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Incomplete protective effect of coronary collateral circulation for acute myocardial infarction patients

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Abstract

The short-term and long-term effects of coronary collateral circulation (CCC) discovered after acute myocardial infarction (AMI) are still debatable. This retrospective cohort study aimed to explore the clinical significance of CCC for AMI patients.

A consecutive series of 323 AMI patients with CCC and 1339 AMI subjects without CCC were enrolled, most of them received percutaneous coronary intervention after AMI. Comparisons between CCC subjects and non-CCC population and between CCC sub-groups were applied regarded to basic clinical characteristics, stenosis extent indicated by Gensini score, myocardial infarction size estimated by peak concentration of troponin I (TnI), and left ventricular function evaluated by peak value of N-terminal pro-brain natriuretic peptide (NT-proBNP). Multiple linear regressions for NT-proBNP and TnI, and Kaplan-Meier curves for 5-years' main cardiovascular event (MACE) were also analyzed.

(1) CCC patient had a greater extent of stenosis and a worse heart function while the estimated infarction size was not larger than non-CCC group;

(2) sub-group analyses showed, for good CCC circulation patient, stenosis extent was heavier, heart function was poorer while estimated infarction size was lower;

(3) regression analyses further indicated: for poorer heart function, stenosis extent and CCC (non, poor, good) were promotive factors; b) for infarction size, stenosis extent was a promotive factor in non-CCC group while it was an inhibitive factor in CCC group, good CCC was an inhibitive factor in CCC sub-group.

(4) Kaplan-Meier curves showed CCC had no obvious protective effect on 5-years' MACE for AMI patients.

CCC might provide incomplete protection by preventing excessive myocardial infarction but not a poorer heart function during AMI and CCC had no obvious protective effect on 5-years' MACE for AMI patients. More attentions should be paid to heart function for CCC patients during AMI.

Abbreviations: AMI = acute myocardial infarction, CCC = coronary collateral circulation, CHD = coronary heart disease, CK-MB = creatine kinase-MB fraction, IABP = intra-aortic balloon pump, MACE = main cardiovascular event, Myo = myoglobin, NT-proBNP = N-terminal pro-brain natriuretic peptide, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction, TnI = troponin I.

Keywords: acute myocardial infarction, coronary collateral circulation, heart function, infarction size

1. Introduction

Coronary heart disease (CHD) is a leading cause of mortality and morbidity worldwide, and parts of CHD patients develop coronary collateral circulation (CCC), which is considered an adaptive response secondary to myocardial ischemia in the presence of significant stenosis in coronary.[1] CCC is a network of arterio-arterial anastomotic connections between vascular branches in different regions of the heart.[2] Its diameter is 100 to 200 μm and closed in physiological state. When the coronary artery is seriously narrowed or occluded, those natural bypass can open up to 100 to 800 μm through a series of internal environment regulations and remodelings.[3] It has been reported that CCC in CHD patients without acute myocardial infarction (AMI) could alleviate episodes of myocardial ischemia, enhance residual myocardial contractility, reduce infarct size, preserve left ventricular function, reduce coronary atherosclerotic progression, and decrease mortality.[1,4,5] However, the short-term and long-term effects of CCC discovered during AMI are still debatable[6–8] especially most of AMI patients received treatment

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of revascularization (thrombolysis, percutaneous coronary intervention [PCI]).[9] Thus, this study sought to explore the clinical significance of CCC for AMI patients under the background of current evidence-based clinical practices in the real world. The main contents of this study include an analysis of basic clinical characteristics, comparisons between CCC and non-CCC subjects for myocardial infarct size as estimated by peak blood concentrations of cardiac-specific enzymes including creatine kinase MB fraction (CK-MB), myoglobin (Myo), and troponin I (TnI),[10] left ventricular function as gauged by echocardiography, peak value of N-terminal pro-brain natriuretic peptide (NT-proBNP), Killip grades, and the intra-aortic balloon pump (IABP) application rate, death rate, as well as the duration of in-hospital stay. Multiple linear regressions for NT-proBNP and TnI, and Kaplan-Meier curves for 5-years' main cardiovascular event (MACE) are also analyzed. It is expected this study would provide some useful hints for clinical practice and future in-depth research in the field of CCC.

2. Patients and methods

2.1. Study Population

This retrospective cohort study reviewed a consecutive series of 2712 patients with AMI who had been admitted to Cardiac Care Unit at Beijing Friendship Hospital from April 2013 to April 2017. Among these subjects, 1662 AMI patients were eligible for this study based on the inclusion and exclusion criteria following with either ST-elevation myocardial infarction (STEMI) or non-STEMI , and those subjects were divided into CCC group with 323 patients and non-CCC group with 1339 subjects respectively. Most of STEMI patients received an emergency PCI as part of reperfusion therapy within 12 hours of the onset of symptoms. For most of non-STEMI patients, initial antithrombotic therapy was instituted and subsequent coronary angiography (delayed PCI) was performed within the first week. Besides the revascularization on culprit vessel, totally 58.51% (189/323) CCC patients, and 47.57% (637/1339) non-CCC patients received PCI on non-culprit vessel with severe stenosis by a second operation or by the delayed PCI planned for culprit vessel at the same time. This study was approved by the local ethics committee of Beijing Friendship Hospital Affiliated to Capital Medical University and was performed in accordance with the Declaration of Helsinki. Informed consents were obtained from all study participants.

2.2. Inclusion and Exclusion Criteria

Patients were included if they met the universal definition of AMI[11] and had no documented history of other cardiovascular diseases (valvular heart diseases, preexisted left ventricular dysfunction, left ventricular hypertrophy, atrial fibrillation), respiratory diseases (pneumonia, chronic obstructive pulmonary disease, asthma, interstitial lung disease, pulmonary hypertension, pulmonary embolism), kidney diseases (glomerular nephritis, nephropathy syndrome, chronic renal failure, dialysis), infectious diseases (tuberculosis, hepatitis B, active infective endocarditis), endocrine diseases (hyperthyroidism, hypothyroidism), rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, vasculitis), hematological diseases (neutropenia, anemia, leukemia, lymphoma, disseminated intravascular coagulation), or varieties of neoplastic disease.

In order to acquire more reliable data, this study excluded patients with any forms of previous PCIs, such as balloon dilation, stent implant, thrombosis aspiration, and so on. Patients who had received only coronary angiography without PCI before the current hospitalization were not excluded. Patients who had been treated with coronary artery bypass grafting previously were also excluded from this study. Because the CCC was reported in relation to CHD and myocardial infarction (MI) histories, patients with CHD and MI histories were not excluded.

2.3. Basic characteristic data

The hospital medical records of the included patients were detailed and intact. Most of the data in this study were extracted from these medical records, including demographic data (age and sex), disease history (CHD, diabetes, and other diseases), conditions for smoking and drinking, family histories (hypertension, diabetes, and CHD), and medications before admission. Body mass index was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

2.4. Biochemical analysis

Serum concentrations of TnI, Myo, CK-MB, and NT-proBNP were measured at admission and at 12-hour intervals during the first 5 days after presentation of AMI (from symptom onset). Peak serum concentrations of TnI, Myo, and CK-MB were used for estimation of infarction size.[10] In addition, blood samples were taken from an antecubital vein after a 12-hour fast to measure total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting plasma glucose levels.

2.5. Echocardiography and coronary angiogram analysis

Transthoracic echocardiography was performed at a median of 5 days after AMI. All images were analyzed by a single investigator, blinded to all clinical data. The coronary angiography was performed via a radial artery approach or a femoral artery approach, and each image was interpreted by 2 independent cardiologists.

CCC grade (ranging from 0 to 3) was based on the Rentrop classification method: grade 0, no filling; grade 1, filling of side branches via collateral channels without visualization of the epicardial segment; grade 2, partial filling of the epicardial major coronary artery via collateral channels; and grade 3, complete filling of the epicardial major coronary artery. If a patient had more than 1 collateral vessel, the highest collateral grade was applied.[12] CCC with Rentrop grades 0 and 1 was defined as poor CCC, and CCC ranged from Rentrop grades 2 to 3 was good CCC.

The Gensini scoring system[13] was employed to evaluate the extent of coronary stenosis, and the most severe stenosis site was defined as the stenosis site for scoring. A stenosis diameter of $<$ 25% was defined as 1 point, 25% to 49% as 2 points, 50% to 74% as 4 points, 75% to 89% as 8 points, 90% to 99% as 16 points, and total occlusion as 32 points. The above scores were multiplied by a corresponding coefficient: 5 for the left main branch; 2.5 and 1.5 for the proximal and middle segment of the left anterior descending artery, respectively; 1 and 0.5 for D1 and D2 in the diagonal branches, respectively; 2.5 and 1 for proximal and distal segment lesions of the left circumflex artery,

respectively; and 1 for proximal, middle, distal, and posterior descending branch lesions of the right coronary artery. The sum of the scores for each lesion was the total score of the degree of coronary artery stenosis for a patient.

2.6. Clinical endpoints and follow-up

The follow-ups were carried out by nurses and doctors in cardiology department with telephones. Adverse events, re-hospitalization, and all-cause death, as well as the manifestations and medications were documented. The telephone follow-ups were performed for all patients at 1, 3, 6, 12, 24, 36, 48, and 60 months after discharge. Early or delayed follow-up was within a week of the scheduled time point. The missing data were addressed with propensity score methods. The major adverse cardiovascular events (MACE) in this study referred to death, re-infarction, repeat revascularization therapy, and cardiovascular related recurrent hospitalization.

2.7. Statistical analysis

All analyses were conducted using SPSS (IBM Corp., Armonk, NY) software version 25. All data were initially analyzed using a Kolmogorov-Smirnov test to assess for normality. Continuous data are presented as mean ± SD when normally distributed and median with interquartile range (IQR) when non-Gaussian in distribution. Unpaired t-tests and Mann-Whitney-U rank sum tests were used for the bivariate analyses of normally and non-normally distributed continuous data, respectively. Non-parametric data characteristics were assessed as a percent (%) and compared among groups using a chi-square test or a Fisher's exact test when appropriate. Multiple linear regressions for log peak value of NT-proBNP, log peak value of TnI, and Kaplan-Meier curves for 5-years' MACE were also performed. A P value $<.05$ was considered statistically significant.

3. Results

For the baseline characteristics (Table 1):

(1) the CHD history rate and MI history rate in CCC group were higher than in the non-CCC group;
(2) there were no significant differences between the CCC group and non-CCC group in age, sex, hypertension prevalence, blood lipids, liver and kidney functions, other cardiovascular risk factors, and medications before in-hospital.

Table 2 showed for CCC patients:

Table 1

Baseline characteristics of patients with acute myocardial infarction.

Item	Non-CCC (n = 1339)	CCC (n = 323)	*P* value
Age, years	63.14 ± 12.35	63.24 ± 12.42	.893
Sex, male (%)	985 (73.56%)	251 (77.71%)	.071
Hypertension, n (%)	819 (61.17%)	203 (62.85%)	.294
SBP (mmHg)	129.05 ± 21.82	126.44 ± 20.98	.053
DBP (mmHg)	73.75 ± 12.28	73.59 ± 12.32	.835
Diabetes, n (%)	375 (28.01%)	92 (28.48%)	.851
Fasting glucose, mmol/h	6.63 ± 2.65	6.67 ± 2.63	.831
HbA1c, %	6.41 ± 1.5	6.49 ± 1.52	.381
BMI (kg/m^2)	25.59 ± 3.55	25.75 ± 3.56	.464
Smoking, n (%)	644 (48.1%)	154 (28.48%)	.922
Alcohol, n (%)	540 (40.33%)	115 (35.6%)	.121
CHD history, n (%)	292 (21.81%)	107 (33.13%)	.000
MI history, n (%)	44 (3.29%)	26 (8.05%)	.000
PCI/CABG history, n (%)	0 (0.00%)	0 (0.00%)	–*
CHD family history, n (%)	399 (29.8%)	105 (32.51%)	.329
Hypertension family history, n (%)	353 (26.36%)	88 (27.24%)	.740
Diabetes family history, n (%)	144 (10.75%)	32 (9.91%)	.666
BUN (mmol/L)	5.57 ± 2.15	5.82 ± 2.12	.061
Creatinine (μmol/L)	85.13 ± 18.5	85.61 ± 17.16	.671
ALT (U/L)	24.00 (16.00–40.00)	27.00 (16.00–42.00)	.357
AST (U/L)	41.80 (22.00–125.00)	42.00 (21.00–112.90)	.774
TC, mmol/L	4.51 ± 0.99	4.57 ± 1.07	.346
TG, mmol/L	1.78 ± 1.42	1.73 ± 1.25	.583
HDL-c, mmol/L	1.07 ± 0.25	1.04 ± 0.25	.065
LDL-c, mmol/L	2.63 ± 0.73	2.71 ± 0.83	.070
Anti-platelet, n (%)	229 (17.1%)	66 (20.43%)	.200
Anti-angina, n (%)	218 (16.28%)	60 (18.58%)	.313
Beta receptor blocker, n (%)	111 (8.29%)	34 (10.53%)	.122
CCB, n (%)	439 (32.79%)	100 (30.96%)	.529
ACEI/ARB, n (%)	229 (17.1%)	53 (16.41%)	.419
Statin, n (%)	163 (12.17%)	41 (12.69%)	.787

ACEI/ARB = angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; ALT = alanine aminotransferase, AST = glutamic-oxaloacetic transaminase, BMI = body mass index, BUN = blood urea nitrogen, CCB = calcium channel antagonists, CCC = coronary collateral circulation; CHD = coronary heart disease; DBP = diastolic blood pressure, HbA1c = hemoglobin A1c, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, MI = myocardial infarction; SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

* In order to acquire more reliable data, this study excluded patients with any form of previous percutaneous coronary interventions (PCIs) and coronary artery bypass grafting (CABG). The significance level was 0.05.

Table 2

Coronary angiography characters and main clinical outcomes during in-hospital.

	Non-CCC (n = 1339)	CCC (n = 323)	*P* value
STEMI, n (%)	756 (56.46%)	167 (51.7%)	.069
LM total occlusion, n (%)	4 (0.30%)	1 (0.31%)	.074
LAD total occlusion, n (%)	246 (18.37%)	105 (32.51%)	.000
LCX total occlusion, n (%)	139 (10.38%)	91 (28.17%)	.000
RCA total occlusion, n (%)	174 (12.99%)	157 (48.61%)	.000
LM stenosis, n (%)	46 (3.44%)	23 (7.12%)	.003
LAD stenosis, n (%)	1158 (86.48%)	299 (92.57%)	.003
LCX stenosis, n (%)	842 (62.88%)	207 (64.09%)	.000
RCA stenosis, n (%)	896 (66.92%)	290 (89.78%)	.000
Gensini score	79.50 (58.50–107.50)	119.50 (89.00–146.00)	.000
NT-proBNP in admission, ng/ml	472.00 (150.00–1562.50)	877.00 (234.00–2453.00)	.000
Peak value of NT-proBNP, ng/mL	1210.50 (454.25–3342.50)	1747.00 (654.00–4306.00)	.000
LVEF, %	62.00 (55.00–66.00)	60.00 (49.00–66.00)	.000
Killip classification ≥2 (n, %)	262 (19.57%)	83 (25.7%)	.010
In-hospital time, day	7.00 (6.00–9.00)	8.00 (7.00–10.00)	.000
Peak value of CK-MB, U/L	54.35 (10.48–168.25)	53.35 (8.02–196.75)	.832
Peak value of Myo, U/L	61.70 (31.70–204.00)	72.70 (32.83–218.75)	.687
Peak value of TnI, ng/ml	5.00 (1.00–17.75)	5.36 (1.01–18.38)	.942
Death, n (%)	26 (1.94%)	4 (1.24%)	.384
Stent implanted, n (%)	1238 (92.46%)	310 (95.98%)	.025
Thrombosis aspiration, n (%)	53 (3.96%)	9 (2.79%)	.319
Use of IABP, n (%)	21 (1.57%)	12 (3.72%)	.013

Significance level was 0.05. CCC = Coronary collateral circulation; ACEI/ARB = angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, CCB = calcium channel antagonists, CK-MB = creatine kinase-MB fraction, IABP = intra-aortic balloon pump, Myo = myoglobin, LAD = left anterior descending coronary artery, LCX = left circumflex coronary artery, LM = left main coronary artery, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-brain natriuretic peptide, RCA = right coronary artery, STEMI = acute ST segment elevation myocardial infarction, TnI = troponin I.

(1) the stenosis extent as indicated by Gensini score and lesions in coronary branches were more obvious;
(2) heart function was poorer as indicated by peak value of NT-proBNP, left ventricular ejection fraction, Killip grade, and IABP application rate;
(3) it was interesting that the estimated infarction size as indicated by peak values of TnI, Myo, and CK-MB was not higher than in non-CCC group;
(4) in-hospital stay was longer, but the death rate was not higher than that of non-CCC patient.

CCC patients were further divided into a poorly developed CCC sub-group (poor CCC: Rentrop grades 0 and 1) and a well-developed CCC sub-group (good CCC: Rentrop grades 2 and 3) and the main outcomes during the hospital stay were compared. The results showed in Table 3 indicated good CCC group had a greater stenosis extent (mainly indicated by Gensini score), worse heart function (indicated by peak value of NT-proBNP, Killip grade, and IABP application rate), but smaller infarction size (mainly represented by TnI).

Multiple linear regression for log peak value of NT-proBNP showed in Table 4:

(1) CCC was a promotive factor for NT-proBNP, which indicated heart function would be worsened moving from non-CCC to poor CCC and to good CCC.

Table 3

Different in-hospital outcomes between poor CCC and good CCC patients.

	Poor CCC (n = 113)	Good CCC (n = 210)	*P* value
Gensini score	109.00 (79.50–133.30)	127.50 (93.75–150.63)	.001
STEMI, n (%)	67 (59.29%)	100 (47.62%)	.045
NT-proBNP in admission, ng/ml	476.00 (134.00–1464.00)	1142.00 (367.00–1142.00)	.000
Peak value of NT-proBNP, ng/mL	1627.00 (584.00–2706.50)	1836.00 (780.00–5494.00)	.025
Killip classification ≥2 (n, %	21 (18.58%)	62 (29.52%)	.032
LVEF, %	60.00 (50.00–67.00)	59.00 (48.75–65.00)	.212
Use of IABP, n (%)	0 (0.00%)	12 (5.71%)	.010
In-hospital time, d	8.82 ± 4.27	8.83 ± 3.49	.113
Peak value of CK-MB, U/L	85.30 (15.00–236.00)	35.80 (5.87–16.00)	.008
Peak value of Myo, U/L	93.30 (39.00–283.00)	60.70 (26.50–199.50)	.027
Peak value of TnI, ng/mL	8.83 (1.89–25.4)	4.74 (0.74–15.00)	.018
Stent implanted, n (%)	110 (97.35%)	200 (95.24%)	.358
Thrombosis aspiration, n (%)	3 (2.65%)	6 (2.86%)	.916
Death, n (%)	20 (1.77%)	2 (0.95%)	.320

Significance level was 0.05. CCC patients were further divided into a poorly developed CCC sub-group (poor CCC: Rentrop grades 0 and 1) and a well-developed CCC sub-group (good CCC: Rentrop grades 2 and 3). CCC = coronary collateral circulation, CK-MB = creatine kinase-MB fraction, IABP = intra-aortic balloon pump, LVEF = left ventricular ejection fraction, Myo = Myoglobin, NT-proBNP = N-terminal pro-brain natriuretic peptide, STEMI = acute ST segment elevation myocardial infarction, TnI = troponin I.

Table 4

Multiple linear regression for the log peak value of NT-proBNP.

Item	Standardization coefficient Beta	95% CI for Beta		*t* value	*P* value
Age, yr	−0.272	−0.334	−0.211	−8.670	.000
Sex, male (%)	0.019	0.017	0.021	16.912	.000
MI history	0.119	−0.013	0.252	1.766	.078
Anti-angina, n (%)	−0.092	−0.163	−0.021	−2.530	.012
Statin, n (%)	−0.086	−0.167	−0.005	−2.078	.038
IABP, n (%)	0.401	0.231	0.572	4.613	.000
STEMI, n (%)	0.153	0.094	0.211	5.137	.000
Neutrophil to lymphocyte ratio	0.021	0.013	0.029	5.075	.000
CCC (non, poor, good)	0.075	0.036	0.115	3.773	.000
Log Gensini score	0.296	0.011	0.580	2.040	.042
Log peak value of TnI	0.135	0.103	0.167	8.305	.000

Significance level was 0.05. CCC = coronary collateral circulation; CI = confidence interval, IABP = intra-aortic balloon pump, MI = myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, STEMI = acute ST segment elevation myocardial infarction, TnI = troponin I.

(2) Gensini score also was a promotive factor for NT-proBNP, which means those with a greater coronary stenosis extent had a worse heart function.

Multiple linear regression for log peak value of TnI showed in Table 5:

(1) for all patients, CCC (non, poor, good) and Gensini score were excluded by this regression model;
(2) for CCC group, the change from poor CCC to good CCC was accompanied by a decreased log peak TnI value;
(3) in non-CCC group Gensini score was a promotive factor for log peak TnI value while in CCC group it was an inhibitive factor (the underlying mechanism might that stenosis was promotive factor for CCC and then CCC offset the infarction-size-promoting effect of stenosis at the same time).

Figure 1 shows CCC did not play a protective role for the 5 years' MACE for all CCC patients (Above), the prognosis for poor CCC sub-group was not different from good CCC sub-group (Below). MACE in this study referred to death, re-infarction, repeat revascularization therapy, and cardiovascular related recurrent hospitalization.

Figure 2 shows CCC did not play a protective role for the 5 years' MACE for CCC patients who had received PCI after AMI

Table 5

Multiple linear regression for the log peak value of TnI.

	Item	Standardization coefficient Beta	95.0% CI for Beta		*t* value	*P* value
All subjects	Sex, male (%)	0.108	0.122	0.323	4.341	.000
	Age, years	−0.061	−0.008	−0.001	−2.251	.025
	STEMI, n (%)	0.320	0.499	0.677	12.962	.000
	Anti-platelet, n (%)	−0.063	−0.268	−0.039	−2.637	.008
	Statin, n (%)	−0.054	−0.288	−0.022	−2.279	.023
	Thrombosis aspiration, n (%)	0.088	0.190	0.600	3.775	.000
	Neutrophil to lymphocyte ratio	0.119	0.020	0.046	4.967	.000
	Log peak value of NT-proBNP	0.230	0.262	0.424	8.290	.000
Non-CCC	Sex, male (%)	0.099	0.093	0.316	3.585	.000
	STEMI, n (%)	0.341	0.531	0.731	12.338	.000
	MI history, n (%)	−0.056	−0.583	−0.022	−2.119	.034
	Anti-platelet, n	−0.056	−0.274	−0.004	−2.019	.044
	Statin, n	−0.058	−0.316	−0.018	−2.204	.028
	Anti-angina, n (%)	0.044	−0.019	0.242	1.670	.095
	IABP, n (%)	−0.050	−0.675	0.003	−1.942	.052
	Thrombosis aspiration, n (%)	0.087	0.158	0.608	3.335	.001
	Neutrophil to lymphocyte ratio	0.112	0.016	0.044	4.214	.000
	Log peak value of NT-proBNP	0.218	0.237	0.421	7.018	.000
	Log Gensini score	0.077	0.248	1.244	2.938	.003
CCC	Sex, male (%)	0.117	0.002	0.482	1.983	.048
	STEMI, n (%)	0.226	0.208	0.594	4.084	.000
	Neutrophil to lymphocyte ratio	0.160	0.017	0.083	2.944	.004
	Alcohol, n (%)	0.114	0.003	0.412	1.996	.047
	CCC (poor, good)	−0.132	−0.425	−0.049	−2.486	.014
	Log peak value of NT-proBNP	0.304	0.277	0.608	5.278	.000
	Log Gensini score	−0.212	−3.353	−1.129	−3.968	.000

Significance level was 0.05.

CCC = coronary collateral circulation, CI = confidence interval, IABP = intra-aortic balloon pump, MI = myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, STEMI = acute ST segment elevation myocardial infarction, TnI = troponin I.

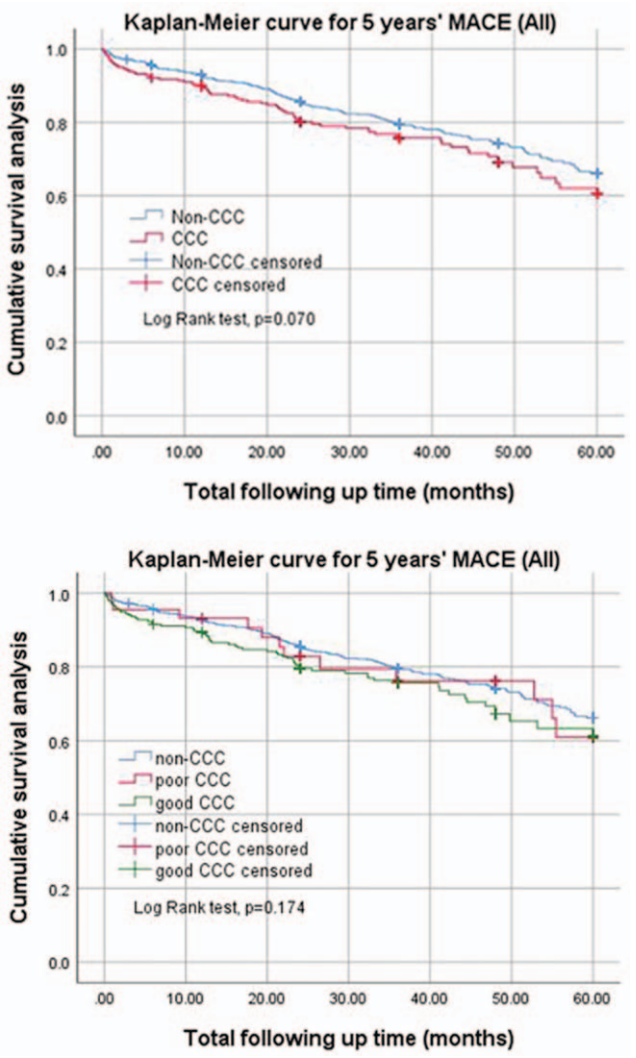

Figure 1. Kaplan-Meier curves of 5-years' MACE for CCC patients. The significance level was 0.05. CCC = coronary collateral circulation; MACE = main cardiovascular event, including total death and recurrent hospitalization, PCI = percutaneous coronary intervention. 1) Above: for all enrolled AMI patients divided into non-CCC group and CCC group; Below: for all enrolled AMI patients divided into non-CCC group, poor CCC group, and good CCC group. 2) Censored cumulative survival for non-CCC and CCC (or poor and good CCC), the average cumulative survival time for non-CCC and CCC (or poor and good CCC), and the log rank test *P* value were: for Above, 79.3%, 73.1%, 49.84±0.59 months, 47.54±1.27 months, .070; for Below, 79.3%%, 72.7%, 73.2%, 49.84±0.59 months, 48.76±2.91 months, 47.21±1.41 months, .174. 3) the following up time was 33.84±16.87 months or 33.27 (24.00-48.00) months; 4) the followed up patients, total subjects and follow up rate were: non-CCC 1160, 1339, 86.63%, CCC 279, 323, 86.38%.

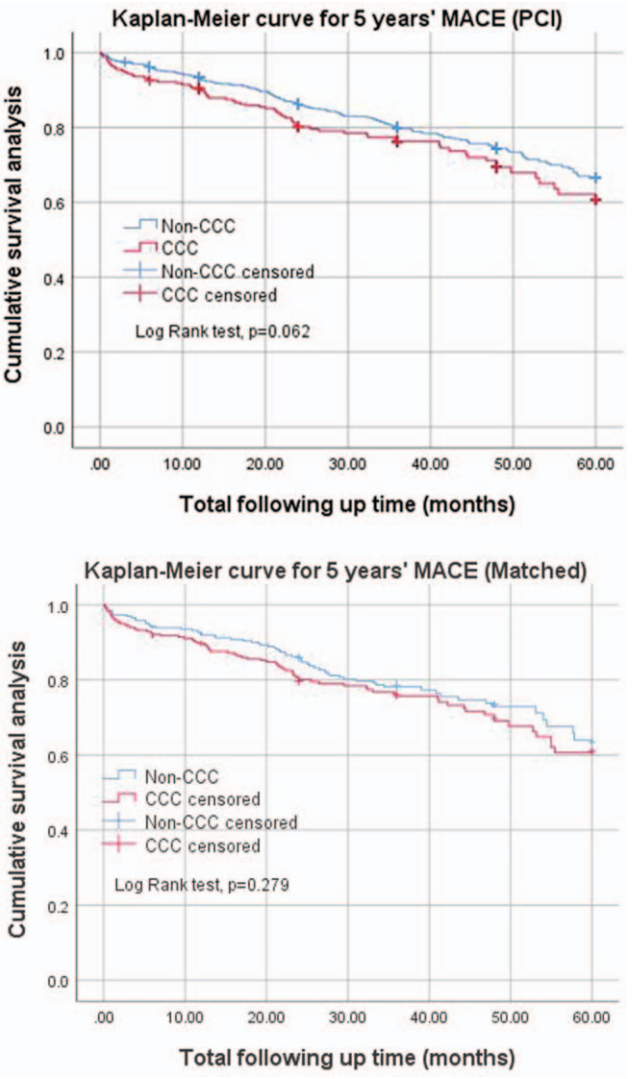

Figure 2. Kaplan-Meier curves for CCC patients received PCI and matched Gensini score. The significance level was 0.05. CCC = coronary collateral circulation; MACE = main cardiovascular event, including total death and recurrent hospitalization, PCI = percutaneous coronary intervention. 1) Above: only including PCI treated patients; Below: by matching the Gensini score between non-CCC and CCC with propensity score matching method by SPSS 25 software. 2) ensored cumulative survival for non-CCC and CCC, the average cumulative survival time for non-CCC and CCC, and the log rank test p value were: Above, 76.0%, 73.1%, 49.38±1.20 months, 47.47±1.26 months, 0.062; Below, 76.0%, 73.1%, 49.38±1.20 months, 47.47±1.26 months, 0.279; 3) the following up time were: Above, 32.18±16.77 months or 33.60 (24.00–48.00) months, Below, 33.82±16.84 months or 36.00 (24.00–48.00) months; 4) the followed up patients, total subjects and follow up rate were: Above, non-CCC 1075, 1328, 80.95%, CCC 270, 310, 87.10%; Below, non-CCC 262, 325, 80.62%, CCC 279, 323, 86.38%.

(Above). After matching Gensini score between non-CCC group and CCC group with 1:1 propensity score matching method by SPSS 25 software (Below), the CCC still did not showed protective role for the 5-years' MACE for CCC patients.

4. Discussion

The clinical significance of CCC discovered during AMI was still controversial in the era of coronary revascularization athough in traditional opinion CCC could reduce the risk of short-term and long-term mortality for CHD patients.[14–15] In this study, a total of 1662 AMI patients were divided into non-CCC and CCC group with balanced baseline data, and most of them received PCI during the in-hospital stay. The main findings were: for AMI patients, CCC was associated with a greater extent of stenosis, a poorer heart function, and without a larger infarction size; good CCC associated with a smaller infarction size; CCC had no obvious protective effect for the 5 years' MACE. Thus main clinical function of CCC might be a protection on the acute phase of AMI by preventing excessive myocardial infarction but not a poorer heart function rather than a protection on the long-term

prognosis. Besides our research, Chu AA found CCC had no significant direct effect on all-cause mortality for STEMI patients during 12-month follow-up,[16] Kurtul A also did not confirm a beneficial role of good CCC in patients with acute coronary syndrome.[17] It reminds us that, for AMI patients with CCC, more attentions should be paid on their poorer heart function, and do not put too many expectations on the long-term prognosis significance of CCC discovered during AMI under current clinical practices.

Why did CCC provide no obvious long-term protection for AMI patients? The possible explanations were:

(1) the worse clinical profiles may mask mortality benefit of CCC[18] because CCC patients have more cardiovascular risk factors which were promotive factors for atherosclerosis,[17,19] and in fact their coronary stenosis were heavier as showed in this research. The more serious the coronary stenosis extent, the greater probability of CCC formation because ischemia and hypoxia were strong stimulative factors for CCC formation.[5]
(2) The CCC developed after AMI was in an unstable status. Most AMI patients would receive revascularization under present evidence-based medicine principles. In this study parts of enrolled patients received a second coronary angiography evaluation during the following up period and the dynamic data showed 66.18% (45/68) CCC patients lost their CCC within 5 years. It was deduced the CCC discovered during AMI would be unstable when the contradiction of insufficient blood supply was resolved. Thus it is urgent to further explore how to promote and maintain CCC for AMI patients in practice.

The main protection effect of CCC discovered during AMI might be to inhibit excessive myocardial infarction. A lower infarction size meant fewer cardiomyocytes were damaged or died ultimately. With the blood supply from CCC, parts of cardiomyocytes in the ischemia area were uninfluenced, parts of cardiomyocytes were influenced by ischemia but a portion of them could recover, parts of cardiomyocytes that would be died because they faced severe and irreversible ischemia had their deaths prevented. CCC found during AMI might be different from CCC produced in CHD patients without AMI. The underlying mechanism for CCC includes angiogenesis and arteriogenesis. Angiogenesis is defined as new capillaries that stem from the budding of preexisting capillary vessels,[20] while arteriogenesis is the remodeling of preexisting arterial vessels through an "anatomic increase in lumen area and wall thickness."[1] It can be deduced that the opening of CCC during AMI was more likely due to arteriogenesis which would be faster than angiogenesis process. The main clinical function of CCC discovered during AMI might be a protection on the acute phase of AMI by preventing a larger infarction size rather than on the long-term prognosis because it might be lack of an adequate mechanism to keep opening of this kind of CCC continuously after revascularization.

Why did the CCC provide no obvious protection for heart function? First, the clinical profiles for CCC were worse than non-CCC patients especially the higher stenosis extent, thus it might be more difficult to fully compensate a worse heart function induced by acute severe ischemia with a narrower coronary even CCC developed subsequently. Secondly, CCC might be appeared too late to protect heart function sufficiently. Rentrop et al found that within 12 hours after the onset of AMI only 33% of the patients had CCC formation.[21] Therefore, the heart function would be affected by acute ischemia before the compensation from a fully developed CCC. Then why was heart function not in parallel with infarction size? In this research, heart function was influenced not only by the total number of dead cardiomyocytes but also by the number of dysfunctional cardiomyocytes. Thus the peak value of NT-proBNP represented the worst heart function during AMI and it did not always consistent with the ultimate fates of the ischemic cardiomyocytes. Thus for short-term significance, the poorer heart function of CCC patients during AMI should be dealt properly because they already accompanied with higher stenosis extent, longer in-hospital stay, higher rate of IABP application although the infarction size and the death rate were not higher than non-CCC patients.

5. Limitations

This study has the following limitations. First, this study was a single-center study and further multi-center collaborations were needed in future to produce more representative results. Second, the precise time point of CCC development was unknown for the AMI patients, and current human ethics do not permit us to design clinical trials to answer these questions, thus we could not determine whether the CCC appeared after AMI or whether it had already existed before AMI. Third, the Rentrop classification method has its own limitations because smaller microvascular caliber vessels less than 100 μm may not be visualized angiographically. Finally we have no data about myocardial perfusion with Thallium or 18F-flurodeoxy glucose after AMI.

6. Future directions

It was necessary to fully stimulate the potentially protective effect of CCC discovered during AMI for CHD patients:

(1) to find out the underlying factors for CCC formation during AMI besides the higher coronary stenosis extent, and to further answer the question why some AMI patients were with CCC but other without;
(2) to explore the approaches for promoting the formation of CCC before and during AMI;
(3) to research the methods for keeping the opening of CCC for a longer time after revascularization. The possible methods of promoting and maintaining CCC included remote ischemic pre-conditioning, stem cell transplant, growth factors injections and so on.

7. Conclusion

In general, the main clinical significance of CCC discovered during AMI might be a protection on the acute phase of AMI rather than a protection on the long-term prognosis because it might be lack of an adequate mechanism to keep the CCC opening continuously after revascularization. CCC might provide incomplete protection through prevention of excessive myocardial infarction but not through inhibition of a poorer heart function during AMI, CCC patient had a poorer heart function which should be dealt with properly. With the accelerated process of population aging worldwide, the prevalence of CHD was increasing in recent years and it was a major public health problem. For some patients, their life quality and prognosis were still unsatisfied although received traditional treatments including lifestyle adjusting, medicines, PCI and

coronary artery bypass grafting. Thus promoting and maintaining CCC are also important strategies for treatment of CHD patients including those with AMI.

Author contributions

Ruifeng Liu and Hongwei Li conceived the study and its design; the data were collected the Cardiovascular Center of Beijing Friendship Hospital Database Bank (CBD Bank) work group at Beijing Friendship Hospital; all authors have read and approved the final manuscript. This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal.

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