In-hospital Major Clinical Outcomes in Patients With Chronic Renal Insufficiency Presenting With Acute Coronary Syndrome: Data From a Registry of 8176 Patients

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OBJECTIVE: To assess the impact of chronic renal insufficiency (CRI) on in-hospital major adverse cardiac events across the acute coronary syndrome (ACS) spectrum.

PATIENTS AND METHODS: From January 29, 2007, through July 29, 2007, 6 adjacent Middle Eastern countries participated in the Gulf Registry of Acute Coronary Events, a prospective, observational registry of 8176 patients. Patients were categorized according to estimated glomerular filtration rate into 4 groups: normal (≥ 90 mL/min), mild (60-89 mL/min), moderate (30-59 mL/min), and severe CRI (< 30 mL/min). Patients' characteristics and in-hospital major adverse cardiac events in the 4 groups were analyzed.

RESULTS: Of 6518 consecutive patients with ACS, 2828 (43%) had mild CRI, 1304 (20%) had moderate CRI, and 345 (5%) had severe CRI. In CRI groups, patients were older and had a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia. On admission, these patients had a higher resting heart rate and frequently had atypical and delayed presentations. Compared with the normal estimated glomerular filtration group, CRI groups were less likely to receive antiplatelet drugs, β -blockers, angiotensin-converting enzyme inhibitors, and statins and were less likely to undergo coronary angiography. In-hospital heart failure, cardiogenic shock, and major bleeding episodes were significantly higher in all CRI groups. In multivariate analysis, mild, moderate, and severe CRI were associated with a higher adjusted odds ratio (OR) of death (mild: OR, 2.1; 95% confidence interval [CI], 1.2-3.7; moderate: OR, 6.7; 95% CI, 3.9-11.5; and severe: OR, 12.0; 95% CI, 6.6-21.7).

CONCLUSION: Across the ACS spectrum, patients with CRI had a worse risk profile, had more atypical and delayed presentations, and were less likely to receive evidence-based therapy. Chronic renal insufficiency of varying stages is an independent predictor of in-hospital morbidity and mortality.

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ACS = acute coronary syndrome; CI = confidence interval; CrCl = creatinine clearance; CRI = chronic renal insufficiency; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; Gulf RACE = Gulf Registry of Acute Coronary Events; MACE = major adverse cardiac event; NSTACS = non-ST-segment elevation ACS; OR = odds ratio; S_{Cr} = serum creatinine; STEMI = ST-segment elevation myocardial infarction

Chronic renal insufficiency (CRI) is a well-established risk factor and predictor of mortality in patients with coronary artery disease.¹⁻⁸ However, the impact of varying stages of CRI in patients with the entire acute coronary syndrome (ACS) spectrum has been less extensively studied.

The objective of the current study was to evaluate the prognostic impact of the CRI stages on the in-hospital mortality and major adverse cardiac events (MACEs) across the ACS population, including patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTACS).

PATIENTS AND METHODS

The data are driven from a prospective, multicenter, observational study of the Gulf Registry of Acute Coronary Events (Gulf RACE).^{9,10} From January 29, 2007, through July 29, 2007, 8176 consecutive patients with ACS were recruited from 64 hospitals in 6 Middle Eastern countries (Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen). Figure 1 shows the Gulf RACE design for the current analysis. The study received ethical approval from the institutional ethical bodies in all participating countries.

Baseline serum creatinine (S_{Cr}) values were available for 6518 patients with ACS on admission and before any intervention. Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease equation: $eGFR = 186 \times S_{Cr}^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).¹¹

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FIGURE 1. Distribution of patients and design of the Gulf Registry of Acute Coronary Events (Gulf RACE). ACS = acute coronary syndrome; eGFR = estimated glomerular filtration rate; NSTACS = non-ST-segment elevation ACS; STEMI = ST-segment elevation myocardial infarction.

Because Gulf RACE did not enroll African black patients, correction for race was not used. Following the National Kidney Foundation Guidelines,¹² we stratified the study population into 4 groups according to eGFR as follows: normal, 90 mL/min or greater (n=2041); mild CRI, 60 to 89 mL/min (n=2828); moderate CRI, 30 to 59 mL/min (n=1304); and severe CRI, less than 30 mL/min (n=345).

The study sample was further divided into 2 subgroups of patients with STEMI and NSTACS. Patients with evidence of ST-segment elevation or left bundle branch block on electrocardiography at time of admission were defined as having STEMI, whereas the remaining patients were categorized as having NSTACS. Demographic and clinical characteristics, reperfusion treatment, pharmacologic treatment, interventional procedures, and incidence of in-hospital MACEs were compared across the creatinine clearance (CrCl) groups for all patients with ACS and separately within the STEMI and NSTACS subgroups.

Moreover, 3 registries from Canada (Canadian ACS I and ACS II registries and Global Registry of Acute Coronary Events [GRACE]) were used to compare in-hospital mortality to that in our study.^{4,8} To compare the outcome in patients with CRI diagnosed using the eGFR formula vs the CrCl method, a subset analysis was done using the Cockcroft-Gault formula^{3,13}: $\text{CrCl (mL/min)} = [(140 - \text{Age}) \times (\text{Weight in Kilograms}) \times (0.85 \text{ for Women})] / [72 \times \text{S}_{\text{Cr}} (\text{mg/dL})]$

STATISTICAL ANALYSES

Data were presented as proportions, medians, or mean $\pm$ SD as appropriate. Differences in categorical variables between respective comparison groups were analyzed using

the χ^2 test. The continuous variables were analyzed using 1-way ANOVA. The association between different levels of eGFR and in-hospital MACEs (mortality, reinfarction, heart failure, cardiogenic shock, stroke, and major bleeding episodes) was examined using univariate and multivariate logistic regression models. Unadjusted and adjusted odds ratios (ORs), with accompanying 95% confidence intervals (CIs), were reported for the respective categories, in comparison with the referent group of patients with an eGFR of 90 mL/min or more (normal renal function). Variables were adjusted for age, sex, treatment differences, and presence of diabetes mellitus. All *P* values were the results of 2-tailed tests and values $<.05$ were considered significant. All data analyses were carried out using the Statistical Package for Social Sciences, version 14 (SPSS, Chicago, IL). Full details of the methods have been published previously.¹⁴ Diagnosis of the different types of ACS (STEMI and NSTACS) and definitions of data variables were based on the American College of Cardiology clinical data standards.^{1,10} The GRACE risk models for hospital mortality were used to stratify the risk status of patients at presentation as low, intermediate, or high.^{4,15}

RESULTS

Baseline characteristics of patients with a diagnosis of ACS at the time of hospital admission are shown in Tables 1 and 2, stratified by the extent of renal dysfunction. Patients with mild, moderate, or severe renal dysfunction were significantly older and had a greater prevalence of previous coronary artery disease, diabetes, hypertension, dyslipidemia, and prior coronary revascularizations. They

TABLE 1. **Baseline Characteristics and Clinical Presentations of Patients With ACS, Stratified by eGFR^{a,b}**

	eGFR (mL/min/1.73 m ²)				P value
	≥90 (n=2041)	60-89 (n=2828)	30-59 (n=1304)	<30 (n=345)	
Age (y)	51±11	56±12	63±11	64±12	<.001
Female	406 (20)	549 (19)	469 (36)	159 (46)	<.001
Family history of CAD	263 (13)	366 (13)	185 (14)	56 (16)	.25
Diabetes mellitus	773 (38)	1025 (36)	647 (50)	235 (68)	<.001
Hypertension	823 (40)	1354 (48)	826 (63)	273 (79)	<.001
Dyslipidemia	529 (26)	862 (30)	533 (41)	171 (50)	<.001
Smoking	951 (47)	1126 (40)	357 (27)	58 (17)	<.001
Prior CAD	794 (39)	1245 (44)	709 (54)	226 (66)	<.001
Prior revascularization	263 (13)	425 (15)	259 (20)	79 (23)	.001
Heart rate (beats/min)	84±21	85.3±22	91.6±26	93±29	<.001
Blood pressure (mm Hg)					
Systolic	139±28	140±30	139±36	142±39	.19
Diastolic	84±17	84±18	82±21	80±21	<.001
Killip class >1	233 (11)	530 (19)	489 (38)	170 (49)	<.001
Body mass index (kg/m ²)	28±5	27±5	28±6	28±6	.22
Initial blood glucose level (mg/dL)	180±234	180±144	216±180	234±144	<.001
Total cholesterol (mg/dL)	189±77	193±84	196±115	185±77	.19
Triglycerides (mg/dL)	168±265	159±97	177±442	177±265	.05
LDL-C (mg/dL)	127±115	127±154	123±270	127±154	.97
HDL-C (mg/dL)	46±38	42±42	42±19	46±115	.14
Initial hemoglobin level (g/dL)	14±33	14±3	13±5	12±7	<.001
Symptom-to-door time (min)	205±202	185±179	217±218	273±304	.003
Typical angina ^c	1766 (87)	2344 (83)	887 (68)	216 (63)	<.001
Dyspnea ^c	98 (5)	214 (8)	262 (20)	70 (20)	<.001
GRACE risk scoring					
Low	949/1571 (60)	908/2126 (43)	147/899 (16)	17/236 (7)	<.001
High	208/1571 (13)	567/2126 (27)	513/899 (57)	176/236 (75)	<.001
LVEF <40%	205/1287 (16)	354/1766 (20)	287/808 (36)	73/217 (34)	<.001
STEMI	836 (41)	1133 (40)	487 (37)	105 (30)	.001

^a Categorical data are provided as number (percentage) of patients and continuous data as mean ± SD. ACS = acute coronary syndrome; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

^b SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; to convert cholesterol values (total cholesterol, HDL-C, LDL-C) to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; and to convert hemoglobin values to g/L, multiply by 10.

^c At presentation.

were less likely to be smokers. The risk factors were seen more often as renal impairment increased. Compared with patients with an eGFR of 90 mL/min, patients with CRI on admission had a higher resting heart rate, had a higher blood glucose level on random testing, and were more likely to have a Killip class greater than 1; however, they were less likely to have chest pain at presentation. Chronic renal insufficiency with an eGFR less than 60 mL/min was a predictor of absence of chest pain in patients with ACS at presentation (OR, 1.35; 95% CI, 1.16-1.61; $P<.001$). Patients with ACS who had moderate or severe CRI were determined to be at high risk, with a GRACE score of 57% and 75%, respectively, compared

with 13% and 27% for patients who had no CRI or who had mild CRI, respectively (Table 1).

MODE OF THERAPY ON ADMISSION AND AT DISCHARGE

The mode of therapy on admission and at discharge is shown in Tables 2 and 3. During the index hospitalization, patients with ACS who had moderate or severe renal dysfunction were less likely to be treated with antiplatelet agents, angiotensin-converting enzyme inhibitors, statins, and glycoprotein IIb/IIIa inhibitors across all ACS subgroups. Angiotensin-converting enzyme inhibitors were more likely to be prescribed to patients with a mild degree of renal dysfunction. Use of β -blockers decreased

TABLE 2. Patient Characteristics, Clinical Presentations, and Outcomes, Stratified by Type of ACS^a

	NSTACS (N=3957)					STEMI (N=2561)				
	eGFR (mL/min/1.73 m ²)				P value	eGFR (mL/min/1.73 m ²)				P value
	≥90 (n=1205)	60-89 (n=1695)	30-59 (n=817)	<30 (n=240)		≥90 (n=836)	60-89 (n=1133)	30-59 (n=487)	<30 (n=105)	
Age (y)	42±11	57±15	65±11	64±12	<.001	50±10	54±11	62±12	68±14	<.001
Female	332 (28)	437 (26)	342 (42)	114 (48)	<.001	74 (9)	112 (10)	127 (26)	45 (43)	<.001
Prior CAD ^b	619 (51)	971 (57)	548 (67)	177 (74)	<.001	175 (21)	274 (24)	161 (33)	49 (47)	<.001
Smoking	429 (36)	534 (32)	152 (19)	31 (13)	<.001	522 (62)	592 (52)	205 (42)	27 (26)	<.001
Diabetes mellitus	519 (43)	699 (41)	460 (56)	173 (72)	<.001	254 (30)	326 (29)	187 (38)	62 (59)	<.001
Hypertension	615 (51)	972 (57)	609 (75)	210 (88)	<.001	208 (25)	382 (34)	217 (45)	63 (60)	<.001
Dyslipidemia	417 (35)	671 (40)	421 (52)	129 (54)	<.001	112 (13)	191 (17)	112 (23)	42 (40)	<.001
Body mass index (kg/m ²)	28±6	28±5	28±6	27±5	.01	26±4	27±4	27±5	29±7	<.001
Resting heart rate (beats/min)	84±21	85±22	92±25	93±27	<.001	83±19	84±22	89±26	92±32	<.001
Blood pressure (mm Hg)										
Systolic	141±26	143±29	145±34	148±36	<.001	136±27	137±29	128±35	126±42	<.001
Diastolic	83±15	84±17	83±19	82±20	.14	85±17	85±20	80±23	76±25	<.001
Initial blood glucose level (mg/dL)	10±16	10±8	12±10	12±8	.001	10±7	11±8	13±10	14±8	<.001
Hemoglobin (g/dL)	14±4	14±3	13±5	12±5	<.001	14±2	15±3	14±7	12±3	<.001
Anginal chest pain ^b	1002 (83)	1319 (78)	496 (61)	147 (61)	<.001	764 (91)	1023 (90)	391 (80)	69 (66)	<.001
Dyspnea ^b	79 (7)	175 (10)	213 (26)	59 (25)	<.001	19 (2)	39 (3)	49 (10)	11 (11)	<.001
Killip class >1 ^b	140 (12)	315 (19)	318 (39)	118 (49)	<.001	93 (11)	215 (19)	171 (35)	52 (50)	<.001
GRACE risk scoring										
Low	497/856 (58)	480/1170 (41)	92/575 (16)	11/157 (7)	<.001	452/717 (63)	428/973 (44)	55/344 (16)	6/75 (8)	<.001
High	127/847 (15)	334/1152 (29)	332/553 (60)	122/158 (77)		81/736 (11)	233/970 (24)	181/341 (53)	54/77 (70)	
Medications										
Aspirin	1190 (99)	1661 (98)	788 (96)	226 (94)	<.001	826 (99)	1114 (98)	475 (98)	100 (95)	.17
Clopidogrel	621 (52)	897 (53)	387 (47)	93 (39)	<.001	457 (55)	725 (64)	309 (63)	61 (58)	<.001
Glycoprotein inhibitors	166 (14)	228 (13)	72 (9)	19 (8)	<.001	84 (10)	100 (9)	19 (4)	5 (5)	<.001
Unfractionated heparin	426 (35)	580 (34)	298 (36)	83 (35)	.72	572 (68)	715 (63)	360 (74)	65 (62)	<.001
ACE inhibitors	718 (60)	1126 (66)	545 (67)	107 (45)	<.001	553 (66)	779 (69)	336 (69)	55 (52)	.005
β-Blockers	903 (75)	1204 (71)	438 (54)	113 (47)	<.001	574 (69)	725 (64)	249 (51)	45 (43)	<.001
Statins	964 (80)	1409 (83)	662 (81)	192 (80)	.16	678 (81)	938 (83)	382 (78)	74 (70)	.01
Hospital stay (d)	4.8±4	5.1±5	5.8±5	6.6±7	<.001	5.8±3	6.1±4	6.8±4	6.7±4	<.001
In-hospital outcomes										
Heart failure	76 (6)	206 (12)	232 (28)	87 (36)	<.001	70 (8)	168 (15)	149 (31)	50 (48)	<.001
Cardiogenic shock	12 (1)	17 (1)	41 (5)	21 (9)	<.001	31 (4)	72 (6)	104 (21)	32 (30)	<.001
Mortality	7 (0.6)	15 (0.9)	29 (4)	18 (8)	<.001	10 (1)	45 (4)	74 (15)	28 (27)	<.001

^a Data are presented as number (percentage) of patients for categorical data and mean ± SD for continuous data. ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; NSTACS = non-ST-segment elevation ACS; STEMI = ST-segment elevation myocardial infarction.

^b On admission.

as renal function worsened, particularly in patients with STEMI (mild CRI, 64%; moderate CRI, 51%; severe CRI, 43%) (Table 2). As renal function worsened, use of thrombolytic therapy and coronary angiography in patients with CRI also declined. In patients with CRI (eGFR <60 mL/min), the reasons for lack of thrombolytic therapy included contraindication (31% vs 12%), missed diagnosis (25% vs 10%), and delayed presentation (18% vs 5%), when compared with patients with an eGFR of 60 mL/min or greater.

IN-HOSPITAL OUTCOMES

Tables 3 and 4 show in-hospital outcomes in patients with ACS, stratified by eGFR. Compared with patients with a normal eGFR, patients with CRI were at a significantly

increased risk of hospital mortality, heart failure, cardiogenic shock, major bleeding, and stroke in both unadjusted and adjusted multivariate analyses. Subsequent multivariate models adjusting for measured covariates yielded similar results. For patients with mild, moderate, or severe CRI, the risk of in-hospital death (adjusted for treatment differences, coronary angiography, Killip class, diabetes mellitus, sex, and age) was greater than for patients with a normal eGFR (mild: OR, 2.1; 95% CI, 1.2-3.7; moderate: OR, 6.7; 95% CI, 3.9-11.5; and severe: OR, 12; 95% CI, 6.6-21.7). The risk of major bleeding episodes increased as renal function worsened. Trends of a greater risk of stroke were noted as renal function worsened throughout all ACS types, and the point estimates of risk were significant in patients

TABLE 3. Management and In-hospital Outcomes in Patients With ACS, Stratified by eGFR^a

	eGFR (mL/min/1.73 m ²)				<i>P</i> value
	≥90 (n=2041)	60-89 (n=2828)	30-59 (n=1304)	<30 (n=345)	
Therapy on admission					
Aspirin	2016 (99)	2775 (98)	1263 (97)	326 (94)	<.001
Clopidogrel	1078 (53)	1622 (57)	695 (53)	154 (45)	<.001
Unfractionated heparin	998 (49)	1295 (46)	658 (50)	148 (43)	.005
LMW heparin	959 (47)	1387 (49)	557 (43)	166 (48)	.002
Glycoprotein inhibitors	250 (12)	328 (12)	91 (7)	24 (7)	<.001
β-Blockers	1477 (72)	1929 (68)	687 (53)	158 (46)	<.001
ACE inhibitors	1271 (62)	1905 (67)	881 (68)	162 (47)	.001
Thrombolysis ^b	508/836 (61)	749/1133 (66)	205/487 (42)	30/105 (29)	<.001
Therapy at discharge					
Aspirin	1981 (97)	2707 (96)	1168 (90)	290 (84)	<.001
Clopidogrel	1020 (50)	1461 (52)	634 (49)	130 (38)	<.001
β-Blockers	1686 (83)	2190 (77)	843 (65)	209 (61)	<.001
ACE inhibitors	1452 (71)	2097 (74)	876 (67)	136 (39)	<.001
Statins	1642 (80)	2347 (83)	1044 (80)	266 (77)	.01
Coronary angiography	420 (21)	593 (21)	185 (14)	34 (10)	<.001
In-hospital outcomes					
Mortality	17 (0.8)	60 (2)	103 (8)	46 (13)	<.001
Recurrent ischemia	169 (8)	256 (9)	127 (10)	37 (11)	.34
Heart failure	146 (7)	377 (13)	381 (29)	137 (40)	<.001
Cardiogenic shock	43 (2)	89 (3)	145 (11)	53 (15)	<.001
Major bleeding episode	9 (0.4)	18 (0.6)	19 (1.5)	6 (1.7)	.002
Stroke	5 (0.2)	14 (0.5)	20 (1.5)	8 (2.3)	<.001
Hospital stay (d), mean ± SD	5.2±4	5.5±5	6.2±5	6.61±6	<.001

^a Data are provided as number (percentage) of patients, unless otherwise indicated. ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; eGFR = estimated glomerular filtration rate; LWM = low-molecular-weight.

^b For patients with ST-segment elevation myocardial infarction.

with moderate or severe CRI (moderate: OR, 6.0; 95% CI, 2.4-16.9; severe: OR, 10.0; 95% CI, 3.1-29.8). There were no significant differences in the occurrence of new coronary ischemic events between the CRI groups. In the

severe CRI group, 61 patients were receiving dialysis, and the mortality rate was nonsignificantly higher in patients receiving dialysis than in those who were not (13% vs 9%; $P=.22$).

TABLE 4. Odds Ratio for In-hospital Outcomes for the Study Population, Stratified by eGFR^a

	eGFR (mL/min/1.73 m ²)	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI) ^b	P value
Death	60-89	2.6 (1.5-4.4)	.001	2.1 (1.2-3.7)	.006
	30-59	10.0 (6.1-17.1)	<.001	6.7 (3.9-11.5)	<.001
	<30	18.0 (10.0-32.4)	<.001	12.0 (6.6-21.7)	<.001
Heart failure	60-89	2.0 (1.6-2.4)	<.001	1.7 (1.4-2.1)	<.001
	30-59	5.3 (4.3-6.6)	<.001	3.6 (2.9-4.5)	<.001
	<30	8.6 (6.6-11.3)	<.001	5.5 (4.1-7.3)	<.001
Cardiogenic shock	60-89	1.5 (1.0-2.2)	.02	1.4 (0.9-2.0)	.09
	30-59	5.8 (4.1-8.2)	<.001	4.6 (3.2-6.7)	<.001
	<30	8.4 (5.5-12.8)	<.001	6.6 (4.2-10.2)	<.001
Major bleeding episode	60-89	1.4 (0.6-3.2)	.36	1.2 (0.5-2.7)	.64
	30-59	3.3 (1.5-7.3)	.003	2.5 (1.0-5.7)	.03
	<30	4.0 (1.4-11.3)	.009	3.1 (1.0-9.2)	.04
Stroke	60-89	1.6 (0.6-4.8) ^k	.35	1.7 (0.6-4.5)	.29
	30-59	6.6 (2.6-16.4)	<.001	4.2 (1.5-11.7)	.006
	<30	8.0 (2.9-26.3)	<.001	5.7 (1.8-18.5)	.004

^a CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio.

^b Variables are adjusted for age, sex, and diabetes mellitus. Referent group is eGFR ≥90 mL/min/1.73 m².

FIGURE 2. In-hospital mortality rate in men and women in whom chronic renal failure was diagnosed using estimated glomerular filtration rate (eGFR) (left) vs creatinine clearance (CrCl) (right).

When we used eGFR or CrCl for the diagnosis of CRI, women with mild or moderate CRI had a nonsignificantly higher mortality rate than men. This mortality difference was also present in patients with severe CRI but only if the CrCl formula was used (Figure 2). When compared with patients who received thrombolytic therapy, patients with CRI who were eligible for thrombolytic therapy but did not receive it had a higher mortality rate (mild CRI: 2.2% vs 4.9%; moderate CRI: 7.0% vs 13.5%; severe CRI: 32.0% vs 7.0%). In patients with mild, moderate, or severe CRI, the mortality rates were significantly higher in patients who did not undergo coronary angiography than in those who did (2.5%, 8.7%, and 15.0% vs 0.7%, 2.7%, and 0.0%, respectively). Data on outcomes after percutaneous coronary intervention were not available in many of the participating centers.

Figure 3 shows that, on admission, patients with late presentation or atypical presentation had a higher mortality rate than those who presented earlier or presented with typical chest pain.

CrCl vs eGFR

The formula by which the degree of renal dysfunction was assessed (eGFR vs CrCl) was not associated with a significant difference in mortality rates (Figure 4). Figure 5 demonstrates that, of 4 ACS studies that used the eGFR formula,^{4,8} the current study and the GRACE study⁴ showed the highest mortality rate in patients with severe CRI, and the current study had the highest mortality rate in the moderate CRI population. The lowest mortality rate in patients with severe CRI was observed in the ACS I and II studies.^{4,8}

FIGURE 3. Left, Mortality rate in patients with acute coronary syndrome and varying stages of renal insufficiency, stratified by the time of presentation. Right, Mortality rate in patients with varying stages of renal insufficiency, stratified by the predominant presenting symptoms. eGFR = estimated glomerular filtration rate.

FIGURE 4. Mortality rate in patients with acute coronary syndrome and varying stages of chronic renal insufficiency (CRI) as defined by estimated glomerular filtration rate (eGFR) vs creatinine clearance (CrCl).

DISCUSSION

To our knowledge, this is the first study in 6 adjacent Middle Eastern countries that demonstrates the prevalence of different stages of CRI in patients presenting with ACS. This multicenter, observational study made a number of key findings. Patients with varying stages of CRI had higher rates of MACEs across the entire ACS spectrum. Despite their higher inherent risk, patients with CRI underwent coronary angiography less frequently and received less evidence-based therapy for any type of ACS than did those without CRI. Chronic renal insufficiency was associated with higher mortality rates in patients with ACS (mild: 3-fold increase; moderate: 10-fold increase; severe: 18-fold increase). The adjusted odds of cardiogenic shock and heart failure were also higher across all

FIGURE 5. In-hospital mortality in different ACS studies, stratified by the estimated glomerular filtration rate (eGFR). Unadjusted P value for all studies, $P < .001$. Referent group is eGFR ≥ 90 mL/min. ACS = acute coronary syndrome; GRACE = Global Registry of Acute Coronary Events; Gulf RACE = Gulf Registry of Acute Coronary Events.

strata of renal dysfunction in patients with STEMI and NSTACS. The MACEs and mortality differences persisted even after adjustment for age and treatment differences. Mortality rates were 4 times higher in CRI patients with STEMI than in those with NSTACS, regardless of the severity of CRI. Stroke and major bleeding episodes were significantly higher in patients with CRI of varying stages with the underuse of antiplatelet therapy. Mortality rates were significantly higher in patients with moderate or severe CRI who presented later than in those who presented earlier. Atypical chest pain and dyspnea were associated with higher rates of poorer outcomes. Moreover, the worse the renal dysfunction, the longer the delay in initiating therapy. Although the eGFR method has not yet been validated in the Arab Middle Eastern population,¹⁶ the in-hospital mortality rate did not differ significantly when we analyzed our patients' data using the eGFR vs the CrCl method.

Chronic renal insufficiency is at least as important as other factors traditionally associated with mortality in patients with coronary artery disease (eg, heart failure). In addition to treatment differences, several mechanisms may contribute to poorer outcomes in patients with CRI after STEMI and NSTACS, including a high prevalence of comorbid conditions and metabolic derangements.^{1,6,17-19} Our study confirmed previous findings^{2,3,6,20} that patients with CRI had an increased prevalence of risk factors in addition to a higher incidence of atypical presentation and prehospital delay. Pitsavos et al²¹ studied 2172 patients with ACS and observed that patients with CRI sought medical attention later than those with normal renal function. This delay in seeking medical attention was attributed to the fact that diabetes mellitus, which may impair sensation of myocardial ischemic pain, was more common among patients with renal dysfunction. Furthermore, in the current study we found that CRI is a predictor of the absence of chest pain in patients with ACS at presentation (OR, 1.35). These findings should alert physicians to the importance of clinical history in patients with CRI.

The risk of stroke was significantly higher in patients with CRI than in patients with an eGFR of 60 mL/min or greater, consistent with the findings of previous studies showing an association between moderate renal dysfunction and stroke.^{3,22,23} Major bleeding episodes were observed more often in CRI groups, probably as a result of the decreased platelet function commonly observed in patients with CRI.^{24,25} The current study did not find significant differences in the rate of recurrent ischemia between CRI groups. This observation may underestimate the occurrence of myocardial ischemia in patients with CRI and may be explained in part by the significantly

higher incidence of angina equivalent in the form of heart failure in these patients.

The actual rate of cardiogenic shock in patients with CRI is poorly defined. In the current study, CRI at any stage was an independent predictor of cardiogenic shock across the entire ACS spectrum. Masoudi et al⁶ reported that the only variable associated with a higher odds of death than severe CRI was cardiogenic shock during the index hospitalization (OR of cardiogenic shock in patients with severe CRI: 10.5 [95% CI, 5.6-19.6] for the study by Masoudi et al vs 8.4 [95% CI, 5.5-12.8] for our study). Furthermore, our study demonstrated that patients with ACS (STEMI and NSTACS) and severe CRI had longer hospital stays with more deterioration of renal function than did those with ACS and normal or mild renal dysfunction (Table 2). This finding demonstrates that CRI constitutes a further burden on hospital resources in patients with ACS.

Several studies have reported an association between more intensive treatment and lower in-hospital or short-term mortality.^{4,6,18,26} These studies, including Gulf RACE, suggested that the presence of renal insufficiency should alert physicians to a significantly increased risk of mortality in all patients with ACS, which may in turn support more aggressive treatment to optimize outcomes. Our study showed less frequent use of coronary angiography in ACS patients with CRI, despite recent data from 5 randomized trials showing an association between an early invasive strategy and nonsignificant reductions in all-cause mortality in patients with CRI.²⁷ Our study also found that evidence-based therapy was used less frequently in CRI groups. Reasons for the observed undertreatment in patients with CRI likely include concerns over comorbid conditions, overestimation of poorer outcomes associated with therapy, underestimation of therapy benefit, lack of prospective clinical trial data, and underrecognition of patients' poor prognosis.^{4,28}

The current study has a few limitations. First, data were collected from an observational study. Second, the study was unable to determine whether the patient had acute renal dysfunction, CRI, or a combination of both. The eGFR during hospitalization may not reflect a steady state in some patients with ACS and may reflect nonrenal factors. Third, although cases of ACS were initially identified, the method of case identification may not have been completely specific, because patients with renal insufficiency may be more likely to have elevated levels of cardiac markers.

CONCLUSION

Consistent with the results of a previous large, community-based study,²² our findings emphasize the clinical and

public health importance of CRI that does not necessitate dialysis. Although patients with CRI had a worse clinical risk profile, they received less aggressive treatment. In patients with ACS, CRI is an independent predictor of not only heart failure and cardiogenic shock but also mortality. Further efforts are warranted to determine whether more aggressive treatment will optimize outcomes in these high-risk patients. It is critical that ACS patients with CRI seek medical care early and that their ACS be recognized and treated without delay.

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