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Percutaneous Coronary Intervention

Predictors of Mortality in Elderly Patients with Non-ST Elevation Acute Coronary Syndrome — Data from Taiwan Acute Coronary Syndrome Full Spectrum Registry

Cheng-Chun Wei[1] and Shih-Huang Lee[1,2]
ACS Full Spectrum Registry Investigators

Background: Some difficulties and variations remain associated with the care of elderly patients with non-ST elevation acute coronary syndrome (NSTE-ACS).

Methods: We included 1470 patients from a Taiwan nationwide registry who fulfilled the criteria of NSTE-ACS, and stratified these patients by age and evaluated the treatment, complications and outcomes in different age groups. Furthermore, we analyzed risk factors and standards of care to determine the predictors of mortality.

Results: Patients ≥ 75 years of age (n = 396) had significantly higher incidences of 90-day mortality [odd ratio (OR) = 4.5 (1.2-16.3), p = 0.023] and 1-year mortality [OR = 4.9 (2.0-12.3), p = 0.001] compared with those patients 45-64 years of age (n = 595). In the patients ≥ 75 years of age, previous myocardial infarction (MI) [OR = 3.3 (1.1-9.8), p = 0.035], statins [OR = 0.35 (0.1-0.9), p = 0.037], left ventricular ejection fraction (LVEF) < 35% [OR = 3.9 (1.5-10.4), p = 0.006] were associated with 90-day mortality. Furthermore, previous MI [OR = 4.0 (1.3-12.6), p = 0.019] was an independent predictor of 90-day mortality. Age [OR = 1.1 (1.03-1.2), p = 0.002], previous MI [OR = 2.2 (1.1-4.4), p = 0.034], angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [OR = 0.5 (0.3-0.9), p = 0.028], and LVEF < 35% [OR = 4.3 (1.9-9.5), p < 0.001] were associated with 1-year mortality. Furthermore, previous MI [OR = 2.6 (1.1-6.5), p = 0.037], LVEF < 35% [OR = 4.7 (1.5-14.4), p = 0.007] and percutaneous coronary intervention(PCI) or not [OR = 0.3 (0.1-0.9), p = 0.021] were independent predictors of 1-year mortality.

Conclusions: Previous MI, LVEF < 35% and PCI or not could predict 1-year mortality in advanced elderly patients with NSTE-ACS. Despite their elevated morbidities and complications, PCI was still beneficial for these patients.

Key Words: Acute coronary syndrome • Age • Outcome • Predictor

INTRODUCTION

Acute coronary syndrome (ACS) is a major cause of death, and the elderly with ACS have poorer outcomes in contrast with the younger patients.[1-4] Despite the publication of ACS guidelines by the European Society of Cardiology and the American Heart Association/American College of Cardiology, some difficulties and variations remain in the care of elderly patients with ACS.[5-7] Some clinical trials have excluded patients with advanced age. Some of these trials suggest it is necessary to follow the guidelines, and others promote conservative treatment rather than standard ACS care for the elderly.[8-10] Therefore, the optimum management proto-

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[1]Division of Cardiology, Department of Internal Medicine, Shin Kong Wu Ho Su Memorial Hospital, Taipei; [2]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan.
Corresponding author: Dr. Shih-Huang Lee, Division of Cardiology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, No. 95, Wen Chang Rd., Shih-Lin District, Taipei, Taiwan. Tel: 886-2-2833-2211 ext. 2091; Fax: 886-2-2834-8910; E-mail: shlee.99888@gmail.com

cols for the elderly with ACS remain the subject of ongoing debate.

The Taiwan ACS Full Spectrum Registry is a nationwide database used to assess real-world clinical practices and outcomes of patients with ACS in Taiwan.[1,2] The present study included the non-ST elevation acute coronary syndrome (NSTE-ACS) patients in this registry. We divided the patients by age and evaluated the treatment, complications and outcomes in short- and medium-term in different age groups. Furthermore, for the advanced elderly (≥ 75 years), we analyzed risk factors and standards of care to determine the predictors of poor outcomes.

METHODS

Study design

The present study was a national, multicenter, and observational design in a Taiwan nationwide registry.[1,2] From October 2008 to January 2010, patients > 20 years of age, who fulfilled the criteria of NSTE-ACS at any of the 39 participating hospitals in Taiwan were included. The criteria included symptoms of typical chest pain or overwhelming shortness of breath, electrocardiogram showing normal findings or pathological Q wave, or persistent or dynamic electrocardiographic change of ST depression > 0.5 mm, or new deep T-wave inversion in more than 2 contiguous leads, and either rise or absence of rise of cardiac markers. The major bleeding was defined as overt clinical bleeding associated with a drop of hemoglobin greater than 5 g/dl, or hematocrit greater than 15%.

Statistical analysis

Continuous variables were shown as means ± standard deviations (SD), and categorical variables were shown as absolute numbers and percentage and compared by use of one-way ANOVA. For categorical variables, the Chi-square or Fisher's exact test was applied. Predictors of in-hospital, 90-day and 1-year mortality were determined by univariate and multivariate logistic regression analysis. Multivariate logistic regression analysis was performed by considering all variables that were identified as $p \leq 0.1$ in the univariate analysis. A p value of < 0.05 was considered to indicate significance for all factors. All analyses were conducted with the use of SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics

In the present study, 1470 patients with NSTE-ACS were included. There were 93 patients (6%) in group I (< 45 years), 595 patients (41%) in group II (45-64 years), 386 patients (26%) in group III (65-74 years) and 396 patients (27%) in group IV (≥ 75 years). There was a significant difference in the sex ratio amongst the four groups; the male ratio was 93%, 81%, 65%, 59%, respectively, $p < 0.001$ (Table 1). There were significant differences among the four groups in the incidence of hypertension (41%, 69%, 76%, 82%, respectively, $p < 0.001$), dyslipidemia (44%, 51%, 45%, 42%, respectively, $p = 0.037$), diabetes (26%, 40%, 50%, 46%, respectively, $p < 0.001$) and smoking (82%, 61%, 42%, 39%, respectively, $p < 0.001$). There were significant differences among the four groups in the incidence of previous coronary artery bypass grafting (CABG) (0%, 3%, 8%, 6%, respectively, $p = 0.03$), previous stroke or transient ischemia attack (2%, 7%, 14%, 21%, respectively, $p < 0.001$), and Killip Class ≥ II (17%, 19%, 27%, 34%, respectively, $p < 0.001$). There were significant differences among the four groups in body mass index (BMI) (29 ± 4, 26 ± 4, 25 ± 4, 24 ± 4 kg/m^2, respectively, $p < 0.001$), peak creatine kinase (718 ± 772, 667 ± 1662, 565 ± 966, 437 ± 1207 U/L, respectively, $p = 0.03$), creatinine (1.1 ± 1.0, 1.9 ± 2.5, 2.1 ± 2.2, 1.8 ± 1.5 mg/dl, respectively, $p < 0.001$), total cholesterol (196 ± 48, 185 ± 45, 173 ± 41, 165 ± 52 mg/dl, respectively, $p < 0.001$), high-density cholesterol (34 ± 7, 38 ± 11, 40 ± 17, 43 ± 33 mg/dl, respectively, $p < 0.001$), low-density lipoprotein (127 ± 42, 116 ± 40, 109 ± 38, 96 ± 32 mg/dl, respectively, $p < 0.001$), triglyceride (233 ± 157, 168 ± 125, 135 ± 84, 113 ± 70 mg/dl, respectively, $p < 0.001$), and thrombolysis in myocardial infarction (TIMI) score (2.5 ± 1.1, 2.7 ± 1.1, 3.8 ± 1.1, 3.8 ± 1.1, respectively, $p < 0.001$).

There were significant differences among the four groups in the incidence of drug treatments in the hospital, including aspirin (94%, 89%, 87%, 83%, respectively, $p = 0.02$), beta-blockers (53%, 45%, 42%, 38%, respec-

Table 1. Baseline characteristics

Number (%) or mean ± SD	Group I (n = 93)	Group II (n = 595)	Group III (n = 386)	Group IV (n = 396)	p-value
Age (years)	39 ± 4	56 ± 5	69 ± 3	81 ± 4	< 0.001
Sex, male	86 (93%)	483 (81%)	249 (65%)	232 (59%)	< 0.001
Hypertension	38 (41%)	405 (69%)	288 (76%)	322 (82%)	< 0.001
*Dyslipidemia	40 (44%)	301 (51%)	172 (45%)	164 (42%)	0.037
Diabetes	24 (26%)	237 (40%)	189 (50%)	180 (46%)	< 0.001
Smoking	75 (82%)	360 (61%)	159 (42%)	151 (39%)	< 0.001
Previous MI	7 (8%)	72 (12%)	55 (14%)	66 (17%)	0.85
Previous PCI	13 (14%)	124 (21%)	102 (26%)	122 (31%)	0.27
Previous CABG	0 (0%)	20 (3%)	30 (8%)	22 (6%)	0.03
Previous stroke/TIA	2 (2%)	39 (7%)	55 (14%)	81 (21%)	< 0.001
Killip class ≥ II	16 (17%)	113 (19%)	106 (27%)	133 (34%)	< 0.001
BMI (kg/m^2)	29 ± 4	26 ± 4	25 ± 4	24 ± 4	< 0.001
Peak CK (U/L)	718 ± 772	667 ± 1662	565 ± 966	437 ± 1207	0.03
Creatinine (mg/dl)	1.1 ± 1.0	1.9 ± 2.5	2.1 ± 2.2	1.8 ± 1.5	< 0.001
Total cholesterol (mg/dl)	196 ± 48	185 ± 45	173 ± 41	165 ± 52	< 0.001
HDL (mg/dl)	34 ± 7	38 ± 11	40 ± 17	43 ± 33	< 0.001
LDL (mg/dl)	127 ± 42	116 ± 40	109 ± 38	96 ± 32	< 0.001
TG (mg/dl)	233 ± 157	168 ± 125	135 ± 84	113 ± 70	< 0.001
TIMI score	2.5 ± 1.1	2.7 ± 1.1	3.8 ± 1.1	3.8 ± 1.1	< 0.001
LVEF < 35%	6 (6%)	21 (4%)	22 (6%)	30 (8%)	0.07

BMI, body mass index; CABG, coronary artery bypass grafting; CK, creatine kinase; HDL, high-density lipoprotein; LDC, low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TG, triglyceride; TIA, transient ischemic attack; TIMI, thrombolysis in myocardial infarction.
*Dyslipidemia, only record yes if patient has been diagnosed with dyslipidemia and/or taking lipid lowering therapy prior to admission to hospital.
Group I (< 45 years); Group II (45-64 years); Group III (65-74 years); Group IV (≥ 75 years).

tively, p = 0.049), statins (54%, 49%, 42%, 35%, respectively, p < 0.001), low molecular weight heparin (48%, 39%, 31%, 32%, respectively, p = 0.003), glycoprotein IIb/IIIa receptor antagonists (16%, 8%, 6%, 5%, respectively, p = 0.001) and adoption of percutaneous coronary intervention (PCI) (79%, 79%, 73%, 71%, respectively, p = 0.01) (Table 2).

Clinical outcomes

There are significant differences among the four groups in the incidence of cardiogenic shock (4%, 1%, 3%, 4%, respectively, p = 0.037), 90-day mortality (0%, 1%, 4%, 8%, respectively, p < 0.001) and 1-year mortality (1%, 2%, 8%, 18%, respectively, p < 0.001); however, there was no difference among the four groups for in-hospital mortality (0%, 1%, 1%, 2%, respectively, p = 0.30) (Table 3).

Table 4 showed the results of logistic regression. There was no case of in-hospital mortality and 90-day mortality in group I, so we set group II as reference, and compared that group with groups III and IV. There were no significant differences of in-hospital mortality [group III versus group II: odds ratio (OR) = 2.1 (0.5-9.3), p = 0.34; group IV versus group II: OR = 3.0 (0.8-12.2), p = 0.12]. In 90-day mortality, there were significantly higher incidences of mortality in group III and group IV, compared with group II [group III versus group II: OR = 4.5 (1.8-11.6), p = 0.002, group IV versus group II: OR = 8.1 (3.3-19.5), p < 0.001]. In 1-year mortality, there were significantly higher incidences of mortality in group III and group IV compared with group II [group III versus group II: OR = 3.6 (1.9-7.1), p < 0.001, group IV versus group II: OR = 9.8 (5.3-17.9), p < 0.001]. We also adjusted variables including sex, hypertension, high-density cholesterol, low-density cholesterol, triglyceride, dyslipidemia, diabetes, smoking, BMI, aspirin, clopidogrel, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, statins, and

Table 2. In-hospital treatments

Variables (n, %)	Group I	Group II	Group III	Group IV	p-value
Aspirin	87 (94%)	529 (89%)	337 (87%)	330 (83%)	0.02
Clopidogrel	89 (96%)	547 (92%)	348 (90%)	353 (89%)	0.16
ACEI or ARB	44 (47%)	261 (44%)	147 (38%)	146 (37%)	0.054
Beta-blockers	49 (53%)	265 (45%)	160 (42%)	152 (38%)	0.049
Statins	50 (54%)	294 (49%)	160 (42%)	138 (35%)	< 0.001
LMWH	45 (48%)	229 (39%)	121 (31%)	127 (32%)	0.003
UFH	58 (62%)	363 (61%)	232 (60%)	227 (57%)	0.65
GpIIb/IIIa	15 (16%)	50 (8%)	24 (6%)	18 (5%)	0.001
PCI	73 (79%)	470 (79%)	281 (73%)	279 (71%)	0.01
Thrombolysis	1 (1%)	4 (1%)	1 (0.3%)	2 (1%)	0.55
CABG	2 (2%)	25 (4%)	27 (7%)	18 (5%)	0.12

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; GpIIb/IIIa, glycoprotein IIb/IIIa receptor antagonists; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

Table 3. Complications and outcomes

Variables (n, %)	Group I	Group II	Group III	Group IV	p-value
Cardiogenic shock	4 (4%)	7 (1%)	12 (3%)	15 (4%)	0.037
Stroke/TIA	2 (2%)	2 (0.3%)	1 (0.3%)	4 (1%)	0.10
Major bleeding	0 (0%)	1 (0.2%)	1 (0.3%)	6 (2%)	0.05
In-hospital mortality	0 (0%)	3 (1%)	4 (1%)	6 (2%)	0.30
90-day mortality	0 (0%)	6 (1%)	17 (4%)	30 (8%)	< 0.001
1-year mortality	1 (1%)	13 (2%)	29 (8%)	71 (18%)	< 0.001

TIA, transient ischemic attack.

Table 4. Age-group as a predictor of in-hospital, 90-day and 1-year mortality

	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
In-hospital mortality						
Group I	NA			NA		
Group II	Reference	–	–	Reference	–	–
Group III	2.1	0.5-9.3	0.34	0.47	0.03-8.3	0.61
Group IV	3.0	0.8-12.2	0.12	0.55	0.04-7.9	0.66
90-day mortality						
Group I	NA			NA		
Group II	Reference	–	–	Reference	–	–
Group III	4.5	1.8-11.6	0.002	2.7	0.7-10.3	0.15
Group IV	8.1	3.3-19.5	< 0.001	4.5	1.2-16.3	0.023
1-year mortality						
Group I	0.49	0.06-3.8	0.49	1.3	0.15-11.0	0.82
Group II	Reference	–	–	Reference	–	–
Group III	3.6	1.9-7.1	< 0.001	2.0	0.74-5.2	0.18
Group IV	9.8	5.3-17.9	< 0.001	4.9	2.0-12.3	0.001

NA, not applicable because of limited numbers. Adjusted for sex, hypertension, high-density cholesterol, low-density cholesterol, triglyceride, dyslipidemia, diabetes, smoking, body mass index, aspirin, clopidogrel, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, statins and thrombolysis in myocardial infarction score.

TIMI risk score and re-analyzed the results. There were no significant differences between group III and group II in 90-day mortality [OR = 2.7 (0.7-10.3), p = 0.15] and 1-year mortality [OR = 2.0 (0.74-5.2), p = 0.18]. However, Group IV had significantly higher incidences of 90-day mortality [OR = 4.5 (1.2-16.3), p = 0.023] and 1-year mortality [OR = 4.9 (2.0-12.3), p = 0.001] compared with group II.

Predictors of outcome in Group IV

Table 5 shows the results of predictors of mortality in group IV in univariate logistic regression. There were no significant predictors of in-hospital mortality. Previous myocardial infarction (MI) [OR = 3.3 (1.1-9.8), p = 0.035], statins [OR = 0.35 (0.1-0.9), p = 0.037], and left ventricular ejection fraction (LVEF) < 35% [OR = 3.9 (1.5-10.4), p = 0.006] were associated with 90-day mortality. Age [OR = 1.1 (1.03-1.2), p = 0.002], previous MI [OR = 2.2 (1.1-4.4), p = 0.034], angiotensin-converting enzyme inhibitor or angiotensin receptor blocker [OR = 0.5 (0.3-0.9), p = 0.028], and LVEF < 35% [OR = 4.3 (1.9-9.5), p < 0.001] were associated with 1-year mortality. Table 6 shows the results of predictors of 90-day and 1-year mortality in group IV in multivariate analysis. Previous MI [OR = 4.0 (1.3-12.6), p = 0.019] was an independent predictor of 90-day mortality. Furthermore, previous MI [OR = 2.6 (1.1-6.5), p = 0.037], LVEF < 35% [OR = 4.7 (1.5-14.4), p = 0.007] and PCI or not [OR = 0.3 (0.1-0.9), p = 0.021] were independent predictors of 1-year mortality.

DISCUSSION

The median age of patients in most NSTE-ACS clinical trials is around 65-68 years, which is almost similar to this study (median age 66 years).[6,11] In worldwide registries data, the incidence of the patients ≥ 75 years

Table 6. Independent predictors of 90-day and 1-year mortality in Group IV (multivariate analysis)

90-day	OR (95% CI)	p-value
Previous MI	4.0 (1.3-12.6)	0.019
Statins	0.3 (0.1-1.2)	0.09
LVEF < 35%	1.3 (0.3-5.4)	0.73
1-year	**OR (95% CI)**	**p-value**
Age (years)	1.1 (1.0-1.2)	0.28
Previous MI	2.6 (1.1-6.5)	0.037
ACEI or ARB	0.4 (0.1-1.2)	0.09
Statins	0.6 (0.2-1.8)	0.39
LVEF < 35%	4.7 (1.5-14.4)	0.007
PCI	0.3 (0.1-0.9)	0.021

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 5. Predictors of in-hospital, 90-day and 1-year mortality in Group IV (univariate analysis)

Variables	In-hospital		90-day		1-year	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	1.1 (0.9-1.3)	0.37	1.0 (1.0-1.1)	0.35	1.1 (1.03-1.2)	0.002
Previous MI	NA		3.3 (1.1-9.8)	0.035	2.2 (1.1-4.4)	0.034
Previous PCI	1.5 (0.1-16.8)	0.74	1.9 (0.6-6.4)	0.28	1.3 (0.6-2.7)	0.46
Diabetes	0.2 (0.03-2.0)	0.19	0.9 (0.4-1.9)	0.80	1.1 (0.7-1.9)	0.67
ACEI or ARB	0.3 (0.04-2.9)	0.32	0.9 (0.4-1.9)	0.68	0.5 (0.3-0.9)	0.028
Beta-blockers	0.3 (0.04-2.7)	0.30	0.7 (0.3-1.5)	0.33	0.8 (0.5-1.4)	0.38
Statins	1.9 (0.4-9.5)	0.44	0.35 (0.1-0.9)	0.037	0.6 (0.3-1.0)	0.07
LVEF < 35%	5.9 (0.95-36.9)	0.06	3.9 (1.5-10.4)	0.006	4.3 (1.9-9.5)	< 0.001
PCI	2.1 (0.2-18)	0.51	0.6 (0.3-1.2)	0.14	0.6 (0.4-1.0)	0.06
Creatinine	1.2 (0.9-1.6)	0.19	1.0 (0.8-1.3)	0.86	1.1 (0.9-1.3)	0.29
CK	0.99 (0.99-1.0)	0.96	0.99 (0.99-1.0)	0.94	0.99 (0.99-1.0)	0.66
Aspirin and clopidogrel	1.4 (0.2-12.3)	0.75	1.44 (0.5-3.9)	0.47	1.0 (0.5-1.8)	0.90

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK, creatine kinase; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable because of limited numbers; PCI, percutaneous coronary intervention.

was 32% in the Grace registry, 37% in the NRMI registry, 38% in the CRUSADE registry, and 27-34% in European registries.[6,12,13] In the present study, 27% of the patients are ≥ 75 years of age, slightly lesser than those in worldwide ACS registries. Older patients with NSTE-ACS usually had poorer outcomes than the younger patients because they are always associated with more comorbidities and complications.[6,13]

The CRUSADE registry showed the incidences of bleeding, congestive heart failure and recurrent myocardial infarction were higher in patients ≥ 75 years.[13] In the present study, the advanced elderly had higher incidences of hypertension, diabetes, previous CABG, previous stroke/transient ischemic attack, Killip Class ≥ II, lower BMI, poor renal function and higher TIMI score but lower incidences of male gender, smokers and dyslipidemia. In the VIGOUR and GRACE registries, the in-hospital mortality rates for patients > 65 years was 1%, but was 10% for patients > 85 years.[6,12] The higher risk for the elderly continued from 30 days to 1 year; the 1-year mortality in the GRACE registry was 15% in patients with 75-84 years and 25% in patients > 85 years.[12] In the present study, the in hospital mortality rate was 1% for patients with age of 65-74 years and 2% for patients ≥ 75 years. Those patients ≥ 75 years had 8% and 18% for their 90-day and 1-year mortality rate, respectively, which were higher compared with patients 45-64 years of age. Furthermore, patients ≥ 75 years had significantly higher 90-day and 1-year mortality rate compared with patients 45-64 years of age, even after variables adjustment.

Evidence from several observational trials suggested that older patients received fewer evidence-based ACS therapies and had higher mortality rates than the younger patients.[14-16] Avezum et al. showed that aspirin, beta-blockers, thrombolytic therapy, statins, and glycoprotein IIb/IIIa inhibitors were prescribed less to elderly patients, and Alexander et al. presented that elderly patients received less clopidogrel and lipid-lowering therapy.[15,16] The present study also showed that the usage of aspirin, beta-blockers, statins, low molecular weight heparin, glycoprotein IIb/IIIa receptor antagonists was significantly less in the advanced elderly. Intensive lipid lowering after ACS has a mortality benefit; furthermore, the Heart protector study concluded that elderly patients (≥ 75 years) treated with statins had the same absolute risk reduction in coronary events and mortality as younger patients.[17,18] In patients > 75 years of age in the present study, statin usage was associated with lower incidence of 90-day mortality. Furthermore, statin usage could nearly predict 90-day mortality (p = 0.09).

In clinical practice, elderly patients are more often managed without invasive care such as diagnostic catheterization and PCI, even if there are no apparent contraindications. The CRUSADE study showed that for each 10 years of advancing age, there was a 20% reduced likelihood of invasive care.[13] Current estimates from community populations for invasive care in patients < 65 versus ≥ 85 years of age are as follows: CRUSADE, 57% versus 21%; NRMI, 65% versus 13%; and GRACE, 69% versus 18%.[6,12,13] In the present study, the incidence of patient ≥ 75 years who underwent PCI was 71%, which was higher than in other registries. In patients ≥ 75 years old, PCI or not could predict 1-year mortality. Therefore, the present study and previous studies suggested that an invasive strategy was favored to reduce the short to medium term mortality in advanced elderly patients without contraindications.[19,20]

Study limitation

The present study should define the causes of mortality or endpoint in the registry. However, the exact causes of mortality were unavailable in the present registry.

CONCLUSIONS

Previous MI, LVEF < 35% and PCI or not could predict 1-year mortality in advanced elderly patients with NSTE-ACS. Despite their high morbidities and complications, PCI was still beneficial in this patient population.

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