Original Article

Invasive treatment strategy in patients aged 80 years or older with non-ST-elevation acute coronary syndromes: a retrospective cohort study

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Background: Invasive treatment is commonly recommended for patients with non-ST-elevation acute coronary syndromes (NSTE-ACS). However, the efficacy of this approach in patients aged ≥80 years remains uncertain.

Methods: We retrospectively assessed consecutive NSTE-ACS patients ≥80 years of age who were hospitalized at our cardiovascular center from December 2012 to July 2019. Patients were divided into two groups based on whether they received invasive treatment (coronary angiography and, if indicated, revascularization) or not. Patients who died in the first 3 days after admission without receiving invasive treatment were excluded. The effect of invasive timed treatment was also explored by dividing patients into timely invasive or delayed invasive groups according to their risk classification. Multivariate COX regression, invasive probability weighting and propensity score matching were used to adjust for confounding variables. The primary outcome was all-cause death during follow-up.

Results: A total of 1,201 patients with a median age of 82.0 (IQR, 81.0–84.0) were divided into two groups: 656 (54.6%) patients in the invasive group and 545 (45.4%) patients in the conservative group. Follow-up survival information was available for up to 6 years (median 3.0 years). During the follow-up, 296 (24.6%) patients died. After adjusting for confounding variables, the invasive treatment strategy was significantly associated with a lower risk of long-term mortality (HR =0.70, 95% CI: 0.54–0.92, P=0.010). No difference was found between timely invasive and delayed invasive interventions with mortality (HR =0.92, 95% CI: 0.57–1.47, P=0.725).

Conclusions: Invasive treatment was associated with lower mortality in patients ≥80 years of age with NSTE-ACS over a median of a 3-year follow-up. The invasive intervention time did not impact the outcome.

Keywords: Non-ST-elevation acute coronary syndromes (NSTE-ACS); elderly; invasive; conservative; mortality

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Introduction

Ischemic heart disease, including acute coronary syndrome (ACS), is the leading cause of mortality both in China and worldwide (1,2). Since age is a major risk factor for ACS, the global disease burden of ACS will inevitably increase in the coming decades due to the aging population. With the advancement of invasive coronary strategies, pharmacological therapies, and lifestyle interventions, the mortality rate of ACS has been gradually reduced over the past decades (3,4). Nevertheless, this reduction has been mostly presented in patients with ST-segment elevation myocardial infarction (STEMI) but not in those with non-ST-elevation acute coronary syndrome (NSTE-ACS) (5).

According to several guidelines, NSTE-ACS patients are recommended to undergo an invasive coronary angiography (CAG), followed by revascularization if necessary, unless their risk stratification is low (6-8). However, patients with advanced age are at higher risk, and thus are less likely to receive invasive treatment (9-11). This treatment-risk paradox may be partly attributed to a higher incidence of comorbidities, which may result in procedure-related complications and mortality in higher-risk patients. Furthermore, the underrepresentation of elderly patients in clinical trials has led to limited evidence for the invasive strategies for those ≥80 years of age. The aim of the present study was to analyze data from a clinical database to determine the impact of invasive treatment strategies on long-term mortality in patients aged 80 years or older presenting with NSTE-ACS. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-650/rc).

Methods

Study population and data collection

The study population in this single-center, retrospective, cohort study was identified from the ACS patient database of the Cardiovascular Center of Beijing Friendship Hospital, a tertiary center with emergency departments, which includes consecutive ACS inpatients over the age of 18 from December 2012 onward. Patients who met the following inclusion criteria were enrolled in the study: ≥80 years old and discharged with non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA) as the principal diagnosis between December 2012 and July 2019. For patients who had more than one record during this period, only the first record that met the inclusion criteria was included.

All clinical data were collected and entered into the database by trained researchers. Data elements collected in this study included patient demographics, medical history, cardiovascular risk factors, blood pressure and heart rate at admission, laboratory test results in the first 24 hours after admission, in-hospital procedures and discharge medications. Barthel index at admission was also collected as a reflection of frailty in elderly patients. To determine the associations between invasive treatment strategies and long-term mortality, patients were divided into invasive and conservative groups, based on whether they received CAG during hospitalization or not, respectively. Patients who died in the first 3 days after admission without receiving invasive treatment were excluded to limit bias. We further divided the invasive intervention group into subgroups to better understand outcomes: timely invasive group (invasive time ≤1 d in high-risk patients or ≤3 d in intermediate risk patients) and delayed invasive group (invasive time >1 d in high-risk patients or >3 d in intermediate-risk patients), based on the guideline recommendation at that time (6-8).

Follow-up survival information was collected by contacting patients and their families at outpatient visits or by phone calls at 1 month, 3 months, 6 months, 1 year and then annually after discharge. The follow-up period ended in April 2020. The primary outcome was all-cause mortality. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Friendship Hospital, Capital Medical University (project number: 2020-P2-083-01) and individual consent for this retrospective analysis was waived.

Definitions

NSTE-ACS was defined according to published guidelines (6-8). Invasive strategy was defined as optimal medical treatment, CAG during hospitalization, with or without further percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Conservative strategy was defined as optimal medical treatment only. Hyperuricemia was defined as serum uric acid >417 μmol/L (7.0 mg/dL) for males and >357 μmol/L (6.0 mg/dL) for female patients. Thrombocytopenia was defined as platelet count $<100\times10^9$/L. Estimate glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation modified for Chinese

population (12). Severe renal insufficiency was defined as end stage renal disease or eGFR <30 mL/min/1.73 m^2 (13).

Statistical analysis

Data are presented as means (standard deviation, SD), medians with interquartile range (IQR) or numbers and percentages where appropriate. Student's *t*-test or Wilcoxon-Mann-Whitney U test was used to compare continuous variables, and the Chi-squared test or Fisher's exact test was used to compare categorical variables between the two groups. The N-terminal pro-brain natriuretic peptide (NT-pro BNP) was transformed to log10 (NT-pro BNP) because of its highly skewed distribution.

Assigning all patients who died during hospitalization without invasive management to the conservative group could cause immortal time bias and lead to results in favor of the invasive group. Some of these patients could have undergone invasive strategy if they had survived. To limit such bias, patients who did not receive invasive management and died within 3 days after admission (which is the median invasive time in the invasive group) were excluded.

Multivariable Cox proportional hazards regression models were used to assess whether treatment strategies were related to long-term mortality. Five adjusted models were built successively. Model 1 adjusted for GRACE risk score (age, systolic blood pressure, heart rate, Killip class, creatinine, ST-segment deviation and elevated troponin). Model 2 adjusted for Model 1 plus cardiovascular risk factors (gender, body mass index, dyslipidemia, hypertension, diabetes mellitus, LDL-c at admission and recent cigarette smoking). Model 3 adjusted for covariates in Model 2 along with high bleeding risk factors in ARC-HBR criteria (13) (hemoglobin <110 g/L, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies and prothrombin activity). Model 4 adjusted for Model 3 plus medications (antiplatelet drug, ACEI/ARBs, β-blockers and statins). Model 5 adjusted for Model 4 plus other important clinical conditions and laboratory test results (prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia and Barthel index). Model 5 also included CAG results for timely versus delayed invasive analysis. The proportional hazards assumption was tested based on Schoenfeld residuals. Covariates that did not meet the proportional hazard assumption were added to the model as strata. Subgroup analysis was performed to test whether the effect of invasive strategies was consistent across groups. The cutoff point for GRACE risk scores used medians because very few patients had GRACE scores <140.

Propensity score matching (PSM) and inverse probability weighting (IPW) were also preformed to control for differences in baseline covariates between groups as sensitivity analysis. The propensity scores (PS) were driven by logistic regression using variables in Model 5. In PSM, we 1:1 matched two groups without replacement, using 0.1 of the standard deviation of the PS as the caliper via the nearest neighbor matching. In IPW, we used stabilized weights to prevent enlarging of sample size and type I error due to weighting (14). The balance of baseline covariates between the two groups in the matched or weighted cohort was assessed by computing absolute standardized mean differences (ASMD), with differences of ≤0.1 indicating a negligible difference in potential confounders between the two groups. Kaplan-Meier curves were plotted to display cumulative survival rates.

For 10 variables with missing data (missing rate between 0.4% and 10.2%, Table S1), 10 imputed datasets were generated using multiple imputations by chained equations (15). Each one of these imputed datasets was independently analyzed, and then pooled together following Rubin's rule (16). All P values are presented for two-tailed tests, and <0.05 was considered statistically significant. All analyses were performed with the R statistical software version 4.0.3 (R Core Team, 2014).

Results

Baseline characteristics

Of the 15,728 consecutive ACS patients who were enrolled in the CBD-BANK database during the study period, 1,829 patients were 80 years or older. After excluding 336 repeated hospitalization records and 287 STEMI patients, the study included 1,206 patients with a median age of 82 years (IQR, 81–84 years). Among them, 656 patients underwent invasive management during hospitalization and 550 patients did not. After excluding 5 patients who died during hospitalization within 3 days without invasive management, 1,201 patients were included in baseline analysis (*Figure 1*).

The patient's clinical characteristics are summarized in *Table 1*. Patients in the conservative group had more comorbidities and worse conditions than the invasive group at admission. The conservative group was older,

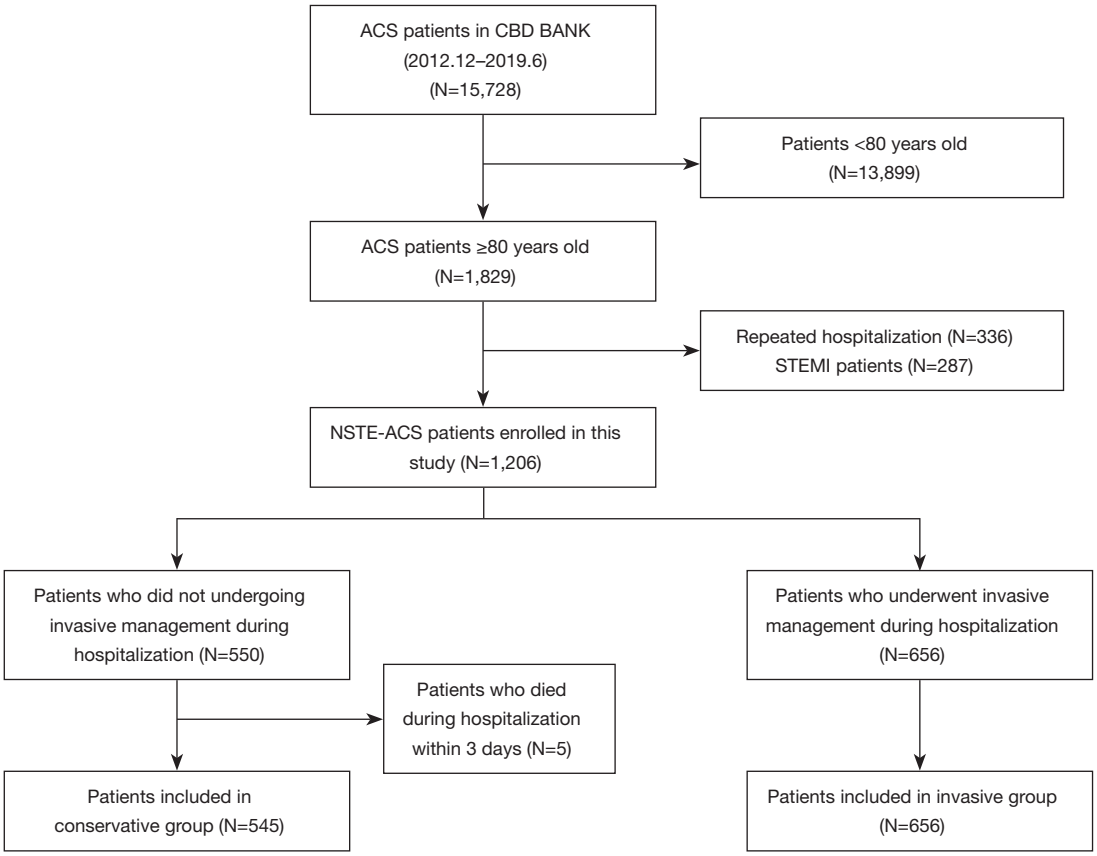

Figure 1 Patient screening flow chart. ACS, acute coronary syndrome; CBD, Cardiovascular Center of Beijing Friendship Hospital Database; NSTE-ACS, non-ST-elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction.

slimmer, had a lower rate of prior revascularization, and a higher prevalence of previous stroke, malignancy, anemia, tachycardia, hyperuricemia and severe renal insufficiency. The conservative group also had higher mean levels of NT-pro BNP, GRACE risk score, as well as lower levels of prothrombin activity and Barthel index.

CAG and revascularization

Most patients (76.1%) in the invasive group showed three-vessel disease and/or left main disease after CAG. In the invasive group, 57.9% patients underwent PCI during hospitalization (n=380), 3.2% were treated with CABG (n=21), and 38.9% did not receive revascularization (n=255). The details of stent implantation and other information are shown in *Table 2*.

Pharmacological treatment and follow-up

Patients who underwent invasive therapy were treated with antiplatelet drugs and statins at discharge more often than the conservative group. The proportion of patients treated with ACEI/ARB, β-blockers, and oral anti-coagulation drugs was similar in both groups. The median follow-up duration was 3.0 years. During the study period, 181 patients (33.2%) in the conservative group and 115 patients (17.5%) in the invasive group died (*Table 1*). The unadjusted Kaplan-Meier curve showed a significant reduction in mortality in the invasive group (HR 0.48, 95% CI: 0.38–0.60, P<0.001, *Figure 2A*).

Following adjustment for GRACE risk score and cardiovascular risk factors, the mortality HR of the invasive group compared to the conservative group was attenuated

Table 1 Baseline characters of the study participants

Variable	Total (n=1,201)	Conservative group (n=545)	Invasive group (n=656)	P value
Female, n (%)	628 (52.3)	291 (53.4)	337 (51.4)	0.522
Age, years, median [IQR]	82.00 [81.00, 84.00]	83.00 [81.00, 85.00]	82.00 [81.00, 84.00]	<0.001*
Body mass index, kg/m^2	24.49 [22.27, 26.95]	24.03 [21.30, 26.31]	24.97 [22.89, 27.34]	<0.001*
Medical history				
Prior myocardial infarction, n (%)	158 (13.2)	77 (14.1)	81 (12.3)	0.41
Prior revascularization, n (%)	316 (26.3)	124 (22.8)	192 (29.3)	0.013*
Prior PCI, n (%)	277 (23.1)	101 (18.5)	176 (26.8)	0.001*
Prior CABG, n (%)	51 (4.2)	28 (5.1)	23 (3.5)	0.21
Dyslipidemia, n (%)	564 (47.0)	229 (42.0)	335 (51.1)	0.002*
Hypertension, n (%)	965 (80.3)	439 (80.6)	526 (80.2)	0.931
Diabetes mellitus, n (%)	467 (38.9)	199 (36.5)	268 (40.9)	0.14
Previous stroke, n (%)	328 (27.3)	174 (31.9)	154 (23.5)	0.001*
Malignancies, n (%)	33 (2.7)	25 (4.6)	8 (1.2)	0.001*
Recent cigarette smoking, n (%)	152 (12.7)	68 (12.5)	84 (12.8)	0.934
Long-term oral anticoagulation, n (%)	18 (1.5)	8 (1.5)	10 (1.5)	1.000
Barthel Index, median [IQR]	80 [55, 90]	75 [50, 90]	85 [60, 90]	<0.001*
Findings on admission				
SBP, mmHg, median [IQR]	135 [123, 149]	134 [123, 148]	135 [123, 149]	0.963
SBP <100 mmHg, n (%)	33 (2.7)	15 (2.8)	18 (2.7)	1.000
Heart rate, bpm, median [IQR]	70 [62, 78]	70 [64, 80]	69 [62, 77]	0.003*
Heart rate >100 bpm, n (%)	44 (3.7)	28 (5.1)	16 (2.4)	0.020*
Killip class, n (%)				
I	356 (29.6)	127 (23.3)	229 (34.9)	<0.001*
II	620 (51.6)	280 (51.4)	340 (51.8)	
III	183 (15.2)	110 (20.2)	73 (11.1)	
IV	42 (3.5)	28 (5.1)	14 (2.1)	
Elevated troponin levels, n (%)	335 (27.9)	157 (28.8)	178 (27.1)	0.563
Hemoglobin, g/L, median [IQR]	123 [113, 133]	120 [109, 132]	126 [117, 134]	<0.001*
Hemoglobin <110 g/L, n (%)	228 (19.0)	142 (26.1)	86 (13.1)	<0.001*
Platelet, 10^9/L, median [IQR]	198 [163, 237]	200 [162, 237]	198 [163, 237]	0.979
Thrombocytopenia, n (%)	19 (1.6)	12 (2.2)	7 (1.1)	0.181
Triglyceride, mmol/L, median [IQR]	1.17 [0.87, 1.58]	1.15 [0.87, 1.48]	1.19 [0.87, 1.66]	0.140
LDL-c, mmol/L, median [IQR]	2.22 [1.76, 2.67]	2.22 [1.76, 2.73]	2.21 [1.75, 2.64]	0.586
NT-pro BNP at admission, pg/mL, median [IQR]	694.0 [273.6, 2,427.0]	1,107.2 [343.0, 4,113.0]	528.0 [242.8, 1,570.3]	<0.001*

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (n=1,201)	Conservative group (n=545)	Invasive group (n=656)	P value
Log10 (NT-pro BNP at admission), median [IQR]	2.84 [2.44, 3.39]	3.04 [2.54,3.61]	2.72 [2.39, 3.20]	<0.001*
PTA, %, median [IQR]	94.0 [84.7, 102.7]	93.00 [82.3, 100.3]	94.71 [86.3, 103.9]	<0.001*
Uric acid, mmol/L, median [IQR]	346.5 [286.9, 414.9]	358.9 [286.9, 426.2]	337.9 [285.9, 401.9]	0.020*
Hyperuricemia, n (%)	428 (35.6)	221 (40.6)	207 (31.6)	0.001*
Creatinine, umol/L, median [IQR]	90.0 [74.6, 107.2]	94.0 [79.4,121.3]	85.0 [71.8, 100.0]	<0.001*
eGFR, mL/min/1.73 m^2, median [IQR]	52.99 [41.72, 63.07]	48.21 [35.82, 59.67]	55.83 [46.46, 65.40]	<0.001*
Severe renal insufficiency, n (%)	108 (9.0)	89 (16.3)	19 (2.9)	<0.001*
GRACE risk score, median [IQR]	168 [151, 190]	173 [157, 195]	164 [146, 184]	<0.001*
>140, n (%)	1,029 (85.7)	486 (89.2)	543 (82.8)	0.006*
108–140, n (%)	170 (14.2)	58 (10.6)	112 (17.1)	
<108, n (%)	2 (0.2)	1 (0.2)	1 (0.2)	
Pharmacological treatment				
Antiplatelet therapy, n (%)				
Single-APT	570 (47.5)	336 (61.7)	234 (35.7)	<0.001*
Dual-APT	544 (45.3)	132 (24.2)	412 (62.8)	
None	87 (7.2)	77 (14.1)	10 (1.5)	
ACEI/ARB, n (%)	664 (55.3)	292 (53.6)	372 (56.7)	0.304
β-blocker, n (%)	798 (66.4)	354 (65.0)	444 (67.7)	0.349
Statin, n (%)	1038 (86.4)	453 (83.1)	585 (89.2)	0.003*
Oral anti-coagulation drug, n (%)	24 (2.0)	14 (2.6)	10 (1.5)	0.28
Follow-up				
Follow-up years, median [IQR]	3.0 [1.2, 4.1]	3.0 [1.1, 4.0]	3.0 [1.2, 4.1]	0.019*
Death during follow-up, n (%)	296 (24.6)	181 (33.2)	115 (17.5)	<0.001*
Death per 100 patient-years	8.5	12	5.8	<0.001*

*, P<0.05. ACEI, angiotensin-converting-enzyme inhibitor; APT, anti-platelet therapy; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; NT-pro BNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PTA, prothrombin activity; SBP, systolic blood pressure.

to 0.58 (95% CI: 0.46–0.74, P<0.001). After adjustment for Model 5, which included risk scores, cardiovascular and bleeding risk factors, drug use, other comorbidities and activities of daily living, patients who underwent invasive management compared with those who were managed conservatively had a 30% reduction in mortality (HR =0.70, 95% CI: 0.54–0.92, P=0.01, *Table 3*). Using IPW and PSM adjustment, we built a good balance between the two groups. The PS and ASMD before and after adjustment were shown in Figures S1,S2. The mortality HR of the invasive with conservative groups was 0.67 (95% CI: 0.53–0.84) after IPTW and 0.69 (95% CI: 0.50–0.94) following PSM adjustment (*Table 3*, *Figure 2B*). *Figure 3* shows the effect of invasive treatment in different subgroups. The invasive treatment seemed to be more efficient in females, patients with elevated cTn at admission, without diabetes, HGB

Table 2 Coronary angiography and revascularization during hospitalization

Variable	Invasive group (n=656)
Coronary angiography result, n (%)	
Normal	2 (0.3)
One-vessel disease	71 (10.8)
Two-vessel disease	84 (12.8)
Three-vessel/LM disease	499 (76.1)
Revascularization	
PCI, n (%)	380 (57.9)
Number of stent implantation	
0[†]	30 (7.9)
1	162 (42.6)
2	126 (33.2)
≥3	62 (16.3)
CABG, n (%)	21 (3.2)
No revascularization, n (%)	255 (38.9)

[†], including 5 unsuccessful PCI procedures and 25 balloon angioplasties. CABG, coronary artery bypass grafting; LM, left main coronary artery; PCI, percutaneous coronary intervention; RCA.

≥110 g/L and with a higher GRACE risk score. However, tests for interaction were insignificant in all subgroups.

The distribution of the number of days from admission to invasive management among patients in the invasive group is shown in Figure S3. The median invasive time was 3 days (IQR, 1–5 days). Only 26.2% of patients underwent CAG within a guideline-recommend time (≤1 day in the high risk group or ≤3 days in the median risk group). The baseline characteristics, results of angiography, revascularization and pharmacological treatment of timely and delayed invasive patients are shown in Table S2. The patients in the two groups were homogeneous, except in the delayed invasive group patients had worse Killip class and higher GRACE risk scores. The crude HR of timely *vs.* delayed invasive therapy was 1.12 (95% CI: 0.77–1.62, P=0.549). After adjustment for Model 5, there was no association between timing of invasive treatment and long-term mortality (HR =0.93, 95% CI: 0.62–1.41, P=0.746, Table S3). The IPW adjusted Kaplan-Meier plot based on model 5 showed

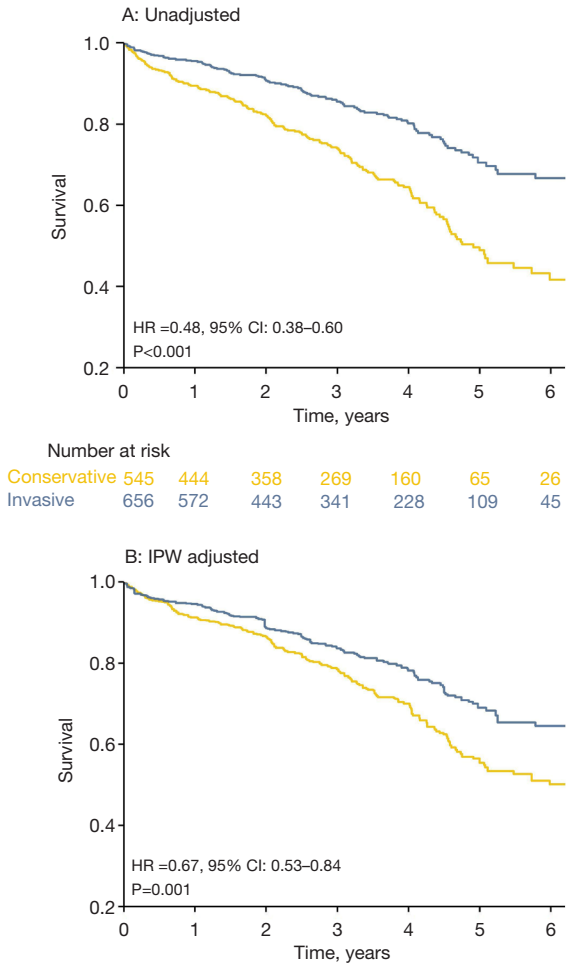

Figure 2 Comparison of unadjusted and adjusted survival curves of patients ≥80 years of age stratified by different strategies. (A) Unadjusted Kaplan-Meier curve. (B) Inverse probability weighted Kaplan-Meier curve. Adjusted for GRACE risk score, gender, body mass index, dyslipidemia, hypertension, diabetes mellitus, LDL-c at admission, recent cigarette smoking, hemoglobin <11 g/dL, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies, prothrombin activity, antiplatelet drug, ACEI/ARBs, β-blockers, statins, prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia and Barthel index. The weight for each patient was calculated though the average propensity score in all imputations. GRACE, global registry of acute coronary events; LDL-c, low-density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; NT-pro BNP, N-terminal pro-brain natriuretic peptide.

Table 3 Associations between invasive strategy and long-term mortality for NSTEMI patients ≥80 years old

Model	Hazard ratio	95% CI	P value
Unadjusted	0.48	0.38–0.60	<0.001
Model 1	0.54	0.43–0.69	<0.001
Model 2	0.58	0.46–0.74	<0.001
Model 3	0.67	0.52–0.86	0.002
Model 4	0.63	0.49–0.82	0.001
Model 5	0.70	0.54–0.92	0.010
PSM	0.69	0.50–0.94	0.019
IPW	0.67	0.53–0.84	0.001

Model 1 adjusted for GRACE risk score (age, systolic blood pressure, heart rate, Killip class, creatinine, ST-segment deviation and elevated troponin). Model 2 = Model 1 plus gender, body mass index, dyslipidemia, hypertension, diabetes mellitus, LDL-c at admission and recent cigarette smoking. Model 3 = Model 2 plus hemoglobin <110 g/L, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies and prothrombin activity. Model 4 = Model 3 plus antiplatelet drug, ACEI/ARBs, β-blockers and statins use. Model 5 = Model 4 plus prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia and Barthel index. Variates in model 5 were used for PSM and IPW adjustment. NSTEMI, non-ST-elevation myocardial infarction; CI, confidence interval; IPW, Inverse probability weighting; PSM, propensity score matching; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.

two closing survival curves for the two groups (*Figure 4*, Figure S4). The difference between patients who had coronary disease but had no further intervention after CAG and those who had revascularization was also explored (Table S4, Figure S5).

Discussion

In the present study, we used a routinely curated clinical database from a large tertiary hospital with emergency departments to estimate the effect of invasive management on long-term survival in patients ≥80 years with NSTE-ACS compared with conservative management. Our data showed that invasive treatment was associated with a 30%-reduction in mortality rates during a median of 3 years follow-up.

In the contemporary reperfusion era, the superiority of invasive treatment for NSTE-ACS has been verified by numerous studies. However, in patients aged 80 years or older, physicians prefer conservative strategies rather than invasive approaches, as advanced age has become an independent predictor for conservative treatment (17). Data from the China Acute Myocardial Infarction (CAMI) registry revealed the same trend in China, where the angiography rate was significantly reduced in NSTEMI patients ≥75 years compared with their younger counterparts (25.4% *vs.* 52.0%) (18). In our study, the invasive rate was 54.4%,

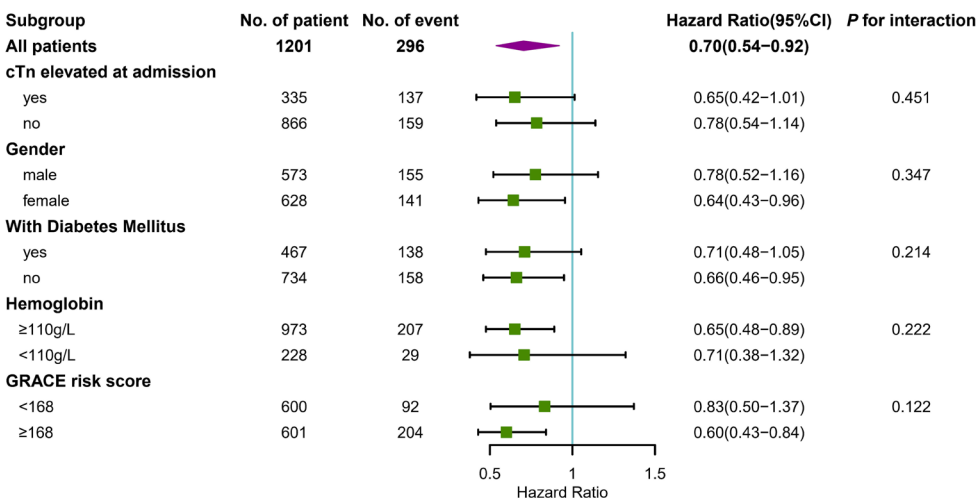

Figure 3 Forest plots for associations of invasive treatment with long-term mortality in subgroup analyses. cTn, cardiac troponin; GRACE, global registry of acute coronary events.

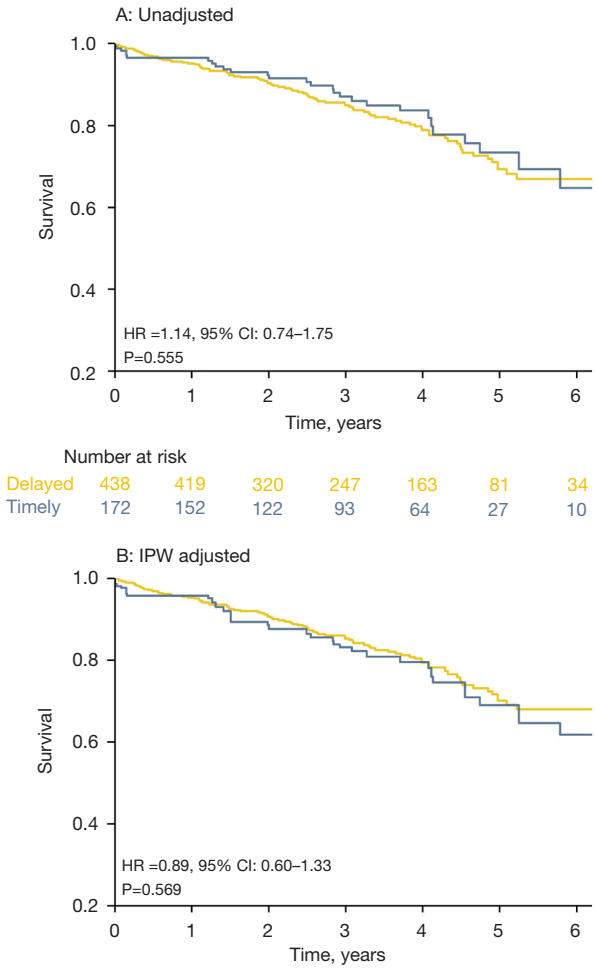

Figure 4 Comparison of unadjusted and adjusted survival curve of patients ≥80 years of age who underwent invasive treatment stratified by different timing of invasive intervention. (A) Unadjusted Kaplan-Meier curve. (B) Inverse probability weighted Kaplan-Meier curve. Adjusted for GRACE risk score, gender, body mass index, dyslipidemia, hypertension, diabetes mellitus, LDL-c at admission, recent cigarette smoking, hemoglobin <11 g/dL, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies, prothrombin activity, antiplatelet drug, ACEI/ARBs, β-blockers, statins, prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia, Barthel index and coronary angiography result. The weight for each patient was calculated though the average propensity score in all imputations. GRACE, global registry of acute coronary events; LDL-c, low-density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; NT-pro BNP, N-terminal pro-brain natriuretic peptide.

similar to previous studies (19,20). Patients who were managed conservatively were more likely older, slimmer, had higher NT-pro BNP levels, more comorbidities, and worse renal function. Such differences indicated a higher risk of complications and a worse outcome, raising the risk-benefit ratio of invasive procedure in those patients.

Few studies have focused on elderly patients, although older individuals comprise a large proportion of NSTE-ACS patients. To the best of our knowledge, the Italian Elderly ACS study (n=313) (21), the After Eighty study (n=457) (22), the MOSCA study (n=106) (23) and the RINCAL trial (n=251) (24) were the only 4 randomized controlled trials focusing on invasive treatment strategies in elderly NSTE-ACS patients. However, the results were contradictory: while the After Eighty study successfully demonstrated the benefit of an invasive strategy in elderly patients (HR =0.48, 95% CI: 0.37–0.63), the other 3 studies showed no difference between the two treatment strategies. Some observational registry studies also focused on this topic (20,25-27). In a meta-analysis published in 2018, researchers pooled results and demonstrated the benefits of an invasive strategy in reducing 12-month mortality compared with the conservative approach. However, none of these studies considered immortal bias (28).

In our cohort, the invasive strategy in elderly patients with NSTE-ACS revealed a significant reduction in all-cause mortality during a median of 3 years follow-up. Compared with the After Eighty study, patients in the present study were younger (medium age: 82 *vs.* 85 years), with a lower rate of previous myocardial infarction (13.2% *vs.* 43.1%) and troponin elevation at admission (27.9% *vs.* 93.0%) (22). These differences reflected a worse condition in patients from the After Eighty study than ours, which might have suppressed the potential benefits of invasive treatment on survival and lead to a negative result of all cause death in the After Eighty study.

In the recently published SENIOR-NSTEMI study, researchers retrospectively analyzed 1,976 NSTEMI patients aged 80 years and older from five UK hospitals. After careful adjustment for observed differences and immortality bias, the study concluded that invasive management improves long-term survival was consistent with our findings (19). The main difference between the two studies was that, in the SENIOR-NSTEMI study, the patients who underwent invasive management after 3 days of peak troponin concentration were assigned to the conservative group, while in our study, the patients who

completed CAG during hospitalization were included in the invasive group.

Based on the guidelines during the study period, an invasive strategy was recommended for patients at high risk within 24 hours and at intermediate risk within 72 hours. However, delayed angiography is common in clinical practice, especially in elderly patients. In the US, 42.5% of NSTEMI patients who were directed to admission to a PCI center underwent delayed angiography, and older patients were more likely to be delayed (29). In China, 44.8% of moderate to very high-risk patients who underwent invasive treatment were delayed for more than 72 hours (30). Meanwhile, the optimal timing of CAG in patients with advanced age remains poorly defined. In one of the largest collaborative meta-analyses that included 5,324 participants from 8 trials, the relationship between early invasive and reduced mortality in patients aged ≥75 years was only described as "might" because of an insignificant statistical result (31). In our study, timing of invasive treatment did not impact long-term mortality in elderly patients (HR =0.93, 95% CI: 0.62–1.41, P=0.746). These findings may suggest that invasive therapy itself, rather than the timing of invasive therapy, might be the key factor for improving late clinical outcomes in elderly patients. An adequate pharmaceutical treatment before delayed catheterization could theoretically stabilize the patient and facilitate further surgery, and thus may be used as an alternative approach for patients over 80 years of age.

In the present study, we used all-cause mortality as the endpoint rather than cardiovascular mortality. Cardiovascular-related death might more directly reflect the impact of cardiovascular treatment. However, elderly patients are complex and vulnerable, and often have frailty and other comorbidities. These factors also affect the choice of treatment strategies and life expectancy, but were not reflected in cardiovascular mortality. Strategies that could only reduce cardiovascular mortality but not all-cause mortality did not benefit the elderly. Therefore, we propose that all-cause mortality would be a more appropriate outcome for this study.

The present study has some limitations that need to be pointed out. First, as a single-center, retrospective, observational study, intervention strategies were not randomized. Although we used multiple strategies to adjust for the observed differences between groups, residual confounding by unmeasured variables may still exist. The results require further validation via prospective cohort studies (32). Second, external validity was limited. Patients in other institutions may have different characteristics. Third, bleeding events were not documented in our database, although previous studies have shown low major bleeding rates and no difference between the two strategies (21,22).

Conclusions

Our data showed that an invasive strategy was associated with lower all-cause mortality in patients ≥80 years with NSTE-ACS during a median of a 3-year follow-up. The timing of invasive treatment did not impact the outcome.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-650/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-650/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-650/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Friendship Hospital, Capital Medical University (project number: 2020-P2-083-01) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Number of participants with missing data at baseline in each variable

	Number of missing (n)	Missing rate (%)
Barthel index	5	0.4
Creatinine	7	0.6
Body mass index	8	0.7
Hemoglobin	20	1.7
Platelet	20	1.7
Triglyceride	41	3.4
LDL-c	41	3.4
Uric acid	50	4.2
PTA	77	6.4
NT-pro BNP at admission	122	10.2

LDL-c, low-density lipoprotein cholesterol; PTA, prothrombin activity.

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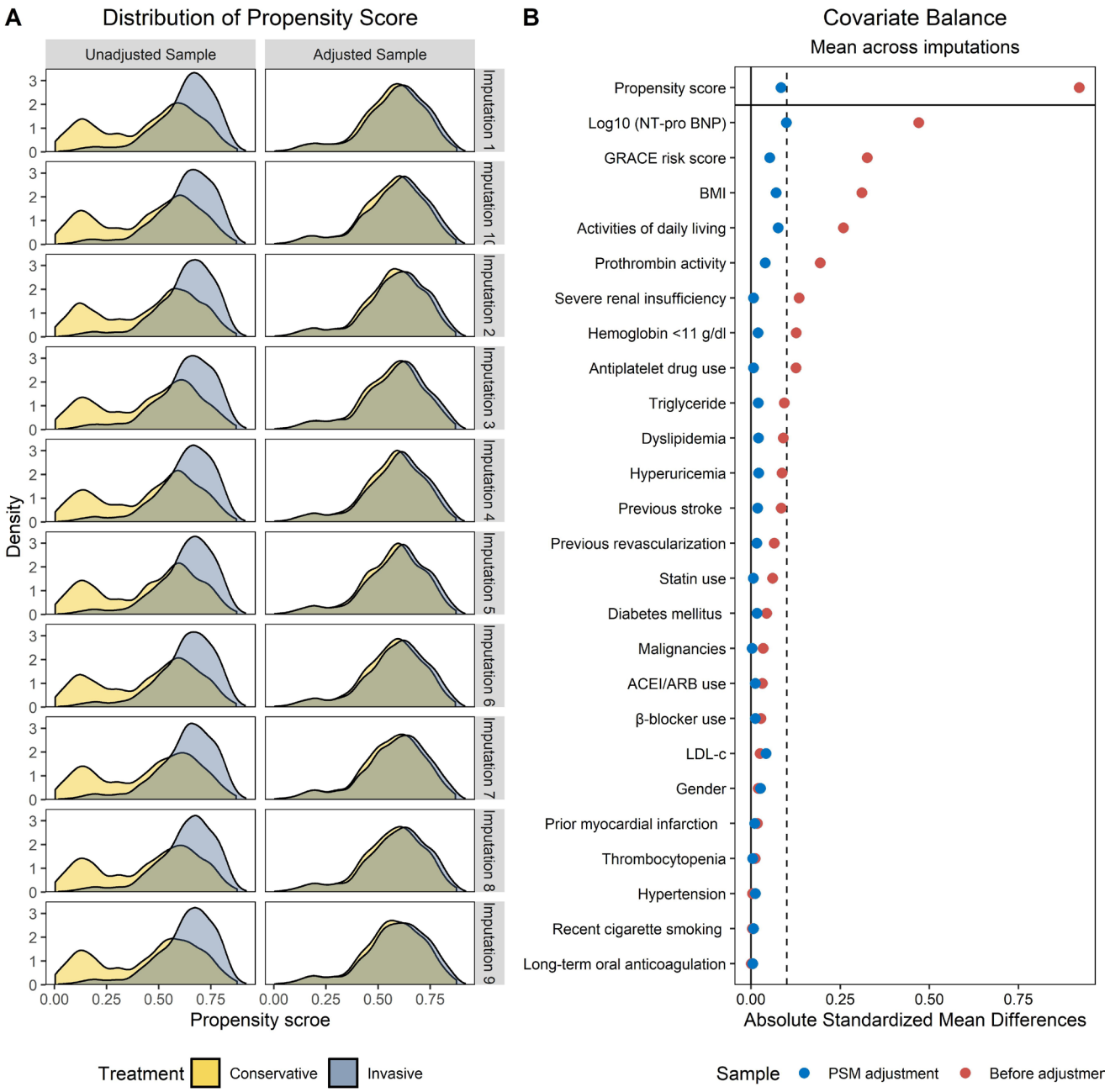

Figure S1 (A)The distribution of propensity score of two treatment group before and after propensity score matching in 10 imputations. (B) the covariates balance before and after propensity score matching. The absolute standardized mean difference (ASMD) was present as mean across imputations in each covariate and ASMD ≤0.1 indicated a good balance between the two groups. ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol.

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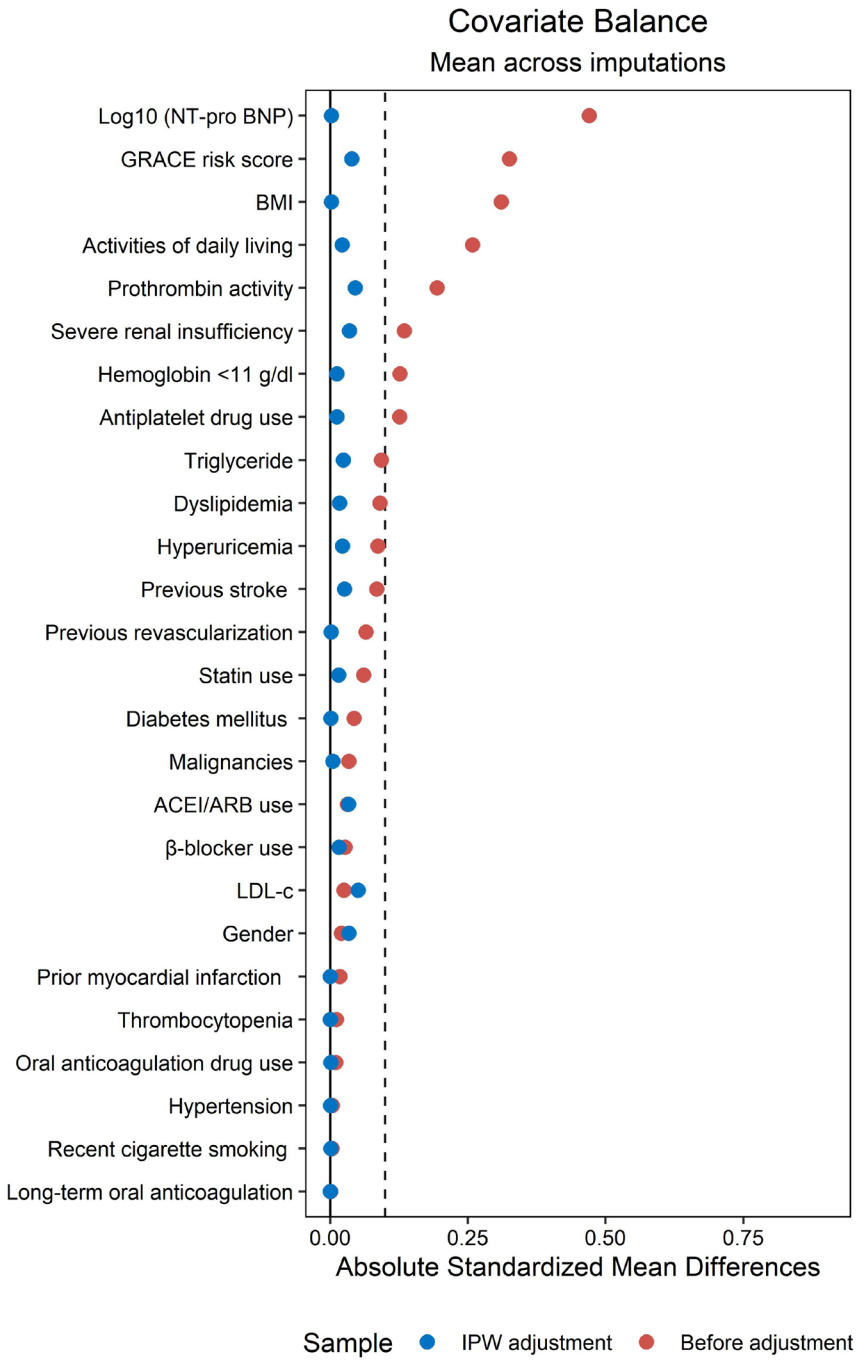

Figure S2 ASMD across covariates before and after IPW between invasive and conservative groups. The ASMD was present as mean across imputations in each covariate and ASMD ≤0.1 indicated a good balance between the two groups. ASMD, absolute standardized mean differences; IPW, inverse probability weighting; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, Body mass index; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol.

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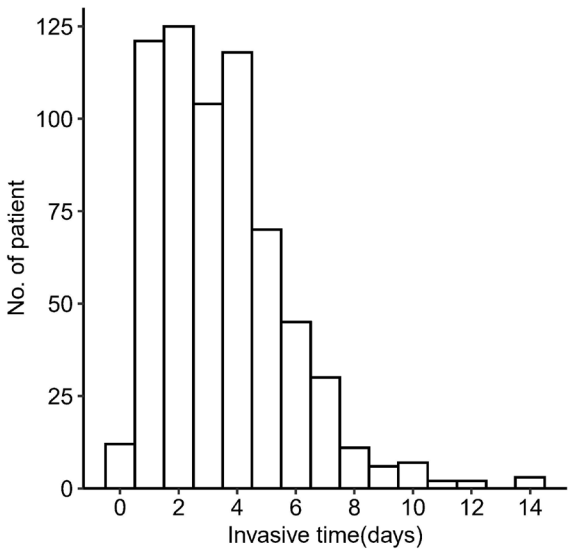

Figure S3 Distribution of the number of days from admission to invasive management among invasive group patients.

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Table S2 Baseline characters, coronary angiography, treatment and follow-up in NSTE-ACS patient ≥80 years underwent invasive treatment

	Overall (n=656)	Timely invasive (n=172)	Delayed invasive (n=484)	P
Female, n (%)	337 (51.4)	84 (48.8)	253 (52.3)	0.493
Age, years, median [IQR]	82.0 [81.0, 84.0]	82.0 [81.0, 83.0]	82.0 [81.0, 84.0]	0.316
Body mass index, kg/m^2	25.15 (3.37)	24.97 (3.17)	25.21 (3.44)	0.423
Medical history				
Prior Myocardial infarction, n (%)	81 (12.3)	17 (9.9)	64 (13.2)	0.313
Prior revascularization, n (%)	192 (29.3)	50 (29.1)	142 (29.3)	1.000
Prior PCI, n (%)	176 (26.8)	48 (27.9)	128 (26.4)	0.786
Prior CABG, n (%)	23 (3.5)	5 (2.9)	18 (3.7)	0.798
Dyslipidemia, n (%)	335 (51.1)	89 (51.7)	246 (50.8)	0.906
Hypertension, n (%)	526 (80.2)	133 (77.3)	393 (81.2)	0.326
Diabetes mellitus, n (%)	268 (40.9)	70 (40.7)	198 (40.9)	1.000
Previous stroke, n (%)	154 (23.5)	36 (20.9)	118 (24.4)	0.417
Malignancies, n (%)	8 (1.2)	3 (1.7)	5 (1.0)	0.438
Recent cigarette smoking, n (%)	84 (12.8)	22 (12.8)	62 (12.8)	1.000
Long-term oral anticoagulation, n (%)	10 (1.5)	1 (0.6)	9 (1.9)	0.416
Barthel Index, median [IQR]	85 [60, 90]	85.00 [65.00, 91.25]	80.00 [60.00, 90.00]	0.665
Findings on admission				
SBP, mmHg, median [IQR]	135 [123, 149]	139 [126, 151]	134 [121, 148]	0.097
SBP<100mmHg (n,%)	18 (2.7)	11 (6.4)	7 (1.4)	0.002*
Heart rate, bpm, median [IQR]	69 [62, 77]	68 [62, 76]	69 [62, 78]	0.437
Heart rate >100 bpm, n (%)	16 (2.4)	5 (2.9)	11 (2.3)	0.861
Killip class (n,%)				
I	229 (34.9)	85 (49.4)	144 (29.8)	<0.001*
II	340 (51.8)	72 (41.9)	268 (55.4)	
III	73 (11.1)	11 (6.4)	62 (12.8)	
IV	14 (2.1)	4 (2.3)	10 (2.1)	
Elevated troponin levels, n (%)	178 (27.1)	50 (29.1)	128 (26.4)	0.572
Hemoglobin, g/L (mean (SD))	125.4 (14.2)	126.0 (14.8)	125.2 (14.0)	0.537
Hemoglobin <110 g/L, n (%)	86 (13.1)	19 (11.0)	67 (13.8)	0.423
Platelet, 10^9/L, median [IQR]	198 [163, 237]	196 [163, 232]	198 [163, 237]	0.842
Thrombocytopenia, n (%)	7 (1.1)	1 (0.6)	6 (1.2)	0.772
Triglyceride, mmol/L, median [IQR]	1.19 [0.87, 1.66]	1.12 [0.87,1.58]	1.21 [0.88, 1.69]	0.275
LDL-c, mmol/L, median [IQR]	2.21 [1.75, 2.64]	2.21 [1.77, 2.57]	2.22 [1.75, 2.69]	0.568
NT-pro BNP at Admission, pg/ml, median [IQR]	528.0 [242.8, 1570.3]	452.2 [228.0, 946.3]	572.0 [245.0, 1734.0]	0.078
Log10 (NT-pro BNP at admission), median [IQR]	2.72 [2.39,3.20]	2.66 [2.36,2.98]	2.76 [2.39, 3.24]	0.078
PTA, %, median [IQR]	94.71 [86.33, 103.90]	94.69 [86.47,102.73]	94.71 [86.10, 104.48]	0.849
Uric acid, mmol/L, median [IQR]	338.0 [286.0, 402.0]	336.0 [293.5, 384.0]	338.00 [285.0, 415.0]	0.367
Hyperuricemia, n (%)	207 (31.6)	49 (28.5)	158 (32.6)	0.362
Creatinine, umol/L, median [IQR]	85.1 [71.9, 100.0]	85.9 [71.1, 99.1]	84.9 [72.2, 100.7]	0.488
eGFR, mL/min/1.73m^2, median [IQR]	55.83 [46.46, 65.40]	56.82 [46.93, 65.22]	55.41 [46.39, 65.49]	0.185
Severe renal insufficiency, n (%)	19 (2.9)	3 (1.7)	16 (3.3)	0.428
GRACE risk score, median [IQR]	164 [146, 184]	160 [138, 181]	165 [149, 186]	0.006*
>140, n (%)	543 (82.8)	121 (70.3)	422 (87.2)	<0.001*
108-140, n (%)	112 (17.1)	51 (29.7)	61 (12.6)	
<108, n (%)	1 (0.2)	0 (0.0)	1 (0.2)	
Invasive treatment				
Coronary angiography result, n (%)				
Normal	2 (0.3)	2 (1.2)	0 (0.0)	0.143
One-vessel disease	71 (10.8)	16 (9.3)	55 (11.4)	
Two-vessel disease	84 (12.8)	24 (14.0)	60 (12.4)	
Three-vessel /LM disease	499 (76.1)	130 (75.6)	369 (76.2)	
Revascularization, n (%)				
CABG	21 (3.2)	5 (2.9)	16 (3.3)	0.174
No revascularization	255 (38.9)	57 (33.1)	198 (40.9)	
PCI	380 (57.9)	110 (64.0)	270 (55.8)	
Number of stent implantation				
0†	30 (7.9)	6 (5.5)	24 (8.9)	0.435
1	162 (42.6)	48 (43.6)	114 (42.2)	
2	126 (33.2)	34 (30.9)	92 (34.1)	
≥3	62 (16.3)	22 (20.0)	40 (14.8)	
Unsuccessful PCI procedural	5 (0.8)	3 (1.7)	2 (0.4)	0.116
Pharmacological treatment				
Antiplatelet therapy, n (%)				
Single-APT	234 (35.7)	53 (30.8)	181 (37.4)	0.253
Dual-APT	412 (62.8)	117 (68.0)	295 (61.0)	
None	10 (1.5)	2 (1.2)	8 (1.7)	
ACEI/ARB, n (%)	372 (56.7)	95 (55.2)	277 (57.2)	0.715
β-blocker, n (%)	444 (67.7)	117 (68.0)	327 (67.6)	0.987
Statin, n (%)	585 (89.2)	157 (91.3)	428 (88.4)	0.373
Oral anti-coagulation drug, n (%)	10 (1.5)	1 (0.6)	9 (1.9)	0.468
Follow-up				
Follow-up years, median [IQR]	3.02 [1.22, 4.10]	3.03 [1.90, 4.09]	3.02 [1.11, 4.10]	0.462
Death during follow-up, n (%)	115 (17.5)	28 (16.3)	87 (18.0)	0.700
Death per 100 patient-years	5.8	5.3	6	0.500

†, including 5 unsuccessful PCI procedures and 25 balloon angioplasties; *, P<0.05. ACEI, angiotensin-converting-enzyme inhibitor; APT, anti-platelet therapy; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; IQR, interquartile range; LDL-c, Low-density lipoprotein cholesterol; LM, left main coronary artery; NT-pro BNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PTA, prothrombin activity; SBP, systolic blood pressure.

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Table S3 Associations between timing of invasive and long-term mortality for NSTEMI patients ≥80 years old who underwent invasive intervention

Model	Hazard ratio	95% CI	P value
Unadjusted	1.137	0.74-1.75	0.555
Model 1	0.986	0.64-1.52	0.95
Model 2	1.014	0.66-1.57	0.949
Model 3	1.001	0.64-1.57	0.995
Model 4	0.979	0.62-1.54	0.926
Model 5	0.92	0.57-1.47	0.725
IPW	0.89	0.60-1.33	0.569

Model 1 adjusted for GRACE risk score (age, systolic blood pressure, heart rate, Killip class, creatinine, ST-segment deviation and elevated troponin). Model 2 = Model 1 plus gender, body mass index, dyslipidemia hypertension, diabetes mellitus, LDL-c at admission and recent cigarette smoking. Model 3 =Model 2 plus hemoglobin <11 g/dl, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies and prothrombin activity. Model 4 = Model 3 plus antiplatelet drug, ACEI/ARBs, β-blockers and statins use. Model 5 = Model 4 plus prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia, Barthel index and coronary angiography result. Variates in model 5 were used for IPW adjustment. CI, confidence interval; IPW, Inverse probability weighting; PSM, propensity score matching.

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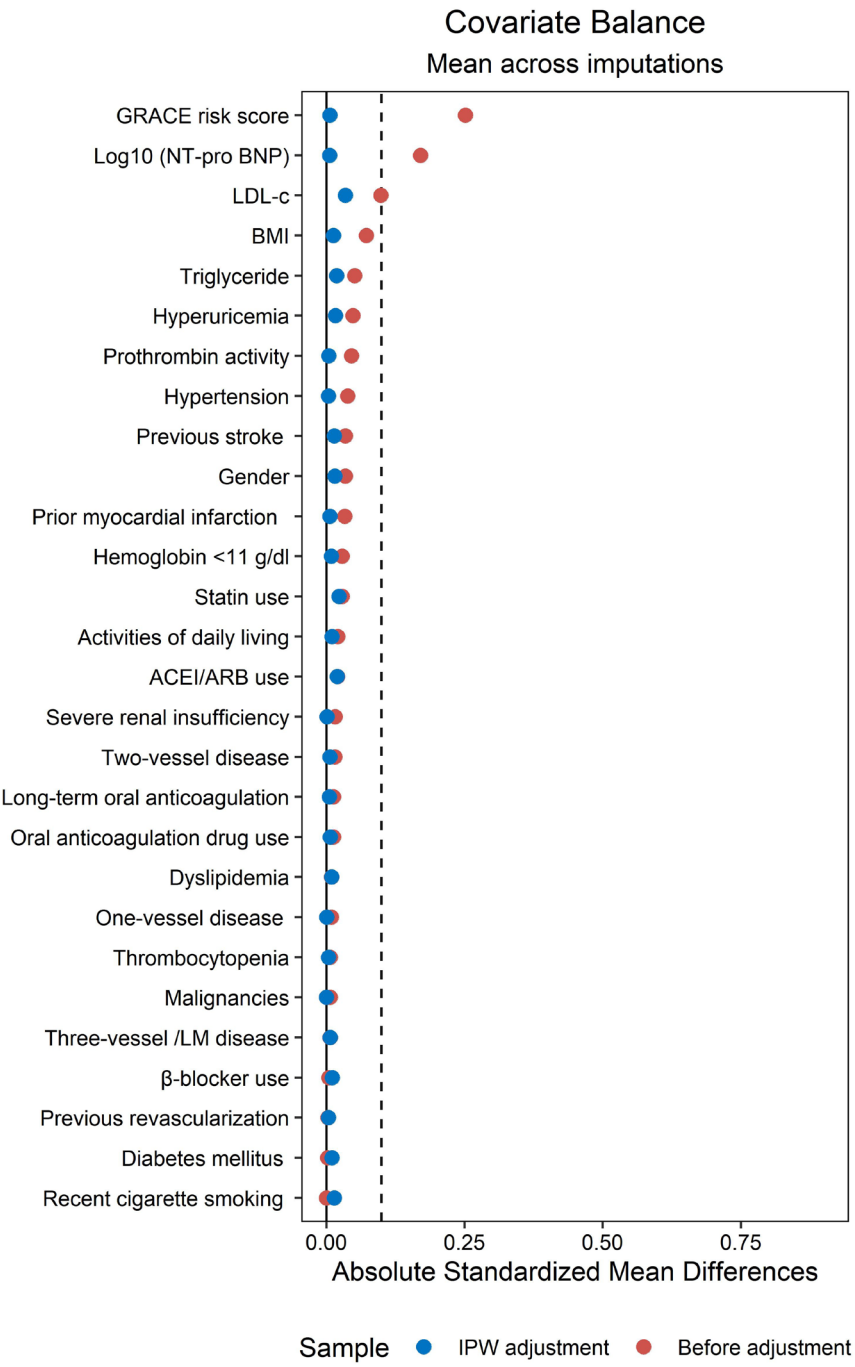

Figure S4 ASMD across covariates before and after IPW between timely and delayed invasive groups. The ASMD was present as mean across imputations in each covariate and ASMD ≤0.1 indicated a good balance between the two groups. ASMD, absolute standardized mean differences; IPW, inverse probability weighting; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LDL-c, low-density lipoprotein cholesterol; LM, left main.

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Table S4 Baseline characters, coronary angiography, treatment and follow-up in NSTE-ACS patients ≥80 years who underwent coronary arteriography and showed at least one-vessel lesions, stratified by further procedures.

	Overall (n=654)	CAG only (n=258)	Revascularization (n=396)	P
Female, n (%)	335 (51.2)	143 (55.4)	192 (48.5)	0.098
Age, years, median [IQR]	82.00 [81.00, 84.00]	82.00 [81.00, 83.00]	82.00 [81.00, 84.00]	0.498
Body mass index, kg/m^2	24.95 [22.87, 27.34]	25.30 [23.04, 27.68]	24.77 [22.86, 26.99]	0.019*
Medical history				
Prior myocardial infarction, n (%)	81 (12.4)	30 (11.6)	51 (12.9)	0.724
Prior revascularization, n (%)	192 (29.4)	90 (34.9)	102 (25.8)	0.016*
Prior PCI, n (%)	176 (26.9)	83 (32.2)	93 (23.5)	0.018*
Prior CABG, n (%)	23 (3.5)	9 (3.5)	14 (3.5)	1.000
Dyslipidemia, n (%)	333 (50.9)	139 (53.9)	194 (49.0)	0.254
Hypertension, n (%)	524 (80.1)	220 (85.3)	304 (76.8)	0.010*
Diabetes mellitus, n (%)	267 (40.8)	101 (39.1)	166 (41.9)	0.533
Previous stroke, n (%)	152 (23.2)	64 (24.8)	88 (22.2)	0.503
Malignancies, n (%)	8 (1.2)	3 (1.2)	5 (1.3)	1.000
Recent cigarette smoking, n (%)	84 (12.8)	29 (11.2)	55 (13.9)	0.384
Long-term oral anticoagulation, n (%)	10 (1.5)	6 (2.3)	4 (1.0)	0.311
Barthel index, median [IQR]	85.00 [60.00,90.00]	85.00 [75.00, 90.00]	80.00 [53.75, 90.00]	<0.001*
Findings on admission				
SBP, mmHg, median [IQR]	135.00 [122.25, 148.00]	134.50 [121.25, 148.00]	135.00 [123.00, 150.00]	0.754
SBP<100 mmHg, n (%)	18 (2.8)	4 (1.6)	14 (3.5)	0.149
Heart rate, bpm, median [IQR]	69.00 [62.00, 77.00]	68.50 [62.00, 78.00]	69.00 [62.75, 77.00]	0.474
Heart rate >100 bpm, n (%)	16 (2.4)	6 (2.3)	10 (2.5)	1.000
Killip class, n (%)				
I	228 (34.9)	73 (28.3)	155 (39.1)	0.022*
II	339 (51.8)	150 (58.1)	189 (47.7)	
III	73 (11.2)	31 (12.0)	42 (10.6)	
IV	14 (2.1)	4 (1.6)	10 (2.5)	
Elevated troponin levels, n (%)	178 (27.2)	37 (14.3)	141 (35.6)	<0.001*
Hemoglobin, g/L, mean (SD)	125.5 (14.2)	125.4 (13.6)	125.5 (14.7)	0.982
Hemoglobin <110 g/L, n (%)	85 (13.0)	31 (12.0)	54 (13.6)	0.629
Platelet, 10^9/L, median [IQR]	198.00 [163.25, 237.00]	198.00 [165.00, 229.00]	197.50 [163.00, 240.00]	0.697
Thrombocytopenia, n (%)	7 (1.1)	3 (1.2)	4 (1.0)	1.000
Triglyceride, mmol/L, median [IQR]	1.19 [0.87, 1.66]	1.20 [0.87, 1.69]	1.19 [0.87, 1.60]	0.902
LDL-c, mmol/L, median [IQR]	2.21 [1.75, 2.64]	2.09 [1.67, 2.59]	2.26 [1.82, 2.70]	0.008
NT-pro BNP at admission, pg/mL, median [IQR]	527.00 [242.26, 1573.44]	390.00 [192.73, 1113.25]	657.62 [291.00, 1751.00]	<0.001*
Log10 (NT-pro BNP at admission), median [IQR]	2.72 [2.38, 3.20]	2.59 [2.28, 3.05]	2.82 [2.46, 3.24]	<0.001*
PTA, %, median [IQR]	94.70 [86.17,103.90]	94.80 [86.58, 105.30]	94.43 [86.05, 103.40]	0.245
Uric acid, mmol/L, median [IQR]	338.00 [286.00, 402.00]	331.00 [284.25, 401.00]	339.00 [288.00, 408.50]	0.745
Hyperuricemia, n (%)	206 (31.5)	81 (31.4)	125 (31.6)	1.000
Creatinine, umol/L, median [IQR]	84.95 [71.82, 100.05]	82.90 [71.20, 99.85]	85.95 [72.90, 100.60]	0.352
eGFR, mL/min/1.73 m^2, median [IQR]	55.87 [46.49, 65.46]	55.57 [46.93, 65.81]	55.93 [46.46, 65.24]	0.977
Severe renal insufficiency, n (%)	19 (2.9)	6 (2.3)	13 (3.3)	0.635
GRACE risk score, median [IQR]	164 [146, 184]	160 [138, 181]	165 [149, 186]	0.006*
>140, n (%)	542 (82.9)	208 (80.6)	334 (84.3)	0.306
108-140, n (%)	111 (17.0)	50 (19.4)	61 (15.4)	
<108, n (%)	1 (0.2)	0 (0.0)	1 (0.3)	
Invasive treatment				
Coronary angiography result, n (%)				
One-vessel disease	71 (10.9)	59 (22.9)	12 (3.0)	<0.001*
Two-vessel disease	84 (12.8)	57 (22.1)	27 (6.8)	
Three-vessel /LM disease	499 (76.3)	142 (55.0)	357 (90.2)	
Revascularization, n (%)				
CABG	21 (3.2)	0 (0.0)	21 (5.3)	NA
PCI-successful	375 (57.3)	0 (0.0)	375 (94.7)	
PCI-unsuccessful	5 (0.8)	5 (1.9)	0 (0.0)	
No revascularization	253 (38.7)	253 (98.1)	0 (0.0)	
Pharmacological treatment				
Antiplatelet therapy, n (%)				<0.001*
Single-APT	233 (35.6)	203 (78.7)	30 (7.6)	
Dual-APT	412 (63.0)	48 (18.6)	364 (91.9)	
None	9 (1.4)	7 (2.7)	2 (0.5)	0.116
ACEI/ARB, n (%)	371 (56.7)	144 (55.8)	227 (57.3)	0.764
β-blocker, n (%)	442 (67.6)	170 (65.9)	272 (68.7)	0.509
Statin, n (%)	584 (89.3)	237 (91.9)	347 (87.6)	0.114
Oral anti-coagulation drug, n (%)	10 (1.5)	7 (2.7)	3 (0.8)	0.096
Follow-up				
Follow-up years, median [IQR]	3.02 [1.22, 4.10]	3.04 [1.81, 4.24]	2.98 [1.12, 4.09]	0.153
Death during follow-up, n (%)	115 (17.6)	42 (16.3)	73 (18.4)	0.547
Death per 100 patient-years	5.8	5.2	6.3	0.3

*, P<0.05. ACEI, angiotensin-converting-enzyme inhibitor; APT, anti-platelet therapy; ARB, angiotensin II receptor blocker; CAG, coronary angiography; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; GRACE, global registry of acute coronary events; IQR, interquartile range; LDL-c, Low-density lipoprotein cholesterol; LM, left main coronary artery; NT-pro BNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PTA, prothrombin activity; SBP, systolic blood pressure.

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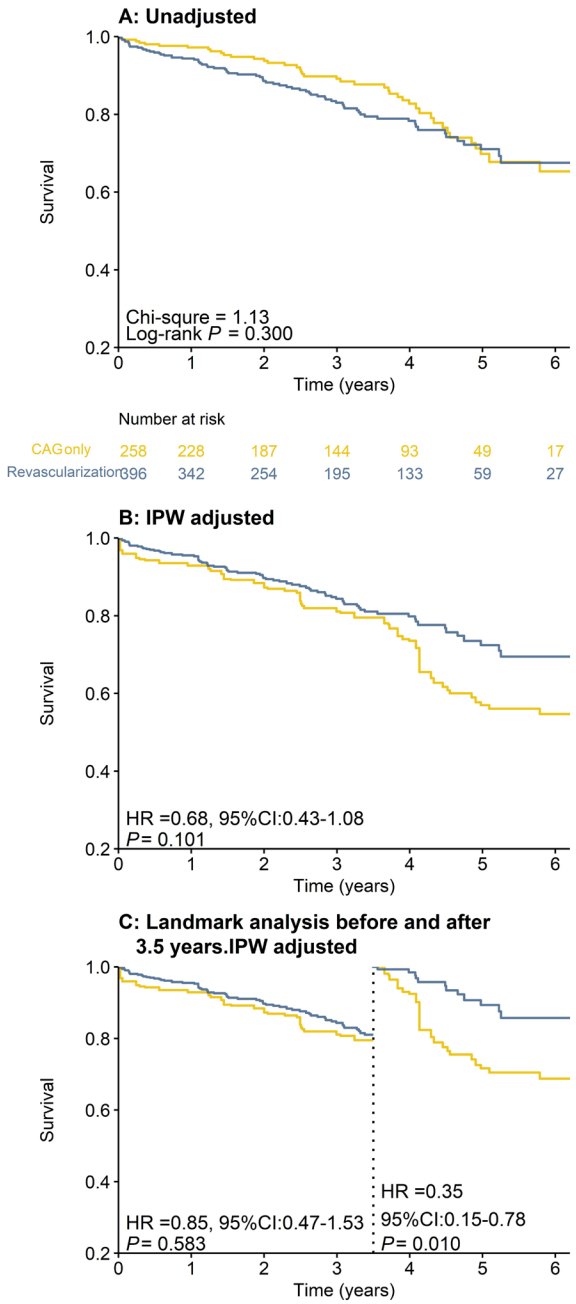

Figure S5 A comparison of unadjusted and adjusted survival curve of patients ≥80 years who underwent coronary arteriography and showed at least one-vessel lesion stratified by following procedure. (A)Unadjusted Kaplan-Meier curve. (B) Inverse probability weighted Kaplan-Meier curve. (C) Landmark analysis discriminating between events occurring before and after 3.5 year of follow-up. Adjusted for GRACE risk score, gender, body mass index, dyslipidemia, hypertension, diabetes mellitus, LDL-c at admission, recent cigarette smoking, hemoglobin <110 g/L, long-term oral anticoagulation, severe or end-stage chronic kidney disease, thrombocytopenia, previous stroke, active malignancies, prothrombin activity, antiplatelet drug, ACEI/ARBs, β-blockers, statins, prior myocardial infarction, prior coronary revascularization, NT-pro BNP at admission, triglyceride, hyperuricemia, Barthel index and coronary angiography result. The weight for each patient was calculated though the average propensity score in all imputations. In general, patients who had elevated troponin, higher NT-pro BNP levels, higher GRACE risk scores, and more complex coronary artery lesions were more likely to require further revascularization (Table S4). The unadjusted Kaplan–Meier curve showed no significant difference in mortality during the follow-up period. After adjusting covariates and landmark analysis, the revascularization group showed a lower mortality rate after 3.5 years (Figure S5).

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