Clinical Outcomes of Elderly Patients with Non ST-Segment Elevation Myocardial Infarction Undergoing Coronary Artery Bypass Surgery

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The aim of this study is to investigate the clinical outcomes of the elderly patients with Non ST-segment elevation myocardial infarction (NSTEMI) undergoing coronary artery bypass surgery (CABG) compared to non-elderly patients. Patients with NSTEMI and undergoing CABG (n=451) who were registered in the Korea Acute Myocardial Infarction Registry between December 2003 and August 2012 were divided into two groups.; the non-elderly group ($<$75 years, n=327) and the elderly group ($\geq$75 years, n=124). In-hospital mortality was higher in the elderly group (4.9% vs. 11.3%, p=0.015), but cardiac death, myocardial infarction, and major adverse cardiovascular events (MACE) including cardiac death, myocardial infarction, percutaneous revascularization, and redo-CABG after a one-year follow up were not different between the two groups. Predictors of in-hospital mortality in patients with NSTEMI undergoing CABG were left ventricular (LV) dysfunction (ejection fraction $\leq$40%) [hazard ratio (HR): 2.76, 95% confidence interval (CI): 1.16-6.57, p=0.022] and age (HR: 1.05, 95% CI: 1.01-1.10, p=0.047). So elderly NSTEMI patients should be considered for CABG if appropriate, but careful consideration for surgery is required, especially if the patients have severe LV systolic dysfunction.

Key Words: Myocardial Infaction; Coronary Artery Bypass; Aged

INTRODUCTION

As the technique and equipment of percutaneous coronary intervention (PCI) have improved, PCI has replaced coronary artery bypass surgery (CABG) for treating patients with acute myocardial infarction (AMI) and complex coronary lesions such as left main and multi-vessel disease. However, CABG is still reserved for left main, and/or 3-vessel disease, failed PCI, and coronary anatomy not amenable to PCI, based on the patient's clinical status, comorbidities, and disease severity including lesion distribution and angiographic lesion characteristics.[1] In other words, PCI dose not completely replace CABG in treating patients with AMI and complex coronary lesions.

In the case of elderly patients, however, they often have, more comorbid conditions[2] so it is not easy for them to undergo surgery, despite the fact that CABG has been getting safer owing to the improvement in surgical techniques and pharmacology. The greatest risk is in the elderly patients for whom the CABG operation may be the best of several high-risk options.[3] It can lead them and their families to hesitate about whether to have the operation.

So the authors investigated the clinical outcomes of the Korean elderly patients with NSTEMI undergoing CABG compared to non-elderly patients. Patients with ST-segment elevation myocardial infarction (STEMI) were excluded in this study, because primary PCI is almost always the main strategy in treating these kinds of patients.

MATERIALS AND METHODS

1. Korea Acute Myocardial Infarction Registry

The Korea Acute Myocardial Infarction Registry (KAMIR) is a Korean prospective multicenter online registry designed to describe characteristics and clinical outcomes of Korean patients with AMI.[4] Data was collected by an experienced study coordinator based on a standardized protocol, and the study was approved by the ethics committee at each participating institution.

2. Study population

From December 2003 to August 2012, 451 NSTEMI patients undergoing CABG during index hospitalization were enrolled from the KAMIR. Patients were divided into two groups according to the age; 327 patients were non-elderly (<75 years), and 124 patients were elderly (≥75 years).

3. Definitions and clinical endpoints

Elderly was defined as individuals ≥75 years of age. The previous American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines categorize elderly patients as a special at-risk group.[1,5,6] Acute myocardial infarction was defined by clinical signs or symptoms, increased cardiac biomarkers, and 12-lead electrocardiographic findings.[7] Non-ST segment elevation myocardial infarction (NSTEMI) was defined as elevated cardiac biomarkers without persistent ST-elevation.[8] Left ventricular ejection fraction (LVEF) was measured by two-dimensional echocardiography using the biplane Simpson's method.[9] And the estimated glomerular filtration rate (eGFR) was measured using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[10] The morphology of the lesion was examined using coronary angiography and was classified using criteria established by ACC/AHA.[11] Failed PCI was defined as

Thrombolysis In Myocardial Infarction (TIMI) flow of grade 0 or I after the procedure.

Clinical follow-up was performed one year after the commencement of the study. Major adverse cardiac events (MACE) included cardiac death, myocardial infarction, percutaneous revascularization, and redo-CABG.

4. Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 21 (SPSS Inc, Chicago, IL, USA). Continuous variables are expressed as means±standard deviations and they were compared by unpaired Student's t-tests or Mann-Whitney rank-sum test. Discrete variables are presented as frequencies and percentages and were compared by chi-square test (or Fisher's exact). All statistical tests were 2-tailed with a statistical significance defined as $p < 0.05$. Survival curves of one-year cardiac death, myocardial infarction, and MACE were calculated by Kaplan-Meier and log rank test was applied to compare the two groups. Furthermore, Cox regression analyses were performed using all available variables considered potentially relevant in determining the impact of different age groups on one-year MACE. Included variables were age (≥75 years), sex, smoking history, atrial fibrillation, previous IHD history, hypertension, diabetes mellitus, dyslipidemia, LV dysfunction (EF ≤40%), and renal insufficiency (estimated GFR <60 mL/min/1.73 m^2), 3-vessel disease, LM lesion, and prescribed medications before discharge. In addition, multivariate logistic regression analyses were performed to identify the predictors of in-hospital mortality. Included variables were age, sex, BMI (≥25 kg/m^2), smoking, shock (systolic blood pressure <90 mmHg) at arrival, atrial fi-
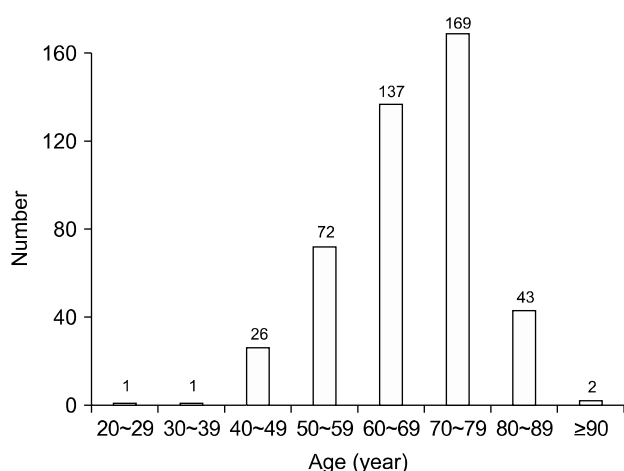

FIG. 1. Graph of age distribution in Non ST-segment elevation myocardial infarction (NSTEMI) patients undergoing coronary artery bypass surgery (CABG).

TABLE 1. Baseline clinical characteristics

	Non-elderly group (n=327)	Elderly group (n=124)	p
Age (years)	62.9±8.5	79.4±4.2	<0.001
BMI (kg/m^2)	24.1±3.2	23.0±2.9	0.486
Sex (Male)	248 (76.1%)	72 (58.9%)	<0.001
Hypertension	181 (55.4%)	80 (65.6%)	0.051
Diabetes mellitus	143 (43.7%)	50 (40.7%)	0.556
Smoking	194 (60.4%)	47 (39.2%)	<0.001
Dyslipidemia	48 (14.7%)	18 (14.6%)	0.981
Family history of CHD	22 (6.8%)	9 (7.5%)	0.794
Previous IHD history	72 (20.0%)	36 (29.3%)	0.109
Atrial fibrillation	9 (2.8%)	6 (4.9%)	0.376
SBP (mmHg)	132.3±26.7	127.0±26.0	0.875
DBP (mmHg)	79.6±15.6	73.7±13.0	0.358
Heart rate (/min)	79.9±19.8	79.2±20.9	0.489
Killip III-IV	30 (12.9%)	18 (21.2%)	0.070

Values are presented as number (%) or mean±standard deviation. BMI: body mass index, CHD: coronary heart disease, IHD: ischemic heart disease, SBP: systolic blood pressure, DBP: diastolic blood pressure.

brillation, previous IHD history, hypertension, diabetes mellitus, dyslipidemia, LV dysfunction (EF ≤40%), and renal insufficiency (estimated GFR < 60 mL/min/1.73 m^2), use of a GP IIb/IIIa inhibitor, failed PCI, 3-vessel disease, LM lesion and Killip class ≥3. Multivariate analyses were performed using the variables showing p<0.1 in univariate analyses. The results are expressed as estimated hazard ratios with 95% confidence intervals (CIs) and p-values with clinical significance defined as p<0.05.

RESULTS

1. Age distribution in NSTEMI patients undergoing CABG

Lots of NSTEMI patients undergoing CABG were included between 60 to 79 years of age (n=306, 67.8%). Of the patients included in this study, the proportion of patients between 70 to 79 years old was largest (n=169, 37.4%), and the next was between 60 to 69 years old (n=137, 30.4%). Approximately, 27% of patients were elderly patients (≥75 years of age) (Fig. 1).

2. Baseline clinical characteristics

In comparing the clinical characteristics of the two groups, the elderly group had less male patients (76.1% vs. 58.9%, p<0.001) and less smokers (60.4% vs. 39.2%, p< 0.001). Furthermore, there were no significant differences in body mass index (BMI), histories of hypertension, diabetes mellitus, dyslipidemia, family history of coronary heart disease (CHD), history of ischemic heart disease (IHD), atrial fibrillation, systolic and diastolic blood pressure, heart rate, or proportion of Killip class III-IV (Table 1).

3. Baseline echocardiographic, laboratory, and coronary angiographic findings

The LVEF measured by 2-dimentional echocardiogram was not significantly different between the two groups. However, Levels of serum creatine kinase (617.6±795.4 vs. 425.3±504.4, p=0.005) and triglyceride (132.6±75.2 vs. 105.4±64.2, p<0.001) were lower in the elderly group. There were no significant differences in the level of serum glucose, creatinine, creatine kinase-MB (CK-MB), troponin I, total cholesterol, high density lipoprotein-cholesterol

TABLE 2. Baseline echocardiographic, laboratory, and coronary angiographic findings

	Non-elderly group (n=327)	Elderly group (n=124)	p
Left ventricular EF (%)	49.3±13.3	50.3±14.2	0.661
Glucose (mg/dL)	174.2±90.6	171.8±74.6	0.137
Creatinine (mg/dL)	1.3±1.7	1.5±2.0	0.386
Creatine kinase (U/L)	617.6±795.4	425.3±504.4	0.005
CK-MB (ng/mL)	45.3±67.2	46.3±75.0	0.465
Troponin I (ng/mL)	16.9±54.0	21.6±87.0	0.186
Total cholesterol (mg/dL)	184.6±49.4	176.8±64.4	0.380
Triglyceride (mg/dL)	132.6±75.2	105.4±64.2	<0.001
HDL-C (mg/dL)	43.9±33.7	42.3±12.5	0.595
LDL-C (mg/dL)	122.3±56.2	111.1±49.9	0.851
Hs-CRP (mg/dL)	7.6±22.6	6.6±15.9	0.509
NT-proBNP (pg/mL)	4,150.7±7,967.7	6,885.6±10,591.2	0.057
HbA1c (%)	7.0±5.0	6.8±1.5	0.299
Number of involved vessels			
2	18 (13.7%)	3 (4.6%)	0.052
3	75 (57.3%)	39 (60.0%)	0.713
Left main	35 (26.7%)	22 (33.8%)	0.301
Target lesion location			
Left main	29 (14.8%)	16 (22.2%)	0.149
LAD	84 (42.9%)	23 (37.5%)	0.430
LCX	31 (15.8%)	15 (20.8%)	0.334
RCA	52 (26.5%)	14 (19.4%)	0.233
ACC/AHA types			
B1	10 (5.7%)	3 (4.5%)	1.000
B2	37 (21.3%)	14 (20.9%)	0.950
C	124 (71.3%)	49 (73.1%)	0.773
Failed PCI	11 (5.2%)	5 (6.3%)	0.774

Values are presented as mean±standard deviation or number (%). EF: ejection fraction, CK-MB: creatine kinase-MB, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, Hs-CRP: high sensitivity C-reactive protein, NT-proBNP: N-terminal pro B-type natriuretic peptide, HbA1c: hemoglobin A1c, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, ACC/AHA: American College of Cardiology/American Heart Association, PCI: percutaneous coronary intervention.

(HDL-C), low density lipoprotein-cholesterol (LDL-C), high sensitivity C-reactive protein (Hs-CRP), N-terminal pro B-type natriuretic peptide (NT-proBNP), or hemoglobin A1c (HbA1c) between the groups (Table 2).

Three vessel disease was the most common in both non-elderly (57.3%) and elderly patients (60%) with NSTEMI who underwent CABG. The next most frequently involved vessels were left main in both groups. The most frequent target vessel was left anterior descending artery (LAD) and the most common morphology of the lesion was type C by ACC/AHA classification in both groups. The proportion of failed PCI was not significantly different between two groups (Table 2).

4. Comparison of the prescribed medications

We compared the prescribed medications during admission. There were no significant differences in prescribed medications including aspirin, clopidogrel, cilostazol, beta-blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEi/ARB), statin, nitrate, nicorandil, or the use of glycoprotein (GP) IIb/IIIa inhibitor (Table 3).

TABLE 3. Comparison of the prescribed medications

	Non-elderly group (n=327)	Elderly group (n=124)	p
Aspirin	316 (96.9%)	122 (98.4%)	0.525
Clopidogrel	286 (88.3%)	113 (91.1%)	0.386
Cilostazol	36 (11.3%)	13 (10.7%)	0.851
Beta-blocker	240 (73.4%)	87 (70.2%)	0.492
ACEi/ARB	249 (76.1%)	89 (71.8%)	0.339
Statin	240 (73.4%)	86 (69.4%)	0.392
Nitrate	205 (64.1%)	68 (55.7%)	0.107
Nicorandil	58 (29.1%)	29 (30.9%)	0.766
GP IIb/IIIa inhibitor	4 (16.0%)	0 (0.0%)	0.278

Values are presented as number (%). ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, GP IIb/IIIa inhibitor: glycoprotein IIb/IIIa inhibitor.
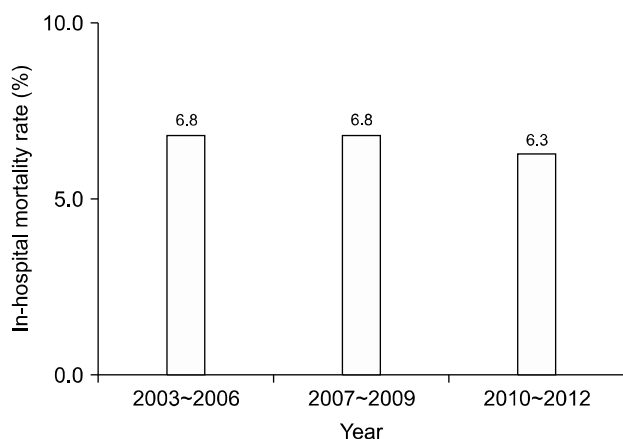

FIG. 2. Trend of in-hospital mortality rate.

5. In-hospital mortality and one-year clinical outcomes

The average in-hospital mortality was 6.6%. The in-hospital mortality rate was 6.8% from 2003 to 2006, 6.8% from 2007 to 2009, and 6.3% from 2010 to 2012 respectively (Fig. 2). The in-hospital mortality was higher in the elderly group (4.9% vs. 11.3%, p=0.015) (Table 4). The causes of in-hospital mortality were not different between two groups. The rate of cardiac in-hospital mortality was 68.8% in the non-elderly group and 71.4% in the elderly group (Table 5). The most common cardiac cause of in-hospital mortality was low-output cardiac failure.

There were no significant differences in the cardiac death, non-cardiac death, myocardial infarction, or MACE at the one-year follow-up, unlike the in-hospital mortality (Table 4). On the basis of the Kaplan-Meier estimates, there were also no significant differences in the occurrence of cardiac death, myocardial infarction, and MACE between the two groups (Fig. 3). Furthermore, the unadjusted and adjusted MACE rates by Cox regression analyses were not different between the two group at the one-year follow-up (Table 6).

6. Predictors of in-hospital mortality

Multivariate logistic analysis was performed to identify the predictors of in-hospital mortality. Among the variables considered potentially relevant, age (HR 1.05, 95% CI 1.01-1.10, p=0.047) and LV dysfunction (EF ≤40%) (HR 2.76, 95% CI 1.16-6.57, p=0.022) were independent predictors of in-hospital mortality. In multivariate analysis, male sex showed a low hazard ratio of less than 1.0, but it was slightly insignificant (Table 7).

TABLE 4. In-hospital mortality and one-year clinical outcomes

	Non-elderly group (n=327)	Elderly group (n=124)	p
In-hospital death	16 (4.9%)	14 (11.3%)	0.015
One-year cardiac death	4 (2.5%)	2 (4.3%)	0.618
One-year non-cardiac death	1 (0.6%)	1 (2.2%)	0.393
One-year myocardial infarction	3 (1.9%)	1 (2.2%)	1.000
One-year MACE	12 (7.5%)	5 (10.6%)	0.545

Values are presented as number (%). MACE: major adverse cardiac event.

TABLE 5. Causes of in-hospital mortality

	Non-elderly group (n=16)	Elderly group (n=14)	p
Cardiac cause	11 (68.8%)	10 (71.4%)	0.873
Non-cardiac cause	5 (31.2%)	4 (28.6%)	

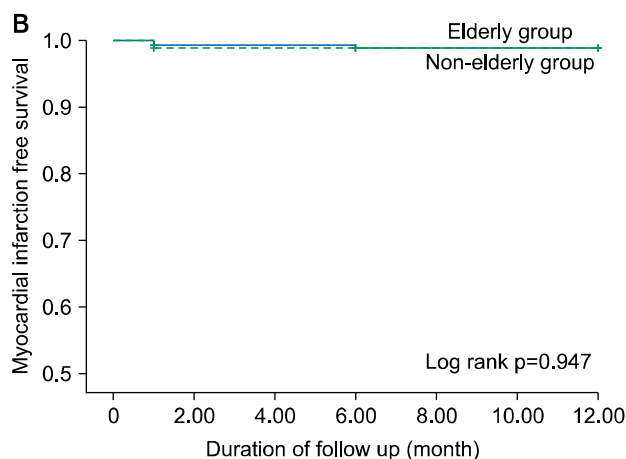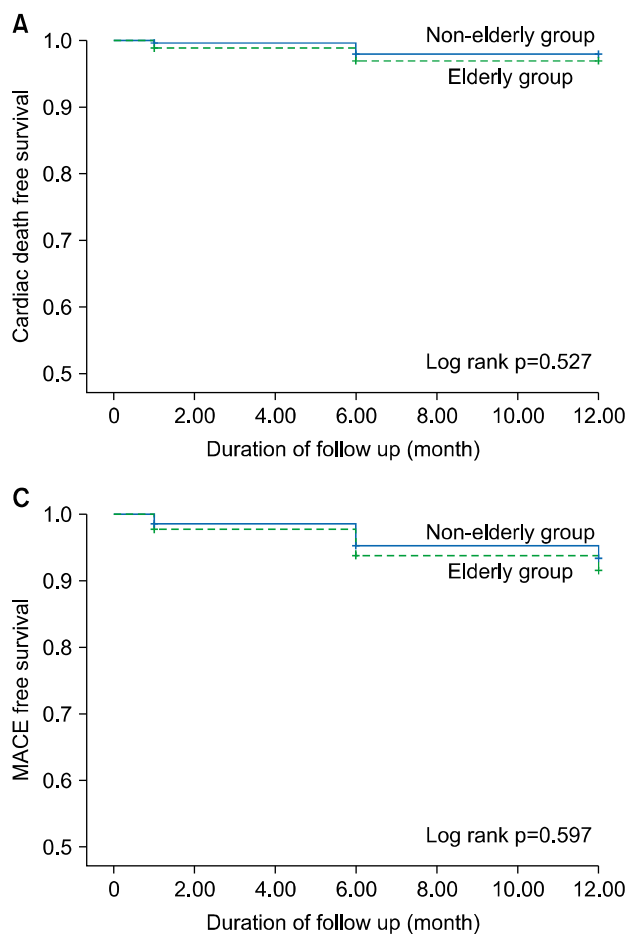Values are presented as number (%).

FIG. 3. Kaplan-Meier estimates of the incidences of (A) cardiac death, (B) myocardial infarction, (C) major adverse cardiac event (MACE) between non-elderly and elderly groups at one-year follow up.

TABLE 6. Cox regression analyses of age difference (non-elderly group vs. elderly group) with one-year MACE

Model	Hazard ratio	95% CI	p
Unadjusted	1.42	0.50-4.04	0.508
Adjusted for sex	1.36	0.47-3.94	0.575
Adjusted for smoking history	1.59	0.54-4.72	0.401
Multivariable adjusted	0.61	0.20-1.84	0.382

MACE: major adverse cardiac event, CI: confidence interval.

TABLE 7. Predictors of in-hospital mortality according to multivariate logistic analysis

Variable	Hazard ratio	95% CI	p
Age	1.05	1.01-1.10	0.047
Sex (Male)	0.43	0.18-1.03	0.058
LV dysfunction (EF ≤40%)	2.76	1.16-6.57	0.022

CI: confidence interval, LV: left ventricle, EF: ejection fraction.

DISCUSSION

This study allows us to know the clinical outcomes and relevant factors for in-hospital mortality in Korean elderly NSTEMI patients undergoing CABG. Therefore, our results can be helpful to guide whether to perform cardiac surgery or to seek other therapeutic strategies. Our result showed that the elderly NSTEMI patients receiving CABG have higher in-hospital mortality, but one-year clinical outcomes were not different compared to non-elderly patients. Furthermore, this study found that left ventricular (LV) dysfunction (ejection fraction ≤40%) and older age was associated with higher in-hospital mortality.

Several studies mentioned the in-hospital mortality of elderly patients undergoing CABG. According to the some reports, the operative mortality rate among the elderly receiving CABG was 2.6% in a population >75 years of age and 11% in a population >80 years of age undergoing urgent or emergency surgery.[12,13] Other studies showed that in-hospital mortality in NSTEMI patients undergoing CABG is approximately 3.7%[14] and operative mortality rates for CABG in patients ≥80 years of age with NSTE-ACS were between 5% and 8% (11% for urgent cases) and increased to approximately 13% at ≥90 years of age.[13,15] In our study, approximately 27% of patients were elderly patients, more than 75 years of age. In-hospital mortality of non-elderly patients was 4.9% and that of elderly patients was 11.3%. In-hospital mortality of the elderly was 2.3 times higher than non-elderly patients in our study.

However, one-year clinical outcomes including one-year cardiac death, myocardial infarction, and MACE were not

significantly different in this study. Although in-hospital outcomes are poorer, the long term outcomes seem to be good for the elderly survivors of surgery. According to an analysis of nearly 25,000 patients >80 years of age who underwent CABG, in those who survived, the long-term survival rate was similar to that of the general population of octogenarians matched for age, sex and race.[16] And Suguru et al. reported that age at operation does not affect long-term outcomes in patients undergoing off-pump CABG (OPCAB) with regard to cardiac death and cardiac events.[17] Hillis et al.[2] also reported that the majority of elderly patients achieve functional improvement after CABG, despite higher rates of in-hospital morbidity and mortality. According to the other studies, elderly patients ≥80 years of age who underwent CABG had improvements in quality of life, as assessed by the Seattle Angina Questionnaire.[18,19] In one of these, angina relief and quality of life improvement scores after CABG did not differ between the patients >75 and ≤75 years of age.[13]

A number of peri-operative factors have been demonstrated to influence the rate of operative mortality after CABG. In our study, the predictors of in-hospital mortality in NSTEMI patients after CABG were age and LV dysfunction (EF ≤40%). Old age was an independent risk factor for poor outcomes after CABG, as mentioned earlier. And the presence of LV dysfunction was one of the important independent predictors of operative mortality after CABG.[20,21] In a prospective observational study of over 8600 patients undergoing CABG, the operative mortality was less than 2% with a LVEF >40%, 3.5 to 4% with an LVEF between 20 and 40%, and approximately 8% with an LVEF <20%.[21] LVEF must be considered in the decision to operate. A low LVEF, especially irreversible, can negate the benefits of surgery.

Although the p-value was not statistically significant, male sex showed a low hazard ratio for in-hospital mortality in this study (hazard ratio 0.43, 95% CI 0.18-1.03, p=0.058). There is controversy regarding the influence of sex on CABG outcomes. Previous studies examining sex differences in mortality after CABG have showed different results. Although most studies have showed higher in-hospital mortality in women compared with men, several studies documented that when an adjustment was made for differences in body size and clinical and angiographic variables, sex was not an accurate predictor.[22,23] In contrast, other studies have continued to show a higher mortality in women that persisted in multivariable analysis.[24-26] In a systemic review of sex differences and mortality after CABG, early mortality differences were reduced but not eliminated after adjustment for comorbidities, procedural characteristics, and body habitus.[27] The impact of sex on in-hospital mortality should be clarified with a well-planned and controlled study.

This study had several limitations. First, the timing and method of CABG during admission were uncertain due to the absent data in this registry, but other baseline clinical characteristics were relatively similar between two groups.

Second, the angina relief and quality of life after CABG is important, however, there was no information about the improvement of angina relief and the quality of life after surgery in this registry data. Third, there may be some bias in choosing elderly NSTEMI patients as candidates for CABG. Fourth, the sample size was relatively small. Therefore, a large-scale and longer-term study is needed including the information about the timing and manner of surgery and the improvement of symptoms.

In conclusion, the elderly patients have higher in-hospital mortality, but one-year outcomes were not different, compared to non-elderly NSTEMI patients receiving CABG. So elderly NSTEMI patients should be considered for CABG if surgery is more appropriate than PCI, but careful evaluation is required for the potential risks and benefits before surgery, especially if the elderly patients have severe LV systolic dysfunction.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST STATEMENT

None declared.

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