Doctor of Medicine

The Value of Coronary Angiography in Out-of-Hospital Cardiac Arrest Survivors without ST-segment Elevation Treated with Targeted Temperature Management

The Graduate School

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The Value of Coronary Angiography in Out-of-Hospital Cardiac Arrest Survivors without ST-segment Elevation Treated with Targeted Temperature Management

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Abstract

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Background

Current international guidelines recommend that emergent coronary angiography (CAG) should be performed for all out-of-hospital cardiac arrest (OHCA) survivors with suspected cardiac etiology of arrest and with ST-segment elevation (STE) on a post-resuscitation electrocardiogram (ECG) in immediate post-cardiac arrest period. In contrast those with STE, the optimal strategy for those without STE remains in debate.

The objectives of this study were (1) to present the CAG findings of all the consecutive adult comatose OHCA survivors without STE who underwent CAG within 24 hours after return of spontaneous circulation (ROSC) and who were treated with targeted temperature management (TTM); (2) to evaluate the rate of 1-month good neurologic outcome and survival; and (3) to evaluate the impact of immediate CAG strategy (< 2 hours after ROSC) versus early CAG strategy (2 – 24 hours after ROSC) on the 1-month neurological performance and survival.

Method

This multicenter retrospective observational registry-based study was conducted at the Emergency Department (ED) of 8 tertiary care university-affiliated teaching hospitals in Korea. Data of adult non-traumatic OHCA patients with no obvious extra-cardiac cause, without STE, who were treated with TTM, and in whom CAG was performed within 24 hours after ROSC between 2010 and 2015 were extracted. Patients were categorized into the immediate (≤2 hours) and early (2–24 hours) CAG groups. To reduce the effect of treatment selection bias and potential confounding factors, patients were propensity score matched. The primary endpoint was 1-month good neurologic outcome, and the secondary endpoint was 1-month survival.

Results

Among 346 patients with TTM and CAG, 119 who underwent CAG after 24 hours were excluded, and 227 patients were finally included. The proportion of the patients who received CAG within 24 hours increased during the 6-year study period. A total of 97 (42.7%) patients had a coronary artery stenosis of at least 50% and subsequent percutaneous coronary intervention and intra-aortic balloon pump insertion was performed in 49 (21.6%) and 18 (7.9%) patients, respectively. Among the 227 included patients, 112 and 115 patients were categorized into the immediate and early CAG groups, respectively. The coronary artery disease extent and subsequent interventions after CAG did not differ between immediate and early CAG groups. In crude model, the patients in early CAG group showed better clinical outcomes including survival at 1 month (58.9% vs. 76.5%; P = 0.005) and good neurologic outcome at 1 month (31.3% vs. 50.4%; P = 0.003). However, after propensity matching, we found no significant difference in clinical outcomes between two groups. Consequently, the timing of CAG (immediate versus early CAG) was not associated

with the survival (odds ratio, 1.600; 95% confidence interval, 0.726–3.526; P = 0.244) and good neurologic outcome at 1 month (odds ratio, 1.917; 95% confidence interval, 0.954–3.852; P = 0.068).

Conclusions

Coronary artery stenosis was found in 42.7% of OHCA survivors without STE who underwent CAG within 24 hours. In crude model, good neurologic outcome and survival at 1 month were higher in early CAG group compared to immediate CAG group, but there was no clear benefit of immediate versus early CAG after propensity score matching. Further randomized clinical trials are warranted to define the guidelines for recommending optimal CAG timing.

Key words

Out-of-hospital cardiac arrest; Cardiopulmonary resuscitation; Coronary angiography; Percutaneous coronary intervention; Outcome

Contents

List of Tables

List of Figures

List of Abbreviations

ACS = acute coronary syndromes;

AHA = American Heart Association;

CAG = coronary angiography;

CI = confidence interval;

CPC = Cerebral Performance Category;

CPR = cardiopulmonary resuscitation;

ECG = electrocardiogram;

ED = emergency department;

EMS = emergency medical service;

ERC = European Resuscitation Council;

IQR = interquartile range;

LBBB = left bundle branch block;

NSTEMI = non-ST-segment elevation myocardial infarction;

OHCA = Out-of-hospital cardiac arrest;

OR = odds ratio;

PCI = percutaneous coronary intervention;

ROSC = return of spontaneous circulation;

SD = standard deviation;

STE = ST-segment elevation;

TIMI = Thrombolysis in Myocardial Infarction;

TTM = targeted temperature management;

UA = unstable angina

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health burden. The global average incidence among adults is 55 OHCAs per 100,000 person-years and an average survival rate is 7%.[1] In Korea, the incidence rate of OHCA increased from 37.5 per 100,000 person-years in 2006 to 46.8 in 2010 according to a nationwide emergency medical service (EMS)-assessed OHCA database.[2] The survival rate of OHCAs in Korea was 3.0% (3.3% for cardiac etiology and 2.3% for non-cardiac etiology), which is lower than that of global average rate.[2] The rate of good neurologic outcome at discharge in Korea was 0.9%, which was much lower than the survival rate.[2] The most important goal of treatment in OHCA is to enhance the survival to discharge rate with a good neurologic outcome.[3-6] Despite the various efforts and medical advances in resuscitation care and post-resuscitation care for over 30 years, the clinical outcomes of OHCA survivors remain dismal and varies between countries and urbanization levels.[2, 7, 8] Further research and implementation of high-quality evidence-based practice are necessary to improve the outcomes of OHCA patients.

The importance of a synchronized set of interdependent actions in resuscitation is emphasized as the “Chain of Survival” to improve the outcomes of OHCA.[9] Especially, the high-quality post-resuscitation care is recognized as a vital link in the “Chain of Survival”.[9] The 2015 European Resuscitation Council (ERC) and the 2015 American Heart Association (AHA) recommend that all OHCA survivors with an initial shockable or non-shockable rhythm who remain unresponsive after return of spontaneous circulation (ROSC) have targeted temperature management (TTM) between 32ºC and 36ºC (Class I).[10, 11] In addition to TTM, the most important changes since 2010 guidelines are about the cardiovascular care. There is a greater emphasis

on the need for urgent or emergent coronary angiography (CAG) and percutaneous coronary intervention (PCI) for OHCA patients with suspected cardiac etiology of arrest in the latest 2015 guidelines.[10, 11]

Current guidelines of ERC and AHA recommend that emergent CAG should be performed for all OHCA survivors with suspected cardiac etiology of arrest and with ST-segment elevation (STE) on a post-resuscitation electrocardiogram (ECG) in immediate post-cardiac arrest period (Class I, level of evidence B-NR).[10, 11] Both the European Society of Cardiology and the American College of Cardiology Foundation/AHA have published the guidelines for the management of acute myocardial infarction in patients presenting STE, and immediate CAG (i.e. <2 hours from hospital admission) and subsequent PCI when indicated, are also recommended for resuscitated OHCA patients (Class I, level of evidence B) regardless of the initial cardiac arrest rhythm.[12-14] However, for those without STE on a post-resuscitation electrocardiogram, emergent CAG is considered selectively (Class IIa, level of evidence B-NR).[10, 11] The decision for invasive strategy in OHCA survivors without STE should carefully weigh the risks and benefits and requires individualized risk stratification and assessment including comorbidities, hemodynamic instability and other patient characteristics.[10, 11]

Generally, very-high-risk patients with non-STE-acute coronary syndromes (ACS) have been excluded from randomized controlled trials, controversy persists on the timing of invasive strategy in OHCA survivors without STE. The European Society of Cardiology recommended immediate invasive strategy (i.e. CAG with subsequent PCI <2 hours from hospital admission) in those patients (Class I, level of evidence C), but the guideline described that comatose OHCA survivors should first be investigated

for non-coronary conditions and CAG should be performed after that investigation.[15, 16] In the American College of Cardiology Foundation/AHA guidelines for the management of patients with Non-STE-ACS, the optimal timing of CAG among immediate, early (i.e. <24 hours from hospital admission) and delayed (i.e. 25 to 72 hours from hospital admission) invasive strategies has not been conclusively defined and there was no specific recommendation for the OHCA patients without STE about the timing of CAG.[17]

Many observational studies were performed to investigate the CAG findings and to evaluate the impact of CAG and/or subsequent PCI in OHCA survivor without STE.[18-25] Among the OHCA survivors without STE, acute coronary artery occlusion was present as approximately 25% to 35%.[18-25] However, those studies were not sufficient to draw a conclusion about the association of early CAG and patients' outcome. Early CAG and/or subsequent PCI were associated with better outcomes in some observational studies;[18, 19, 21-23, 26] however, other studies demonstrated conflicting outcome data.[24, 25, 27] Those studies should be interpreted in the context of the inherent biases of observational studies. Also, the broad definition of "early" CAG from 2 hours to 72 hours limited the value of their findings.

The primary benefit of emergent CAG is the timely revascularization by identifying the patients who really have an acute coronary artery occlusion that results in cardiac arrest or who need coronary reperfusion treatment to salvage myocardial tissue and function.[15-17, 28] Ultimately, this could prevent the occurrence of re-arrest and improve the short-term and long-term outcomes in OHCA survivors. However, performing immediate CAG in immediate post-cardiac arrest period has the potential risks. The mobilization of the patients at a time of hemodynamic instability from the

Emergency Department (ED) to cardiac catheterization laboratory and exposure to contrast are inevitable to perform CAG.[29, 30] Also, the possibility of delayed diagnosis of other possible non-coronary causes of cardiac arrest and incorrect therapeutic decisions might be increased with routine immediate invasive strategy.[29-31] Considering these risks and benefits of early CAG, the optimal timing of CAG has not yet been settled.

The objectives of this study were (1) to present the CAG findings of all the consecutive adult comatose OHCA survivors without STE on a post-resuscitation ECG in immediate post-cardiac arrest period who underwent CAG within 24 hours after ROSC and who were treated with TTM in 8 Korean tertiary care hospitals between 2010 and 2015; (2) to evaluate the rate of 1-month neurological performance and survival of those patients; and (3) to evaluate whether the immediate CAG strategy (i.e. performing CAG <2 hours after ROSC) would impact the 1-month neurological performance and survival of those patients compared to the early CAG strategy (i.e. performing CAG between 2 hours and up to 24 hours after ROSC with optimal medical therapy and evaluation).

Subjects and methods

I. Study design and patient population

This retrospective observational cohort study, using the data of prospectively collected OHCA registry, was conducted at the 8 EDs, which were university-affiliated, tertiary referral hospitals in Korea. The OHCA registry enrolled all persons aged ≥ 18 years who experienced non-traumatic OHCA and were treated with TTM since January 2010.[31] Data were extracted from the OHCA registry between January 2010 and December 2015. The Institutional Review Board of the University of Ulsan College of Medicine reviewed the study protocol and approved the study (IRB approval number. 2016-1038). Informed consent was waived due to the retrospective nature of this study.

Patients who met the following criteria were included in this study: no obvious extra-cardiac cause of OHCA such as hanging, drowning, asphyxia, and poisoning; post-resuscitation ECG demonstrating no significant STE or new-onset left bundle branch block; and CAG performed within 24 hours after sustained ROSC (defined as return of evident signs of circulation for more than 20 consecutive minutes). STE (measured at the J-point) was defined as following criteria: at least 2 contiguous leads with STE ≥ 2.5 mm in men < 40 years, ≥ 2.0 mm in men ≥ 40 years, or ≥ 1.5 mm in women in leads V_2 and V_3 and/or ≥ 1.0 mm in the other leads.[32] Patients were excluded if their post-resuscitation ECG was lost, or if they did not undergo CAG within 24 hours after ROSC.

Patients were categorized into two groups based on the time to CAG after ROSC: immediate and early CAG groups. Immediate CAG group was defined as the

OHCA survivors who underwent CAG < 2 hours after ROSC or the ED presentation.[15-17] Early CAG group was defined as the OHCA survivors who underwent CAG between 2 and 24 hours after ROSC or the ED presentation.[16, 17, 33] An interventional cardiologist on duty determined the timing of CAG and the decision for revascularization treatment was based on the CAG findings as well as the cardiologist's judgement throughout the study period.

II. Patient management

Patients in this study received post-resuscitation care in accordance with the then current Advanced Cardiac Life Support guidelines of 2005 or 2010.[3, 34] In Korea, EMS system were encouraged to provide field resuscitation attempts of at least 5 minutes in compliance with the standard protocols for EMS providers. Then, they bring the patients to the ED while administering cardiopulmonary resuscitation (CPR) during ambulance transport. EMS providers are legally prohibited to declare death in the field by themselves, except if patients show obvious signs incompatible with life.

In all unconscious OHCA survivors, TTM was induced using cooling devices such as the Blanketrol II (Cincinnati Subzero Products, Cincinnati, OH, USA), Arctic Sun Energy Transfer Pad (Medivance Corp., Louisville, CO, USA), or an endovascular cooling device (Thermoguard; ZOLL Medical Corporation, Chelmsford, MA, USA). The target temperature in the range between 33ºC and 36ºC was maintained for at least 24 hours. After maintenance period, patients were gradually rewarmed to 37ºC in hourly increments of 0.25ºC. After the intervention period, the body temperature was maintained normothermia until 72 hours from ROSC. The core

body temperature was monitored using an esophageal or rectal probe. During the intervention period, all patients were sedated, and the use of sedatives and analgesics such as propofol, benzodiazepine, and opioids were at the discretion of the treating physician. When patients developed shivering during the intervention period, they received systemic interventions to control shivering according to the Columbia Anti-Shivering Protocol.[35] The treating physician performed standard intensive care at the discretion of the institution.

III. Data collection

Demographic and clinical data, including age, sex, comorbidities (previous history of cardiac arrest and acute myocardial infarction, coronary arterial disease, congestive heart failure, hypertension, diabetes mellitus, chronic lung disease, stroke, chronic kidney disease, and liver cirrhosis), witness on collapse, bystander CPR, initial documented rhythm (ventricular fibrillation, pulseless ventricular tachycardia, asystole, pulseless electrical activity, and unknown), time from collapse to ROSC, duration of resuscitation, interventions before CAG (vasopressor use and extracorporeal life support) and interventions after CAG (PCI, coronary artery bypass graft, and intra-aortic balloon pump) were obtained (Figure 1). Initial documented rhythm was collected by EMS provider at the scene or treating physician at the ED. The first interpretable 12-lead ECG in immediate post-cardiac arrest period and coronary angiographic findings were retrieved from the patients' electronic medical records. The time interval from ROSC to CAG and the time interval from ROSC to PCI, if indicated, were also retrieved.

Figure 1. Case report form of this study

병원/환자 일련번호	/	성별	□남 □여	BMI		나이 (내원시)	
Date of arrest	□□년 □□월□□일	Witnessed	□ Yes □ No	Bystander CPR	□ Yes □ No		
Time factor	No-flow time (arrest ~ CPR시작까지 시각) / Low-flow time (CPR 시작 ~ ED 도착 시각)				□□□min/□□□min		
Initial rhythm (병원전)	□VF □VT □PEA □Asystole □unknown shockable □unknown unshockable □unknown						
과거력	□No past medical history						
	□ Previous Cardiac arrest □ Previous AMI □ Previous Heart failure □ Previous PCI □ Previous CABG □ Hypertension □ DM □ Chronic lung disease (COPD, ILD) □ Stroke □ Neurological disease other than CVA □ Renal failure □ LC						
	□ Current aspirin use □ Current clopidogrel use □ Current warfarin use						
병원전 ROSC후 내원	□ Yes □ No	타원 ROSC후 ER전원	□ Yes □ No	Initial rhythm (ER)	□VF □VT □PEA □Asystole		
ED resuscitation time (ED 도착시각 ~ Sustained ROSC 시각): non-sustained ROSC기간은 제외					□□□min		
Immediate Post-resuscitation state	GCS (E: /V: /M:) Total:			EKG findings	□STE □STD or T change □Others		
	CAG전 brain CT	□ Yes (□뇌출혈 □WNL) □ No		ECMO insertion	□ Yes □ No		
	Lab after ROSC (within 20 min)	Lactic acid	mmol/L	CK-MB		TnI /TnT	____ / ___
		BNP		PT (INR)		platelet	
	CAG전 IV 약물	□ NE □ Vasopressin □ Epinephrine □ Dopamine □ Dobutamine □ Nitrate □ Heparin					
	CAG전 PO 약물	□ Aspirin □ Clopidogrel □ b-blocker □ others _____					
CAG/PCI 시간	ROSC후 □□□hr / ROSC후 □□□hr			ROSC-to-catheterization lab time / ROSC-to-balloon time	□□□□min / □□□□min		
Angiographic disease extent	□1VD □2VD □3VD □Vasospasm			IABP	□ Yes □ No	GP IIb/IIIa inhibitor	□ Yes □ No

	Lesion location	Lesion type (ACC/AHA classification)	Stent insertion	Total occlusion	Long lesion (≥20mm)
□ Lt main	□Ostial □Prox. □Mid □Distal	□A □B □C □in-stent restenosis	□ Yes □ No □ Failure	□ Yes □ No	□ Yes □ No
□ LAD	□Ostial □Prox. □Mid □Distal	□A □B □C □in-stent restenosis	□ Yes □ No □ Failure	□ Yes □ No	□ Yes □ No
□ LCX	□Ostial □Prox. □Mid □Distal	□A □B □C □in-stent restenosis	□ Yes □ No □ Failure	□ Yes □ No	□ Yes □ No
□ RCA	□Ostial □Prox. □Mid □Distal	□A □B □C □in-stent restenosis	□ Yes □ No □ Failure	□ Yes □ No	□ Yes □ No
□ Others	□Ostial □Prox. □Mid □Distal	□A □B □C □in-stent restenosis	□ Yes □ No □ Failure	□ Yes □ No	□ Yes □ No

PCI	□ Yes (□stent/□balloon) □ No (진행하지 못한 원인: □Vasospasm □Lt main □3VD □prior CABG □anatomy not amenable □unsuccessful dilation □dissection □incomplete revascularization)						
CABG	□ Yes(ROSC후__시간) □ No	TTM target Temp.	____ ℃	PCI후 LVEF	□□%	PCI후 Vfib	□ Yes□ No
ICU 입원기간	□□□days	전체입원기간	□□□days	30 일 사망	□ 사망 □ 생존	30 day CPC	___ 점
퇴원시상태	□ 사망 □ 생존 (퇴원시 CPC ___ 점)						
사망일시	□□년 □□월□□일			6개월 사망	□ 사망 □ 생존		
사망원인	□ Brain injury □ Cardiac cause (□MI □arrhythmia) □ Shock □ Respiratory failure □ CVA(ischemia, hemorrhage)						

IV. Primary and secondary outcomes

The primary outcome was good neurologic outcome at 1 month, defined as a Cerebral Performance Category (CPC) score of 1 or 2.[36] Neurologic performance was classified according to the CPC scale.[36] The CPC scale included five categories, with CPC 1 representing conscious and alert with good cerebral performance or minor disability; CPC 2 conscious and alert with moderate cerebral performance; CPC 3 conscious with severe cerebral disability; CPC 4 comatose or in a persistent vegetative state; and CPC 5 brain death or dead by traditional criteria.[36] CPC score at 1 month was determined from an in-hospital visit, from electronic medical records, or from telephone contact with patient or relative as a primary caregiver. The secondary outcome was 1-month survival. The date of patient's death was obtained from electronic medical records, or from the National Health Insurance Service in South Korea.[37]

V. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) when normally distributed or median with interquartile range (IQR) when non-normally distributed. Variables were tested for normal distribution using the Kolmogorov–Smirnov test. Categorical variables are presented as absolute numbers and percentages. Due to the number of the subgroups, we reported our trend data by an interval of 6 months and the frequencies of each period were calculated.

Student's *t*-test was used to compare the means of normally distributed continuous variables, and Mann–Whitney U test was used to compare the values of

non-normally distributed continuous variables. Differences between categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. The temporal trends were analyzed by the Mantel-Haenzsel test for trend. Paired t-test or sign test were used to compare continuous variables in propensity-score-matched groups, and McNemar's test was used for categorical variables.

To reduce the effect of treatment selection bias and potential confounding factors inherent in an observational study, we adjusted for differences in the patients' baseline characteristics using propensity score matching. The propensity scores were estimated without regard to outcomes through a multiple logistic regression analysis. A full non-parsimonious model was developed that included variables including age, sex, comorbidities (hypertension, diabetes mellitus, previous medial history of acute myocardial infarction, coronary artery disease, congestive heart failure, chronic kidney disease), witness on collapse, bystander CPR, initial shockable rhythm, time from collapse to ROSC, and interventions before CAG (vasopressor use and extracorporeal life support). The discrimination and calibration abilities of each propensity score model were assessed using the C-statistic and the Hosmer–Lemeshow statistic.[38]

Propensity score–matched pairs were created by matching between patients in the immediate and early CAG groups on the logit of the propensity score using calipers of width equal to 0.2 of the standardized difference of the logit of the propensity score. Using the matched set, we examined the similarities between the immediate and early CAG groups by calculating standardized differences for each of the baseline variables including age, sex, comorbidities (hypertension, diabetes mellitus, previous medial history of acute myocardial infarction, coronary artery disease, congestive heart

failure, chronic kidney disease), witness on collapse, bystander CPR, initial shockable rhythm, time from collapse to ROSC, and interventions before CAG (vasopressor use and extracorporeal life support). The C-statistic of the propensity score model was 0.760, while the P value of the Hosmer–Lemeshow statistics was 0.247.

In this crude model, good neurologic outcome at 1 month and 1-month survival were compared using the logistic regression model. Survival in immediate and early CAG groups was assessed by nonparametric Kaplan-Meier survival analysis and compared by log-rank tests. In the propensity-matched analysis, good neurologic outcome at 1 month and 1-month survival were compared using the conditional logistic regression model for matched pairs data.

All reported P values are two-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA).

Results

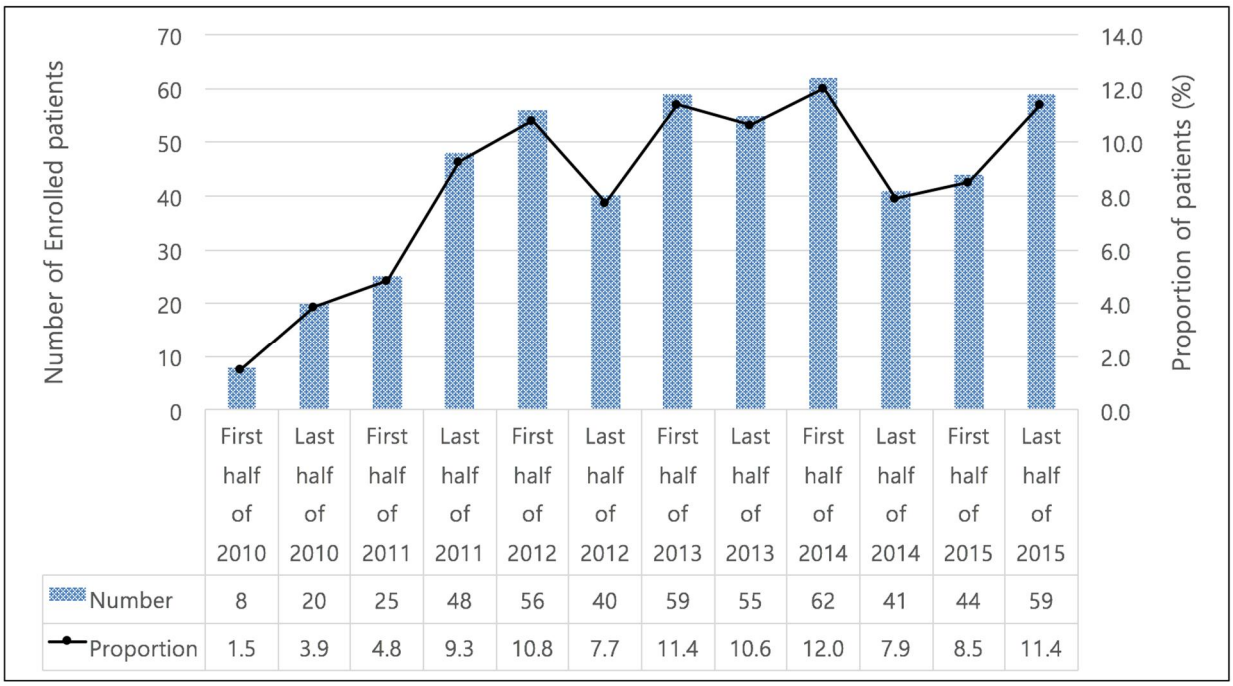
I. Patients enrollment and inclusion

During the study period from January 2010 to December 2015, 517 non-traumatic OHCA survivors without obvious extra-cardiac cause of OHCA underwent CAG and were admitted to be treated with TTM (Table 1). Regarding the first 18 months as the implementation period of 2010 guidelines for post-resuscitation care, 40 to 60 cases per period were consistently enrolled throughout the study period, as presented in Figure 2.

Table 1. Enrolled patients according to participating hospitals

Hospitals	Number of Enrolled Patients (%)
A	22 (4.3)
B	96 (18.6)
C	70 (13.5)
D	30 (5.8)
E	76 (14.7)
F	158 (30.6)
G	9 (1.7)
H	56 (10.8)
Total	517 (100.0)

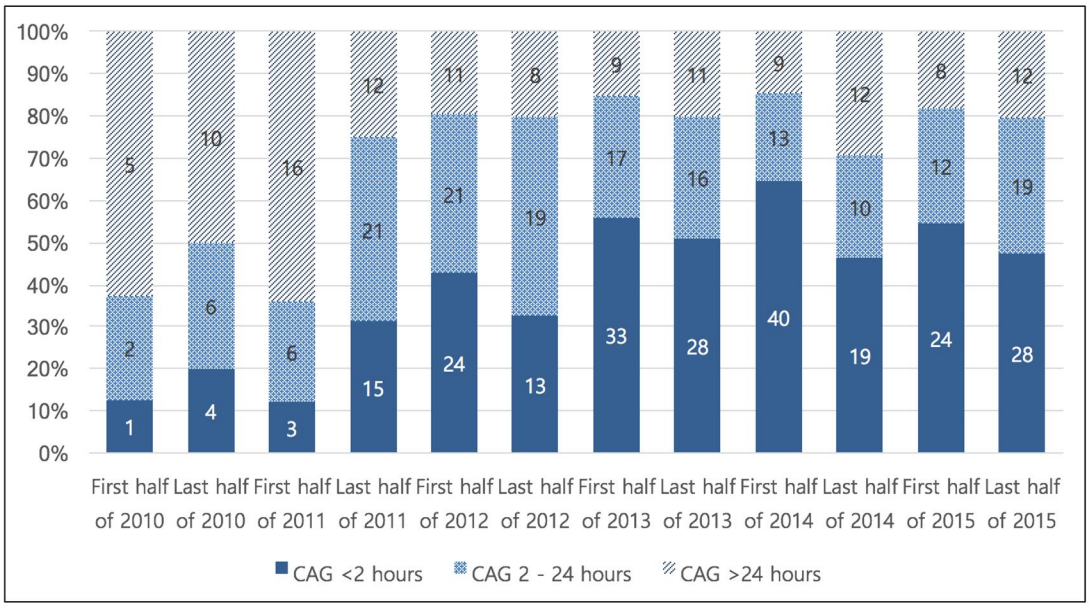
Figure 2. Patient enrollment by period



	First half of 2010	Last half of 2010	First half of 2011	Last half of 2011	First half of 2012	Last half of 2012	First half of 2013	Last half of 2013	First half of 2014	Last half of 2014	First half of 2015	Last half of 2015
Number	8	20	25	48	56	40	59	55	62	41	44	59
Proportion	1.5	3.9	4.8	9.3	10.8	7.7	11.4	10.6	12.0	7.9	8.5	11.4

Among the 517 enrolled patients from 8 hospitals, we excluded 123 patients because they received CAG after 24 hours. The proportion of the patients who received CAG within 24 hours among the enrolled OHCA patients increased by 278.7%, from 28.6% in the first half of 2010 to 79.7% in the last half of 2015, and the number of the patients who received CAG within 24 hours rose from 3 to 47 during the same time period ($P < 0.001$) (Figure 3).

Figure 3. Number and proportion of enrolled patients according to CAG timing during the study period.

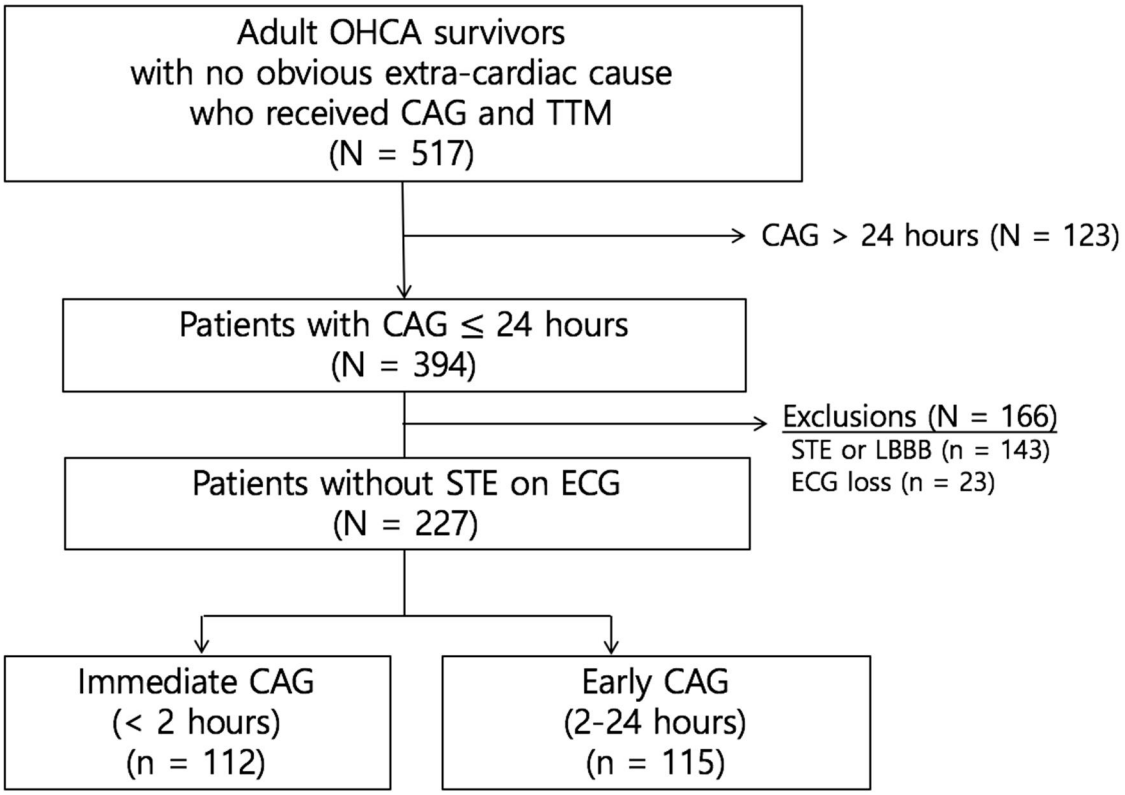


CAG, coronary angiography.

Of the remaining 394 patients, a total of 166 patients were excluded from the study because they had STE or left bundle branch block (LBBB) on their post-resuscitation ECG (n = 143), or their post-resuscitation ECG was lost (n = 23) (Figure 4). A total of 227 patients were finally included. The proportion of the patients who received CAG within 2 hours among the finally included OHCA patients increased from 0.0 % in the first half of 2010 to 58.3% in the last half of 2015, and the number of the patients who received CAG within 2 hours rose from 0 to 14 during the same time period (P = 0.012) (Figure 5).

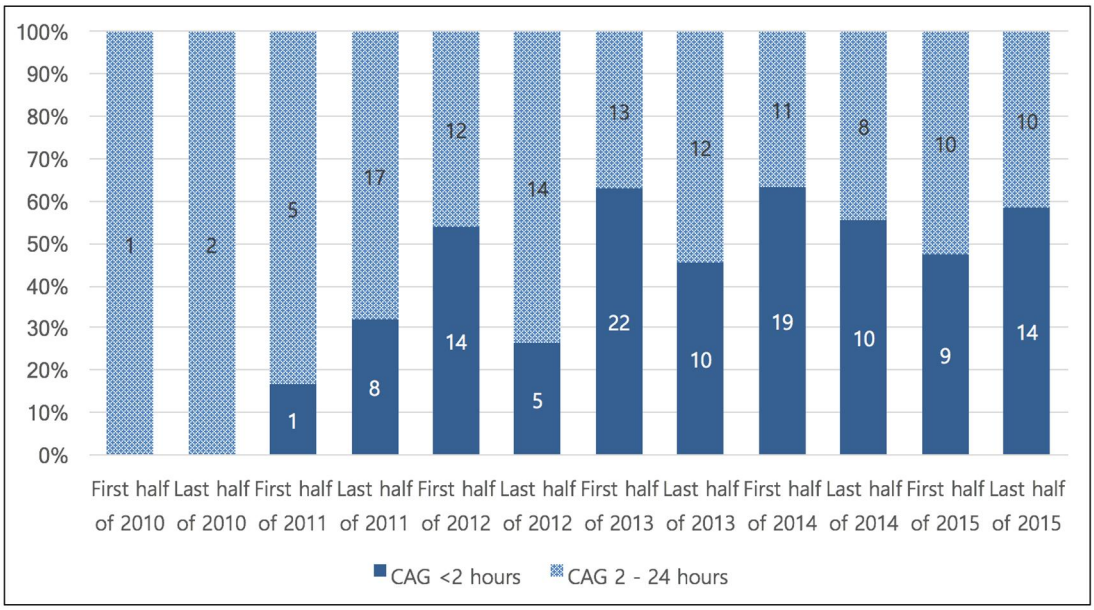
The proportion of the ECG findings in the patients who underwent CAG within 24 hours according to participating hospitals is shown in Table 2. There was no patient who underwent CAG within 24 hours without STE on postresuscitation ECG in hospital G. Thus, a total of 227 patients of 7 hospitals were finally included in the study. Patients were categorized into an immediate CAG group (n = 112, 49.3%) and early CAG group (n = 115, 50.7%).

Figure 4. Patient flow diagram



OHCA, out-of-hospital cardiac arrest; CAG, coronary angiography; TTM, targeted temperature management; STE, ST-segment elevation; LBBB, left bundle branch block; ECG, electrocardiogram.

Figure 5. Number and proportion of included patients according to CAG timing during the study period.



CAG, coronary angiography.

Table 2. The proportion of the electrocardiographic findings in the patients who underwent coronary angiography within 24 hours according to participating hospitals

Hospitals	Electrocardiographic findings		
	STE or LBBB	No-STE	ECG loss
A	5	4	0
B	25	68	1
C	2	45	18
D	12	9	0
E	33	12	1
F	41	71	0
G	6	0	3
H	20	18	0
Total	144	227	23

STE, ST-segment elevation; LBBB, left bundle branch block; ECG, electrocardiogram

II. Baseline characteristics of the study patients

The demographic and baseline characteristics of the study patients are summarized in Table 3. The mean age was 57.2 years (SD, ± 13.3 years), with a range of 18 to 91 years. A total of 170 (74.9%) patients were male.

Among the 227 patients, 111 (48.9%) had no previous medical illness before their cardiac arrest events. Hypertension (n = 89, 39.2%) and diabetes mellitus (n = 54, 23.8%) were the most common comorbid disease. Coronary artery disease, previous PCI and acute myocardial infarction were present in 24 (10.6%), 15 (6.6%), 14 (6.2%) patients, respectively. Other data of comorbid disease were outlined in table 3.

Less than 10% of the study patients already took aspirin (n = 21, 9.3%), antiplatelet agent (i.e. clopidogrel, ticagrelor, or prasugrel) (n = 8, 3.5%) and warfarin, an oral anticoagulant agent (n = 5, 2.2%), respectively. The median Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina (UA)/ non-ST-segment elevation myocardial infarction (NSTEMI) was 1.0 (IQR, 1.0-2.0), and 121 (55.3%) patients were assessed as low risk of death according to the TIMI risk score.

Table 3. Demographic and baseline characteristics of the out-of-hospital cardiac arrest survivors without ST-segment elevation who received coronary angiography within 24 hours and targeted temperature management

Variables	Total patients (n = 227)
Demographics	
Age, years	57.2 ± 13.3
Male	170 (74.9%)
Comorbid disease	
No previous medical illness	111 (48.9%)
Hypertension	89 (39.2%)
Diabetes mellitus	54 (23.8%)
Previous cardiac arrest	2 (0.9%)
Acute myocardial infarction	14 (6.2%)
Coronary artery disease	24 (10.6%)
Previous PCI	15 (6.6%)
Congestive heart failure	11 (4.8%)
Cerebrovascular disease	7 (3.1%)
Chronic lung disease	4 (1.8%)
Chronic kidney disease	14 (6.2%)
Liver cirrhosis	0 (0%)
Concurrent use of medication	
Aspirin	21 (9.3%)
Oral antiplatelet agents*	8 (3.5%)
Warfarin	5 (2.2%)

Table 3. Cont'd

TIMI risk score for UA/NSTEMI	1.0 (1.0-2.0)
TIMI risk score for UA/NSTEMI assessment	
Low risk (0 or 1)	121 (55.3%)
High risk (> 1)	106 (46.7%)

Variables are expressed as mean number ± standard deviation, median (interquartile ranges), or number (%) as appropriate.

* Oral antiplatelet agents include clopidogrel, ticagrelor, and prasugrel.

PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; NSTEMI; Non-ST-segment elevation myocardial infarction.

Table 4 shows the arrest and resuscitation characteristics of the study patients. A total of 156 patients (68.7%) were witnessed arrest. Bystander CPR was performed in 50.7% (n = 115). Ventricular fibrillation (n = 78, 34.4%) was the most frequently documented arrest rhythm at prehospital state, followed by unknown rhythm (n = 52, 22.9%) and asystole (n = 39, 17.2%). The prehospital shockable rhythm including ventricular fibrillation, pulseless ventricular tachycardia, and unknown shockable rhythm by automatic external defibrillator was noted in 104 of 227 patients (45.8%). By contrast, asystole (n = 79, 34.8%) was the most frequently documented initial rhythm at the ED, followed by sinus rhythm after ROSC (n = 52, 22.9%) and ventricular fibrillation (n = 42, 18.5%). The proportion of the shockable rhythm decreased from 45.8% (n = 104) at prehospital state to 23.3% (n = 53) at ED.

The mean duration of arrest was 32.4 min (SD, ± 16.33 min). Two thirds of the patients (n = 158, 69.6%) showed the ST-segment depressions on their post-resuscitation ECG. A total of 184 patients (81.1%) underwent brain computed tomography before CAG. Vasopressor was administrated in 66.5% (n = 151) and extracorporeal life support was performed in 10.6% (n = 24).

Table 4. Arrest and resuscitation characteristics of the out-of-hospital cardiac arrest survivors without ST-segment elevation who received coronary angiography within 24 hours and targeted temperature management

Variables	Total patients (n = 227)
Arrest characteristics	
Witnessed	156 (68.7%)
Bystander CPR	115 (50.7%)
Prehospital initial documented rhythm	
Ventricular fibrillation	78 (34.4%)
Pulseless ventricular tachycardia	7 (3.1%)
Unknown shockable rhythm	19 (8.4%)
Pulseless electrical activity	18 (7.9%)
Asystole	39 (17.2%)
Unknown unshockable rhythm	14 (6.2%)
Unknown	52 (22.9%)
Initial documented rhythm at the ED presentation	
Ventricular fibrillation	42 (18.5%)
Pulseless ventricular tachycardia	11 (4.8%)
Pulseless electrical activity	33 (14.5%)
Asystole	79 (34.8%)
Unknown	10 (4.4%)
ED presentation after ROSC	52 (22.9%)
Prehospital no flow time, min	5.0 (0.0-9.0)

Table 4. Cont'd

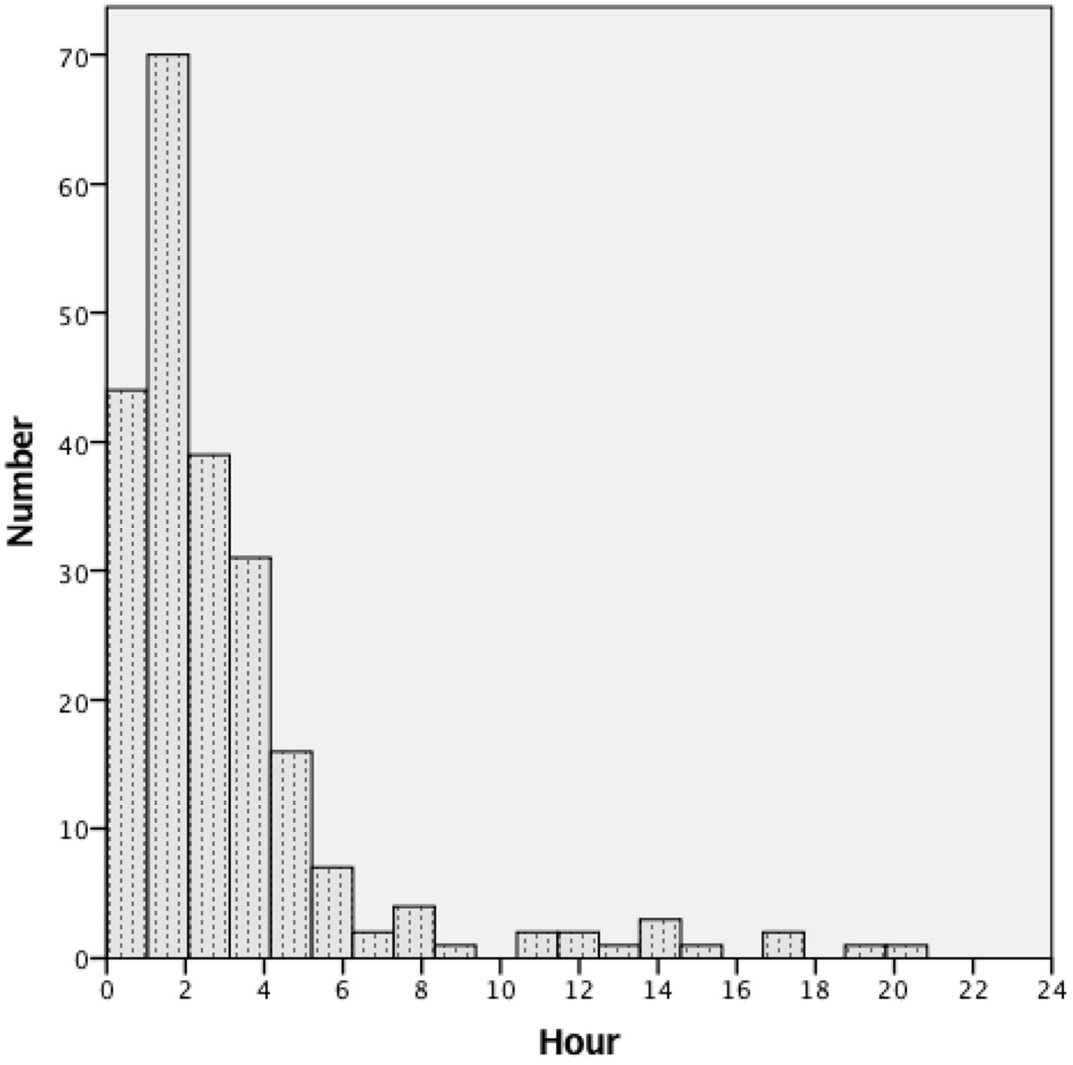
Prehospital low flow time, min	15.0 (8.0-20.0)
Resuscitation duration at the ED	9.0 (1.0-16.5)
Time from collapse to ROSC, min	32.4 ± 16.33
ECG findings at immediate post-resuscitation duration	
ST-segment depression	158 (69.6%)
No or insignificant ST-segment changes	69 (30.4%)
Interventions at immediate post-resuscitation duration before CAG	
Brain computed tomography	184 (81.1%)
Administration of vasopressor	151 (66.5%)
Extracorporeal life support	24 (10.6%)

Variables are expressed as mean number ± standard deviation, median (interquartile ranges), or number (%) as appropriate.

CPR, cardiopulmonary resuscitation; ED, emergency department; ROSC, return of spontaneous circulation; ECG, electrocardiogram; CAG, coronary angiography.

Figure 6 presents a histogram of the timing of CAG. The median time from ROSC or the ED presentation to CAG was 2.1 hours (IQR, 1.23-3.88, hours).

Figure 6. The distribution of the timing of coronary angiography



III. Comparison of clinical characteristics

Among the 227 patients, 112 patients (49.3%) underwent immediate CAG and the other 115 (50.7%) received early CAG. We used propensity score matching and matched 146 propensity score–matched pairs. The demographic and clinical characteristics between the immediate and early CAG groups before and after propensity score matching are summarized in Table 5 and Table 6, respectively.

Demographic characteristics did not differ between the immediate and early CAG groups (Table 5). Cardiovascular comorbid disease including acute myocardial infarction, coronary artery disease and previous PCI treatment also did not show significant difference between two groups. The patients in the immediate CAG group had higher rates of non-cardiaovascular diseases including diabetes mellitus (29.5% vs. 18.3%; P = 0.048) and chronic kidney disease (9.8% vs. 2.6%; P = 0.024). The concurrent medication use of aspirin, antiplatelet agents and warfarin and TIMI risk score for UA/NSTEMI did not differ between two groups. Table 6 showed that a propensity score matching analysis achieved the intergroup balance between two groups.

Table 5. Comparison of demographic and baseline characteristics between the patients in the immediate and early coronary angiography groups

Characteristic	Immediate group (<2 hours) (n = 112)	Early group (2-24 hours) (n = 115)	P value
Demographics			
Age, years	57.3 ± 13.3	57.2 ± 13.4	0.989
Male	85 (75.9%)	85 (73.9%)	0.731
Comorbid disease			
Hypertension	44 (39.3%)	45 (39.1%)	0.981
Diabetes mellitus	33 (29.5%)	21 (18.3%)	0.048
Acute myocardial infarction	6 (5.4%)	8 (7.0%)	0.617
Coronary artery disease	12 (10.7%)	12 (10.4%)	0.945
Previous PCI	7 (6.3%)	8 (7.0%)	0.830
Congestive heart failure	6 (5.4%)	5 (4.4%)	0.723
Cerebrovascular disease	4 (3.6%)	3 (2.6%)	0.719
Chronic lung disease	2 (1.8%)	2 (1.7%)	>0.999
Chronic kidney disease	11 (9.8%)	3 (2.6%)	0.024
Concurrent use of medication			
Aspirin	11 (9.8%)	10 (8.7%)	0.770
Oral antiplatelet agents*	4 (3.6%)	4 (3.5%)	>0.999

Table 5. Cont'd

Warfarin	2 (1.8%)	3 (2.6%)	>0.999
TIMI risk score for UA/NSTEMI	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.246
TIMI risk score for UA/NSTEMI assessment			0.094
Low risk (0 or 1)	66 (58.9%)	55 (47.8%)	
High risk (> 1)	46 (41.1%)	60 (52.2%)	

Values are expressed as mean ± standard deviation, median (interquartile ranges) or n (%) as appropriate.

* Oral antiplatelet agents include clopidogrel, ticagrelor, and prasugrel.

PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; NSTEMI; Non-ST-segment elevation myocardial infarction.

Table 6. Comparison of demographic and baseline characteristics between the patients in the immediate and early coronary angiography groups after propensity score matching

Variables	Total patients after matching (n = 146)	Immediate group (<2 hours) (n = 73)	Early group (2-24 hours) (n = 73)	Standardized difference of means
Demographics				
Age, years	56.8 ± 13.4	56.7 ± 14.1	56.8 ± 12.8	0.006
Male	119 (81.5%)	58 (79.5%)	61 (83.6%)	0.106
Comorbid disease				
Hypertension	49 (33.6%)	24 (32.9%)	25 (34.3%)	0.029
DM	25 (17.1%)	12 (16.4%)	13 (17.8%)	0.036
AMI	8 (5.5%)	4 (5.5%)	4 (5.5%)	<0.001
CAD	14 (9.6%)	8 (11.0%)	6 (8.2%)	0.093
CHF	4 (2.7%)	2 (2.7%)	2 (2.7%)	<0.001
CKD	5 (3.4%)	2 (2.7%)	3 (4.1%)	0.075

Values are expressed as mean ± standard deviation, or n (%).

AMI, acute myocardial infarction; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus.

Table 7 shows the arrest and resuscitation characteristics of the study patients. Patients in the immediate CAG group had a higher rate of witnessed arrest (75.0% vs. 62.6%, P = 0.044). However, there was no significant difference between the immediate and early CAG groups, in terms of bystander CPR (50.9% vs. 50.4%; P = 0.945) and initial shockable rhythm at the scene (43.8% vs. 47.8%; P = 0.538). The mean duration of arrest in the immediate and early CAG groups was not significantly different (34.0 vs. 30.8 min; P = 0.141).

ST-segment depression on the post-resuscitation ECG was predominant in early CAG group contrast to immediate CAG group (58.0% vs. 80.9%; P < 0.001) and brain computed tomography was performed more frequently in early CAG group than immediate CAG group (70.5% vs. 91.3%; P < 0.001). While the patients in immediate CAG group received vasopressor more frequently than those in early CAG group without statistical significance (72.3% vs. 60.9%; P = 0.068), they received significantly more extracorporeal life support in the ED (18.8% vs. 2.6%; P < 0.001).

Table 7. Comparison of arrest and resuscitation characteristics between the patients in the immediate and early coronary angiography groups

Characteristic	Immediate group (<2 hours) (n = 112)	Early group (2-24 hours) (n = 115)	P value
Arrest characteristics			
Witnessed	84 (75.0%)	72 (62.6%)	0.044
Bystander CPR	57 (50.9%)	58 (50.4%)	0.945
Initial shockable rhythm	49 (43.8%)	55 (47.8%)	0.538
Prehospital no flow time, min	5.0 (0.0-9.0)	5.0 (0.0-8.0)	0.759
Prehospital low flow time, min	15.0 (7.0-22.0)	15.0 (8.0-20.0)	0.683
Resuscitation duration at the ED, min	9.0 (4.0-18.5)	9.5 (0.0-16.0)	0.226
Time from collapse to ROSC, min	34.0 ± 17.24	30.8 ± 15.27	0.141
ECG findings at immediate post-resuscitation duration			<0.001
ST-segment depression	65 (58.0%)	93 (80.9%)	
No or insignificant ST-segment changes	47 (42.0%)	22 (19.1%)	
Interventions before CAG			
Brain computed tomography	79 (70.5%)	105 (91.3%)	<0.001

Table 7. Cont'd

Administration of vasopressor	81 (72.3%)	70 (60.9%)	0.068
Extracorporeal life support	21 (18.8%)	3 (2.6%)	< 0.001

Values are expressed as mean ± standard deviation, median (interquartile ranges) or n (%) as appropriate.

CPR, cardiopulmonary resuscitation; ED, emergency department; ROSC, return of spontaneous circulation; ECG, electrocardiogram; CAG, coronary angiography.

The arrest and resuscitation characteristics between the immediate and early CAG groups after propensity score matching are summarized in Table 8. Significant variables which possibly affect the clinical outcomes of OHCA were examined such as witness on collapse, bystander CPR, initial shockable rhythm, time from collapse to ROSC, and interventions before CAG (vasopressor use and extracorporeal life support).

Table 8. Comparison of arrest and resuscitation characteristics between the patients in the immediate and early coronary angiography groups after propensity score matching

Variables	Total patients after matching (n = 146)	Immediate group (<2 hours) (n = 73)	Early group (2-24 hours) (n = 73)	Standardized difference of means
Arrest characteristics				
Witnessed	101 (69.2%)	52 (71.2%)	49 (67.1%)	0.089
Bystander CPR	76 (52.1%)	38 (52.1%)	38 (52.1%)	< 0.001
Initial shockable rhythm	75 (51.4%)	38 (52.1%)	37 (50.7%)	0.027
Time from collapse to ROSC, min	31.4 ± 15.46	31.8 ± 15.73	30.9 ± 15.27	0.060
Interventions at immediate post-resuscitation duration before CAG				

Table 8. Cont'd

Administration of vasopressor	100 (68.5%)	51 (69.9%)	49 (67.1%)	0.059
Extracorporeal life support	8 (5.5%)	5 (6.9%)	3 (4.1%)	0.121

Values are expressed as *n* (%)

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; CAG, coronary angiography.

IV. Coronary angiographic findings

The coronary angiographic findings of our study patients are presented in Table 9. Among the 227 patients, significant coronary stenosis, defined as coronary artery at least 1.5 mm in diameter with stenosis of 50% or more,[39] was present in 97 (42.7%) patients, whereas 72 (31.7%) patients had normal coronary artery. Of the 97 patients with clinically significant coronary artery stenosis, single-vessel disease was most common (n = 38, 39.2%), followed by 3-vessel or left main artery disease (n = 34, 35.1%) and 2-vessel disease (n = 25, 25.8%). A total of 49 patients (21.6%) received subsequent PCI and 18 patients (7.9%) were inserted intra-aortic balloon pump.

The location of coronary stenosis according to the number of vessel disease is presented in Figure 7. Left anterior descending artery was the most common artery with significant stenosis, but the proportion was not significantly different.

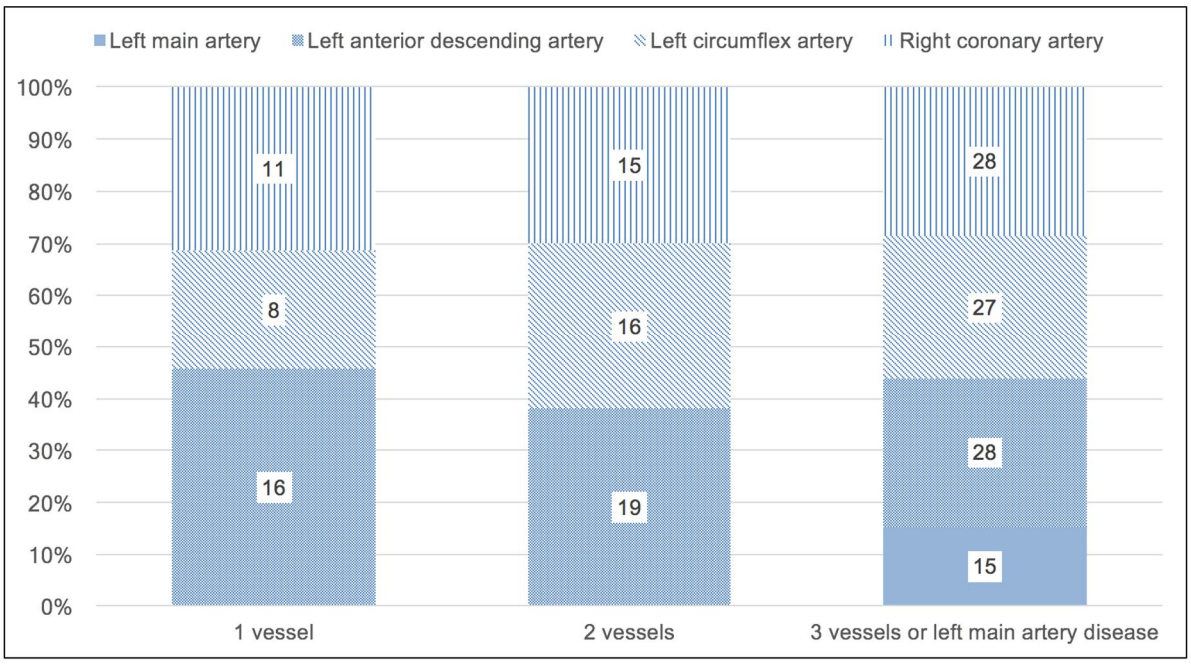
Table 9. Coronary angiography findings of the out-of-hospital cardiac arrest survivors without ST-segment elevation who received coronary angiography within 24 hours and targeted temperature management

Angiography findings	Total patients (n = 227)
Normal	72 (31.7%)
Vasospasm	33 (14.5%)
Insignificant stenosis	24 (10.6%)
Significant stenosis*	97 (42.7%)
Disease extent	
1 vessel	38/97 (39.2%)
2 vessels	25/97 (25.8%)
3 vessels or left main artery disease	34/97 (35.1%)
Disease location	
Left main artery	15/97 (15.5%)
Left anterior descending artery	63/97 (64.9%)
Left circumflex artery	51/97 (52.6%)
Right coronary artery	54/97 (55.7%)
Interventions after coronary angiography	
Subsequent percutaneous coronary intervention	49 (21.6%)
Intra-aortic balloon pump insertion	18 (7.9%)

Values are expressed as n (%).

* Significant coronary artery stenosis is defined as the vessel at least 1.5 mm in diameter with stenosis of 50% or more.[39]

Figure 7. Disease location of the study patients with significant coronary stenosis according to number of vessel disease



The median time from ROSC to CAG of the immediate and early CAG groups were 1.2 hours (IQR, 1.0-1.7 hours) and 3.8 hours (IQR, 2.8-5.1 hours; ranges, 2.0-20.8), respectively. The coronary angiographic findings of the patients in the immediate and early coronary angiography groups are presented in Table 10. Coronary spams were more frequently documented in patients of early CAG group compared to those of immediate CAG group (8.9% vs. 20.0%; P = 0.048); whereas patients in immediate CAG group more frequently had at least one significant coronary artery stenosis episode without statistical significance (48.2% vs. 37.4%; P = 0.099). The rate of subsequent PCI was not significantly different between the immediate and early CAG groups (25.0% vs. 18.3%; P = 0.217) and the requirement of intra-aortic balloon pump insertion also showed no difference between two groups (7.1% vs. 8.7%; P = 0.665).

Table 10. Comparison of coronary angiography findings between the patients in the immediate and early coronary angiography groups

Angiography findings	Immediate group (<2 hours) (n = 112)	Early group (2-24 hours) (n = 115)	P value
Normal or insignificant stenosis	48 (42.9%)	49 (42.6%)	0.970
Vasospasm	10 (8.9%)	23 (20.0%)	0.018
Significant stenosis*	54 (48.2%)	43 (37.4%)	0.099
Disease extent			0.217
1 vessel	17/54 (31.5%)	21/43 (48.8%)	
2 vessels	16/54 (29.6%)	9/43 (20.9%)	
3 vessels or left main artery disease	21/54 (38.9%)	13/43 (30.2%)	
Disease location			
Left main artery	9/54 (16.7%)	6/43 (14.0%)	0.714
Left anterior descending artery	38/54 (70.4%)	25/43 (58.1%)	0.284
Left circumflex artery	31/54 (57.4%)	20/43 (46.5%)	0.286
Right coronary artery	34/54 (63.0%)	20/43 (46.5%)	0.105
Interventions after coronary angiography			
Subsequent percutaneous coronary intervention	28 (25.0%)	21 (18.3%)	0.217

Table 10. Cont'd

Intra-aortic balloon pump insertion	8 (7.1%)	10 (8.7%)	0.665

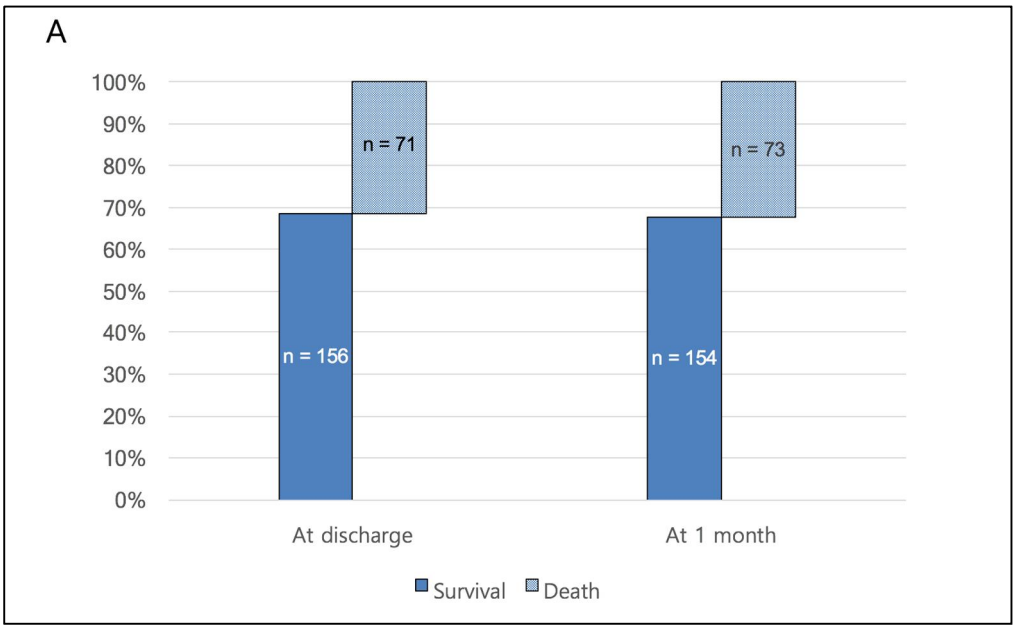
Values are expressed as n (%).

* Significant coronary artery stenosis is defined as the vessel at least 1.5 mm in diameter with stenosis of 50% or more.[39]

V. **Clinical outcomes including neurologic outcome and survival**

Figure 8 shows the clinical outcomes of the study patients. A total 156 patients (68.7%) survived to hospital discharge, and 154 patients (67.8%) survived till 1 month (Figure 8A). However, only 94 (41.4%) and 93 patients (41.0%) had good neurologic outcomes at discharge and at 1 month, respectively (Figure 8B). Three patients discharged with bad neurologic outcome died within 1 month, and 1 patient was hospitalized more than 1 month with bad neurologic outcome.

Figure 8. (A) Survival at discharge and at 1 month of the study patients. (B) Neurologic outcome at discharge and at 1 month of the study patients.



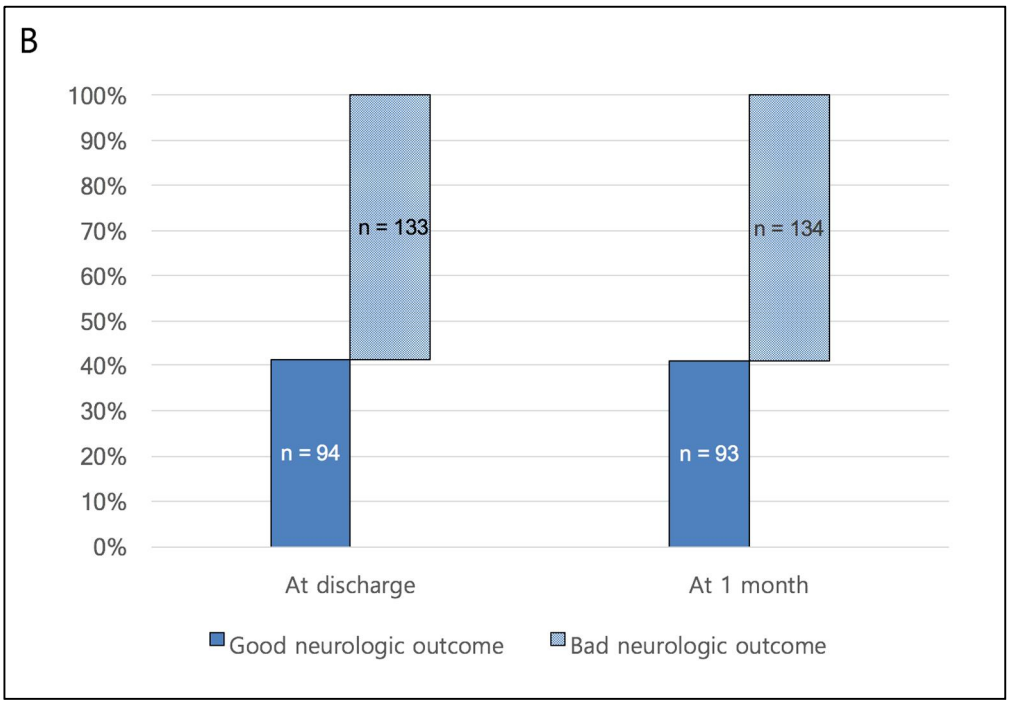
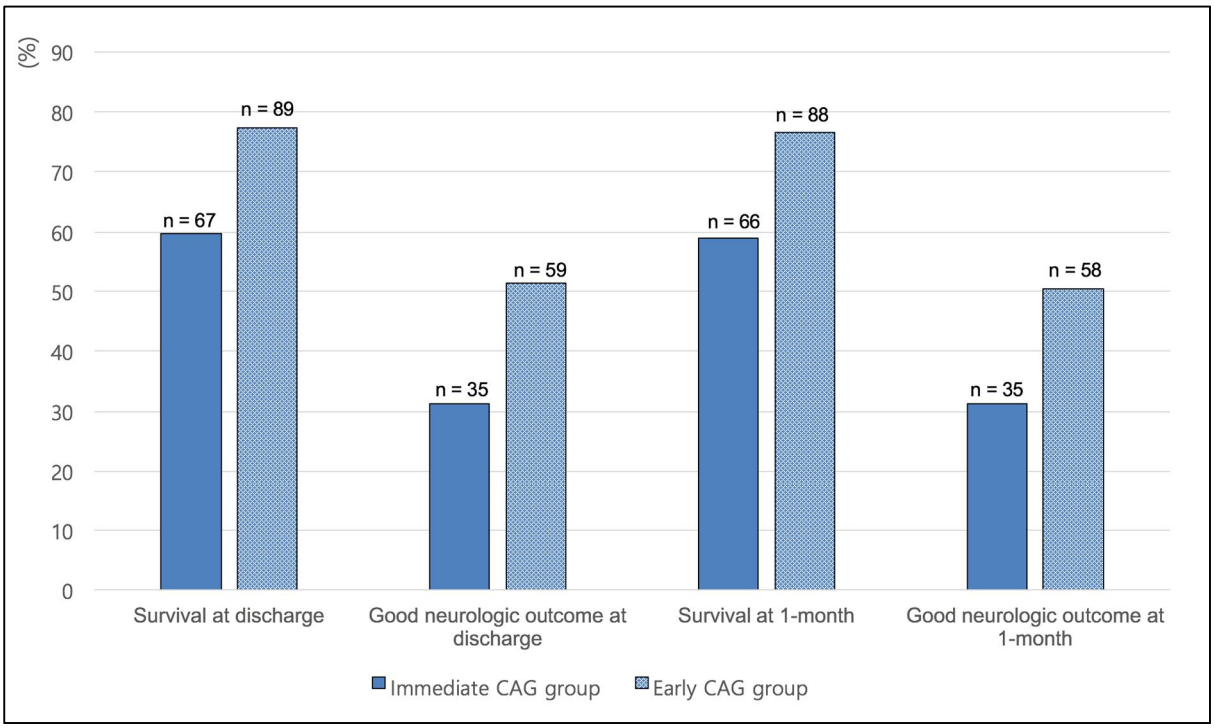


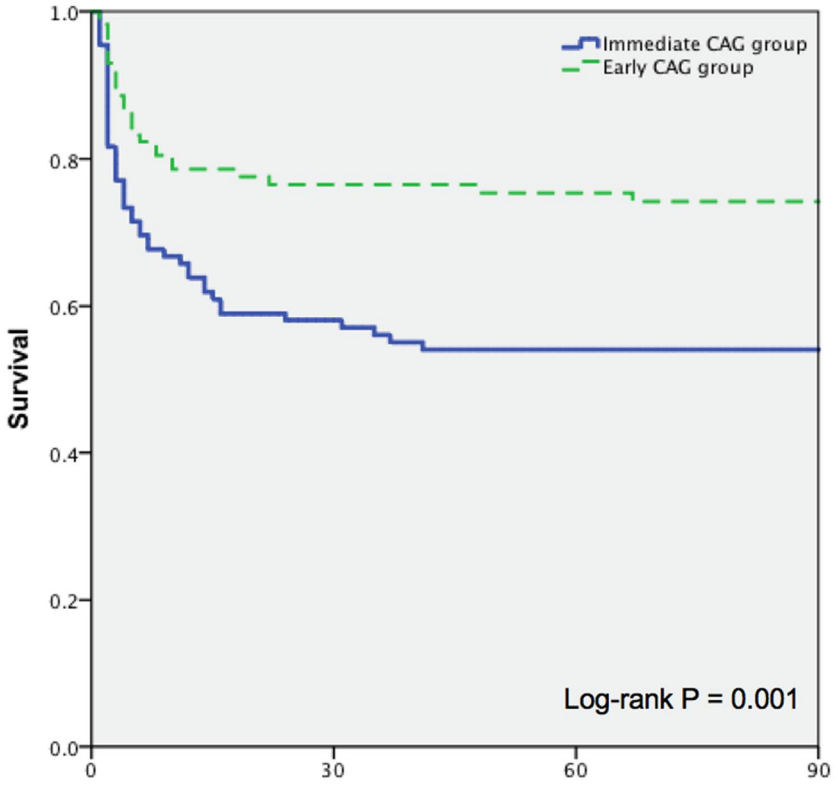
Figure 9 compares the clinical outcomes of patients in the immediate and early coronary angiography groups at discharge and 1 month after ROSC. The survival rates were significantly higher in the early CAG group than in the immediate CAG group at discharge (59.8% vs. 77.4%; P = 0.004) and at 1 month (58.9% vs. 76.5%; P = 0.005). Also, good neurologic outcome was more frequent in the early CAG group than in the immediate CAG group at discharge (31.3% vs. 51.3%; P = 0.002) and at 1 month (31.3% vs. 50.4%; P = 0.003). The estimated 3-month survival rate was also significantly higher in patients of the immediate CAG group than those of the early CAG group (49.7% vs. 73.0%, P = 0.001, log-rank test) (Figure 10).

Figure 9. Comparison of clinical outcomes between the patients in the immediate and early coronary angiography groups



CAG, Coronary angiography.

Figure 10. Kaplan-Meier survival curves of the study patients according to timing of coronary angiography. (P = 0.001, Log-rank test)

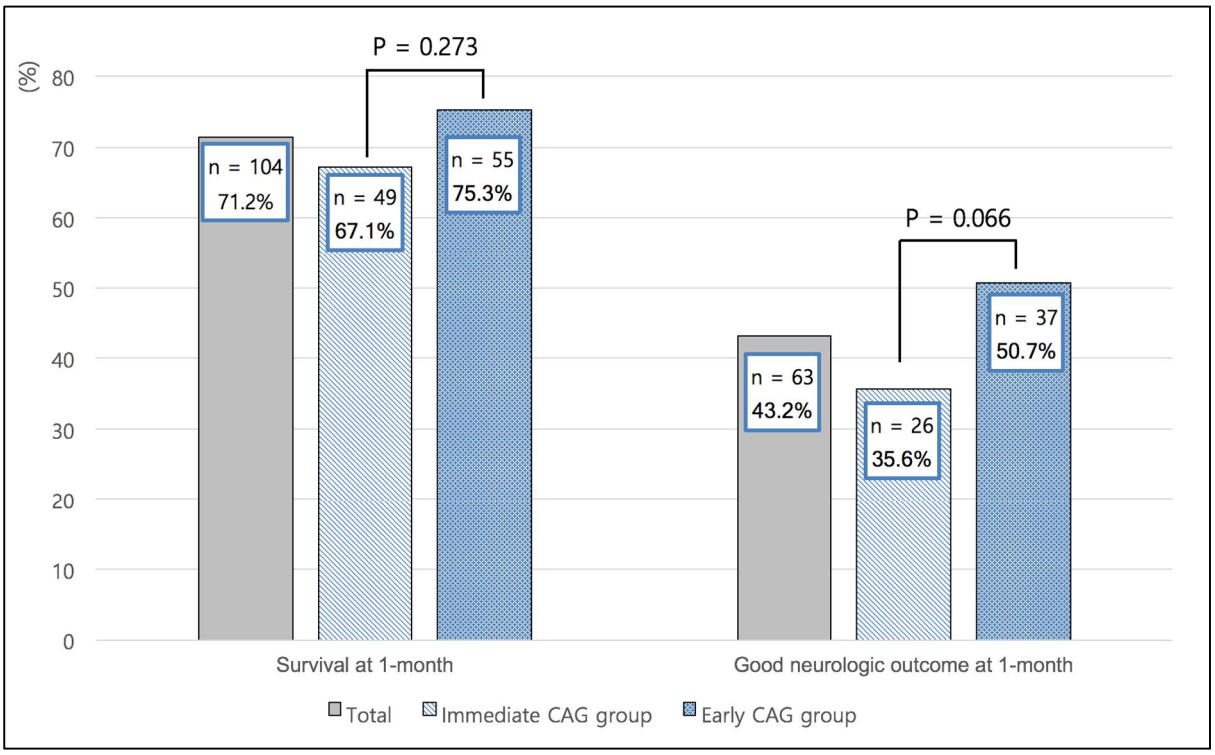


Number at risk				
Immediate CAG	109	79	57	56
Early CAG	114	91	85	84

CAG, coronary angiography.

Figure 11 compares the clinical outcome at 1 month after propensity score matching. In contrast to crude comparison before propensity score matching, 1-month survival rate (67.1% vs. 75.3%; P = 0.273) and 1-month good neurologic outcome rate (35.6% vs. 50.7%; P = 0.066) did not differ significantly between the immediate and early coronary angiography groups after propensity score matching.

Figure 11. Clinical outcomes at 1 month between the patients in the immediate and early coronary angiography groups after propensity score matching



CAG, coronary angiography.

VI. Impact of the early CAG on the clinical outcomes compared to immediate CAG

Table 11 shows the impact of the early CAG on the clinical outcomes compared to immediate CAG. The clinical outcomes in immediate and early CAG groups showed significant difference before propensity score matching, but they did not differ after propensity score matching (Figure 8, Figure 10). Likewise, early CAG versus immediate CAG was associated with survival at 1 month (odds ratio (OR), 2.272; 95% confidence interval (CI), 1.289–4.063; P = 0.005), and early CAG was also independently associated with good neurologic outcome at 1 month (OR, 2.238; 95% CI, 1.309–3.872; P = 0.004) in crude model. However, after propensity score matching, CAG timing was not independently associated with clinical outcomes including survival at 1 month (OR, 1.600, 95% CI, 0.726–3.526, P = 0.244) and good neurological outcomes at 1 month (OR, 1.917, 95% CI, 0.954–3.852, P = 0.068) on the logistic regression model of the matched groups.

Table 11. Odds ratios of the early versus Immediate coronary angiography for survival and good neurologic outcome at 1 month in out-of-hospital cardiac arrest survivors without ST-segment elevation who received coronary angiography within 24 hours and targeted temperature management

Outcome	Before matching (n = 227)			After matching (n = 146)		
	OR	95% CI	P value	OR	95% CI	P value
Survival at 1 month	2.272	1.289-4.063	0.005	1.600	0.726-3.526	0.244
Good neurologic outcome at 1 month	2.238	1.309-3.872	0.004	1.917	0.954-3.852	0.068

OR, odds ratio; CI, confidence interval.

Discussion

In this multicenter registry-based study, we aimed to describe the CAG findings and clinical outcomes of all the consecutive adult OHCA survivors without STE on a post-resuscitation ECG who underwent CAG within 24 hours after ROSC and were treated with TTM due to their comatose mentality after ROSC in Korea between 2010 and 2015. Additionally, we aimed to evaluate whether immediate versus early CAG impacts clinical outcomes including survival and good neurologic outcome at 1 month of those patients.

The proportion of the patients who received CAG within 24 hours increased during the 6-year study period for both OHCA survivors with STE and without STE. Among the 227 included patients, a total of 97 (42.7%) patients had a coronary artery stenosis of at least 50% and subsequent PCI and Intra-aortic balloon pump insertion was performed in 49 (21.6%) and 18 (7.9%) patients, respectively. The coronary artery disease extent and subsequent interventions after CAG did not differ between immediate and early CAG groups. In crude model, the patients in early CAG group showed better clinical outcomes including survival at 1 month (58.9% vs. 76.5%; P = 0.005) and good neurologic outcome at 1 month (31.3% vs. 50.4%; P = 0.003). However, after propensity matching, we found no significant difference in clinical outcomes between two groups, and consequently the timing of CAG (immediate versus early CAG) was not an independent factor for the survival and neurologic outcome at 1 month.

Acute coronary syndrome constitutes a major cause of OHCA.[40] CAG and subsequent reperfusion therapy is one of the cornerstones of post-cardiac arrest

care,[10, 11] emphasized as the fifth chain of survival. CAG is gold standard test for coronary artery disease.[41] Immediate CAG can evaluate the cause of OHCA without obvious extra-cardiac cause. In addition to the diagnostic value of CAG, CAG with subsequent reperfusion therapy when indicated can minimize the myocardial ischemic injury; salvage the myocardium;[41] and consequently, avoid recurrent arrest. Also, prompt reperfusion therapy in OHCA caused by acute coronary syndrome contribute to preserve left ventricular function and prevent heart failure.[41] In contrast, the potential disadvantages still argued such as increased cardiovascular instability in OHCA patients with a risk of fatal dysrhythmia due to unnecessary mobilization at a time of important monitoring; delay in TTM and other appropriate diagnostic examination such as brain computed tomography; and the CAG-related complications that are inherent to the test including contrast-induced nephropathy, vascular injury and bleeding from adjunctive medication.[29, 30, 42, 43]

The patient's previous medical history, observed symptoms before collapse are important diagnostic clues, but taking accurate information of the OHCA patient at the ED is impossible in most cases. Also, the laboratory tests are inaccurate with high false positive or negative rate and time-consuming. A 12-lead ECG at the immediate post-resuscitation period is a key investigation for assessment of the resuscitated OHCA patients without obvious extra-cardiac cause. The 2010 guidelines of AHA recommended obtaining a 12-lead ECG as soon as possible after ROSC to identify the presence of STE.[3] Although 12-lead ECG is an essential step in the diagnostic flow, many previous studies revealed that ECG findings have poor diagnostic accuracy.[3, 32, 44-46] In OHCA patients without obvious extra-cardiac cause, the combination of an unremarkable medical history with the nonspecific, or even

normal findings on post-resuscitation ECG and negative laboratory tests cannot be used to exclude the presence of an acute coronary artery obstruction, which is responsible for OHCA reliably.[18, 26, 46]

According to international guidelines of ERC and AHA, performing immediate CAG (i.e. <2 hours from hospital admission) and subsequent PCI, when indicated, for patients with OHCA of suspected cardiac etiology and STE on their post-resuscitation ECG are Class I recommendation,[10-14] despite no randomized study about performing CAG in OHCA survivors with STE or LBBB on their post-resuscitation ECG. The recommendation is based on several observational studies demonstrated the association between early invasive management (i.e. early CAG followed by subsequent PCI when indicated) and good neurologic outcome in OHCA survivors with STE or LBBB on their post-resuscitation ECG.[41, 47, 48] Although the selection bias of the study patients of those observational studies with high proportion of witnessed arrest with initial shockable rhythm and relatively short resuscitation duration was inevitable, the potential benefit of early invasive strategy is reasonable and clinically relevant considering the high prevalence (90% to 96%) of acute coronary occlusion of the OHCA survivors with STE or presumed new LBBB on their post-resuscitation ECG.[10-14, 41, 49, 50]

In contrast to patients with OHCA of suspected cardiac etiology and STE on their post-resuscitation ECG, the optimal strategy for the OHCA survivors without STE on their post-resuscitation ECG is still debatable due to the conflicting results of observational studies and lack of randomized study. However, a recent consensus statement from the European Association for Percutaneous Cardiovascular Interventions emphasized that CAG should be performed immediately in OHCA

patients with the presence of STE and considered as soon as possible (< 2 hours) in other patients without obvious non-coronary cause, particularly if they are hemodynamically unstable.[15, 18, 24, 27] Despite the consensus statement, controversies and concerns remain that performing immediate CAG possibly do a harm in small percentage of OHCA patients initially presented without obvious extra-cardiac cause but also whose etiology of arrest was not cardiovascular cause with delaying other diagnostic and therapeutic procedures.[51]

In our study, the patients in early CAG group showed better clinical outcomes compared to those in immediate CAG group; however, it should be noticed that after adjusting clinical significant factors such as age, cardiac arrest characteristics and interventions during the postresuscitation period, the differences in clinical outcomes were not evident between two groups. The patients in the immediate group were more frequently treated with extracorporeal life support and vasopressor, which implied that the patients who underwent CAG immediately were highly suspected of cardiogenic shock, and these could contribute the differences of clinical outcomes in our crude model.

In our study, 42.7% (n = 97) of OHCA patients without STE had at least 1 significant coronary artery stenosis, of whom 21.6% (n = 49) were amendable to subsequent PCI. These results are comparable to those of other previous studies. Dumas et al. analyzed the data from the Parisian Region Out of hospital Cardiac ArresT (PROCAT) prospective registry. Among 435 patients with no obvious extra-cardiac cause who underwent CAG at admission, 176 of 301 (58.5%) OHCA patients without STE had at least 1 significant coronary artery stenosis, and subsequent PCI was attempted in 92 (30.6%) patients with a successful PCI rate of 84.8% (n = 78).[26]

Jentzer et al. conducted a prospective two-center observational study of 599 OHCA patients, and 158 of 577 patients (26.4%) received CAG and subsequent PCI.[52] Another prospective observational study reported 157 of 524 OHCA patients without STE who underwent CAG (30.0%) were treated with PCI.[21] According to the recent meta-analysis of 23 observational studies, 38.7% of resuscitated OHCA patients without STE who underwent CAG within 24 hours received reperfusion treatment such as PCI (34.6%) and coronary artery bypass grafting (4.1%).[43] Data from our study and previous studies imply that almost one third of OHCA survivors without STE on ECG will have an acute culprit lesion that can potentially benefit from emergent PCI. In other words, data suggests that it is not necessary for the other two thirds of OHCA survivors without STE to undergo CAG.

Identifying the etiology of cardiac arrest is mandatory to improve the outcome of OHCA patients.[53] It is challenging to identify the exact cause of arrest, and about 40% of OHCA patients could be remained without clear etiological diagnosis even after extensive investigations including CAG, computed tomography and laboratory tests.[51] Acute coronary syndrome is a major cause of cardiac arrest, but there are other important extra-cardiac and non-coronary cardiac causes, for which CAG and subsequent PCI are not expected to improve the outcome.[54] Furthermore, immediate CAG is associated with potential risks in OHCA survivors in whom the coronary pathology is not responsible for the arrest.[15] Unnecessary and potentially harmful catheterization lab admissions at a time of important monitoring and exposure to contrast could be potentially harmful to those patients. Also, adjunctive antiplatelet/anticoagulation drugs before excluding cerebral hemorrhage of arrest could lead to critical complications.[31] Thus, a diagnostic strategy for OHCA survivors

without STE would be needed to identify patients who will benefit the most from PCI.

Despite the current recommendations from international guidelines to perform early CAG in OHCA survivors without STE, how early it should be provided remains unclear. Dankiewicz et al. performed a post-hoc analysis from the TTM trial to investigate the impact of early CAG, defined as being performed on admission or < 6 hours after arrest, and early CAG was not associated with improved survival in the patients without STE after OHCA of a presumed cardiac etiology.[24] Another prospective observational study performed by Bro-Jeppesen et al. also demonstrated no clinical benefits of early CAG, defined as being performed on admission or < 12 hours after OHCA, on 30-day and 1-year survival in patients with OHCA of suspected cardiac cause presenting no STE.[27] A recent study using the Swedish CAG registry of 4,308 sudden cardiac arrest patients found no clear benefit of early CAG (< 6 hours) on 30-day survival.[25] Additionally, a retrospective study from Netherlands reported that early CAG ($\leq$ 3 hours), as compared to non-early CAG (> 3 hours), was not associated with reduced 30-day mortality in OHCA patients without no obvious extra-cardiac cause.[55]

In line with recent reports and trends, our study consistent with previous studies. Good neurologic outcome and survival rates at 1 month did not differ between immediate (< 2 hours) and early (2–24 hours) CAG groups in our study patients, the OHCA survivors without STE, who received CAG within 24 hours and TTM. These results imply that until the results of ongoing randomized trials are available,[56, 57] the benefit of immediate CAG in OHCA patients without STE will remain in debate but that performing immediate CAG may be reasonable in selected patients with suspected culprit lesions rather than all resuscitated patients without STE.

This study has several strengths. First, to reduce survivorship bias, we excluded OHCA patients who received CAG after 24 hours. The treatment intensity would be affected by the clinical course of the patients. Although early prognostication in OHCA patients is challenging, physicians and the families tend to avoid invasive treatment when patients are expected to have very poor outcomes, particularly those after prolonged resuscitation or those with old age. Second, our study used good neurologic outcome at 1 month as the primary endpoint, which may be more clinically significant and applicable. Lastly, all the study patients were treated with TTM according to the current guidelines in high-volume centers by well-experienced physician in TTM for OHCA survivors.[58]

The current study has several limitations. First, owing to the observational nature of our study, a causal relationship between CAG timing and outcomes cannot be established, but only an independent association between them. The estimated effects of well-conducted observational studies may be consistent with the results of clinical trials, but generally cautious interpretation is required for the results. Second, decisions to perform in-hospital interventions such as extracorporeal life support and PCI are not standardized among the participating hospitals, and selection bias favoring subjects undergoing immediate CAG is obvious. We performed a propensity score matching analysis to achieve intergroup balance, but it is likely that some bias remains. Third, although the attending physician made the clinical decisions according to the guidelines, post-resuscitation care could be a potential confounding factor. Additionally, the epidemiology of OHCA shows regional differences and the patient eligibility of our study might be subject to selection bias; which might limit the generalizability. Lastly, we did not adjust for the extent of coronary artery disease from

CAG findings or rate of subsequent PCI treatment, which may have affected the outcome. However, the CAG findings and rate of subsequent PCI treatment did not show significant differences between the patients of immediate and early CAG groups, and those results cannot be predicted before CAG.

Conclusion

In Korea, the proportion of OHCA patients without STE who received CAG within 24 hours after ROSC and TTM increased during 2010 to 2015. Significant coronary artery stenosis was found in 42.7% of those patients, of whom subsequent PCI was performed in 21.6%. Immediate CAG (< 2 hours after resuscitation) versus early CAG (2 – 24 hours after resuscitation) in OHCA patients without STE who were treated with TTM was not associated with 1-month survival or good neurologic outcome in our propensity score–matched cohort. Physicians would perform immediate CAG and subsequent PCI, if required, in selected patients most likely to benefit from immediate CAG among OHCA survivors without STE. Further randomized clinical trials are warranted to define the guidelines for recommending optimal CAG timing.

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국문요약

병원 밖 심정지로 목표체온유지치료를 받은 ST 분절 상승이 없는 환자들에서 관상동맥조영술의 임상적 의의

배경

현재 국제적 지침은 응급 관상동맥조영술을 심인성 심정지가 의심되고, 소생 직후 심전도에서 ST 분절 상승이 확인되는 모둔 병원밖심정지 생존자들에게 시행할 것을 권고하고 있다. ST 분절 상승이 확인된 환자들과 대조적으로, ST 분절 상승 소견이 없는 환자들에 대한 최선의 치료 방침에 대해서는 여전히 논란이 있다. 본 연구의 목적은 (1) 목표체온치료를 받고, 자발순환회복 후 심전도에서 ST 분절 상승을 보이지 않았으나 24시간 이내 관상동맥조영술을 시행 받은 모든 성인 병원밖심정지 환자들의 관상동맥조영술의 결과를 확인하고; (2) 1개월 후 좋은 신경학적 치료 결과 비율 및 생존율을 평가하고; (3) 1개월 후 좋은 신경학적 치료 결과 및 생존에 대해 즉각적인 관상동맥조영술 방침 (자발순환회복 후 2시간 이내)이 조기 관상동맥조영술 방침 (자발순환회복 후 2 – 24 시간 사이)과 비교하여 효과가 있는지 검증하는 것이다.

방법

본 다기관 레지스트리 기반 후향적 관찰 연구는 한국의 8개 3차 진료 대학 부속 병원 응급실에서 시행되었다. 2010년부터 2015년 사이 명백한 심장 외 원인이

없고, ST 분절 상승이 없으며, 외상이 아니며 목표체온치료를 받고, 자발순환회복 후 24시간 이내 심혈관조영술을 시행 받은 성인 병원밖심정지 환자들의 자료를 추출하였다. 환자들은 즉각적인 관상동맥조영술 군 (자발순환회복 후 2시간 이내)과 조기 관상동맥조영술 군 (자발순환회복 후 2 – 24 시간 사이)으로 분류되었다. 치료 선택 비뚤어짐과 잠재적 교란 요인의 영향을 줄이기 위해 환자들은 성향 점수를 일치시켰다. 일차적인 평가 지표는 1개월 좋은 신경학적 치료 결과이고, 이차적인 평가 지표는 1개월 생존이었다.

결과

목표체온치료와 관상동맥조영술을 시행 받은 346명 중, 24시간 이후 관상동맥조영술을 시행한 119명의 환자를 제외하여 최종적으로 227명의 환자들이 포함되었다. 6년의 연구 기간 동안 24시간 이내 관상동맥조영술을 받은 환자들의 비율은 증가하였다. 총 97명 (42.7%)의 환자들이 최소 50% 이상의 관상동맥 협착 소견을 보였고, 이 환자들은 후속적으로 경피적 관상동맥중재술을 49명 (21.6%)에서, 대동맥 풍선 펌프 삽입술을 18명 (7.9%)에서 각각 시행 받았다. 연구에 포함된 227명의 환자들 중 112명과 115명이 각각 즉각적 관상동맥조영술 군과 조기 관상동맥조영술 군으로 분류되었다. 관상동맥질환 정도와 관상동맥조영술 후의 후속적인 처치는 즉각적 관상동맥조영술 군과 조기 관상동맥조영술 군 간의 차이를 보이지 않았다. 성향 점수를 일치 전 분석 시에는, 조기 관상동맥조영술 군 환자들이 1개월 생존 (58.9% vs. 76.5%; P = 0.005)과 1개월 좋은 신경학적 치료 결과 (31.3% vs. 50.4%; P = 0.003)에서 더 좋은 임상적 치료 결과를 보였다. 그

러나, 성향 점수를 일치시켜 분석을 시행하였을 때, 양 군간의 임상적 치료 결과는 유의한 차이가 없었다. 결과적으로 관상동맥조영술의 시점 (즉각적 대 조기 관상동맥조영술)은 1개월 생존 (교차비, 1.600; 95% 신뢰 구간, 0.726-3.526; P = 0.244) 및 1개월 좋은 신경학적 치료 결과 (교차비, 1.917; 95% 신뢰 구간, 0.954-3.852; P = 0.068)와 유의한 관련성이 없었다.

결론

관상동맥협착은 24시간 이내 관상동맥조영술을 시행 받은 ST 분절 상승이 없는 병원밖심정지 생존자들의 42.7%에서 확인되었다. 전체 환자군에서 1개월 좋은 신경학적 치료 결과와 1개월 생존은 즉각적인 관상동맥조영술 군에 비해 조기 관상동맥조영술 군에서 더 높았으나, 성향 점수 일치 후에는 즉각적 대 조기 관상동맥조영술의의 명확한 이득은 없었다. 향후, ST 분절 상승 소견이 없는 병원밖심정지 환자들에게서 적절한 관상동맥조영술 시행 시점을 확립하기 위한 대규모 무작위 대조 시험이 필요할 것이다.

중심 단어

병원밖심정지; 심폐소생술; 관상동맥조영술; 경피적관상동맥중재술; 치료 결과