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Original Article

Cardiac rehabilitation improves the clinical outcomes of patients with chronic kidney disease after percutaneous coronary intervention: a propensity match analysis

Hongmei Qin[1], Qingqiang Shi[2]

[1]*Department of Physical Examination,* [2]*Emergency Department, First People's Hospital of Chongqing Liangjiang New Area, Chongqing 401121, China*

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Abstract: Background: Patients with chronic kidney disease (CKD) suffer a higher incidence of coronary artery disease (CAD) and mortality after percutaneous coronary intervention (PCI). Coronary rehabilitation (CR) has been reported to benefit patients undergoing PCI. This study aimed to investigate the effect of CR in patients with CKD undergoing PCI. Methods: A retrospective investigation was adopted to collect the clinical data of patients undergoing PCI due to CAD, while the patients with CKD were screened for further analysis. According to whether they had treatment for CR or not, the patients enrolled were divided into the CR group or the nCR group. Baseline characteristics were compared between the two groups before and after the propensity score match. A Cox hazard ratio model and survival plot were adopted to analyze the benefit of CR when the primary endpoint of all-cause mortality and secondary endpoint of complications were recorded. Results: A total of 246 patients with CKD who received PCI from Jan 2007 to Jan 2012 in our hospital were enrolled in this study, with 106 cases receiving CR after the procedure. After the propensity score match, there were 89 pairs of patients left with no significant differences in their demographical and clinical characteristics (All $P > 0.05$). CR participation was associated with a significantly lower risk of all-cause mortality (HR 0.465, 95% CI 0.233-0.926, $P = 0.029$) and cardiac complications (HR 0.532 95% CI 0.287-0.984, $P = 0.044$). A survival analysis showed that there was a significant difference between the CR group and the nCR group in survival rates ($P = 0.024$). Conclusion: For patients with CKD who receive PCI, a significant benefit for long term survival and reduction of cardiac events can be achieved when they receive cardiac rehabilitation.

Keywords: Cardiac rehabilitation, coronary artery disease, chronic kidney disease, percutaneous coronary intervention, clinical outcome

Introduction

The estimated mortality of coronary artery disease (CAD) has been decreasing, thanks to the development of intervention techniques and drugs [1-3]. However, we are still facing a severe burden of cardiac death and recurrence, which necessitates a comprehensive treatment for CAD. Cardiac rehabilitation (CR) is a broad measure offered to patients with heart disease, which comprises health education, advice on cardiovascular risk reduction, physical activity, and stress management [4]. Especially for patients with CAD, a well-designed and long-term executed CR, which involves medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling, can significantly reduce mortality and morbidity in a very cost-effective way [5-7]. However, the participation rates of CR remain unsatisfying varying from 20%~40%, in comparison with the great benefits and low cost it provides [8]. In China, the situation is worse due to the relatively poor social-economic conditions, which mandate more clinical promotion and practice [9].

Chronic kidney disease (CKD) has roused attention when complicated with CAD because it can increase the incidence of CAD [10] and the long term risks of cardiac events [11]. CR is strongly recommended for patients with ACS-including ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina-and all patients undergoing reperfusion [12]. However, there is limited data on the benefits of CR on ACS patients with CKD. In this

study, we analyzed the effects of CR on the long-term outcomes of patients undergoing percutaneous coronary intervention (PCI) using a retrospective propensity match study, which provided more evidence of CR's benefits and indications.

Materials and methods

Study population

We retrospectively collocated the clinical data of patients meeting the following criteria: 1. Patient diagnosed with ACS who received the PCI treatment, according to the 2011 ACCF/AHA/SCAI guideline for PCI [13]; 2. Patients with a previous history of CKD, or their eGFR was lower than 60 mL/min/1.73 m^2; 3. Patients had no contra-indications of CR, including unstable angina, severe heart failure (with LVEF < 30%), or uncontrolled ventricular arrhythmia [14]; 4. Patients who fulfilled the routine follow-up. A total of 246 patients with CKD who received PCI from Jan 2007 to Jan 2012 in our hospital were enrolled in this study and divided into the CR group, which was given CR treatment, and the nCR group which wasn't given CR treatment.

Demographic characteristics, clinical data, and the long-term outcome results from the electronic database of the hospital were collected for analysis, with the informed consent signed by the patients at admission. This study was also approved by the Medical Ethics Committee of First People's Hospital of Liangjiang New District.

Cardiac rehabilitation

According to BACPR Standard 2 [15], the CR program was launched in the Department of Cardiology, First People's Hospital of Liangjiang New District in Feb 2010, when the CR group was formed, which includes cardiologists, nurse specialists, physiotherapists, dietitians, psychologists, exercise specialists, occupational therapists, and clerical administrators. A particular CR plan was made for every patient who was willing to receive the treatment, which included the following components: 1. Health behavior change and education; 2. Lifestyle risk factor management (Physical activity and exercise, diet, smoking cessation); 3. Psychosocial health; 4. Medical risk factor management; 5. Cardioprotective therapies; 6. Long term management; 7. Audit and evaluation. The patients were required to attend the CR session within three months after PCI, and the multidisciplinary program had to last more than one year (more than three courses of CR).

Follow-up and endpoints

The follow-up lasted from Jan 2010 to Jan 2017, and it was done by telephone or in the outpatient clinics. Every patient was given an annual inquiry of their conditions. Self-dropout or missed contact was considered to be censored data.

Primary and secondary endpoints were studied as follows: the primary endpoint was defined as all-cause mortality during the follow-up, while the secondary endpoint was identified as a composite of adverse events including myocardial infarction, unscheduled revascularization.

Statistical analysis

In this study, SPSS version 19.0 (SPSS, Inc, Armonk, NY) was used for the statistical analysis. The normality distribution test of the variables was conducted first to check the variables' distribution conditions. Continuous variables meeting the normal distribution were presented as the mean ± standard deviations, and categorical variables were presented as proportions.

A comparison of the continuous variables of different groups was conducted with the *t*-test of independent samples. A chi-square test was performed in the different evaluations of categorical variables. The propensity score was calculated with a multivariable logistic regression used by taking into account the demographical and clinical variables. Patients with the closest propensity scores were matched using the "greedy match" method. Following the propensity score match, a Student's *t*-test of paired samples and a McNemar test were adopted in the analysis.

As for the survival analysis, the Cox hazard ratio (HR) model was adopted as the regression method to compare the relative hazard for endpoints between the CR and nCR groups. A univariate analysis between covariates and endpoints was conducted. Kaplan-Meier survival curves and log-rank tests were used to compare the survival status of the CR and nCR

Table 1. Demographical characteristics and clinical data of the CR and nCR groups before the propensity score match

Variables	CR group (n = 106)	nCR group (n = 140)	*P*-value
Demographics			
Age (y, Mean ± SD)	58.4 ± 17.5	65.7 ± 17.2	0.001
Gender (% male)	65 (61.3%)	76 (54.3%)	0.299
BMI (kg/m^{-2})	22.8 ± 3.1	24.0 ± 3.2	0.003
Smoking (%)	37 (34.9%)	48 (34.3%)	1.000
Most recent MI			0.011
< 24 h	24 (22.6%)	54 (38.6%)	
1-7 d	17 (16.0%)	19 (13.6%)	
> 7 d	25 (23.6%)	15 (10.7%)	
Never	40 (37.7%)	52 (37.1%)	
Unstable angina	76 (71.7%)	92 (65.7%)	0.336
Prior PCI	16 (15.1%)	32 (22.9%)	0.145
Prior CABG	13 (12.3%)	25 (17.9%)	0.286
Contemporary PCI			0.001
Emergency PCI	23 (21.7%)	51 (36.4%)	
Urgent PCI	43 (40.6%)	65 (46.4%)	
Elective PCI	40 (37.7%)	24 (17.1%)	
Drug-eluting stent	48 (45.3%)	39 (27.9%)	0.007
GP IIb/IIIa Use	66 (62.3%)	76 (54.3%)	0.241
LVEF	49.1 ± 12.2	53.3 ± 11.4	0.006
Comorbidities			
Heart failure	31 (29.2%)	19 (13.6%)	0.004
Hypertension	66 (62.3%)	65 (46.4%)	0.015
Diabetes mellitus	22 (20.8%)	27 (19.3%)	0.872
Chronic lung disease	26 (24.5%)	31 (22.1%)	0.760
Cerebrovascular disease	1 (0.9%)	6 (4.3%)	0.244
Tumor	8 (7.5%)	5 (3.6%)	0.249

Abbreviations: BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction.

groups. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

There was a total of 246 patients included in this study, including 106 patients who joined the CR program (the CR group) and 140 patients who did not undergo CR treatment (the nCR group). The demographical characteristics and clinical data between the two groups are shown in **Table 1**. In the demographical part, the patients in the CR group were significantly younger than those in the nCR group (P = 0.001), and their BMI was lower than the BMI of the nCR group (P = 0.003). However, there was no significant difference in gender or smoking status (P > 0.05). There was also a considerable difference in the time of most recent MI (P = 0.011) and contemporary PCI type (P = 0.001). As for the subsequent treatment, more patients in the CR group received drug-eluting stents (P = 0.007). In terms of the comorbidities, the CR group had a higher proportion of heart failure (P = 0.004) and hypertension (P = 0.015), but there was no statistical difference in the ratio of diabetes mellitus, chronic lung disease, cerebrovascular disease, or tumors (P > 0.05). After the propensity match, there was no statistical difference in the variables listed in **Table 2** (all P > 0.05).

Primary endpoint

During the average follow-up of (38.9 ± 22.5) months, a total of 37 episodes of the primary endpoint (all-cause death) occurred, including 28 cases of cardiovascular death and 9 cases of non-cardiovascular death. As shown in **Table 3**, the hazard ratio (HR) of CR for the primary endpoint was 0.465 95% CI (0.233-0.926) (P = 0.029). The survival analysis also demonstrated that the CR group had a higher survival rate than the nCR group (P = 0.024), as shown in **Figure 1**.

Secondary endpoint

There were 44 episodes of secondary endpoints initiated during the follow-up, including 18 cases of myocardial infarction and 26 instances of emergent revascularization. The CR group had a significantly lower risk of developing cardiac events compared with the nCR group, with an HR of 0.532 95% CI (0.287-0.984) (P = 0.044), but there was no statistical significance in the subgroup analysis of myocardial infarction and emergent revascularization (P > 0.05). The Kaplan-Meier survival curve demonstrated that the CR group had fewer cardiovascular events than the nCR group (O = 0.039), as shown in **Figure 2**.

Discussion

To our knowledge, this study is the first to demonstrate that CR is effective in decreasing the

Table 2. Demographical characteristics and clinical data of the CR and nCR groups after the propensity score match

Variables	CR group (n = 89)	nCR group (n = 89)	*P*-value
Demographics			
Age (y, Mean ± SD)	59.9 ± 17.7	61.3 ± 17.8	0.517
Gender (% male)	59 (66.3%)	64 (71.9%)	0.219
BMI (kg/m^{-2})	23.1 ± 3.0	23.5 ± 3.1	0.406
Smoking (%)	29 (32.6%)	27 (30.3%)	0.872
Most recent MI			0.503
< 24 h	24 (27.0%)	30 (33.7%)	
1-7 d	17 (19.1%)	15 (16.9%)	
> 7 d	15 (16.9%)	9 (10.1%)	
Never	33 (37.1%)	35 (39.3%)	
Unstable angina	61 (68.5%)	56 (62.9%)	0.528
Prior PCI	12 (13.5%)	14 (15.7%)	0.832
Prior CABG	11 (6.7%)	19 (21.3%)	0.160
Contemporary PCI			0.301
Emergency PCI	23 (25.6%)	30 (33.7%)	
Urgent PCI	33 (37.1%)	35 (39.3%)	
Elective PCI	33 (37.1%)	24 (27.0%)	
Drug-eluting stent	34 (38.2%)	28 (31.5%)	0.432
GP IIb/IIIa Use	51 (57.3%)	52 (58.4%)	1.000
LVEF	49.8 ± 12.3	51.9 ± 12.4	0.243
Comorbidities			
Heart failure	24 (27.0%)	19 (21.3%)	0.484
Hypertension	50 (56.2%)	42 (47.2%)	0.294
Diabetes mellitus	19 (21.3%)	18 (20.2%)	1.000
Chronic lung disease	15 (16.9%)	10 (11.2%)	0.389
Cerebrovascular disease	1 (1.1%)	5 (5.6%)	0.211
Tumor	1 (1.1%)	2 (2.2%)	1.000

Abbreviations: BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; GP, glycoprotein; LVEF, left ventricular ejection fraction.

Table 3. Hazard ratio (HR) of the endpoint for patients treated with CR compared with patients without CR

	HR	95% CI	*P*-value
Primary endpoint	0.465	0.233-0.926	0.029
Secondary endpoint			
Myocardial infarction	0.465	0.174-1.239	0.125
Emergent revascularization	0.482	0.264-1.285	0.180
Overall	0.532	0.287-0.984	0.044

all-cause mortality and cardiac events for patients with CKD after undergoing PCI, by retrospectively comparing the patients receiving CR and patients without CR treatment. Notably, the propensity score match was used in this study to eliminate the baseline bias, which made the conclusions more convincing than an isolated comparison.

Previous studies have provided strong links between CR training and lower all-cause mortality. A systematic review and meta-analysis with 148 randomized controlled trials in 97,486 participants included consolidating the reduction of mortality by CR for patients with coronary heart disease [16]. However, there are still some controversies over the indications and risks of CR, especially for patients at high risk. Some studies found that CR was less effective for diabetics [17, 18], but one study found that CR was as effective in DM patients as it was in those without DM [19]. Those controversies necessitate more studies to focus on specific patients, especially patients with some complications.

CKD is an independent risk factor for CAD, and CAD is the leading cause of morbidity and mortality in patients with CKD [20-22]. For patients undergoing PCI, the complication of CKD leads to significantly more procedure complications, restenosis, and future cardiac events, even in the drug-eluting stent era [23]. Patients with both CKD and CAD are at a higher risk of death and cardiac events compared with patients with isolated CKD or CAD. Some studies investigated the effectiveness of CR in patients with CAD, which demonstrated that CR could lead to improved significant renal function and lower coronary risk profiles for patients with CKD [24-27]. However, there is no previous study observing the long-term effects of CR on patients with CKD. The propensity score match eliminated the baseline characteristics which might influence the survival rates, including age, BMI, the PCI emergency, MI history, cardiac function, and other complications. After the propensity match, there was no statistical difference between the two groups, so a univariate Cox regression analysis was conducted to compare the CR group and the nCR group in all-cause mortality and cardiac events. The results were positive, which we think resulted from two significant mechanisms. On the

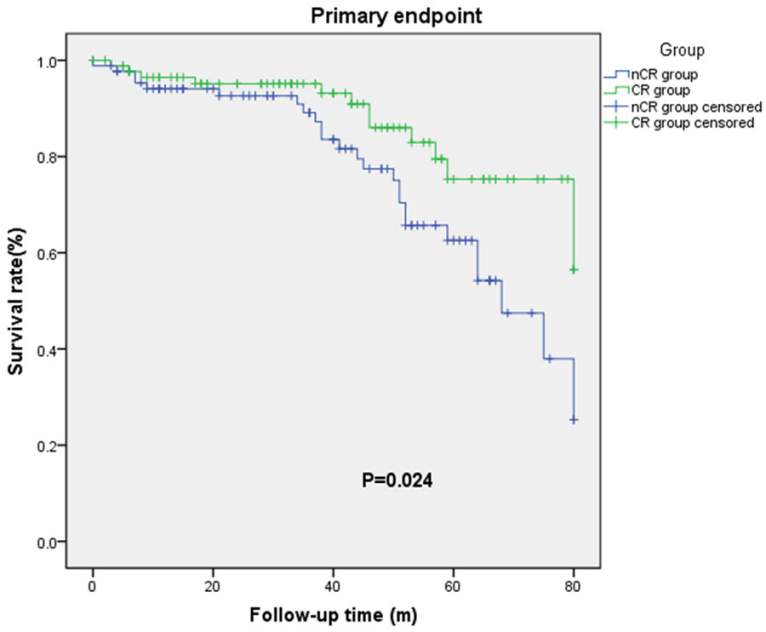

Figure 1. Kaplan-Meier curve for the primary endpoint of the CR and nCR groups.

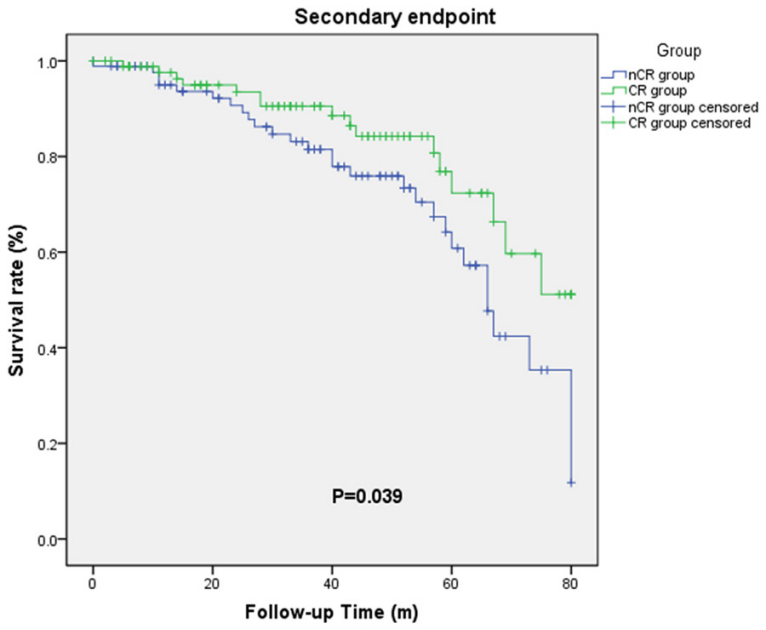

Figure 2. A Kaplan-Meier curve for the secondary endpoint of the CR and nCR groups.

one hand, the CR composite including exercising, smoking cessation, and weight loss has been shown to benefit the endothelial functions, which may play a role in renal function improvement and coronary revascularization [28]. On the other hand, some studies have demonstrated that CR can reduce the oxidized low-density lipoprotein (ox-LDL) level, which is critical for the development and worsening of CAD [29].

No matter how great the benefits of CR are, without the participation and compliance of the patients, the outcome will be nonsense. Despite years of promotion, the participation rate of CR remains low, especially in countries with undeveloped medical conditions. According to research conducted by the Canadian Institutes of Health Research, only 38.8% of countries have cardiac rehabilitation programs, including 68.0% of high-income and 23% of low- and middle-income countries [12]. In China, a survey showed that only 30 out of 124 (24%) reported that they had launched a CR program [30]. The significant barriers hindering the CR program lie in reduced referral rates, Poor patient adherence, the lack of an endorsement from a doctor, obesity, multiple morbidities, poor exercise habits, cigarette smoking, depression, problems with transport, poor social support, lack of leave from work [31]. In this study, about 46% (106 out of 246) patients with CKD got involved in the CR program, which was higher than the average level, and which could be attributed to the complete CR team.

Several limitations of this study should also be noted. First, the retrospective design was the primary reason affecting the strength of the evidence. Second, the follow-up data was not as good as in cohort studies, which have a relative higher proportion of censored data, which might have some bias against the final results. Last, due to

the incomplete clinical data of CKD, the CKD stage information was absent from this study.

Conclusions

In summary, this study demonstrated that CR is associated with a lower risk of death and cardiac events for patients with CKD by comparing patients receiving CR or not. More efforts are needed to promote CR in patients with CAD, especially for those with CKD.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qingqiang Shi, Emergency Department, First People's Hospital of Chongqing Liangjiang New Area, Chongqing 401-121, China. E-mail: 569770664@qq.com

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