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Research article

Effects of cardiac rehabilitation on cognitive function in patients with acute coronary syndrome: A systematic review

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ABSTRACT

Background: Construction of an intervention method for the cognitive dysfunction of patients with acute coronary syndrome (ACS) is needed. Exercise-based comprehensive cardiac rehabilitation is a potentially effective approach that can improve cognitive function in ACS patients. This study aimed to investigate the effect of cardiac rehabilitation on cognitive function in ACS patients through a systematic review.
Methods: A systematic review was conducted of studies on PubMed, MEDLINE, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) on September 13, 2022, to identify those reporting the effects of cardiac rehabilitation on cognitive function in ACS patients. Data that reported exercise-based comprehensive cardiac rehabilitation and cognitive function (even if not main results and any type of cognitive function assessment was used) were extracted.
Results: In total, six studies were included that comprised a total of 1085 ACS patients. Overall positive effects of cardiac rehabilitation on cognitive function in ACS patients were reported across the six studies. All studies included aerobic exercise, resistance exercise, and patient education in cardiac rehabilitation. Meta-analysis could not be undertaken because each dataset used different methods to evaluate cognitive function, and the outcomes were different.
Conclusions: This systematic review showed that cardiac rehabilitation could have positive effects on cognitive function in ACS patients. Our results support the efficacy of cardiac rehabilitation for cognitive function in ACS patients. Additional well-designed clinical trials of exercise-based

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comprehensive cardiac rehabilitation should be conducted to clarify the true effect on cognitive function in ACS patients.

1. Introduction

Cardiovascular disease and cognitive impairment are socioeconomic problems that require countermeasures in aging societies [1,2]. In particular, the pandemic of heart failure (HF) is a serious problem [3]. Cognitive impairment makes the secondary prevention of future cardiac events difficult and increases readmission for HF in cardiovascular disease patients [4]. We reported that even if cognitive impairment was mild, it had an impact on unplanned readmission in coronary artery disease patients [5]. Therefore, early interventions for cognitive dysfunction in acute coronary syndrome (ACS) are necessary because such interventions could prevent the onset of future HF and other cardiac events.

The risk of developing cognitive impairment and dementia is increased in ACS patients [6,7]. It was reported that the prevalence rate of cognitive impairment during hospitalization and over a 5-year period ranged from 9 to 85 % in ACS patients [6]. Methods of evaluation and intervention that specifically address the cognitive dysfunction of ACS patients must be established. As one method to resolve these problems, cardiac rehabilitation could be an effective intervention for cognitive dysfunction in ACS patients because it is a multidomain comprehensive intervention that includes the aid of many professions as well as exercise.

As an intervention for cognitive dysfunction in older people, the efficacy of multidomain intervention including diet, exercise, cognitive training, and vascular risk monitoring was shown in a double-blind randomised controlled trial (RCT) [8]. To prevent cognitive dysfunction in older people, intervention involving many aspects including nutrition, exercise, and disease control is more important than intervention for cognitive dysfunction alone. Moreover, it is important that aerobic exercise is included in the multicomponent intervention because of its potential positive effect on global cognitive function in patients with mild cognitive impairment or dementia [9]. Exercise-based comprehensive cardiac rehabilitation is a multicomponent intervention involving these many aspects that is reported to be associated with prognostic benefits in ACS patients and patients with HF, regardless of their age, sex, comorbidities, frailty, and ejection fraction [10,11]. Moreover, cardiac rehabilitation offers many beneficial aspects that affect cardiopulmonary function, physical activity, muscle strength, cardiovascular risk factors/test parameters, mental health, and quality of life [12,13]. A few studies have reported the effect of cardiac rehabilitation on cognitive function as an outcome in cardiovascular disease patients [14–16]. On the basis of these findings, we hypothesised that exercise-based comprehensive cardiac rehabilitation could have positive effects on cognitive function in ACS patients. However, its true effect on cognitive function is uncertain as no studies have systematically reviewed the effects of exercise-based comprehensive cardiac rehabilitation on cognitive function in ACS patients. We expect that establishing intervention methods for cognitive function can lead to secondary prevention in ACS patients.

Therefore, this systematic review aimed to elucidate the effect of cardiac rehabilitation on the cognitive function of ACS patients via a comprehensive search and evaluation of the current literature. This systematic review supports the building of clinical intervention strategies to improve cognitive dysfunction in ACS patients by elucidating the effects of cardiac rehabilitation on their cognitive function.

Table 1
PubMed search strategy on September 13, 2022.

("Cardiac Rehabilitation"[MeSH Terms] OR "cardiovascular rehabilitation"[Title/Abstract] OR "Rehabilitation"[MeSH Terms] OR "rehabilitation"[MeSH Terms] OR "rehabilitating"[Title/Abstract] OR "Physical and Rehabilitation Medicine"[MeSH Terms] OR "Rehabilitation Nursing"[MeSH Terms] OR "Hospitals, Rehabilitation"[MeSH Terms] OR "Psychiatric Rehabilitation"[MeSH Terms] OR "Neurological Rehabilitation"[MeSH Terms] OR "Exercise Therapy"[MeSH Terms])
AND
("Acute Coronary Syndrome"[MeSH Terms] OR "Kounis Syndrome"[MeSH Terms] OR "Myocardial Infarction"[MeSH Terms] OR "Non-ST Elevated Myocardial Infarction"[MeSH Terms] OR "ST Elevation Myocardial Infarction"[MeSH Terms] OR "MINOCA"[MeSH Terms] OR ("Myocardial Ischemia"[MeSH Terms] OR "Angina, Unstable"[MeSH Terms] OR "Coronary Artery Disease"[MeSH Terms] OR "Cardiovascular Diseases"[MeSH Terms] OR "heart attack*"[Title/Abstract])
AND
("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "Randomized Controlled Trials"[MeSH Terms] OR "Random Allocation"[MeSH Terms] OR "Double-Blind Method"[MeSH Terms] OR "Single-Blind Method"[MeSH Terms] OR "clinical trial"[Publication Type] OR "Clin* NEAR/25 Trial*"[Title/Abstract] OR "Cohort Studies"[MeSH Terms] OR "Follow-Up Studies"[MeSH Terms] OR "Longitudinal Studies"[MeSH Terms] OR "Prospective Studies"[MeSH Terms] OR "Retrospective Studies"[MeSH Terms] OR "Comparative Study[MeSH Terms]" OR "Cross-Sectional Studies"[MeSH Terms])
AND
("Cognition"[MeSH Terms] OR "Cognition Disorders"[MeSH Terms] OR "Cognitive Behavioral Therapy"[MeSH Terms] OR "Mental Status and Dementia Tests"[MeSH Terms] OR "Neuropsychological Tests"[MeSH Terms] OR "Cognitive Psychology"[MeSH Terms] OR "Cognitive Restructuring"[MeSH Terms] OR "Postoperative Cognitive Complications"[MeSH Terms] OR "Cognitive Dysfunction"[MeSH Terms] OR "Cognitive Reserve"[MeSH Terms] OR "Cognitive Science"[MeSH Terms] OR "Cognitive Remediation"[MeSH Terms] OR "Cognitive Neuroscience"[MeSH Terms] OR "Cognitive Aging"[MeSH Terms] OR "Neuropsychological Tests"[MeSH Terms] OR "Memory Disorders"[MeSH Terms] OR "Wechsler Memory Scale"[MeSH Terms] OR "Executive Function"[MeSH Terms] OR "Neurocognitive Disorders"[MeSH Terms] OR "cognitive function*"[Title/Abstract] OR "cognitive impairment*"[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR "cognitive decline*"[Title/Abstract])

2. Methods

2.1. Literature search strategy

The present systematic review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [17] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement [18]. A comprehensive literature search of PubMed, MEDLINE, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) was conducted on September 13, 2022, by one researcher (K.I.). The search was aimed at identifying published studies assessing the effect of cardiac rehabilitation on the cognitive function of ACS patients. An advanced search strategy was formulated using search terms related to "cardiac rehabilitation", "ACS", "study design", and "cognition" (Tables 1–3). The search was performed to identify any type of intervention that could be a part of the cardiac rehabilitation process. In addition, various types of cognition were included in the search strategy to assess global cognitive function. The researcher who conducted the comprehensive literature search also conducted a manual search. However, no additional studies were found. We contacted four authors to obtain the full-text reports before conducting a second screening, and we received a reply from two authors. We used Rayyan for literature management after searching [19].

2.2. Selection criteria

Studies were included if they met the following inclusion criteria: (a) investigated ACS patients only or isolated and reported results for an ACS subgroup; (b) reported on exercise-based comprehensive cardiac rehabilitation defined as a comprehensive intervention including aerobic exercise, resistance exercise, or patient education; and (c) reported on cognitive function even if it was not a main result and was evaluated by any means used to evaluate cognitive function. Studies were excluded if they met the following exclusion criteria: (a) not published in English; and (b) not narrative or systematic reviews, study protocols, case reports, editorial or opinion articles, grey literature, or conference papers.

2.3. Data extraction

Two reviewers (K.I. and M.K.) independently conducted screenings of the titles and abstracts of all search results against the selection criteria to identify potentially related articles. We retrieved and reviewed the full-text articles to detect eligibility for inclusion. The screening results from the two independent reviewers were compared, and any conflicts were mediated by a third party (Y.K.). We extracted data on country, study design, disease, sample size, age, ratio of males, outcome measures, frequency, intensity, time, duration, type, control type, and results from the text, figures, and tables of each article.

2.4. Data synthesis

We created a data extraction sheet to extract results from the included studies. If the study mixed various cardiac diseases, we extracted only the data on ACS patients from the study's database and analysed it by the method similarly used in the original study. Although we considered performing a meta-analysis, we could not combine the data because a different evaluation of cognitive function was performed for each data set. In addition, the data contained different scores, and the time points of measurement were different between the studies. Hence, we conducted a narrative review as we considered this to be the most appropriate method to summarize the results of observational studies and RCTs.

Table 2
Medline and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) search strategy via EBSCO on September 13, 2022.

Abstract ("Cardiac Rehabilitation" OR "cardiovascular rehabilitation" OR "Rehabilitation" OR "rehabilitation" OR "rehabilitating" OR "Physical and Rehabilitation Medicine" OR "Rehabilitation Nursing" OR "Hospitals, Rehabilitation" OR "Psychiatric Rehabilitation" OR "Neurological Rehabilitation" OR "Exercise Therapy")
AND
Abstract ("Acute Coronary Syndrome" OR "Kounis Syndrome" OR "Myocardial Infarction" OR "Non-ST Elevated Myocardial Infarction" OR "ST Elevation Myocardial Infarction" OR "MINOCA" OR ("Myocardial Ischemia" OR "Angina, Unstable" OR "Coronary Artery Disease" OR "Cardiovascular Diseases" OR "heart attack*")
AND
Publication Type ("randomized controlled trial" OR "controlled clinical trial" OR "Randomized Controlled Trials" OR "Random Allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "clinical trial" OR "Clin* NEAR/25 Trial*" OR "Cohort Studies" OR "Follow-Up Studies" OR "Longitudinal Studies" OR "Prospective Studies" OR "Retrospective Studies" OR "Comparative Study" OR "Cross-Sectional Studies")
AND
Abstract ("Cognition" OR "Cognition Disorders" OR "Cognitive Behavioral Therapy" OR "Mental Status and Dementia Tests" OR "Neuropsychological Tests" OR "Cognitive Psychology" OR "Cognitive Restructuring" OR "Postoperative Cognitive Complications" OR "Cognitive Dysfunction" OR "Cognitive Reserve" OR "Cognitive Science" OR "Cognitive Remediation" OR "Cognitive Neuroscience" OR "Cognitive Aging" OR "Neuropsychological Tests" OR "Memory Disorders" OR "Wechsler Memory Scale" OR "Executive Function" OR "Neurocognitive Disorders" OR "cognitive function*" OR "cognitive impairment*" OR "mild cognitive impairment" OR "cognitive decline*")

Table 3
Web of Science search strategy on September 13, 2022.

Topic ("Cardiac Rehabilitation" OR "cardiovascular rehabilitation" OR "Rehabilitation" OR "rehabilitation" OR "rehabilitating" OR "Physical and Rehabilitation Medicine" OR "Rehabilitation Nursing" OR "Hospitals, Rehabilitation" OR "Psychiatric Rehabilitation" OR "Neurological Rehabilitation" OR "Exercise Therapy")
AND
Topic ("Acute Coronary Syndrome" OR "Kounis Syndrome" OR "Myocardial Infarction" OR "Non-ST Elevated Myocardial Infarction" OR "ST Elevation Myocardial Infarction" OR "MINOCA" OR ("Myocardial Ischemia" OR "Angina, Unstable" OR "Coronary Artery Disease" OR "Cardiovascular Diseases" OR "heart attack*")
AND
Topic ("randomized controlled trial" OR "controlled clinical trial" OR "Randomized Controlled Trials" OR "Random Allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "clinical trial" OR "Clin* NEAR/25 Trial*" OR "Cohort Studies" OR "Follow-Up Studies" OR "Longitudinal Studies" OR "Prospective Studies" OR "Retrospective Studies" OR "Comparative Study" OR "Cross-Sectional Studies")
AND
Topic ("Cognition" OR "Cognition Disorders" OR "Cognitive Behavioral Therapy" OR "Mental Status and Dementia Tests" OR "Neuropsychological Tests" OR "Cognitive Psychology" OR "Cognitive Restructuring" OR "Postoperative Cognitive Complications" OR "Cognitive Dysfunction" OR "Cognitive Reserve" OR "Cognitive Science" OR "Cognitive Remediation" OR "Cognitive Neuroscience" OR "Cognitive Aging" OR "Neuropsychological Tests" OR "Memory Disorders" OR "Wechsler Memory Scale" OR "Executive Function" OR "Neurocognitive Disorders" OR "cognitive function*" OR "cognitive impairment*" OR "mild cognitive impairment" OR "cognitive decline*")

2.5. *Quality assessment*

Two researchers (K.I. and M.K.) independently assessed the risk of bias of the included studies in this systematic review, and any conflicts were mediated by a third party (Y.K.). The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [20] was used to assess the risk of bias for the observational studies. The Cochrane Risk of Bias tool [21] was used to assess the quality of evidence for the RCTs. RoBANS consists of six domains of bias evaluated as "low risk", "unclear risk", or "high risk" [20]. The Cochrane Risk of Bias tool consists of seven domains that are evaluated by the same three grades [21].

3. Results

3.1. *Study identification*

The search process is shown in Fig. 1. In total, 2066 studies were identified from searching of the databases, and no additional studies were identified from manual searching. Initially, 49 duplicate studies were removed, and 1940 studies were excluded based on the inclusion and exclusion criteria after screening of their titles and abstracts. After assessment of 77 full-text articles for eligibility, six

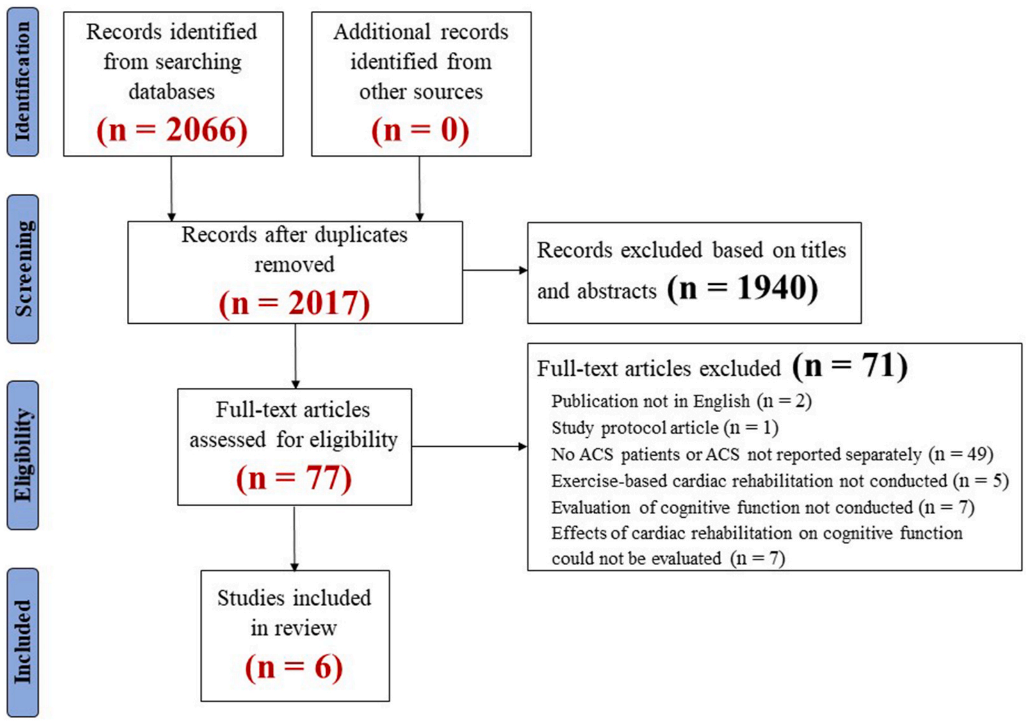

Fig. 1. Search strategy for the effects of cardiac rehabilitation on cognitive function in patients with acute coronary syndrome (ACS).

studies were finally included in this systematic review.

3.2. Characteristics of included studies

The six studies included in this review that assess the effects of cardiac rehabilitation on cognitive function in patients with ACS [22–27] are summarized in Table 4. Among the total of 1085 ACS patients included in the six studies, the numbers ranged from 15 [27] to 496 [23] patients across the studies. The mean age of patients ranged from 55 [23,24,27] to 77 [22] years, and the proportion of males ranged from 63 % [26] to 80 % [23,24]. Two studies were undertaken in Germany [23,24] and one each in Japan [22], Australia [25], China [26], and Portugal [27]. Study designs included prospective observational studies (n = 4) [22–25] and RCTs (n = 2) [26,27]. The included studies were published from 2017 [23] to 2021 [25,26]. The six studies were approved by appropriate ethics committees and conformed to the ethical guidelines of the Declaration of Helsinki [22–27]. No guideline information such as that of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) and Consolidated Standards of Reporting Trials (CONSORT) was provided in any of the six studies [22–27].

Bivariate analysis was used to examine the effect of cardiac rehabilitation on the cognitive function of ACS patients in all six studies [22–27], and analysis of variance and the multiple comparison test were used in one study [27]. The six studies included p values in statistical reporting [22–27], two studies included effect sizes [22,24], and one study included the confidence interval (CI) [22]. Among the prospective observational studies (n = 4) [22–25], one study conducted comparison between two groups with bivariate analysis to examine the effect of cardiac rehabilitation on the cognitive function of ACS patients and showed no differences in patient characteristics between the two groups [22]. The other three studies conducted comparisons before and after cardiac rehabilitation using bivariate analysis in one group [23–25]. In the RCTs (n = 2) [26,27], one study conducted comparison between two groups using bivariate analysis to examine the effect of cardiac rehabilitation on the cognitive function of ACS patients [26], and the other conducted comparison between three groups using analysis of variance and the multiple comparison test [27].

3.3. Cardiac rehabilitation

Cardiac rehabilitation in all of the studies included aerobic exercise, resistance exercise, and patient education [22–27]. Three studies included stretching [22,26,27], and two included psychological care and nutritional advice [23,24]. One study included sports therapy [24], another a home-based program [25], and a third promoted activities of daily living and breathing exercises [26]. The intensity of aerobic exercise and resistance exercise was 65–70 % of the heart rate reserve in one study [27]. However, the other five studies did not report on exercise intensity [22–26]. The length of the cardiac rehabilitation programs ranged from 3 to 26 weeks [22–27], including 1 to 3 sessions per week [25,27], and 30–86 min per session [22,25,27]. Only one study fully reported on frequency, intensity, time, and type of exercise [27].

Patient education was included in all studies to improve coronary risk factors and disease management [22–27]. Three studies included diet in patient education [22,25,27], while two studies addressed increased physical activities in patient education [22,27]. One study included stress management, medications, and exercise [25], and another smoking in patient education [27].

3.4. Assessment of cognitive function

The Montreal Cognitive Assessment (MoCA) [23,24] and Trail Making Test (TMT) [25,27] were used to assess cognitive function in two studies. One study assessed cognitive function with the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) [22]; one with the Rey Auditory Verbal Learning Test (RAVLT), Cogstate identification task (Cogstate ID), and Cogstate detection task (Cogstate DET) [25]; one with the Coronary Revascularization Outcome Questionnaire for determination of quality (CROQ-PTCA-Post) for the domain of cognitive function [26]; and one with the Verbal Digit Span (VDS) test and Stroop test [27].

The MoCA and MMSE were assessments of cognitive function used to evaluate multiple cognitive domains such as orientation, registration, recording, writing, visual construction, and other items related to cognitive function based on a 30-point scale [22–24]. The other tests used to assess cognitive function in the six studies included the following: TMT for evaluation of processing speed and executive function based on time taken to complete the test [25,27]; FAB for evaluation of the function of the prefrontal cortex based on an 18-point scale [22]; RAVLT for evaluation of verbal learning based on a potential range of 0–45 [25]; Cogstate ID and Cogstate DET for evaluation of processing speed based on reaction time and visual attention time taken to complete the test, respectively [25]; CROQ-PTCA-Post for evaluation of cognitive function as it relates to quality of life based on a 100-point scale [26]; VDS test for evaluation of executive function working memory based on a 14-point scale [27]; and Stroop test for evaluation of selective attention and conflict resolution ability based on a total score [27].

3.5. Effects of cardiac rehabilitation on cognitive function

Overall, the six studies reported positive effects of cardiac rehabilitation on cognitive function in the ACS patients (Table 4). The methods used to evaluate cognitive function and each of the outcome measures were different, but a positive effect of cardiac rehabilitation was found in the improvement of cognitive function of the patients in all six studies.

In the prospective observational study of Fujiyoshi et al. [22], 26 weeks of cardiac rehabilitation (30 min/session) comprising stretching, aerobic and resistance exercise, and patient education (diet, physical activity promotion, improvement of coronary risk factors and disease management) for myocardial infarction patients was conducted, and its effects on the change in MMSE and FAB

Table 4
Characteristics and results of the included studies.

Study (country)	Study design	Disease	Sample size (Lost)	Mean age (years)	Male (%)	Outcome measures	Frequency (days/week)	Intensity	Time	Duration (weeks)	Type	Control type	Results
Fujiyoshi et al., 2020 (Japan)	Prospective observational study	MI	19	77	68	MMSE FAB	–	–	30 min/ session	26	- Aerobic exercise - Resistance exercise - Patient education - Stretching	–	Change in MMSE score was greater in the monthly CR group than in the non-monthly CR group (2.4 ± 2.9 vs. −0.9 ± 2.2 points; 95 % CI −5.7 to −0.8; r = 0.56; p = 0.01). Change in FAB score was greater in monthly CR group than in non-monthly CR group (1.6 ± 1.7 vs. −0.5 ± 2.3 points; 95 % CI −4.1 to −0.1; r = 0.47; p = 0.04).
Salzwedel et al., 2017 (Germany)	Prospective observational study	ACS	496	55	80	MoCA	–	–	–	3	- Aerobic exercise - Resistance exercise - Patient education - Psychological care - Nutritional advice	–	Rate of cognitive impairment was reduced from 36.7 % to 32.9 % after CR ($p < 0.001$).
Salzwedel et al., 2019 (Germany)	Prospective observational study	ACS	401	55	80	MoCA	–	–	–	3	- Aerobic exercise - Resistance exercise - Patient education - Psychological care - Nutritional advice	–	MoCA scores (unadjusted and education-adjusted) were improved after CR (standardized effect size = 0.1, $p = 0.010$).

(*continued on next page*)

Table 4 (*continued*)

Study (country)	Study design	Disease	Sample size (Lost)	Mean age (years)	Male (%)	Outcome measures	Frequency (days/week)	Intensity	Time	Duration (weeks)	Type	Control type	Results
Gallagher et al., 2021 (Australia)	Prospective descriptive study	ACS	40 (10)	66	70	RAVLT TMT-A TMT-B Cogstate ID Cogstate DET	1–2	–	60 min/ session	6	- Sports therapy - Aerobic exercise - Resistance exercise - Patient education - Home-based programme	–	Rates of mild cognitive impairment in a single domain and multiple domains were reduced across CR timepoints ($p \leq 0.05$). Specific domains of cognitive impairments (verbal learning, processing speed, and visual attention) were reduced across CR timepoints ($p < 0.05$).
Jiang et al., 2021 (China)	RCT	AMI	I: 49 (0) C: 49 (0)	I: 59 C: 60	I: 63 C: 67	CROQ-PTCA-Post; cognitive function	–	–	–	26	- Aerobic exercise - Resistance exercise - Patient education - Stretching - Activities of daily living promotion - Breathing exercises	Routine care	Scores of cognitive function were higher for progressive exercise in the kinetic energy group than in the routine care group ($t = 7.2$, $p < 0.001$).
Vieira et al., 2018 (Portugal)	RCT	ACS	I1: 15 (4) C: 16 (5)	I1: 55 C: 59	I1: C:	TMT VDS Stroop test	3	65–70 % of the heart rate reserve	71–86 min/ session	26	- Aerobic exercise - Resistance exercise - Patient education - Stretching	Usual care	Executive function, selective attention, and conflict resolution ability were improved with virtual reality exercise in the Kinect group (intervention group 1) than in the usual care group ($p < 0.05$).

ACS, acute coronary syndrome; AMI, acute myocardial infarction; C, control group; CI, confidence interval; Cogstate DET, Cogstate detection task; Cogstate ID, Cogstate identification task; CR, cardiac rehabilitation; CROQ-PTCA-Post, coronary revascularization outcome questionnaire for determination of quality; FAB, Frontal Assessment Battery; I, intervention group; MI, myocardial infarction; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; RCT, randomized controlled trial; TMT, Trail Making Test; VDS, Verbal Digit Span test.

score were evaluated. The results showed that the change in MMSE score was significantly greater in the myocardial infarction patients with versus those without monthly cardiac rehabilitation (2.4 ± 2.9 vs. −0.9 ± 2.2 points; 95 % CI −5.7 to −0.8; r = 0.56; p = 0.01), and the change in FAB score was also significantly greater in the myocardial infarction patients with versus those without monthly cardiac rehabilitation (1.6 ± 1.7 vs. −0.5 ± 2.3 points; 95 % CI −4.1 to −0.1; r = 0.47; p = 0.04). In this study, 66 elderly patients (≥70 years old) with cardiovascular diseases were prospectively enroled [22]. For these results, we extracted only the myocardial infarction patients (n = 19) from the S1 Database of supporting information of the study and analysed the data by the same method used in the original study [22].

In the prospective observational study of Salzwedel et al. [23], a 3-week cardiac rehabilitation program including aerobic and resistance exercise, patient education (improvement of coronary risk factors and disease management), psychological care, and nutritional advice for ACS patients was conducted, and its effects on the change in the rate of cognitive impairment were evaluated with MoCA. The results showed that the rate of cognitive impairment declined significantly to 32.9 % from 36.7 % after cardiac rehabilitation (p < 0.001). In this study, 496 patients with ACS were prospectively enroled and were examined within 14 days of discharge from the hospital following a 3-week inpatient cardiac rehabilitation program [23]. In a follow-up study of this patient cohort by Salzwedel et al. [24], they also reported that the MoCA score (unadjusted and education-adjusted score) was significantly improved after cardiac rehabilitation (standardized effect size = 0.1, p = 0.010). In this later study, 401 ACS patients at two inpatient rehabilitation centres who were followed up by mail at six months after cardiac rehabilitation were analysed [24].

The prospective observational study of Gallagher et al. [25] consisted of a 6-week cardiac rehabilitation program (1–2 days/week, 60 min/session) of aerobic and resistance exercise, a home-based program (30 min of exercise, 5 days/week), and patient education (diet, stress management, medications, exercise) for ACS patients, and its effects on the change in the rate of mild cognitive impairment and specific domains of cognitive impairments were evaluated using the RAVLT, TMT-A, TMT-B, Cogstate ID, and Cogstate DET. Their results showed that the rate of mild cognitive impairment in a single domain and in multiple domains declined across cardiac rehabilitation timepoints (p ≤ 0.05), and the specific domains of cognitive impairments that were reduced across the measured timepoints were verbal learning, processing speed, and visual attention (p < 0.05). This study prospectively enroled 40 ACS patients without diagnosed dementia, and 30 patients completed the cardiac rehabilitation follow-up [25].

The RCT of Jiang et al. [26] assessed 26 weeks of cardiac rehabilitation for acute myocardial infarction patients that consisted of stretching (5 min/time), aerobic and resistance exercise (10 repetitions/set, 3 sets/day), patient education, activities of daily living promotion, and breathing exercises (5–6 times/min for 10 min), and its effects on the change of cognitive function scores were evaluated using the CROQ-PTCA-Post for the domain of cognitive function. The results showed that the scores for cognitive function in the progressive exercise of kinetic energy group were higher than those in the routine care group ($t = 7.2$, p < 0.001). This study prospectively enroled 98 patients with AMI who were randomly allocated to either the progressive exercise of kinetic energy group (n = 49) or the routine care group (n = 49) [26]. Patients in the routine care group only received health education, facilitation in getting out of bed, and sports education [26].

Finally, Vieira et al. [27] conducted a RCT of a 26-week cardiac rehabilitation program (3 days/week, 71–86 min/session) of stretching, aerobic and resistance exercise (65–70 % of heart rate reserve), and patient education (diet, smoking, physical activity promotion, improvement of coronary risk factors and disease management) for ACS patients using virtual reality. The TMT, VDS, and Stroop test were used to evaluate its effects on the change of specific domains of cognitive impairments. Virtual reality exercise with the Kinect (intervention group 1) revealed significant improvements in executive function, selective attention, and conflict resolution ability of this group compared with the usual care group (p < 0.05). In this study, 46 patients with ACS were prospectively enroled and randomly assigned to one of three groups: intervention group 1 (home-based cardiac rehabilitation program using virtual reality exercise with the Kinect, n = 15); intervention group 2 (home-based cardiac rehabilitation program using a paper booklet, n = 15); and usual care group (n = 16) [27]. Patients in the usual care group received education on cardiovascular risk factors and were encouraged to take daily walks [27].

Table 5
Quality assessment with the Risk of Bias Assessment Tool for Non-randomized Studies.

Author	Selection bias		Performance biases	Detection biases	Attrition biases	Reporting biases	Overall risk of bias
	The selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting	
Fujiyoshi et al., 2020	Low	High	Low	Low	Low	High	Low
Salzwedel et al., 2017	Low	Low	Low	Low	High	Low	Low
Salzwedel et al., 2019	Low	Low	Low	Low	High	Low	Low
Gallagher et al., 2021	Low	High	Low	Low	High	High	High

Table 6
Quality assessment with the Cochrane Risk of Bias Tool.

Author	Selection bias		Performance bias	Detection bias	Attribution bias	Reporting bias	Other bias	Overall risk of bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	
Jiang et al., 2021	High	Unclear	High	High	Low	Unclear	High	High
Vieira et al., 2018	Low	Unclear	High	High	Low	Low	Unclear	High

3.6. Quality assessment

No studies were excluded based on the quality assessment. However, we paid careful attention to the interpretation of the results of each study because studies with a high risk of bias were included. Of the four cohort studies [22–25], three [22–24] showed a low risk of bias and one [25] an overall high risk of bias according to RoBANS (Table 5). In the risk of bias domain in RoBANS, the risk was high in three studies [23–25] due to incomplete outcome data and in two studies [22,25] due to confounding variables and selective outcome reporting. Both of the RCTs [26,27] had an overall high risk of bias according to the Cochrane Risk of Bias tool (Table 6) in terms of blinding of participants and personnel and blinding of outcome assessment. One study [26] was evaluated as having high risk due to random sequence generation and other sources of bias.

4. Discussion

4.1. Effects of cardiac rehabilitation on cognitive function

To our best knowledge, this is the first systematic review to show the effects of cardiac rehabilitation on cognitive function in ACS patients. Among the six studies identified through our systematic literature search, although the methods of assessing cognitive function and each outcome measure were different, all six showed validity effects of cardiac rehabilitation on cognitive function in the ACS patients. Thus, cardiac rehabilitation appeared to be effective in improving and maintaining cognitive function in these patients.

Although the exact reasons for the validity effects of cardiac rehabilitation on cognitive function are unclear, one promising factor is that cardiac rehabilitation is an exercise-based multidomain intervention aided by many professions. The efficacy of the multidomain intervention for cognitive function has been shown by several large-scale RCTs in older adults [8,28–31]. These trials showed that a multidomain intervention that included diet, exercise, cognitive training, and vascular risk monitoring could slow cognitive decline and reduce incident dementia in older adults at high risk for dementia [8,28–31]. In addition, a recent systematic review and meta-analysis indicated the importance of including aerobic exercise in the multicomponent intervention [9]. The six studies we identified all have aerobic exercise, resistance exercise, and patient education in common [22–27]. Patient education to improve coronary risk factors and disease management was included in all of the studies [22–27], with diet included in three studies [22,25,27] and increasing physical activities included in two studies [22,27]. As compared with large-scale RCTs [8,28–31], multidomain intervention in our six identified studies was insufficient because only two studies included nutritional advice [23,24] and none included cognitive function training.

However, all six studies included aerobic exercise, resistance training, and patient education, which contribute to improvement in cognitive function. Previous reviews showed that exercise intervention and lifestyle improvement programs were beneficial for cognitive function in older adults and those with Alzheimer's disease [32,33]. Exercise acts to promote secretion of brain-derived neurotrophic factor, which promotes neurogenesis, synaptogenesis, and dendritogenesis [34]. Moreover, exercise improves mitochondrial function, which is related to a neuroprotective role through both brain plasticity and angio-neurogenesis ways [35]. In addition, exercise and patient education improve risk factors (arteriosclerosis, obesity, diabetes) associated with a worse prognosis of cognitive dysfunction [36]. The results of our systematic review indicate that comprehensive intervention carried out via exercise-based cardiac rehabilitation in real-world clinical practice support its effectiveness in improving and maintaining cognitive function. Moreover, there is room for exercise-based comprehensive cardiac rehabilitation to further improve cognitive function by adding appropriate nutrition intervention and cognitive function training.

Although the six identified studies did not fully describe in detail the contents of their exercise programs, such as frequency, intensity, and time, some information was provided. Two studies reported that the frequency of exercise was 1–2 days/week [25] and 3 days/week [27]. One study described intensity as 65–70 % of the heart rate reserve [27]. The duration of each session length was described in three studies as 30 min/session [22], 60 min/session [25], and 71–86 min/session [27]. In patients with Alzheimer's disease, for example, 30–60 min sessions combining both aerobic and resistance exercises for 2 or 3 days/week maintained for at least 2 months, and ideally for at least 6 months, are recommended to preserve and improve cognitive function [32]. Additional investigation is needed to determine the details of exercise-based comprehensive cardiac rehabilitation that is effective in improving the cognitive function of ACS patients.

4.2. Assessment of cognitive function

The evaluation methods and outcomes of cognitive function varied in the six identified studies. Two studies each used the MoCA [23,24] and TMT [25,27] to assess cognitive function, and one study each used the MMSE and FAB [22]; RAVLT, Cogstate ID, and Cogstate DET [25]; CROQ-PTCA-Post for the domain of cognitive function [26]; and the VDS test and Stroop test [27]. The MoCA and MMSE measure multiple cognitive domains such as visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, orientation, registration, recording, and writing [37–40]. The TMT measures processing speed and executive function [41], the FAB frontal lobe functions [42], and the RAVLT verbal learning [43]. Cogstate ID measures processing speed and Cogstate DET measures visual attention [44,45]. The cognitive function domain of the CROQ-PTCA-Post measures cognitive function as it relates to the quality of life [46]. The VDS test measures executive function working memory [47], and the Stroop test measures selective attention and conflict resolution ability [48]. Because of the wide variety of parameters measured by these tests, we could not combine the data on cognitive function across the studies for meta-analysis. An optimal screening method is particularly required for the identification of cognitive dysfunction in cardiovascular disease patients [6,49]. The results of our systematic review also indicate that the identification of an optimal screening method is an important problem that should be resolved rapidly to allow integration of results and to grasp the true situation of cognitive impairment in ACS patients.

4.3. Limitations

Our systematic review has several limitations. First, there was heterogeneity in the evaluation methods and outcomes of cognitive function and a lack of stratification of the ACS patients in the reviewed studies. The methods used to assess cognitive function and each outcome measure differed across the studies, and most did not describe effect sizes or CIs. Characteristics of the reviewed studies included small sample size, middle-aged and older patients, a high percentage of men, and unknown disease severity. Thus, we could not combine the data (for meta-analysis) on or show the details of cognitive function, so we reported the various outcomes regarding cognitive function as a whole. Second, only two RCTs and four prospective observational studies were examined, and studies with high risk of bias were included. Therefore, we paid close attention to interpretation of the results. Third, our systematic review did not show publication bias, the effect of the absence of cognitive function training, or the details of the cardiac rehabilitation program conducted in each study and follow-up. Finally, we did not use the Physiotherapy Evidence Database (PEDro) as one of the searched databases, and we only included papers published in English. Thus, our systematic review lacks studies reported in other languages and those that might only be collected in PEDro.

4.4. Strengths and implications

Our systematic review has some strengths and implications. First, it was conducted based on solid methodology to comply with the standardized protocols of PRISMA and MOOSE. Thus, a comprehensive search and meticulous selection process were conducted. Second, our systematic review included two study designs (prospective descriptive studies and RCTs), diverse racial populations, and various exercise-based comprehensive cardiac rehabilitation interventions and cognitive function assessments (even if not reported in the main results and evaluation was by any means). These factors are useful in the overall understanding of the impact of cardiac rehabilitation on cognitive function in ACS patients. Third, the risk of bias in the included studies was assessed using risk of bias tools appropriate for each study design. The risk of bias was solidly assessed, and interpretations of the results of the risk of bias in the included studies were provided. Finally, our systematic review showed validity effects of cardiac rehabilitation on the cognitive function of ACS patients for the first time, to our knowledge. Previous studies have not shown whether multidomain interventions such as cardiac rehabilitation are effective for cognitive function in patients with ACS. Our results showed that comprehensive cardiac rehabilitation, particularly exercise-based rehabilitation, could be an effective multidomain intervention strategy to improve the cognitive function of these patients. Moreover, such an intervention strategy could contribute to preventing the onset of future HF and other cardiac events in ACS patients. Our findings also suggest that the addition of appropriate nutritional intervention and cognitive training is necessary to build more effective exercise-based comprehensive cardiac rehabilitation to improve cognitive function in ACS patients. Well-designed clinical trials will improve risks of bias (attrition, performance, and detection biases), and standardized evaluations of cognitive function will need to be used in future trials. These strengths and implications can contribute to the development of intervention strategies for cognitive function in ACS patients.

5. Conclusion

This systematic review showed validity effects of cardiac rehabilitation on the cognitive function of ACS patients and that comprehensive cardiac rehabilitation, particularly exercise-based rehabilitation, could be an effective multidomain intervention to improve the cognitive function of these patients. The addition of appropriate nutritional intervention and cognitive training is necessary to build more effective exercise-based comprehensive cardiac rehabilitation that can improve the cognitive function of ACS patients. Moreover, well-designed clinical trials that improve risks of bias and use of standardized cognitive function evaluations will be needed in the future.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author. No data for review are included in the article itself or supplemental material referenced in the article.

CRediT authorship contribution statement

Kodai Ishihara: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kazuhiro P. Izawa:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Masahiro Kitamura:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Yuji Kanejima:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Masato Ogawa:** Writing – review & editing, Supervision. **Ryo Yoshihara:** Writing – review & editing, Supervision. **Tomoyuki Morisawa:** Writing – review & editing, Supervision. **Ikki Shimizu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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