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Original article

Age and clinical outcomes in patients presenting with acute coronary syndromes☆

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A B S T R A C T

Context: Elderly patients have more cardiovascular risk factors and a greater burden of ischemic disease than younger patients.
Aims: To examine the impact of age on clinical presentation and outcomes in patients presenting with acute coronary syndrome (ACS).
Methods and material: Collected data from the 2nd Gulf Registry of Acute Coronary Events (Gulf RACE-2), which is a prospective multicenter study from six adjacent Arab Middle Eastern Gulf countries. Patients were divided into 3 groups according to their age: ≤50 years, 51–70 years and >70 years and their clinical characteristics and outcomes were analyzed. Mortality was assessed at one and 12 months.
Statistical analysis used: One-way ANOVA test for continuous variables, Pearson chi-square (X^2) test for categorical variables and multivariate logistic regression analysis for predictors were performed.
Results: Among 7930 consecutive ACS patients; 2755 (35%) were ≤50 years, 4110 (52%) were 51–70 years and 1065 (13%) >70 years old. The proportion of women increased with increasing age (13% among patients ≤50 years to 31% among patients > 70 years). The risk factor pattern varied with age; younger patients were more often obese, smokers and had a positive family history of CAD, whereas older patients more likely to have diabetes mellitus, hypertension, and dyslipidemia. Advancing age was associated with under-treatment evidence-based therapies. Multivariate logistic regression analysis after adjusting for relevant covariates showed that old age was independent predictors for re-ischemia (OR 1.29; 95% CI 1.03–1.60), heart failure (OR 2.8; 95% CI 2.17–3.52) and major bleeding (OR 4.02; 95% CI 1.37–11.77) and in-hospital mortality (age 51–70: OR 2.67; 95% CI 1.86–3.85, and age >70: OR 4.71; 95% CI 3.11–7.14).
Conclusion: Despite being higher risk group, elderly are less likely to receive evidence-based therapies and had worse outcomes. Guidelines adherence is highly recommended in elderly.

1. Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide, particularly in elderly patients.[1] Previous studies addressed the need to define the impact of age across the spectrum of acute coronary syndromes (ACS).[2] According to the American Heart Association (AHA) statistics, 83% of CAD deaths were in patients' ≥65 years of age.[3] The expected mortality rates from ACS

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increase by an odds ratio of 1.7 for each 10-year increment over age 65 years.[4] Elderly patients have more cardiovascular risk factors and a greater burden of ischemic disease than younger patients and therefore, they derive a greater absolute benefit from evidence-based therapies including revascularization. However, they are also more likely to experience procedural complications, owing to age-related physiological changes, frailty, and comorbidities.

Although the American College of Cardiology/American Heart Association (ACC/AHA) guidelines clearly state that a patient's age should not influence decisions about cardiac care, elderly patients are much less likely to receive evidence-based therapies compared to their younger counterparts.[5,6] Despite increasing prevalence and burden of CAD, the elderly are often underrepresented in many cardiovascular clinical trials, and the proportion of the elderly included in clinical registries remains low.[7] Therefore, relatively little is known about the management and outcomes of ACS in the elderly. Furthermore, the vast majority of studies was conducted in the developed world and mainly included Caucasian patients. Data on the outcome of elderly ACS patients among other ethnicities are scarce. In the current study we evaluate the impact of age on clinical presentation and short- and long-term clinical outcomes in the Arab Middle Eastern population.

2. Materials and methods

Data were collected from a prospective, multicenter study of the 2nd Gulf Registry of Acute Coronary Events (Gulf RACE-2) between October 2008 and June 2009. We recruited 7930 consecutive ACS patients from six adjacent Middle Eastern Gulf countries (Bahrain, Kingdom of Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen). Patients diagnosed with ACS, including unstable angina (UA) and non-ST- and ST-elevation myocardial infarction (NSTEMI and STEMI, respectively), were enrolled from 65 hospitals. On-site cardiac catheterization laboratory was available in 43% of the participating hospitals. There were no exclusion criteria, and thus, all the prospective patients with ACS were actually enrolled. The study received ethics approval from the institutional review boards in all participating countries. Diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology (ACC) clinical data standards.[8] A Case Report Form (CRF) for each patient with suspected ACS was filled out upon hospital admission by assigned physicians and/or research assistants using standard definitions and was completed throughout the patient's hospital stay. All CRFs were verified by a cardiologist and then sent online to the principal coordinating center, where the forms were further checked for mistakes before submission for final analysis.[9]

2.1. Statistical analysis

Data were presented as proportions or mean ± standard deviation (SD) as appropriate. Baseline demographic characteristics, past medical history, clinical presentation, medical therapy, cardiac procedures and clinical outcomes were compared between the three age groups (≤50, 51–70, and >70 years).[10] Statistical analyses were conducted using one-way ANOVA test for continuous variables and Pearson chi-square (X^2) test for categorical variables. The clinical hospital outcomes included recurrent ischemia, myocardial reinfarction, heart failure (HF), shock, stroke, major bleedings and mortality. Mortality was assessed also at 1 month and 12 months after discharge. In order to assess the independent association of age with clinical outcomes, a multivariate logistic regression analysis was performed. We included important variables in the analysis that predicted the outcomes of interest. These variables included age, sex, diabetes mellitus, hypertension, dyslipidemia, current smoking, renal failure, and medications. All *P*-values were the results of two-tailed tests and values <0.05 were considered significant. Data analysis was carried out using the Statistical Package for Social Sciences Version 18 (SPSS Inc. USA).

3. Results

3.1. Baseline patient characteristics

The clinical characteristics of 7930 patients are presented in Table 1 according to age group. The patients' ages ranged from 21 to 105 years with a mean age of 57 ± 13 years; 2755 (35%) were ≤50 years old, 4110 (52%) were 51–70 years old and 1065 (13%) >70 years old. Women were increasingly represented with increasing age comprising 13% of patients ≤50 years and reaching 31% of patients >70 years ($P = 0.001$). In all age groups, ischemic chest pain was the most frequent symptom at hospital admission. Elderly patients were more likely to have diabetes mellitus, hypertension and dyslipidemia ($P = 0.001$). Current smoking and family history of CAD were more prevalent in patients ≤50 years and were least in those >70 years ($P = 0.001$). A higher diastolic blood pressure and body mass index were prevalent in patients ≤70 years ($P = 0.001$). Also, a higher total cholesterol, serum triglyceride and low-density lipoprotein were more prevalent in patients ≤70 years ($P = 0.001$). Conversely, elderly patients were more likely to have comorbidities such as renal failure, prior myocardial infarction (MI), prior coronary artery bypass graft surgery (CABG), prior stroke and prior peripheral arterial disease (PAD) ($P = 0.001$). Fasting blood sugar was higher in patients ≤70 years ($P = 0.001$), but there was no difference in hemoglobin A1c between elderly patients and patients ≤50 years ($P = 0.09$).

3.2. Clinical presentation

Elderly patients presented less frequently with typical ischemic chest pain in comparison to the other age groups ($P = 0.001$). Atypical chest pain was more prevalent (6.6%) in patients >70 years old than in other age groups ($P = 0.001$). Presentation with dyspnea was less frequent in the youngest age group when compared to the elderly (3.3% and 14% respectively). The proportion of patients with Killip class >1 increased with age ($P = 0.001$). However, the interval from chest pain onset to emergency department arrival was not influenced by age ($P = 0.49$).

3.3. Acute coronary artery syndrome type

Of the 7930 patients, 3613 (46%) presented with STEMI, 2386 (30%) with NSTEMI and 1931 (24%) with UA. STEMI decreased with increasing age from 55% of patients aged <50 years to 32% of patients >70 years ($P = 0.001$). Conversely, NSTEMI increased with increasing age from 24% of patients aged ≤50 years to 42% of patients >70 years ($P = 0.001$). Unstable angina (UA) was lesser in frequency (20%) in patients ≤50 years of age than in other age groups (25–27%; $P = 0.001$).

3.4. Management

The proportion of patients who received in-hospital management in a specific age group is shown in Table 2. The use of aspirin, clopidogrel, beta-blockers and statins was more prevalent in patients ≤70 years of age ($P = 0.001$ for all). The use of angiotensin converting enzyme (ACE) inhibitors/angiotensinogen receptor blockers (ARBs) was similar among age groups ($P = 0.08$). Elderly patients with STEMI were less likely (28%) to receive thrombolytic therapy than in other age groups (47%–61%, $P = 0.001$). Also, they

Table 1
Baseline demographic and clinical characteristics.

Variables	≤50 Years	51–70 Years	>70 Years	*P*-value
Number (%)	2755 (35%)	4110 (52%)	1065 (13%)	
Sex (females)	12.5	24.7	30.8	0.001
Diabetes mellitus	30.9	44.9	45.6	0.001
Hypertension	34	53.8	59.7	0.001
Dyslipidemia	29.9	41	42.8	0.001
Current smoker	67.3	48.1	33.7	0.001
Renal failure	1.3	4.5	9.5	0.001
Family history of CAD	13.4	11.1	8.6	0.001
Prior MI	14.1	21.9	26.6	0.001
Prior PCI	6.5	11	9.5	0.001
Prior CABG	1.5	5.1	7.9	0.001
Prior stroke	1.7	4.8	9.3	0.001
Prior PAD	0.8	2.1	3.7	0.001
Heart rate (beats/min) (mean ± SD)	83.6 ± 18	84.8 ± 20.9	85.6 ± 22	0.001
Systolic blood pressure (mmHg) (mean ± SD)	132.9 ± 26	137 ± 30	136 ± 31	0.001
Diastolic blood pressure (mmHg) (mean ± SD)	82.7 ± 17.5	81.2 ± 17.8	77.9 ± 18	0.001
Body mass index (Kg/m^2) (mean ± S.D)	27 ± 5	27.2 ± 5.5	26 ± 5.4	0.001
Fasting blood sugar (mmol/l) (mean ± S.D)	7.2 ± 3.3	7.5 ± 3.2	7.1 ± 2.9	0.001
Total cholesterol (mmol/l) (mean ± S.D)	5.0 ± 1.3	4.9 ± 1.6	4.7 ± 2.1	0.001
Serum triglyceride (mmol/l) (mean ± S.D)	2.0 ± 1.3	1.8 ± 1.05	1.5 ± 0.8	0.001
Low-Density Lipoprotein (mmol/l) (mean ± S.D)	3.3 ± 1.2	3.1 ± 1.4	2.8 ± 1.2	0.001
High-Density Lipoprotein (mmol/l) (mean ± S.D)	1.01 ± 0.5	1.1 ± 0.5	1.1 ± 0.4	0.001
Troponin T (mean ± S.D)	1.21 ± 0.4	1.3 ± 0.44	1.24 ± 0.42	0.001
Hemoglobin A1c (mean ± S.D)	7.6 ± 2.4	7.8 ± 2.4	7.5 ± 2.2	0.09
Killip class >1	14.3	24.9	62.1	0.001
Symptom >12 h	58.3	59	54.9	0.49
Ischemic chest pain	90.2	82.9	73.0	0.001
Atypical chest pain	4.1	5.3	6.6	0.001
Dyspnea	3.3	7.7	14.1	0.001
ST-elevation MI	55.4	40.7	31.6	0.001
NST-elevation MI	23.8	31.3	41.7	0.001
Unstable angina	20.3	26.9	25.1	0.001

CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, PAD = peripheral arterial disease, NST = non-ST.

were less likely to receive glycoprotein (GP) inhibitors and heparin. On discharge, elderly patients >70 years old were less likely to be treated by aspirin (89% vs. 95%), clopidogrel (58% vs. 76%), beta-blockers (72% vs. 83%) and statins (87% vs. 94%) than those ≤50 years ($P = 0.001$ for all). The use of ACE inhibitors/ARBs was not significantly influenced by age ($P = 0.24$).

Elderly patients were less likely to have coronary angiography (27%) than in other age groups (33–35%, $P = 0.001$). Single-vessel

Table 2
Medical therapy, cardiac procedures and interventions.

Variables	≤50 Years	51–70 Years	>70 Years	*P*-value
1st 24 h therapy in %				
Aspirin	98.8	98.3	97.3	0.009
Clopidogrel	82.8	74	67.2	0.001
Beta-blockers	78.1	73.6	67.4	0.001
ACE inhibitors/ARBs	73.9	78.3	75.7	0.08
Statins	96.3	94.4	92.4	0.001
Thrombolytic therapy	60.5	46.9	27.7	0.001
GP inhibitors	7.4	6.6	4.7	0.013
Heparin	14.6	12.5	11.5	0.004
LMWH	41	38	39	0.04
Coronary angiography %	34.7	32.5	26.5	0.001
1-vessel CAD	12.3	8.6	6.4	0.001
2-vessel CAD	8.3	8.4	4.8	0.001
3-vessel CAD	7.8	10.4	12.0	0.001
PCI %	17	14.1	11	0.001
CABG %	2.3	3.2	3.7	0.001
Echocardiogram %	77.8	75.6	76.3	0.12
Mild LV dysfunction (LVEF 40–50%)	42.6	40.7	36.8	0.001
Moderate LV dysfunction (LVEF 30–39%)	15.5	18.6	21.9	0.001
Severe LV dysfunction (LVEF 30%)	6	8.5	14.6	0.001
Discharge medications %				
Aspirin	95.4	92.2	88.6	0.001
Clopidogrel	75.7	65.1	58.7	0.001
Beta-blockers	82.9	78.6	72.2	0.001
ACE inhibitors/ARBs	77.6	78.3	75.9	0.24
Statins	93.9	90.7	86.8	0.001

Table 3
In-hospital and long-term outcomes.

Variables (%)	≤50 Years	51–70 Years	>70 Years	*P*-value
Re-ischemia	13.9	16	17.5	0.007
Re-infarction	1.9	2.1	3.2	0.04
Congestive heart failure	7.4	14.4	23.3	0.001
Cardiogenic shock	3.8	6	10	0.001
Stroke	0.4	0.8	1	0.05
Major bleeding	0.3	0.6	1.3	0.001
In-hospital mortality	2	5	10	0.001
1-month mortality	4	9	15	0.001
12-month mortality	6	13.5	25	0.001

disease was more common in patients ≤50 years old, while three-vessel disease was more prevalent with increasing age ($P = 0.001$). Patients >70 years old were less likely to be treated by percutaneous coronary intervention (PCI) (11%) than in other age groups (14%–17%, $P = 0.001$) and CABG increased from 2% among patients ≤50 years to 4% in patients >70 years ($P = 0.001$). Older patients had significantly lower left ventricular ejection fraction (LVEF) than younger patients.

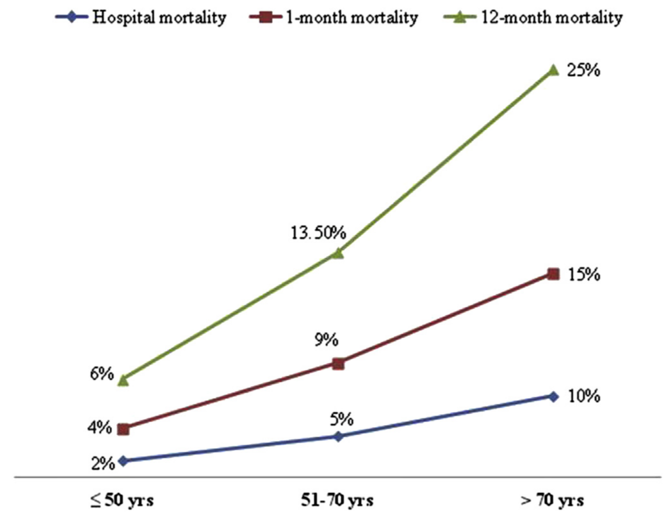

Fig. 1. Hospital, 1-month and 12-month mortality in patients presenting with acute coronary syndrome according to age groups.

3.5. Clinical outcomes

Elderly patients had more unfavorable hospital outcomes compared with younger patients in terms of myocardial re-ischemia, heart failure, cardiogenic shock, stroke, major bleeding and mortality when compared to patients ≤50 years (Tables 3 and 4). Multivariate logistic regression analysis after adjusting for relevant covariates showed that old age was independent predictors for re-ischemia (OR 1.29; 95% CI 1.03–1.60), heart failure (OR 2.8; 95% CI 2.17–3.52) and major bleeding (OR 4.02; 95% CI 1.37–11.77).

One- and twelve-month mortality rate was higher in elderly ($P = 0.001$ for all) (Fig. 1). Age >50 was independent predictor for in-hospital mortality (OR 2.67; 95% CI 1.86–3.85, for age 51–70 and OR 4.71; 95% CI 3.11–7.14, for age >70).

4. Discussion

The current study demonstrates the paradox of under-treatment of older higher risk ACS Middle Eastern patients with evidence-based therapies. Older patients had higher risk of adverse hospital outcomes, short- and long-term mortality rates when compared to younger patients.

Patients in the current registry (Gulf RACE-2), with a mean age of 57 years were of comparable age to those in the CREATE (Treatment and outcomes of acute coronary syndromes in India) registry,[10] and 6 years younger than patients in the Euro Heart Surveys of ACS.[11,12] This difference in age at presentation may be due to the higher prevalence of CAD risk factors in our study. As in a previous study,[2] the proportion of women increased with increasing age and the risk factor pattern also varied with age. The most prevalent CAD risk factors in the younger patients were smoking; higher body mass index and a higher prevalence of positive family history of CAD, whereas history of diabetes mellitus, hypertension, dyslipidemia, prior cardiovascular disease and prior cerebrovascular events were more often seen in elderly patients. This variation in risk factor patterns in young and elderly patients highlights the urgent need for a real effort and international awareness of primary and secondary prevention of CAD.

4.1. Clinical presentation and ACS type

Elderly ACS patients were more likely to present with atypical chest pain than younger patients putting them at increased risk for

Table 4
Multivariate Logistic regression for in-hospital, 1- and 12-month mortality.

Variable	In-hospital mortality		1-Month mortality		12-Month mortality	
	OR	95% C.I	OR	95% C.I	OR	95% C.I
Gender male	0.70	0.51–0.95	0.75	0.58–0.96	0.84	0.67–1.04
Diabetes mellitus	1.28	0.95–1.73	1.17	0.92–1.49	1.29	1.05–1.59
Hypertension	1.06	0.80–1.39	0.98	0.79–1.22	1.05	0.87–1.28
Dyslipidemia	0.60	0.43–0.79	0.74	0.58–0.93	0.85	0.69–1.04
Renal failure	1.55	0.95–2.53	1.55	1.03–2.31	1.49	1.05–2.12
Smoking	0.92	0.70–1.24	1.06	0.84–1.34	0.90	0.73–1.10
Aspirin	0.62	0.34–1.15	0.71	0.41–1.25	0.77	0.45–1.33
Clopidogrel	1.34	1.0–1.79	1.21	0.95–1.53	1.00	0.82–1.23
β-Blocker	0.26	0.20–0.34	0.34	0.28–0.41	0.44	0.37–0.53
ACE inhibitor	0.29	0.22–0.37	0.51	0.41–0.63	0.61	0.50–0.75
Statin	0.43	0.30–0.62	0.52	0.38–0.72	0.56	0.41–0.76
PCI	0.51	0.30–0.86	0.54	0.36–0.79	0.53	0.38–0.74
Age group[a]						
51–70 Years	2.67	1.86–3.85	2.31	1.75–3.03	2.16	1.70–2.85
>70 Years	4.71	3.11–7.14	3.74	2.71–5.17	4.10	3.10–5.42

CI = confidence interval, OR = odd ratio, PCI = percutaneous coronary intervention.
[a] The reference group is age ≤50 years.

misdiagnosis. Previous studies[13–19] demonstrated that between 0.4% and 10% of patients who have acute MI were incorrectly discharged from the emergency department. Moreover, four subgroups of patients were at greater risk for misdiagnosis, including the very young and very old patients, women, as well as diabetics. Because of atypical presentation, a high index of suspicion for ACS is advisable in the elderly.

The presence of heart failure increased significantly with increasing age as shown in other registries.[7,18,20] Similar to previous studies[2,19] our study demonstrated that elderly with MI were more likely to have NSTEMI and the proportion of STEMI decreased with increasing age. Also, Mehta et al, demonstrated that STEMI accounted only for ≤30% of all elderly patients admitted with ACS.[21]

4.2. Hospital management and outcomes

Age is the most important determinant of ACS outcomes.[22] Although elderly patients were more likely to have worse clinical profile; they were less likely to receive guideline-recommended medical and interventional therapies. Previous studies[13,19,23–25] reported similar age-dependent results. The ACC/AHA guidelines (2004) on the management of STEMI and the 2007 ACC/AHA focused update did not recommend an age limitation to fibrinolytic therapy, and prompt reperfusion for patients with STEMI is a Class I guideline recommendation and has been shown to reduce mortality.[6] In the present study, elderly patients with STEMI were less likely to receive thrombolysis than younger patients. Only, 28% of STEMI patients >70 years of age received thrombolytic therapy. In TIMI III registry,[26] elderly patients were shown to receive less aggressive anti-ischemic therapy and were less likely to undergo coronary angiography, with fewer revascularization procedures than their younger counterparts. Although most elderly patients will benefit from thrombolysis, the risk/benefit ratio has to be evaluated on a case-by-case basis to optimize outcome. Also, in the present study, the proportion of ACS patients treated by PCI decreased significantly with age.

In CRUSADE (Can Rapid stratification of Unstable angina Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines) database[7,23] showed that although elderly patients (>90 years old) had a higher risk of bleeding from aggressive treatment, the benefit still outweighed this risk. So, advanced patient age should not be a contraindication for aggressive treatment. Lower rate of in-hospital mortality was found in those who were treated with early coronary angiography and revascularization than who were treated with a more delayed conservative approach. Consistent with previous studies[13,23] the use of evidenced-based medical therapies at hospital discharge was less often with increasing age except, the use of ACE inhibitors/ARBs was not significantly influenced by patient age. In the present study, coronary artery bypass grafting (CABG) was more prevalent in patients >70 years of age than in other age groups and this may be due to the fact that they more likely presented with more severe and extensive CAD hence warranting consideration of surgical revascularization.[27] Similar findings were observed in a prior study,[19] where the rate of CABG surgery was the highest among patients aged 65–74 years.

Consistent with previous studies,[4,13,19,22] the risk of myocardial re-ischemia, reinfarction, heart failure, cardiogenic shock, major bleeding and in-hospital mortality was more prevalent in the elderly than in the other age group. Consistent with findings from GRACE (Global registry of acute coronary events),[18] the risk of 12-month mortality increased with increasing patient age. After adjustment for patient and hospital factors, the odds ratio of 12-month mortality for older age groups compared with age ≤50 was 2.16 for patients aged 51–70 years, 4.10 for those aged >70 years (Table 4).

The overall worse prognosis in the elderly is likely due to multiple factors that include increasing age itself,[2,22] greater comorbidity, extensive CAD disease, impaired left ventricular systolic function[28] and the under-use of Guideline-recommended medical and interventional therapies.[2,22,23] The magnitude of the effect of adherence to guideline-recommended therapies was illustrated in an observational study. Every 10% increase in composite adherence to ACC/AHA guideline-recommended therapies was associated with a 10% reduction of in-hospital mortality.[29]

4.3. Limitations

Our data were collected from an observational study. The fundamental limitations of observational studies cannot be eliminated because of the nonrandomized nature and unmeasured confounding factors. However, well-designed observational studies provide valid results and do not systemically overestimate the results compared with the results of randomized controlled trials.

5. Conclusions

Despite being a high-risk group, elderly patients presenting with ACS were less likely to receive guideline-recommended therapies. They had a high rate of adverse hospital outcomes and short- and long-term mortality. Guidelines' adherence and improvement in hospital care for elderly patients with ACS may potentially improve the outcomes and save a substantial number of patients.

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Conflicts of interest

All authors have none to declare.

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