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ORIGINAL ARTICLE

Social Determinants of Health and Mortality After Premature and Non-premature Acute Coronary Syndrome

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Abstract

Objective: To describe and compare the determinants of 1-year mortality after premature vs non-premature acute coronary syndrome (ACS).

Patients and Methods: Participants presenting with ACS were enrolled in a prospective registry of 29 hospitals in 4 countries, from January 22, 2012 to January 22, 2013, with 1-year of follow-up data. The primary outcome was all-cause 1-year mortality after premature ACS (men aged <55 years and women aged <65 years) and non-premature ACS (men aged ≥55 years and women aged ≥65 years). The associations between the baseline patient characteristics and 1-year mortality were analyzed in models adjusting for the Global Registry of Acute Coronary Events (GRACE) score and reported as adjusted odds ratio (aOR) (95% CI).

Results: Of the 3868 patients, 43.3% presented with premature ACS that was associated with lower 1-year mortality (5.7%) than those with non-premature ACS. In adjusted models, women experienced higher mortality than men after premature (aOR, 2.14 [1.37-3.41]) vs non-premature ACS (aOR, 1.28 [0.99-1.65]) ($P_{interaction}$=.047). Patients lacking formal education vs any education had higher mortality after both premature (aOR, 2.92 [1.87-4.61]) and non-premature ACS (aOR, 1.78 [1.36-2.34]) ($P_{interaction}$=.06). Lack of employment vs any employment was associated with approximately 3-fold higher mortality after premature and non-premature ACS ($P_{interaction}$=.72). Using stepwise logistic regression to predict 1-year mortality, a model with GRACE risk score and 4 characteristics (education, employment, body mass index [kg/m^2], and statin use within 24 hours after admission) had higher discrimination than the GRACE risk score alone (area under the curve, 0.800 vs 0.773; $P_{comparison}$=.003).

Conclusion: In this study, women, compared with men, had higher 1-year mortality after premature ACS. The social determinants of health (no formal education or employment) were strongly associated with higher 1-year mortality after premature and non-premature ACS, improved mortality prediction, and should be routinely considered in risk assessment after ACS.

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Premature myocardial infarction (MI) typically refers to MI in men aged younger than 55 years and women aged younger than 65 years, whereas non-premature MI refers to MI at older ages.[1,2] Describing the determinants of mortality after premature and non-premature MI may improve risk stratification and guide interventions for secondary cardiovascular prevention.

Premature and non-premature coronary events (MI or acute coronary syndrome [ACS]) differ by the type and magnitude of risk factors.[1,3] In studies based on North American, European, and Middle Eastern cohorts, premature MI or ACS, compared with non-premature MI or ACS, was associated with a higher prevalence of smoking, lower prevalence of hypertension and diabetes, and variable prevalence of dyslipidemia.[1] In

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comparison, there is relatively sparse information on the determinants of mortality after premature or non-premature events. The Global Registry of Acute Coronary Events (GRACE) study developed a risk score to determine short-term and long-term outcomes, such as mortality, after ACS.[4] However, the association of risk factors that are not included in the GRACE risk score (eg, social determinants of health) with mortality after ACS is unknown.

To address these knowledge gaps, we evaluated the determinants of mortality (such as social determinants of health) after premature and non-premature ACS in patients who presented with ACS events in the Gulf COAST prospective registry of 29 hospitals in 4 countries (Bahrain, Kuwait, Oman, and United Arab Emirates) and followed up for 1 year. The objective of the study was to describe and compare the determinants of mortality after ACS to inform risk prediction among patients with ACS.

PATIENTS AND METHODS

Study Design and Population

Gulf COAST is a prospective, observational registry of 4044 citizens (aged ≥18 years) presenting with ACS across 29 hospitals in Bahrain (n=631), Kuwait (n=1234), Oman (n=1488), and the United Arab Emirates (n=691).[5,6] The participants provided written informed consent and were enrolled from January 22, 2012 to January 22, 2013, with a 1-year follow-up in a clinic or by telephone. For this analysis, we excluded participants with unavailable data on mortality and/or GRACE risk score to yield a cohort of 3868 participants.

Participant Characteristics

At enrollment, trained study staff collected information on demographic and clinical characteristics using a standardized case report form. For this analysis, we categorized the variables as follows: any education (below secondary school, secondary school, any college or vocational school, graduate from college, or postgraduate degree) vs no formal education; any employment (part-time or full-time) vs lack of employment; non-governmental (private or military) or governmental health insurance; married vs not married (single, divorced, separated, or widowed); and ever-smokers vs never-smokers. Hypertension, diabetes, and dyslipidemia were defined using the American College of Cardiology and American Heart Association criteria.[6,7] A family history of premature coronary artery disease was defined as ≥1 first-degree relative with angina, MI, or sudden death without an obvious cause, before the age of 55 years.[8]

The study staff collected information on admission characteristics from the patient and/or electronic medical record, such as transportation mode, symptoms, and medications received within 24 hours after admission (aspirin, clopidogrel, prasugrel, ticagrelor, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins).

Anthropometric Measurements

At enrollment, participant's height, weight, and waist circumference (at the level of iliac crest) were measured by the study staff, as previously described. The body mass index (BMI; kg/m^2) was calculated as the weight in kilograms divided by the height in meters squared. We defined the following obesity measures: obesity by BMI (≥30.0 kg/m^2) or nonobesity (lower); obesity by waist circumference (≥94.0 cm [men] and ≥80.0 cm [women]) or nonobesity (lower) using the values for Middle Eastern populations; and obesity by waist-to-height ratio (ratio ≥0.5) or nonobesity (lower).[6]

Premature and Non-premature ACS

Premature ACS was defined as ACS in men aged <55 years or women aged < 65 years, and non-premature ACS was defined as ACS in men aged ≥55 years or women aged ≥65 years.[1,3,9]

Mortality

The all-cause 1-year mortality (primary outcome) and hospital mortality (secondary outcome) after ACS were documented by the study staff. Mortality at 1-year included hospital mortality.

Statistical Analyses

Within each ACS category, we compared characteristics based on mortality status using the

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Fisher exact test (categorical variables) and Wilcoxon rank sum test (continuous variables). The associations between the baseline characteristics and mortality were evaluated using logistic regression in crude models (odds ratio [OR] and [95% CI]) and models adjusted for the GRACE risk score (adjusted odds ratio [aOR] and 95% CI), which comprised 8 variables (age, heart rate, systolic blood pressure, initial creatinine levels, Killip class, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzyme levels). The OR for continuous variables (age, BMI, and waist circumference) were reported per SD increment. For hospital mortality, crude ORs were reported because the rate precluded evaluation using adjusted models. The *P* value for interaction was from characteristic × ACS category analyses. We developed a model for all-cause 1-year mortality in randomly split 60% derivation and 40% validation cohorts using forward stepwise logistic regression ($P<.05$ to enter and $P<.01$ to stay). The model performance was evaluated using receiver operating characteristic curves (model discrimination; area under the curve [AUC]) and the Hosmer-Lemeshow test (model calibration).

Splines were generated using the *splines* package in R (version 4.0.3). The statistical analysis was completed using SAS 9.4 (SAS Institute) with a statistical significance at 2-tailed of $P<.05$.

Ethics Approval

Gulf COAST was approved by the institutional review boards of participating centers, and this study was deemed exempt by the institutional review board at Mayo Clinic, Rochester, MN.

RESULTS

Acute coronary syndrome was diagnosed as ST-elevation MI or left bundle branch block MI (n=968) and unstable angina or non−ST-elevation MI (n=2900). In the cohort, 43.3% of the participants (n=1675/3868) presented with premature ACS. The cumulative incidence of 1-year mortality was lower in the premature ACS (5.7%; n=96/1675) than that in the non-premature ACS (17.6%; n=385/2193) category (Table 1). Within both ACS categories, the proportion of baseline demographic characteristics (eg, women, no formal education, and lack of employment) and admission characteristics (eg, Killip classes II-IV) was higher in participants with 1-year mortality than that in participants who were alive (Table 1). Clinical characteristics, such as BMI and ever smoked, were lower in participants with 1-year mortality, whereas clinical characteristics, such as diabetes mellitus and hypertension, were more prevalent only in participants with 1-year mortality after premature ACS.

Demographic Characteristics and 1-Year Mortality

In the univariate analysis, women, compared with men, had higher mortality after premature ACS (OR, 2.99; 95% CI, 1.95-4.67; $P<.0001$) vs non-premature ACS (OR, 1.49; 95% CI, 1.18-1.89; $P<.01$) ($P_{interaction}=.01$) (Table 2). Of all characteristics, lack of employment, compared with any employment, had the strongest association with mortality after both premature ACS (OR, 4.52; 95% CI, 2.69-8.08; $P<.0001$) and non-premature ACS (OR, 3.98; 95% CI, 2.49-6.83; $P<.0001$) ($P_{interaction}=.74$). The lack of formal education, compared with any education, was associated with higher mortality after premature ACS vs non-premature ACS ($P_{interaction}=.01$) (Table 2). After adjusting for GRACE risk score, most of the associations were preserved but attenuated. Women had higher mortality after premature ACS (aOR, 2.14; 95% CI, 1.37-3.41; $P<.01$) vs non-premature ACS (aOR, 1.28; 95% CI, 0.99-1.65) ($P_{interaction}=.047$) (Table 2 and Figure). Lack of employment and lack of formal education were associated with similar approximately 2-fold higher mortality after premature and non-premature ACS ($P_{interaction}>.05$, for both) (Table 2).

Clinical Characteristics and 1-Year Mortality

In the univariate analysis, ever smoked, compared with never smoked, was associated with lower mortality after premature ACS (OR, 0.40; 95% CI, 0.24-0.64; $P<.0001$) vs non-premature ACS (OR, 0.78; 95% CI, 0.62-0.99; $P<.01$) ($P_{interaction}=.01$) (Table 2). Body mass index and obesity by waist-to height ratio showed similar lower mortality with premature and non-premature ACS, whereas diabetes was associated with higher mortality

TABLE 1. Baseline Characteristics and All-Cause 1-Year Mortality After ACS[a]

	Premature ACS (n=1675)		Non premature ACS (n=2193)	
	Dead at 1y (n=96)	Alive at 1y (n=1579)	Dead at 1y (n=385)	Alive at 1y (n=1808)
Demographic characteristics				
Age, (y)	53 (50-59)[d]	50 (44-54)	72 (66-78)[d]	67 (61-73)
Women	64 (66.7)[d]	633 (40.1)	133 (34.6)[c]	472 (26.1)
No formal education	61 (63.5)[d]	458 (29.0)	294 (76.4)[d]	1064 (58.9)
Lack of employment	80 (83.3)[d]	829 (52.5)	368 (95.6)[d]	1527 (84.5)
Non-government health insurance	4 (4.2)	126 (8.0)	11 (2.9)[b]	100 (5.5)
Not married	18 (18.8)[b]	181 (11.5)	93 (24.2)[c]	306 (16.9)
Clinical characteristics				
Ever smoked	23 (24.0)[c]	694 (44.0)	122 (31.7)[b]	673 (37.2)
Hypertension	65 (67.7)[b]	867 (54.9)	286 (74.3)	1299 (71.9)
Dyslipidemia	56 (58.3)	833 (52.8)	212 (55.1)[b]	1096 (60.6)
Diabetes	62 (64.6)[c]	759 (48.1)	218 (56.6)	1040 (57.5)
Family history of premature coronary artery disease	6 (6.3)[c]	339 (21.5)	32 (8.3)	202 (11.2)
Body mass index, (kg/m^2)	26.2 (23.5-29.7)[d]	29.0 (25.9-32.9)	26.0 (23.5-29.8)[c]	27.3 (24.5-30.9)
Waist circumference, (cm)	95.0 (83.0-110.0)[c]	100.0 (90.0-110.0)	90.0 (84.0-105.0)[d]	98.0 (88.0-109.0)
Obesity, by body mass index	22 (24.2)[c]	663 (42.2)	88 (24.1)[b]	537 (30.0)
Obesity, by waist circumference	74 (79.6)	1224 (78.2)	204 (56.4)[d]	1207 (68.2)
Obesity, by waist-to-height ratio	77 (84.6)[b]	1435 (91.8)	294 (81.2)[d]	1583 (89.5)
Admission characteristics				
Non-ambulance transportation to the hospital	69 (71.9)	1224 (77.5)	262 (68.1)[c]	1398 (77.3)
Previous angina	41 (42.7)	539 (34.1)	167 (43.4)	770 (42.6)
Symptom other than typical chest pain	31 (32.3)[c]	259 (16.4)	171 (44.4)[d]	453 (25.1)
Non-sinus cardiac rhythm	8 (8.3)	71 (4.5)	39 (10.1)	142 (7.9)
ST-elevation MI	28 (29.2)	427 (27.0)	107 (27.8)[b]	406 (22.5)
Killip classes II-IV	36 (37.5)[d]	180 (11.4)	186 (48.3)[d]	433 (24.0)
Medications received within 24 h after admission				
Aspirin	94 (97.9)	1564 (99.1)	368 (95.6)[c]	1776 (98.2)
Clopidogrel or prasugrel or ticagrelor	68 (70.8)[b]	1276 (80.8)	289 (75.1)[c]	1497 (82.8)
β-Blocker	59 (61.5)[d]	1317 (83.4)	245 (63.6)[d]	1394 (77.1)
Angiotensin-converting enzyme inhibitor	55 (57.3)[b]	1083 (68.6)	206 (53.5)[d]	1249 (69.1)
Angiotensin receptor blocker	9 (9.4)	175 (11.1)	43 (11.2)	266 (14.7)
Statin	87 (90.6)[c]	1538 (97.4)	357 (92.7)[d]	1769 (97.8)

[a]ACS, acute coronary syndrome; MI, myocardial infarction.

[b]$P<.05$, [c]$P<.01$, [d]$P<.0001$ for dead at 1y vs alive at 1y within each ACS category based on the Wilcoxon rank sum test (continuous variables) and Fisher exact test (categorical variables).

Data are presented as median (interquartile range) and frequency (%). Missing data for premature ACS (body mass index [n=13], waist circumference [n=17], and corresponding obesity measures; obesity by waist-to-height ratio [n=20]) and non-premature ACS (body mass index [n=39], waist circumference [n=61], and corresponding obesity measures; obesity by waist-to-height ratio [n=63]).

only after premature ACS ($P_{interaction}$=.004) (Table 1). In models adjusted for GRACE risk score, ever smoked, compared with never smoked, had lower mortality after premature ACS (aOR, 0.47; 95% CI, 0.29-0.77; $P<.01$) but not non-premature ACS (aOR, 0.83; 95% CI, 0.64-1.06) ($P_{interaction}$=.047) (Table 2 and Figure). A family history of premature coronary artery disease was associated with lower mortality after premature ACS (aOR, 0.26; 95% CI, 0.10-0.56) but not non-premature ACS (aOR, 0.91; 95% CI, 0.59-1.37) ($P_{interaction}$=.01) (Table 2 and Figure).

Admission Characteristics and 1-Year Mortality

In the univariate analysis, symptoms other than chest pain, compared with typical chest

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TABLE 2. Association of Baseline Characteristics With All-Cause 1-Year Mortality After ACS[a]

	Premature ACS OR (95% CI)[b] (n=96/1675)	Non-premature ACS OR (95% CI)[b] (n=385/2193)	$P_{interaction}$[c]
Demographic characteristics			
Age (y), per SD increment			
Crude	2.26 (1.59-3.28)[f]	2.19 (1.87-2.58)[f]	.87
Women (vs men)			
Crude	2.99 (1.95-4.67)[f]	1.49 (1.18-1.89)[e]	.01
Adjusted	2.14 (1.37-3.41)[e]	1.28 (0.99-1.65)	.047
No formal education (vs any education)			
Crude	4.27 (2.79-6.61)[f]	2.26 (1.76-2.92)[f]	.01
Adjusted	2.92 (1.87-4.61)[f]	1.78 (1.36-2.34)[f]	.06
Lack of employment (vs any employment)			
Crude	4.52 (2.69-8.08)[f]	3.98 (2.49-6.83)[f]	.74
Adjusted	3.09 (1.81-5.61)[f]	2.71 (1.66-4.74)[f]	.72
Non-government health insurance (vs government insurance)			
Crude	0.50 (0.15-1.23)	0.50 (0.25-0.90)[d]	1.00
Adjusted	0.56 (0.16-1.42)	0.51 (0.25-0.96)	.90
Not married (vs married)			
Crude	1.78 (1.02-2.98)[d]	1.56 (1.20-2.03)[e]	.67
Adjusted	1.42 (0.78-2.45)	1.18 (0.89-1.57)	.52
Clinical characteristics			
Ever smoked (vs never smoked)			
Crude	0.40 (0.24-0.64)[f]	0.78 (0.62-0.99)[d]	.01
Adjusted	0.47 (0.28-0.77)[e]	0.83 (0.64-1.06)	.047
Hypertension			
Crude	1.72 (1.12-2.70)[d]	1.13 (0.88-1.46)	.10
Adjusted	1.53 (0.98-2.44)	1.19 (0.91-1.56)	.34
Dyslipidemia			
Crude	1.25 (0.83-1.91)	0.80 (0.64-0.99)[d]	.06
Adjusted	1.12 (0.72-1.74)	0.85 (0.67-1.08)	.27
Diabetes			
Crude	1.97 (1.29-3.06)[e]	0.96 (0.77-1.21)	.004
Adjusted	1.52 (0.98-2.41)	0.93 (0.74-1.19)	.05
Family history of premature coronary artery disease			
Crude	0.24 (0.09-0.52)[f]	0.72 (0.48-1.05)	.02
Adjusted	0.26 (0.10-0.56)[e]	0.91 (0.59-1.37)	.01
Body mass index (kg/m^2), per SD increment			
Crude	0.54 (0.36-0.79)[e]	0.71 (0.58-0.87)[e]	.23
Adjusted	0.59 (0.39-0.86)[e]	0.78 (0.63-0.96)[d]	.21
Waist circumference (cm), per SD increment			
Crude	0.82 (0.65-1.02)	0.75 (0.66-0.84)[f]	.49
Adjusted	0.92 (0.73-1.14)	0.83 (0.73-0.95)[e]	.52
Obesity, by body mass index			
Crude	0.44 (0.26-0.70)[e]	0.74 (0.57-0.96)[d]	.06
Adjusted	0.44 (0.26-0.72)[e]	0.78 (0.59-1.02)	.06
Obesity, by waist circumference			
Crude	1.09 (0.66-1.87)	0.60 (0.48-0.76)[f]	.04
Adjusted	1.13 (0.67-2.00)	0.68 (0.53-0.87)[e]	.09
Obesity, by waist-to-height ratio			
Crude	0.49 (0.28-0.93)[d]	0.51 (0.37-0.69)[f]	.95
Adjusted	0.64 (0.35-1.28)	0.65 (0.47-0.90)[e]	.95

Continued on next page

TABLE 2. Continued

	Premature ACS OR (95% CI)[b] (n=96/1675)	Non-premature ACS OR (95% CI)[b] (n=385/2193)	$P_{interaction}$[c]
Admission characteristics			
Non-ambulance transportation to the hospital (vs ambulance)			
Crude	0.74 (0.47-1.19)	0.63 (0.49-0.80)[e]	.52
Adjusted	1.16 (0.71-1.93)	0.91 (0.70-1.20)	.51
Previous angina			
Crude	1.44 (0.94-2.18)	1.03 (0.83-1.29)	.17
Adjusted	1.50 (0.96-2.32)	1.23 (0.96-1.56)	.45
Symptom other than typical chest pain (vs typical chest pain)			
Crude	2.43 (1.54-3.77)[e]	2.39 (1.90-3.00)[f]	.95
Adjusted	1.18 (0.69-1.94)	1.23 (0.95-1.60)	.90
Non-sinus cardiac rhythm (vs sinus)			
Crude	1.93 (0.84-3.91)	1.32 (0.90-1.90)	.38
Adjusted	0.91 (0.37-1.99)	0.72 (0.47-1.07)	.52
ST-elevation MI (vs other ACS event)			
Crude	1.11 (0.70-1.73)	1.33 (1.03-1.70)[d]	.50
Killip classes II-IV (vs class I)			
Crude	4.66 (2.98-7.22)[f]	2.97 (2.37-3.73)[f]	.07
Medications within 24 h after admission (vs not)			
Aspirin			
Crude	0.45 (0.13-2.89)	0.39 (0.22-0.73)[e]	.86
Adjusted	0.61 (0.14-4.36)	0.41 (0.21-0.82)[e]	.69
Clopidogrel or prasugrel or ticagrelor			
Crude	0.58 (0.37-0.92)[d]	0.63 (0.48-0.82)[e]	.76
Adjusted	0.69 (0.43-1.14)	0.74 (0.55-0.98)[d]	.77
β-Blockers			
Crude	0.32 (0.21-0.49)[f]	0.52 (0.41-0.66)[f]	.049
Adjusted	0.50 (0.31-0.80)[e]	0.88 (0.68-1.15)	.03
Angiotensin-converting enzyme inhibitor			
Crude	0.61 (0.41-0.94)[d]	0.52 (0.41-0.64)[f]	.47
Adjusted	0.68 (0.44-1.06)	0.70 (0.55-0.89)[e]	.87
Angiotensin receptor blockers			
Crude	0.83 (0.38-1.59)	0.73 (0.51-1.02)	.74
Adjusted	1.00 (0.46-1.97)	0.79 (0.54-1.13)	.59
Statin			
Crude	0.26 (0.13-0.58)[e]	0.28 (0.17-0.47)[f]	.85
Adjusted	0.41 (0.18-1.05)	0.33 (0.19-0.57)[f]	.71

[a]ACS, acute coronary syndrome; OR, odds ratio.

[b]Odds ratio (95% CI) of all-cause 1-year mortality after ACS obtained from logistic regression analysis in crude models or models adjusted for GRACE risk score (comprised 8 variables: age, heart rate, systolic blood pressure, initial creatinine levels, Killip class, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzyme levels). Only crude odds ratio reported for variables in the GRACE risk score.

[c]*P* values for (characteristic × ACS category) interaction.

[d]$P<.05$

[e]$P<.01$

[f]$P<.0001$

Standard deviation: age (12.7 years), body mass index (9.03 kg/m^2), and waist circumference (16.1 cm).

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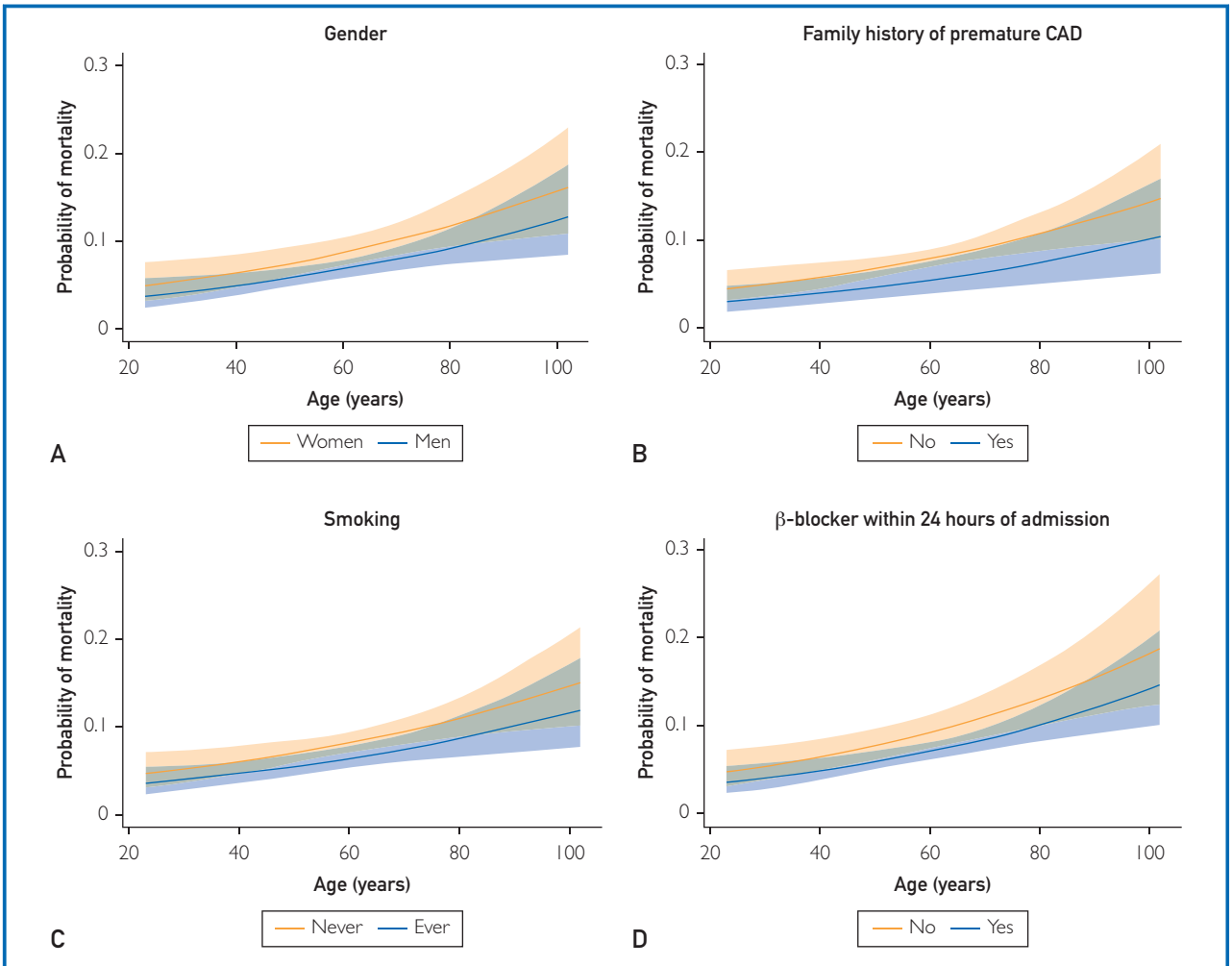

FIGURE. Probability of all-cause 1-year mortality after ACS event, as a function of age. Depiction of factors with different associations with mortality after premature ACS vs non-premature ACS ($P_{interaction}$<.05) in models adjusted for GRACE risk score (Table 2). ACS, acute coronary syndrome; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events.

pain, were associated with similar, higher mortality after premature ACS (OR, 2.43; 95%CI, 1.54-3.77; *P*<.01) and non-premature ACS (OR, 2.39; 95% CI, 1.90-3.00; *P*<.0001) ($P_{interaction}$=.95) (Table 2). Of all admission characteristics, Killip classes II-IV, compared with class I, were associated with the highest, similar mortality after premature ACS (OR, 4.66; 95% CI, 2.98-7.22; *P*<.001) and non-premature ACS (OR, 2.97; 95% CI, 2.37-3.73; *P*<.0001) ($P_{interaction}$=.07). Of the cardiovascular medications given within 24 hours after admission, statins were associated with approximately 75% lower mortality after both premature ACS and non-premature ACS ($P_{interaction}$=.85). In models adjusted for GRACE risk score, β-blockers were associated with lower mortality after premature ACS (aOR, 0.50; 95% CI, 0.31-0.80; *P*<.01) but not non-premature ACS (aOR, 0.88; 95% CI, 0.68-1.15) ($P_{interaction}$=.03) (Table 2 and Figure). Other cardiovascular medications were associated with lower mortality after non-premature ACS but not premature ACS (Table 2). Angiotensin receptor blocker medications showed no association with mortality after premature and non-premature ACS (Table 2).

TABLE 3. Association of Baseline Characteristics With All-Cause Hospital Mortality After ACS[a]

	Premature ACS crude OR (95% CI)[b] (n=36/1675)	Non-premature ACS crude OR (95% CI)[b] (n=129/2193)	$P_{interaction}$[f]
Demographic characteristics			
Age (y), per SD increment	2.14 (1.22-3.88)[d]	1.62 (1.27-2.07)[d]	.39
Women (vs men)	3.27 (1.64-6.97)[d]	1.06 (0.71-1.56)	.01
No formal education (vs any education)	5.27 (2.64-11.23)[e]	1.77 (1.20-2.68)[d]	.01
Lack of employment (vs any employment)	6.95 (2.74-23.42)[d]	2.86 (1.42-6.82)[d]	.18
Non-government health insurance (vs government insurance)	0.33 (0.02-1.57)	0.28 (0.05-0.90)	.89
Not married (vs married)	1.20 (0.41-2.87)	1.46 (0.95-2.19)	.72
Clinical characteristics			
Ever smoked (vs never smoked)	0.32 (0.13-0.69)[d]	0.87 (0.59-1.26)	.03
Hypertension	2.43 (1.18-5.51)[c]	0.57 (0.39-0.82)[d]	.001
Dyslipidemia	2.34 (1.16-5.12)[c]	0.69 (0.49-0.99)[c]	.004
Diabetes	2.76 (1.36-6.04)[d]	0.79 (0.56-1.13)	.003
Family history of premature coronary artery disease	0.11 (0.01-0.50)[c]	0.54 (0.24-1.05)	.14
Body mass index (kg/m^2), per SD increment	0.79 (0.44-1.13)	0.69 (0.48-0.96)[c]	.67
Waist circumference (cm), per SD increment	0.96 (0.68-1.33)	0.76 (0.61-0.93)[d]	.24
Obesity, by body mass index	0.59 (0.27-1.20)	0.61 (0.37-0.96)[c]	.93
Obesity, by waist circumference	0.97 (0.46-2.30)	0.52 (0.35-0.76)[d]	.17
Obesity, by waist-to-height ratio	0.43 (0.19-1.17)	0.52 (0.33-0.87)[d]	.71
Admission characteristics			
Non-ambulance transportation to the hospital (vs ambulance)	0.40 (0.21-0.81)[d]	0.44 (0.30-0.63)[e]	.85
Previous angina	0.94 (0.45-1.86)	0.61 (0.41-0.88)[c]	.28
Symptom other than typical chest pain (vs typical chest pain)	2.78 (1.35-5.47)[d]	3.02 (2.11-4.38)[e]	.83
Non-sinus cardiac rhythm (vs sinus)	1.87 (0.44-5.36)	1.38 (0.75-2.38)	.66
ST-elevation MI (vs other ACS event)	2.45 (1.25-4.77)[d]	2.52 (1.74-3.62)[e]	.95
Killip classes II-IV (vs class I)	9.20 (4.70-18.30)[e]	3.88 (2.71-5.60)[e]	.03
Medications within 24 h after admission (vs not)			
Aspirin	—[g]	0.31 (0.15-0.72)[d]	—
Clopidogrel or prasugrel or ticagrelor	0.63 (0.31-1.39)	0.64 (0.43-0.98)[c]	.97
β-Blockers	0.13 (0.06-0.25)[e]	0.23 (0.16-0.33)[e]	.14
Angiotensin-converting enzyme inhibitors	0.37 (0.19-0.72)[d]	0.40 (0.28-0.58)[e]	.82
Angiotensin receptor blocker	0.73 (0.18-2.07)	0.50 (0.24-0.91)[c]	.57
Statin	0.23 (0.09-0.80)[d]	0.22 (0.12-0.42)[e]	.92

[a]ACS, acute coronary syndrome; MI, myocardial infarction; OR, odds ratio.
[b]Odds ratio (95% CI) of all-cause hospital mortality after ACS event obtained from univariate logistic regression models.
Statistical significance at
[c]$P<.05$
[d]$P<.01$
[e]$P<.0001$ levels.
[f]P values for (characteristic × ACS category) interaction.
[g]Insufficient events in aspirin vs no aspirin groups.
Standard deviation: age (12.7 years), body mass index (9.03 kg/m^2), and waist circumference (16.1 cm).

Model for 1-Year Mortality

Many characteristics had similar associations with mortality after premature and non-premature ACS. To develop a prediction model for mortality and to compare performance with the GRACE risk score model, we used characteristics that were not included in the GRACE risk score (Supplemental Table 1,

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available online at http://www.mcpiqojournal.org). In stepwise logistic regression models, the following variables were identified: GRACE risk score, education, employment, BMI, and statin use within 24 hours after admission (full model). In the derivation cohort, the AUC (95% CI) of the full model was 0.811 (95% CI, 0.784-0.838). In the validation cohort, the full model had a higher discrimination (AUC, 0.800; 95% CI, 0.769-00.832) than the "GRACE risk score" model (AUC, 0.773; 95% CI, 0.737-0.809) (AUC comparison, *P*=.0033) (Supplemental Figure, available online at http://www.mcpiqojournal.org) and adequate calibration (*P*=.46) (Supplemental Table 2, available online at http://www.mcpiqojournal.org).

Hospital Mortality

The incidence of hospital mortality was lower in the premature ACS (2.1%; n=36/1675) compared with non-premature ACS (5.9%; n=129/2193) categories (Supplemental Table 3, available online at http://www.mcpiqojournal.org). Within both ACS categories, the differences in the baseline characteristics based on hospital mortality were similar to those based on 1-year mortality. In univariate analyses, women, lack of employment, no formal education, symptom other than typical chest pain, ST-elevation MI, and Killip classes II-IV were associated with higher mortality after both premature and non-premature ACS (Table 3). Most cardiovascular medications administered within 24 hours after admission were associated with lower mortality (Table 3).

DISCUSSION

In this study of mortality after premature and non-premature ACS, women compared with men had 2-fold higher 1-year mortality after premature ACS but not after non-premature ACS. The social determinants of health, particularly, lack of employment or formal education, were associated with 2-fold to 3-fold higher mortality after both premature and non-premature ACS in both women and men. A model with GRACE risk score plus social determinants of health had adequate calibration and higher discrimination than the GRACE risk score alone. Together, these results highlight the potential effects of social determinants of health in mortality after ACS and should be routinely considered in patients presenting with ACS.

Previous studies on sex-based ACS outcomes have yielded mixed results. In the Atherosclerosis Risk in Communities study in 4 US communities, men and women (aged 35-54 years) had similar 1-year mortality rates after MI.[10] In a community study in Olmsted County, women aged 18-65 years had 63% reduced risk in 5-year death after MI, whereas men aged 18-55 years showed no change.[9] In the Mass General Brigham Young-MI registry, women aged <50 years with MI had a higher mortality rate over a median of 11.2 years of follow-up than similarly aged men.[11] In a pooled analysis of 7 Gulf registries, which included Gulf COAST, young women vs men (both aged ≤65 years) had a 1.9-fold higher mortality that was higher than the 1.5-fold higher risk for older women vs men (both aged >65 years).[12] The differences in sex-based ACS outcomes may be related to incompletely understood genetic factors, sociocultural factors, differences in use of evidence-based therapies, and adherence to secondary prevention therapies. Furthermore, young women are more likely to experience atypical symptoms and present with MI with nonobstructive coronary arteries than similarly aged men, which may delay the use of evidence-based therapies.[9,13] Further studies are required to characterize the contribution of these and other factors to sex-based ACS outcomes.

Previously, we reported that lack of formal education was associated with higher 1-year mortality after ACS.[14] The present study extends those findings and shows that lack of formal education and lack of employment were associated with higher 1-year mortality after both premature and non-premature ACS. The INTERHEART study examined the association of 3 socioeconomic status measures with the risk of MI.[15] Across world regions, and notably in high-income countries, a low level of education (ie, ≤8 years) was associated with a higher MI risk, compared with other measures (family income, possessions in household, and occupation).[15] Other studies have shown mixed results on the association of socioeconomic disadvantage and health literacy with cardiovascular

mortality.[16-20] In the present study, reasons for the higher mortality in those lacking employment are unclear. Gulf COAST included national citizens, who have access to health services. In this cohort, lack of formal education and lack of employment may not necessarily reflect lower socioeconomic status but rather suboptimal adherence to secondary prevention measures. Interventions tailored to health literacy may improve adherence to secondary prevention measures.

The association of ever-smoking vs never-smoking with lower 1-year and hospital mortality after premature ACS, but not after non-premature ACS, was intriguing. Studies on the smoker paradox and cardiac outcomes have yielded mixed results.[21-25] In the Malaysian National Cardiovascular Database-Acute Coronary Syndrome registry, smoking was associated with a lower relative risk of hospital and 30-day mortality after ACS.[25] In the Gulf Acute Heart Failure Registry, smoking was associated with lower hospital mortality.[22] However, this association was abrogated with propensity matching, suggesting that the paradox was likely because of residual confounding.[22] In a systematic review of smoker paradox and ACS, only 6 of the 17 studies observed the smoker paradox.[24] Cigarette smoking may reduce platelet reactivity and confer short-term protection[23]; however, smoking is associated with vascular conditions and cancers that increase morbidity and mortality[26] and the present study does not endorse the initiation or continuation of smoking.

Previously, we reported the complex association of obesity indices and ACS outcomes.[6] We extend these findings and show that these associations depend on the ACS category: peripheral obesity (ie, BMI) was associated with lower mortality after premature ACS, whereas central obesity (ie, waist circumference and waist-to-height ratio) was associated with lower mortality after non-premature ACS. However, interaction analyses showed no association between obesity indices and ACS category. Similar to the smoker paradox, studies have described an obesity paradox, in which obesity confers short-term mortality protection after ACS. Despite potential short-term benefits, the overall evidence shows that obesity is associated with higher long-term morbidity and mortality.[6]

The study has limitations. The study was based on national citizens and generalizability to other residents requires evaluation.[14] Participants presenting to the hospital with ACS were included but not those who died after out-of-hospital ACS. The study has several strengths. This is the first Middle East registry with robust follow-up of participants from several countries. The inclusion of national citizens increased homogeneity and mitigated potential confounding by access to health care that is free for citizens. The registry is based on enrollment in 2012 and 2013 with follow-up through 2014. Despite enrollment approximately 10 years ago, to our knowledge, this registry remains the most recent Middle East multinational ACS registry with 1-year follow-up. Therefore, the registry offered a unique opportunity to evaluate the association of baseline characteristics with mortality after an ACS event. Taken together, this registry enabled us to describe and compare characteristics associated with mortality after premature and non-premature ACS and provided a foundation for secondary prevention interventions. Identifying the social determinants of health and reducing associated health inequities may help to improve the cardiovascular health.[27]

CONCLUSION

In this observational prospective study, women, compared with men, had a higher 1-year mortality after premature ACS. Social determinants of health (no formal education or employment) were strong determinants of 1-year mortality after premature and non-premature ACS, improved mortality prediction, and should be routinely considered in risk assessment of patients presenting with ACS.

POTENTIAL COMPETING INTEREST

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACS,** acute coronary syndrome; **aOR,** adjusted odds ratio; **AUC,** area under the curve; **BMI,** body mass index; **GRACE,** Global Registry of Acute Coronary Events; **MI,** myocardial infarction; **OR,** odds ratio

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