexibility training: Stretching of major muscle groups of the upper and lower limbs, 5 repetitions of 30 sec hold for 2 to 3 sets

Aerobic training: 40-60% THR, 30 to 40 mins (including warm-up & cool down)

Resistance training: 60-70% 1RM, 2-3 sets, of major muscle groups of bilateral upper and lower limbs.

Group B

IMT: 30 to 60% of MIP, 10 repetitions of 3-5 sets, with 1 min rest in between.

Eligibility criteria

Inclusion criteria

- Diagnosed CKD patients with Type 4 cardiorenal syndrome
- Age 30–65 years, of both genders.
- Patients should be able to complete 6 min walk test
- Resting SPO2 ≥ 90%
- Chronicity of disease (more than 3 months)
- Medically stable and able to participate in an exercise program
- Willing to provide written informed consent

Exclusion criteria

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- Unstable angina, recent myocardial infarction (<6 weeks), decompensated heart failure (NYHA IV).
- Uncontrolled arrhythmia, severe uncontrolled hypertension.
- Symptomatic peripheral arterial disease conditions limiting exercise.
- Musculoskeletal conditions limiting exercise.
- Active infection, recent kidney transplant (<6 months)

Outcome measures

Cardiovascular function

- LVEF
- HRR

Functional capacity

- 6MWT

HRQOL

- Kancas City Cardiomyopathy Questionnaire (KCCQ).
- Kidney Disease Quality of Life (KDQOL)

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (version 29.0). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequencies. Normality of distribution for each outcome variable was assessed using the Shapiro-Wilk test. Baseline comparability between the experimental and control groups was tested using the independent samples t-test or Mann-Whitney U test for continuous variables, depending on distribution, and the Chi-square test for categorical variables. Within-group change from pre- to post-intervention was analyzed using the paired t-test for normally distributed difference scores and the Wilcoxon signed-rank test where the assumption of normality was not met. Between-group comparison of the magnitude of change (Δ=post−pre) was performed using the independent samples t-test or Mann-Whitney U test, as appropriate, and confirmed using Analysis of Covariance (ANCOVA) with the baseline (pre-intervention) score entered as a covariate. Effect sizes were calculated using Cohen's d for paired comparisons, Hedges' g for independent group comparisons, and the r statistic for non-parametric tests. A p-value of less than 0.05 was considered statistically significant for the overall analysis; given that five primary outcome measures were tested, a Bonferroni-corrected threshold of α=0.01 (0.05/5) was additionally applied to guard against inflation of Type I error, and all between-group comparisons remained significant at this stricter threshold. All analyses were performed on data from 52 participants (26 per group), with no missing values.

Results

Baseline characteristics and comparability of groups

A total of 52 participants with CKD-associated Type 4 Cardiorenal Syndrome were enrolled and allocated equally to the Experimental group (n=26) and Control group (n=26). Baseline demographic and clinical characteristics of the two groups are summarised in Table 1. No statistically significant differences were observed between groups for age, gender distribution, CKD stage, or any of the baseline outcome measures (all p>0.05), confirming that the groups were comparable at the outset and that subsequent between-group differences can reasonably be attributed to the intervention rather than to pre-existing imbalance.

Table 1. Baseline demographic and clinical characteristics of the experimental and control groups.

Variable	Experimental (n=26)	Control (n=26)	p-value
Age (years), mean ± SD	51.2 ± 10.2	52.5 ± 10.4	0.647
Gender, n (M/F)	19 / 7	17 / 9	0.764
CKD Stage, n (3/4/5)	6 / 9 / 11	10 / 9 / 7	0.389
LVEF (%)	46.47 ± 3.71	46.39 ± 3.38	0.932
HRR (bpm)	12.69 ± 2.13	12.38 ± 2.35	0.480
6MWD (m)	328.58 ± 22.79	325.23 ± 20.79	0.420
KDQOL score	53.38 ± 5.81	54.58 ± 5.29	0.409
KCCQ score	52.15 ± 4.07	51.35 ± 3.86	0.466

Continuous variables reported as mean ± SD, compared using independent t-test or Mann-Whitney U test as appropriate; categorical variables compared using Chi-square test.

Within-group change following intervention

Both groups demonstrated statistically significant improvement from baseline to post-intervention across all outcome measures (p<0.001 for all comparisons), as shown in Table 2. In the Experimental group, LVEF improved from 46.47±3.71% to 52.38±4.00% (Δ=5.91%, 95% CI 5.40–6.42, d=4.70), and 6MWD increased from 328.58±22.79 m to 416.92±17.72 m (Δ=88.35 m, 95% CI 76.18–100.51, d=2.93). The Control group also improved significantly, though the magnitude of change was consistently smaller across every measured domain. Effect sizes within the Experimental group ranged from large to very large (d=2.67–4.70), while those in the Control group were moderate to large (d=1.09–2.74).

Table 2. Within-group comparison of pre- and post-intervention outcome measures.

Outcome	Group	Pre (mean ± SD)	Post (mean ± SD)	Mean change (95% CI)	Test statistic	p-value	Effect size
LVEF (%)	Experimental	46.47 ± 3.71	52.38 ± 4.00	5.91 (5.40–6.42)	t(25) =23.95	<0.001	d=4.70
	Control	46.39 ± 3.38	48.87 ± 3.16	2.48 (2.11–2.84)	t(25) =13.99	<0.001	d=2.74
HRR (bpm)	Experimental	12.69 ± 2.13	21.08 ± 1.98	8.38 (7.28–9.49)	t(25) =15.67	<0.001	d=3.07
	Control	12.38 ± 2.35	16.65 ± 1.60	4.27 (3.20–5.34)	t(25) =8.23	<0.001	d=1.61
6MWD (m)	Experimental	328.58 ± 22.79	416.92 ± 17.72	88.35 (76.18–100.51)	t(25) =14.96	<0.001	d=2.93

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Table 2 (continued)

Outcome	Group	Pre (mean ± SD)	Post (mean ± SD)	Mean change (95% CI)	Test statistic	p-value	Effect size
	Control	325.23 ± 20.79	362.85 ± 13.56	37.62 (25.95–49.28)	t(25)= 6.64	<0.001	d=1.30
KDQOL	Experimental	53.38 ± 5.81	74.62 ± 4.17	21.23 (18.02–24.44)	t(25)= 13.62	<0.001	d=2.67
	Control	54.58 ± 5.29	63.12 ± 4.29	8.54 (5.37–11.71)	t(25)= 5.55	<0.001	d=1.09
KCCQ[a]	Experimental	52.15 ± 4.07	73.69 ± 5.52	21.00 (median)	W=0.0	<0.001	r=0.88
	Control	51.35 ± 3.86	61.50 ± 4.59	10.15 ± 6.50	t(25)= 7.97	<0.001	d=1.56

[a]For KCCQ in the experimental group, the difference score violated the assumption of normality (Shapiro-Wilk p=0. 047); the Wilcoxon signed-rank test was therefore used and the median change is reported. d = Cohen's d; r = matched-pairs rank-biserial correlation (Figure 1-5).

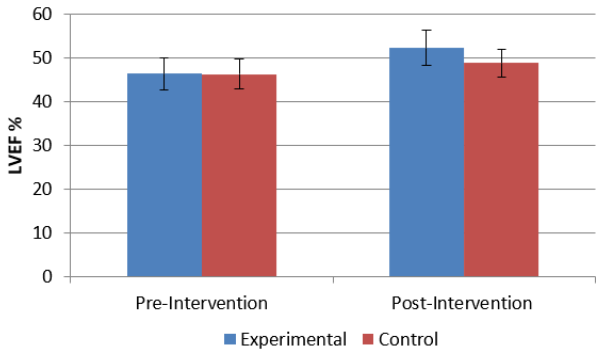

Figure 1. Comparison of LVEF% between the experimental & control groups at pre- and post- intervention.

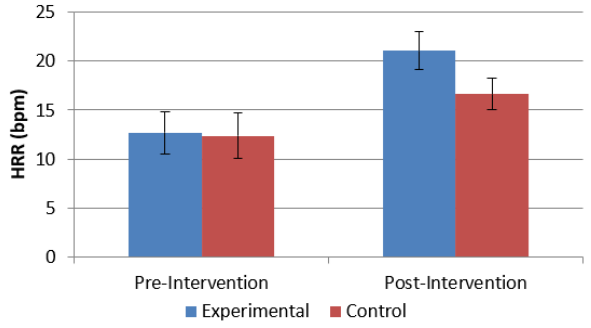

Figure 2. Comparison of Heart rate recovery (bpm) between the experimental & control groups at pre- and post- intervention.

Between-group comparison of treatment effect

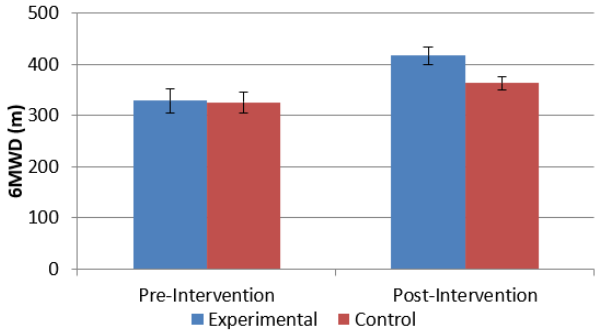

Figure 3. Comparison of 6-min walk distance between the experimental and control groups at pre- and post- intervention.

To evaluate the differential effect of the two interventions, change scores (Δ=post−pre) were compared between groups (Table 3). The experimental group showed a significantly greater improvement than the control group on every outcome measure. The largest between-group difference was observed for LVEF (mean difference 3.43%, 95% CI 2.82–4.04, t(50)=11.30, p<0.001, g=3.09), followed by 6MWD (mean difference 50.73 m, 95% CI 34.29–67.17, t(50)=6.20, p<0.001, g=1.69). KCCQ change scores were compared using the Mann-Whitney U test owing to non-normal distribution in the experimental group, and again favoured the experimental group (median Δ=21.00 vs 10.00, U=608.5, p<0.001, r=0.69). Effect sizes for all between-group comparisons were in the large-to-very-large range (g/r=1.51–3.09), indicating that the addition of flexibility, aerobic, and resistance training to IMT conferred a clinically and statistically meaningful advantage over IMT alone.

Table 3. Between-group comparison of change scores (Δ=Post−Pre).

Outcome (Δ)	Experimental Δ	Control Δ	Test statistic	p-value	Effect size
ΔLVEF (%)	5.91 ± 1.26	2.48 ± 0.90	t(50)=11.30	<0.001	g=3.09
ΔHRR (bpm)	8.38 ± 2.73	4.27 ± 2.65	t(50)=5.52	<0.001	g=1.51
Δ6MWD (m)	88.35 ± 30.12	37.62 ± 28.89	t(50)=6.20	<0.001	g=1.69
ΔKDQOL	21.23 ± 7.95	8.54 ± 7.84	t(50)=5.80	<0.001	g=1.58
ΔKCCQ[b]	21.00 (median)	10.00 (median)	U=608.5	<0.001	r=0.69

[b]KCCQ change scores were non-normally distributed in the experimental group; median values and the Mann-Whitney U test are reported. g = Hedges' g; r = rank-biserial correlation effect size.

Sensitivity analysis: Analysis of Covariance (ANCOVA)

As a sensitivity analysis, and to statistically adjust for any residual influence of baseline scores on the post-intervention outcome, an ANCOVA was performed for each outcome measure with the post-intervention score as the dependent variable, group as the fixed factor, and the corresponding pre-intervention score entered as a covariate. This approach corroborated the change-score analysis in Table 3, after adjustment for baseline values, the experimental group showed significantly higher adjusted post-intervention means than the control group for every outcome (all p<0.001), as summarized in Table 4. The pattern and magnitude of the adjusted between-group differences closely matched the unadjusted change-score comparisons,

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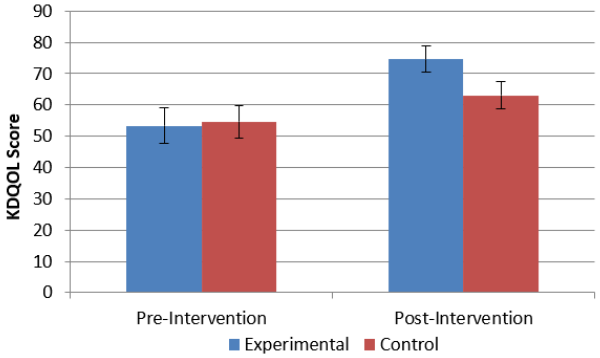

Figure 4. Comparison of KDQOL Scores between the experimental & control groups at pre- & post- intervention.

strengthening confidence that the observed treatment effect is not attributable to baseline imbalance or regression to the mean.

Table 4. ANCOVA: Adjusted post-intervention group means, controlling for baseline (pre) score.

Outcome	Adjusted exp. mean	Adjusted ctrl. mean	Adjusted mean diff (95% CI)	F / t statistic	P-value
LVEF (%)	52.34	48.91	3.43 (2.82–4.05)	t(49)=11.26	<0.001
HRR (bpm)	21.06	16.67	4.39 (3.38–5.40)	t(49)=8.77	<0.001
6MWD (m)	417.18	362.59	54.59 (45.88–63.30)	t(49)=12.60	<0.001
KDQOL	74.48	63.25	11.24 (8.94–13.53)	t(49)=9.85	<0.001
KCCQ	73.63	61.56	12.08 (9.22–14.93)	t(49)=8.50	<0.001

Adjusted means calculated at the grand mean of the baseline covariate. Adjusted mean difference = experimental − control, adjusted for pre-intervention score.

Summary of findings

The two treatment groups were well matched at baseline. Both the multimodal exercise programme combined with IMT (experimental group) and IMT alone (control group) produced statistically significant within-group improvements in cardiovascular function, functional capacity, and QOL. The magnitude of improvement was consistently and significantly greater in the experimental group across all five outcome measures, with effect sizes ranging from large to very large, and this finding held even after Bonferroni correction for multiple comparisons and after adjustment for baseline scores using ANCOVA. These findings support the hypothesis that a multimodal exercise programme combined with IMT confers superior benefit over IMT alone in patients with CKD-associated Type 4 Cardiorenal Syndrome.

Discussion

This study evaluated whether the addition of a multimodal exercise programme (flexibility, aerobic, and resistance training) to IMT would produce greater improvement in cardiovascular recovery, functional capacity, and QOL than IMT delivered alone, in patients with CKD-associated Type 4 Cardiorenal Syndrome. Both the experimental and control groups improved significantly on every outcome measure, confirming that even a single-modality respiratory intervention

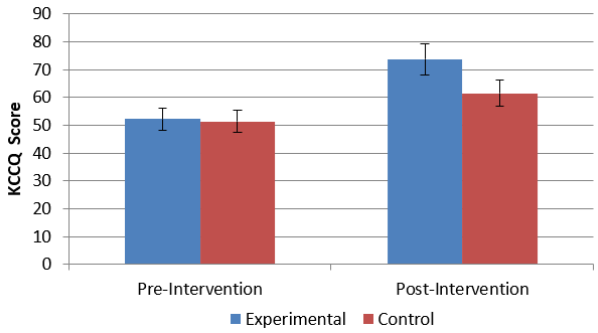

Figure 5. Comparison of KCCQ scores between the experimental & control groups at pre- and post- intervention.

confers meaningful benefit in this population. However, the magnitude of improvement was consistently and substantially greater in the experimental group across LVEF, HRR, 6MWD, KDQOL, and KCCQ, with effect sizes in the large-to-very-large range. This pattern persisted after Bonferroni correction for multiple comparisons and after ANCOVA adjustment for baseline scores, indicating that the observed advantage of combined training is unlikely to reflect chance findings, pre-existing group imbalance, or regression to the mean. These results support the study hypothesis and add to a still-limited body of evidence on combined rehabilitation strategies in cardiorenal populations.

Cardiovascular recovery: LVEF and heart rate recovery

The larger gain in LVEF observed in the experimental group is consistent with the broader literature on exercise-based cardiac rehabilitation in kidney disease. The 2024 Clinical Consensus Statement of the European Association of Preventive Cardiology and the European Association of Rehabilitation in CKD summarised multiple randomised trials in which combined aerobic and resistance training produced favourable changes in left ventricular structure and function in patients with CKD and those on haemodialysis, attributing this partly to restoration of cardiac autonomic balance and improved arterial compliance [14]. The CYCLE-HD trial, a cluster-randomised trial of intradialytic cycling alone in haemodialysis patients, reported a statistically significant six-month reduction in left ventricular mass of approximately 11 g, together with reductions in myocardial fibrosis markers and aortic stiffness, but no significant change in physical function or QOL [15]. The present findings extend this picture: whereas CYCLE-HD tested a single aerobic modality and observed benefit confined largely to cardiac structure, the addition of resistance and flexibility work to inspiratory training in the current study appears to have produced concurrent gains in cardiac function, functional capacity, and QOL, suggesting that a broader stimulus across muscular, cardiovascular, and respiratory systems may be needed to translate structural cardiac change into functional and perceptual benefit.

The greater improvement in HRR in the Experimental group is compatible with reports that combined training modalities produce more consistent gains in cardiac autonomic indices than aerobic training alone. A recent systematic review and meta-analysis of exercise interventions in haemodialysis patients found that heart rate variability indices improved more reliably in trials using concurrent aerobic-plus-resistance protocols than in those using aerobic training in isolation, although the certainty of evidence for several individual indices remained low to moderate [16]. This is broadly consistent with the between-group difference in ΔHRR observed here (8.38 bpm in the Experimental group versus 4.27 bpm in the Control group), and lends support to the interpretation that multimodal loading, rather than respiratory training alone, is the more effective stimulus for autonomic reconditioning in this population.

Functional capacity

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The substantial between-group difference in 6MWD (88.35 m versus 37.62 m) parallels findings from the Tunisian randomised controlled trial of Frih and colleagues, in which four months of combined endurance-resistance training in chronic haemodialysis patients produced large improvements in walking distance and other physical performance measures relative to usual care, with an effect size for the 6-minute walk test of similar magnitude to that reported here [17]. The consistency of direction across these two trials, conducted in different renal populations using different comparator conditions, strengthens the inference that combining aerobic and resistance loading with a respiratory or usual-care comparator reliably outperforms single-modality or no-exercise control in restoring walking capacity. The somewhat larger effect size in the present study may reflect the fact that both groups here received IMT as a common respiratory foundation, potentially amplifying the incremental contribution of the additional flexibility, aerobic, and resistance components in the Experimental arm.

Quality of life

Both disease-specific instruments used in this study, the KDQOL and the KCCQ, showed markedly greater improvement in the Experimental group. This finding contrasts somewhat with the DiaTT trial, the largest randomized trial of intradialytic combined endurance-resistance training to date, which reported improvement in the physical component of generic quality-of-life scores but no significant change in the mental component summary after twelve months [14]. One explanation for the more uniform quality-of-life benefit observed in the present study may be that participants had CKD-associated Type 4 Cardiorenal Syndrome rather than end-stage disease on maintenance dialysis, and were therefore able to tolerate a more demanding combined training load; another is that the simultaneous targeting of cardiovascular, musculoskeletal, and respiratory impairment addresses a wider range of symptom domains captured by disease-specific quality-of-life instruments than aerobic training alone. Taken together with the consistent pattern seen in the Frih trial for physical and psychosocial outcomes, the present results suggest that the breadth of the training stimulus, rather than its duration or setting alone, may be an important determinant of quality-of-life response in cardiorenal and renal populations [17].

Comparison with similar trials

Comparing the present findings with those of Frih et al. and the CYCLE-HD trial highlights both convergence and divergence [15,17]. All three trials agree that combined or multimodal exercise produces functional and, where measured, cardiac benefits exceeding those of a single-modality or usual-care comparator. They diverge, however, in the consistency of quality-of-life response: CYCLE-HD found no significant quality-of-life change despite a clear structural cardiac benefit, whereas both Frih et al. and the present study found quality-of-life gains accompanying functional improvement [15,17]. This divergence may be attributable to differences in patient population (ambulatory CKD versus maintenance haemodialysis), intervention duration, and the specific comparator condition used, and underscores that the relationship between exercise-induced physiological change and patient-reported outcome is not uniform across the spectrum of kidney disease severity.

Conclusion

This study demonstrates that adding a multimodal exercise programme comprising flexibility, aerobic, and resistance training to IMT produces significantly greater improvement in cardiovascular recovery, functional capacity, and QOL than IMT alone in patients with CKD-associated Type 4 Cardiorenal Syndrome. Both groups improved meaningfully from baseline, confirming that IMT alone confers real benefit in this population; however, the Experimental group showed consistently larger gains across LVEF, HRR, 6MWD, KDQOL, and KCCQ, with effect sizes in the large-to-very-large range that remained robust after Bonferroni correction and ANCOVA adjustment for baseline scores.

These findings support the incorporation of multimodal exercise alongside IMT as a more comprehensive rehabilitation strategy for this high-risk cardiorenal population, addressing cardiovascular, musculoskeletal, and respiratory impairment concurrently rather than in isolation. Given the study's single-center design, convenience sampling, and 12-week duration, larger multicenter trials with longer follow-up are warranted to confirm these findings and establish their durability and generalizability before wider clinical adoption.

Data Availability Statement

The data supporting the findings of this study can be obtained from the corresponding author on reasonable request. Because of institutional data-sharing policies and the need to protect participant privacy, the dataset itself has not been made publicly available.

Funding Statement

No external funding was received. Institutional support was provided in the form of free investigation & treatment facilities.

Ethics Declaration

This study was conducted in accordance with the ethical standards of the Institutional Ethics Committee.

- Name - Institutional Ethics Committee of MIPT,
- Approval number – IEC/PG – 2024-25/2026,
- Date of approval — 25/11/2025

AI Disclosure

During the preparation of this work, the authors used ChatGPT to assist with statistical cross-checking, literature search support, and language refinement of portions of the manuscript text. Following the use of this tool, the authors reviewed, verified, and edited the content as needed and take full responsibility for the accuracy, integrity, and interpretation of the content of this publication.

Author Contribution Statement

Dr. Minaz Naik: Conceptualization, methodology, data collection, formal analysis, investigation, writing – original draft preparation.

Dr. Vishvnath Pawadshetty: Conceptualization, supervision, methodology guidance, resources, writing – review and editing, project administration.

Both authors read and approved the final manuscript.

Ethical Consent

Written informed consent was obtained from all individual participants included in the study prior to enrolment. Participants were informed of the study's purpose, procedures, potential risks and benefits, and their right to withdraw at any time without effect on their ongoing clinical care. All data were anonymized prior to analysis to protect participant confidentiality.

Conflict of Interest

The authors declare that they have no conflict of interest

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