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Aerobic Exercise and Long-Term Major Adverse Cardiovascular Events in Chronic Heart Failure: A Single-Center Retrospective Cohort Study

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Abstract

Background: Exercise-based cardiac rehabilitation improves functional capacity in chronic heart failure (CHF), but evidence on long-term major adverse cardiovascular events (MACE) in Chinese populations remains limited. Methods: This single-center retrospective cohort study included 547 CHF patients undergoing cardiopulmonary exercise testing. Aerobic exercise was defined as ≥150 min/week of activity sustained for ≥3 months. The primary outcome was MACE. Incidence was compared with Kaplan–Meier and log-rank tests. Associations were estimated using univariable and progressively adjusted multivariable Cox models. Results: Over a median follow-up of 757 days, 309 MACE events occurred. Aerobic exercise was associated with a lower MACE risk (HR = 0.771; 95% CI = 0.611–0.972; $p = 0.028$). All-cause mortality showed a borderline association (HR = 0.671; 95% CI = 0.448–1.005; $p = 0.053$). Conclusions: Aerobic exercise was independently associated with reduced MACE incidence in Chinese CHF patients.

Keywords: chronic heart failure; aerobic exercise; major adverse cardiovascular events; retrospective cohort study; cardiopulmonary exercise testing; prognosis

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1. Introduction

Heart failure remains one of the leading cardiovascular conditions worldwide, and its burden in China has grown considerably. An estimated 8.9 million Chinese adults aged 35 years and older live with heart failure, a figure roughly 44% higher than in 2000 [1]. The syndrome is not only common but disabling, with cardiovascular death and repeated hospitalizations accounting for much of its public health impact. In Asian populations, heart

failure appears even more prevalent than the global average, and among Asian countries China carries the highest age-standardized rate [2,3].

For patients with chronic heart failure (CHF), exercise intolerance is one of the most distressing symptoms [4]. Even with contemporary pharmacologic therapy, many patients still face recurrent admissions, declining quality of life, and a 5-year mortality reportedly as high as 53% [5].

In 2026, the European Society of Cardiology published its first dedicated guidelines on cardiac rehabilitation [6], which emphasize that comprehensive CR is essential to improve not only objective clinical outcomes but also functioning and health-related quality of life (HRQoL) in patients with heart failure. The guidelines further highlight that cardiopulmonary exercise testing (CPET) is the reference standard for assessing exercise intolerance, guiding individualized exercise prescriptions, and enabling the early and safe initiation of training in CHF patients. Despite robust evidence supporting the benefits of exercise-based rehabilitation in improving exercise capacity and quality of life in HF, its effect on long-term hard clinical endpoints, particularly major adverse cardiovascular events (MACEs), remains inconsistent [6–9]. Meta-analyses of cardiac rehabilitation trials have not shown a clear survival advantage, but these conclusions are limited by small samples, few deaths, and follow-up periods usually shorter than 12 months.

By contrast, a large American observational study of over 40,000 heart failure patients linked exercise-based cardiac rehabilitation to lower all-cause mortality [10]. However, whether a similar association holds in China has not been well established. With that background, we set out to examine the relationship between self-reported aerobic exercise and long-term outcomes in a Chinese CHF cohort, focusing on major adverse cardiovascular events (MACEs).

2. Materials and Methods

2.1. Study Design and Population

This was a single-center retrospective cohort study, reported in accordance with the STROBE statement. Details of the rationale and study design have been published previously [11,12]. We identified consecutive patients with CHF who underwent cardiopulmonary exercise testing in Tongji Hospital Cardiac Rehabilitation Department Affiliated to Tongji University between March 2007 and December 2018 as shown in Figure 1. Cardiopulmonary exercise testing was performed on patients at cardiac rehabilitation center, and We used the MasterScreen series of the lung function test system produced by CareFusion of Germany, the Cardiosoft motion test system produced by GE Medical of Germany, and the Viasprint 150 electric bicycle produced by ergoline of Germany (Bitz, Germany) in this study. Inclusion criteria include CHF diagnosed in accordance with the "Chinese Heart Failure Diagnosis and Treatment Guidelines 2018" with a medical history of more than 3 months; age $\geq$ 18 years; NYHA heart function level 1–3; and ability to cooperate to complete the CPET. Exclusion criteria include chronic obstructive pulmonary disease, pulmonary heart disease or pulmonary vascular disease; acute myocardial infarction; second- or third-degree atrioventricular block; acute pericarditis, rheumatic heart disease; thrombophlebitis or intracardiac thrombosis; severe supraventricular or ventricular arrhythmia; and uncontrolled hypertension. According to the criteria of acceptance, 1589 patients were excluded, and 547 patients with HF were finally included. The study protocol was approved by the ethics committee of Tongji Hospital Affiliated to Tongji University [LL(H)-08-04] and registered in the Chinese Clinical Trials Registry (accessed on 4 November 2026, https://www.chictr.org.cn/showproj.html?proj=9292.) under the unique identifier ChiCTR-TNRC-08000235.

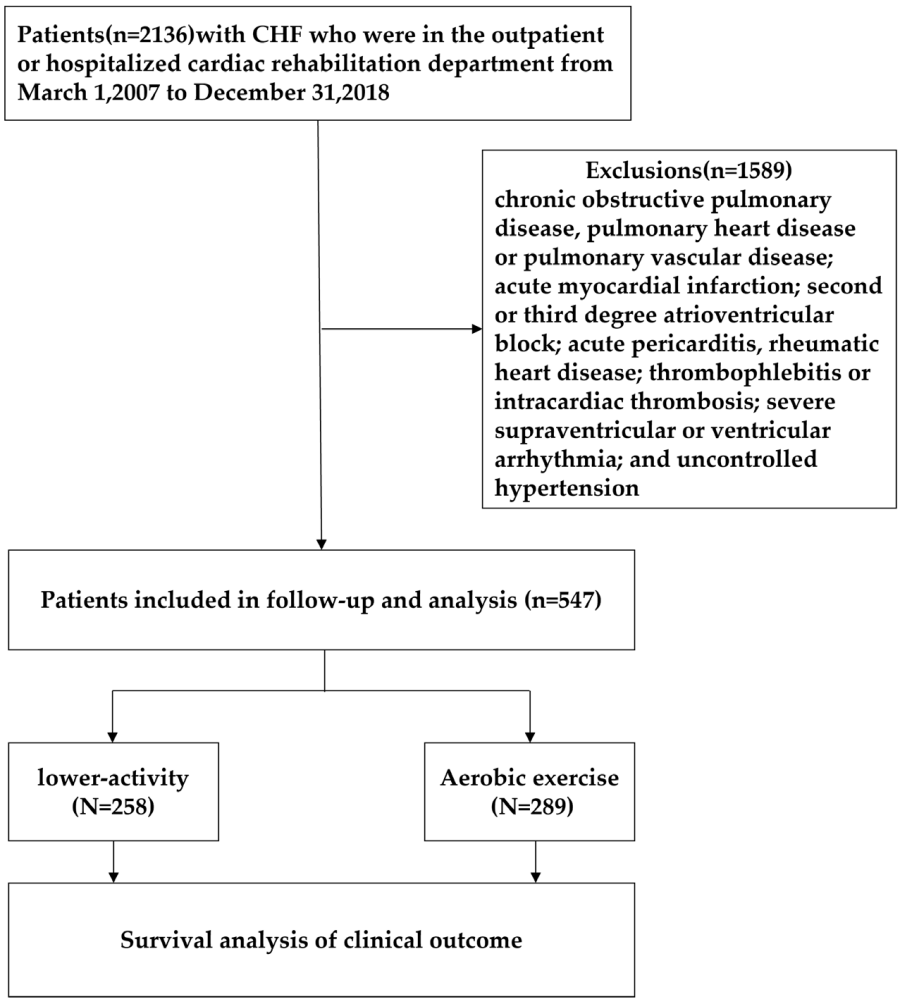


Figure 1. Flowchart illustrating the study population.

2.2. Aerobic Exercise Exposure

Aerobic exercise was assessed by a structured interview administered by a trained research doctor at baseline and updated at roughly six-month intervals by telephone. The questionnaire captured exercise type, frequency, duration, and perceived exertion (Borg scale). Aerobic exercise was defined as brisk walking, running, or similar activities associated with a Borg rating of 12–13, consistent with the AHA physical activity recommendations. No formal cardiac rehabilitation program was specifically targeted; both supervised and unsupervised activity were counted if the reported intensity and duration met the threshold. Patients were placed in the aerobic-exercise group if they described at least 150 min per week of aerobic activity, such as brisk walking, and if this pattern had persisted for at least three months. Everyone else was assigned to the non-exercise group. Information on exercise was updated by telephone or from medical records at roughly six-month intervals. In the primary analysis, long-term stable exercise was used as the exposure variable, because this reflects the prespecified study question regarding the prognostic value of long-term habitual aerobic activity.

2.3. Clinical Outcome and Follow-Up

The primary endpoint was MACE. MACE was defined as the first occurrence of any of the following: cardiovascular death, acute myocardial infarction, acute heart failure, percutaneous coronary intervention, unstable angina, cardiac ablation, cardioversion, implanted

cardioverter defibrillator placement, pacemaker placement, ischemic stroke, hemorrhagic stroke. Events were identified from medical records, death certificates, and discharge summaries, and were independently adjudicated by two cardiologists blinded to exercise status. Disagreements were resolved by consensus or by a third adjudicator. Only the first event per patient was counted for the primary time-to-event analysis. The composite of all-cause mortality or readmission and all-cause mortality are designated as secondary outcomes. Readmission was all-cause unplanned hospitalization and only the first hospitalization was counted for the composite endpoint. Follow-up was conducted every six months by telephone or outpatient visits. A wrong telephone number, lack of response, and refusal to follow up were considered as being lost to follow-up. The time of hospitalization or mortality was recorded by the follow-up staff. It is worth noting that a cardiopulmonary exercise test was performed at the index date and that exercise exposure was classified on the basis of the follow-up. Because the cardiopulmonary exercise test-derived measurements predate neither the exposure nor the outcome, they were treated as baseline severity indicators.

2.4. Statistical Analysis

The primary outcome measure of this study was MACE. According to previous similar literature, the control group was 69% and the intervention group was 44%, with $\alpha = 0.05$, power = 0.90, and a loss to follow-up rate of 20% [13]. The sample size was calculated by PASS 15.0 software to be at least 191 cases, with a total of 382 cases. Measurement data conforming to normal distribution were expressed as mean ± SD, measurement data not conforming to normal distribution were expressed as median (IQR), and count data were expressed as rate or component ratio (%). Descriptive statistics were used for baseline characteristics. Chi-square test was used to compare disordered variables between groups. For comparison of measurement data between groups, t test was used when the data were in line with normal distribution and had homogeneous variances. Non-parametric rank sum tests were used when the data were not normally distributed and/or had uneven variances. In survival analysis, Kaplan–Meier curves were used to compare clinical outcome between groups, and log-rank was used to test differences in survival curves. Univariable and multivariable Cox proportional risk models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI). The associations between aerobic exercise and different clinical outcomes after multivariable Cox regression analysis were presented in forest plots. Variables with $p < 0.05$ in the univariable Cox analysis were included in the multivariable Cox model. Four progressively adjusted models were fitted, with the final model including demographic, clinical, and cardiopulmonary exercise testing variables. $p < 0.05$ was considered statistically significant. The α test level was 0.05. Statistical analysis was performed by SPSS 24.0 software, and figures were created by GraphPad Prism 9.5.

3. Results

3.1. Baseline Characteristics

All patients were divided into two groups based on aerobic exercise (lower-activity, $n = 258$; aerobic exercise, $n = 289$). Detailed baseline data are shown in Table 1. There were statistically significant differences in age, sex, peak oxygen uptake and the slope of ventilation relative to carbon dioxide production between the two groups, but no significant differences in body mass index, left ventricular ejection fraction, etiology of heart failure, combined disease (hypertension, atrial fibrillation and diabetes mellitus), medication (digoxin, diuretic, aldosterone-antagonists, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor, beta-blockers, anti-platelet, statins), and cardiopulmonary exercise test outcomes (oxygen uptake at anaerobic threshold).

Table 1. Baseline characteristics of study patients.

Variables	Total (N = 547)	Lower-Activity (N = 258)	Aerobic Exercise (N = 289)	p
Age, y	63.0 (13.0)	65.0 (15.0)	61.0 (11.0)	<0.001
Male (%)	447 (81.7)	195 (75.6)	252 (87.2)	<0.001
BMI, kg/m^2	25.2 (2.9)	25.2 (2.8)	25.2 (3.2)	0.165
LVEF, %	45.0 (16.0)	45.0 (15.0)	45.0 (17.0)	0.050
Heart failure subtypes (%)				0.207
HFrEF	170 (31.1)	88 (34.1)	82 (28.4)	
HFmrEF	222 (40.6)	105 (40.7)	117 (40.5)	
HFpEF	155 (28.3)	65 (25.2)	90 (31.1)	
Etiology of heart failure (%)				0.862
ICM	333 (60.9)	156 (60.5)	177 (61.2)	
DCM	171 (31.3)	83 (32.2)	88 (30.4)	
Others	43 (7.9)	19 (7.4)	24 (8.3)	
Combined disease (%)				
HBP	386 (70.6)	187 (72.5)	199 (68.9)	0.353
AF	81 (14.8)	35 (13.6)	46 (15.9)	0.440
DM	158 (28.9)	66 (25.6)	92 (31.8)	0.107
Medication (%)				
Digoxin	98 (17.9)	52 (20.2)	46 (15.9)	0.197
Aldosterone-antagonists	193 (35.3)	100 (38.8)	93 (32.2)	0.108
ACEI/ARB/ARNI	434 (79.3)	199 (77.1)	235 (81.3)	0.228
Beta-blockers	464 (84.8)	221 (85.7)	243 (84.1)	0.608
Anti-platelet	414 (75.7)	195 (75.6)	219 (75.8)	0.957
Statins	414 (75.7)	196 (76.0)	218 (75.4)	0.884
Cardiopulmonary exercise test				
VO_2 AT, ml·min^{-1}·kg^{-1}	10.7 (3.1)	10.7 (2.9)	10.7 (3.5)	0.057
VO_2 peak, ml·min^{-1}·kg^{-1}	14.7 (4.6)	14.1 (4.1)	14.8 (4.7)	<0.001
VE/VCO_2 slope	34.9 (8.5)	35.8 (9.5)	33.3 (7.9)	<0.001

Values are median (IQR) or n (%). BMI = body mass index; LVEF = left ventricular ejection fraction; ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy; HBP = hypertension; AF = atrial fibrillation; DM = diabetes mellitus; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; VO_2 AT = oxygen uptake at anaerobic threshold; VO_2 peak = peak oxygen uptake; VE/VCO_2 slope = the slope of ventilation relative to carbon dioxide production.

3.2. Clinical Outcomes

The median duration of follow-up was 757 days and the loss to follow-up rate was 11.0%. During follow-up, 389 all-cause mortality or readmission incidents, 309 MACEs and 116 all-cause mortality incidents were identified.

Kaplan–Meier survival analyses showed there were statistically significant differences in MACE and all-cause mortality between the two groups at the follow-up, with the lower incidence in aerobic-exercise patients (MACE: log-rank = 8.887, $p = 0.003$; all-cause mortality: log-rank = 12.115, $p < 0.001$) (Figure 2A,C). However, there was no statistically significant difference in the incidence of all-cause mortality or readmission between the two groups (Figure 2B).

The univariable results are presented in Figure 2, Table 2 and Supplementary Table S1. In univariable Cox regression analysis, aerobic exercise was associated with a lower hazard of MACE (HR = 0.713, 95% CI = 0.570–0.892) and of all-cause mortality (HR = 0.458, 95% CI = 0.314–0.670) compared with the lower-activity group. In multivariable Cox regression analysis with adjustment for age, aerobic-exercise patients had the lower risk of MACE (HR = 0.768; 95% CI = 0.612–0.964) and all-cause mortality (HR = 0.523; 95%

CI = 0.355–0.770) in comparison to lower-activity patients. In multivariable Cox regression analysis with adjustment for VO_2 peak and VE/VCO_2 slope, aerobic-exercise patients had the lower risk of MACE (HR = 0.767; 95% CI = 0.610–0.964) and all-cause mortality (HR = 0.561; 95% CI = 0.379–0.828) in comparison to lower-activity patients. In the fully adjusted model, adjusting for meaningful variables in univariable Cox analysis in this study, aerobic exercise was associated with a lower likelihood of MACE incidence (HR = 0.771; 95% CI = 0.611–0.972).

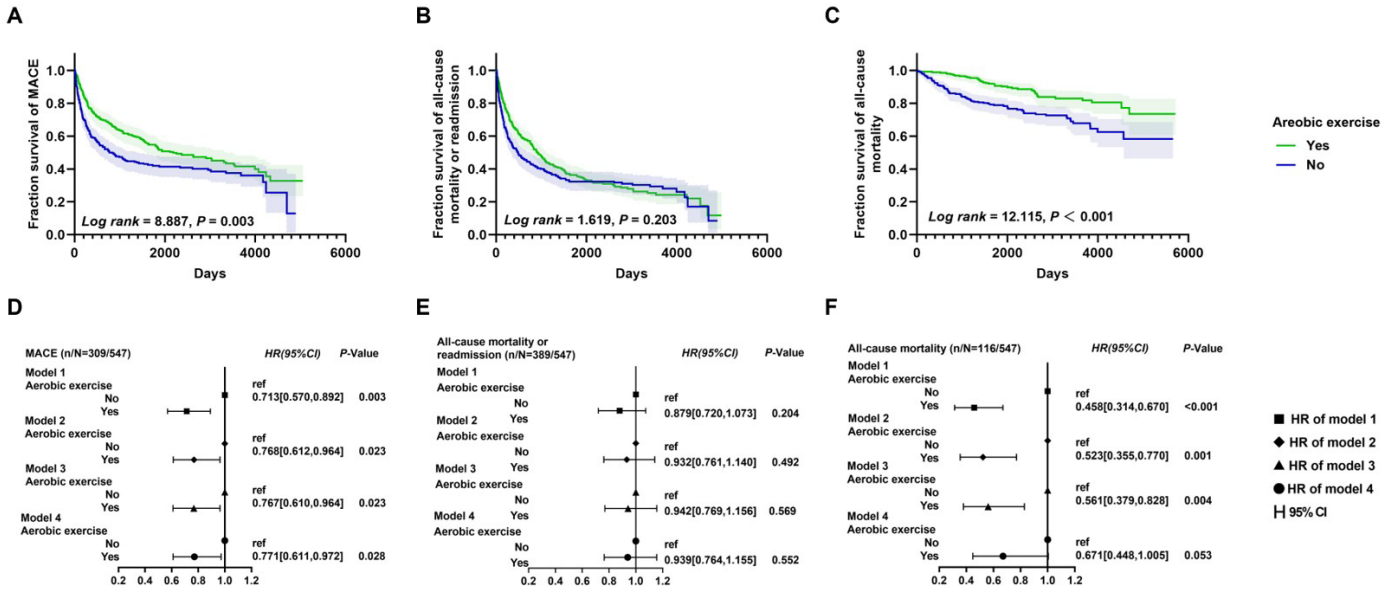


Figure 2. Aerobic exercise and different clinical outcomes during follow-up: panels (**A**,**D**) show major adverse cardiovascular events (MACE); panels (**B**) and (**E**) show all-cause mortality or readmission; panels (**C**,**F**) show all-cause mortality. Panels (**A**–**C**) show Kaplan–Meier curves of incident clinical outcome in association with aerobic exercise. Panels (**D**–**F**) show forest plots of incident clinical outcome in association with aerobic exercise.

Table 2. Multivariable Cox regression analyses for different outcomes according to aerobic exercise.

Outcomes	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
MACE (n/N = 309/547)								
No	1.00	0.003	1.00	0.023	1.00	0.023	1.00	0.028
Yes	0.713 [0.570, 0.892]		0.768 [0.612, 0.964]		0.767 [0.610, 0.964]		0.771 [0.611, 0.972]	
All-cause mortality or readmission (n/N = 389/547)								
No	1.00	0.204	1.00	0.492	1.00	0.569	1.00	0.552
Yes	0.879 [0.720, 1.073]		0.932 [0.761, 1.140]		0.942 [0.769, 1.156]		0.939 [0.764, 1.155]	
All-cause mortality (n/N = 116/547)								
No	1.00	<0.00	1.00	0.001	1.00	0.004	1.00	0.053
Yes	0.458 [0.314, 0.670]		0.523 [0.355, 0.770]		0.561 [0.379, 0.828]		0.671 [0.448, 1.005]	

Model 1 was univariable analysis; Model 2 was adjusted for age; Model 3 was adjusted for age, peak oxygen uptake (VO_2 peak), the slope of ventilation relative to carbon dioxide production (VE/VCO_2 slope); and Model 4 (fully adjusted) was adjusted for age, auricular fibrillation, diabetes mellitus, VO_2 peak, VE/VCO_2 slope, etiology of heart failure, left ventricular ejection fraction, which were variables with $p < 0.05$ in the univariable analysis. n/N: events/participants.

4. Discussion

CHF is a severe end-stage manifestation of various cardiovascular diseases, and remains a leading cause of morbidity and mortality globally [3]. Current guidelines universally

recommend comprehensive cardiac rehabilitation as an important therapeutic strategy for CHF [5,6], yet its adoption remains low, and its impact on hard clinical outcomes in real-world settings is still debated [3,14]. Our study contributes to this evidence by demonstrating that regular aerobic exercise is associated with a significantly lower risk of MACE in a Chinese CHF cohort, even after comprehensive adjustment for measured covariables for demographic features, comorbidities, and baseline cardiopulmonary fitness.

Our results show that in univariable survival analysis, exercise significantly reduced MACE (HR = 0.713; 95% CI = 0.570–0.892; $p = 0.003$) and all-cause mortality (HR = 0.458; 95% CI = 0.314–0.670; $p < 0.001$). After full multivariable adjustment, the association with MACE remained robust (HR = 0.771; 95% CI = 0.611–0.972; $p = 0.028$). However, the present study evaluated self-reported habitual aerobic activity, not a structured cardiac rehabilitation program. Although both share an exercise component, formal cardiac rehabilitation additionally includes comprehensive risk-factor management, patient education, psychological support, and medical supervision. Our findings therefore extend the evidence base for habitual activity, but they should not be interpreted as establishing the efficacy of formal cardiac rehabilitation programs.

Importantly, our study employed CPET-derived parameters, including VO_2 peak and VE/VCO_2 slope. The 2026 ESC guidelines on cardiac rehabilitation highlight the essential role of CPET in developing individualized exercise prescriptions (FITT-VP) and performing appropriate risk stratification before training initiation [6]. In the present cohort, the beneficial association between aerobic exercise and a lower risk of major adverse cardiovascular events remained statistically significant after adjustment for these physiological parameters (Model 4: HR = 0.771; 95% CI = 0.611–0.972; $p = 0.028$). This suggests that aerobic exercise is associated with a reduced risk of MACE.

Pharmacotherapy is a fundamental determinant of prognosis in patients with heart failure, and we fully acknowledge its importance [3,6]. In this study, baseline use of major GDMT classes was balanced between groups (Table 1). We did not include these medications in the primary model because medication status, particularly at baseline, is a coarse indicator that does not capture dose titration, adherence, or drug changes during follow-up. Furthermore, regular exercise may indirectly improve tolerance to and uptake of GDMT, placing medication use on the causal pathway from exercise behavior to clinical outcomes. Adjusting for variables on the causal pathway can lead to overadjustment bias and underestimation of the total effect of exercise. We therefore selected a model that estimates the total association between aerobic exercise and MACE. Nevertheless, because data on medication dosing and longitudinal changes were unavailable, residual confounding by pharmacotherapy cannot be fully excluded, and this remains an important limitation.

Healthy-user bias is a well-recognized concern in observational studies of physical activity [15]. Patients who regularly exercise may also have greater functional reserve, better health literacy, stronger social support, and better access to care, all of which could reduce MACE independently of the exercise behavior itself. Although we adjusted for demographic, clinical, and CPET-derived variables, residual confounding by socioeconomic status, frailty, depression, diet, and healthcare quality cannot be excluded. The present findings should therefore be interpreted as hypothesis-generating rather than causal.

Despite the benefits of exercise for CHF patients, participation in CR programs remains poor [6,14]. The 2026 ESC guidelines emphasize the urgent need to improve enrollment and adherence to exercise-based CR [6]. In this regard, our finding that even self-reported aerobic exercise, not necessarily formal center-based CR, is associated with significantly reduced MACE provides strong, motivating evidence for both clinicians and patients, and may help enhance the traditionally low participation rates in cardiac rehabilitation.

This study has several limitations inherent to its single-center retrospective design. First, exercise was self-reported, without objective monitoring (e.g., accelerometry). Second, patients able to sustain aerobic exercise may have greater functional reserve, less congestion, fewer symptoms, stronger social support, better health literacy, and better access to medical care. These characteristics may account for at least part of the observed association, and the possibility of residual bias from unmeasured changes in clinical status cannot be excluded. Third, phenotype-specific analyses were not performed, because the reduced sample size and event count in each phenotype would have made multivariable Cox models potentially unreliable. Furthermore, the presence of loss to follow-up is a further limitation. Patients who were lost during follow-up may have systematically differed from those retained, which could introduce attrition bias that cannot be fully excluded. Finally, although the exercise status was updated every six months, the research results only indicated the prognostic value of long-term regular exercise for MACE. Therefore, residual exposure misclassification could not be completely ruled out. Future prospective studies, including our ongoing multicenter HF-EI trial, should incorporate CPET-guided individualized exercise prescriptions, serial CPET assessments, and PROMs to confirm these findings and capture the full spectrum of exercise-derived benefits in CHF patients [12].

5. Conclusions

In conclusion, we found that aerobic exercise is associated with a lower incidence of MACE in CHF patients in this retrospective study. In this single-center retrospective cohort, self-reported aerobic exercise at or above 150 min per week was associated with a lower adjusted hazard of first MACE in Chinese patients with chronic heart failure. Residual confounding by unmeasured severity, healthy-user factors, medication changes, and socioeconomic variables cannot be excluded. This association should be considered hypothesis-generating; prospective multicenter studies with device-based activity monitoring and standardized endpoint adjudication are required to establish causality.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcdd13110608/s1, Table S1: Relationship between aerobic exercise and clinical outcome after separate adjustment for each of the other significant variables.

Author Contributions: Conceptualization, L.W. and Y.S.; methodology, Q.L., G.L. and Y.J.; software, Q.L., G.L., Y.J. and L.Z.; validation, T.S., D.L. and M.Z.; formal analysis, Q.L., G.L. and Y.J.; investigation, Q.L., G.L., Y.J., T.S., D.L., M.Z., W.X., Y.F., Y.Z. and L.L.; resources, L.W. and Y.S.; data curation, Q.L., G.L. and Y.J.; writing—original draft preparation, Q.L., G.L. and Y.J.; writing—review and editing, T.S., D.L., M.Z., W.X., Y.F., Y.Z., L.L., L.W., B.T., L.Z. and Y.S.; visualization, Q.L., G.L., Y.J. and L.Z.; supervision, L.W., B.T., L.Z. and Y.S.; project administration, B.T., L.Z. and Y.S.; funding acquisition, Q.L. and Y.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Tongji Hospital Affiliated to Tongji University (protocol code: LL(H)-08-04; date of approval: 16 June 2008). The design of this project includes both a prospective intervention component and a retrospective analysis of previous medical records. During the review process, the ethics committee explicitly approved the retrospective extraction and analysis of patient data that meet the inclusion criteria. Therefore, this retrospective study falls entirely within the scope authorized by the original ethics approval, and no separate application is required.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy and ethical reasons.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

HF	Heart failure
CHF	Chronic heart failure
MACE	Major adverse cardiovascular event
BMI	Body mass index
LVEF	Left ventricular ejection fraction
ICM	Ischemic cardiomyopathy
DCM	Dilated cardiomyopathy
HBP	Hypertension
AF	Atrial fibrillation
DM	Diabetes mellitus
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
CPET	Cardiopulmonary exercise test
VO_2 AT	Oxygen uptake at anaerobic threshold
VO_2 peak	Peak oxygen uptake

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