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ORIGINAL RESEARCH ARTICLE

Incidence and impact of cardiorenal anaemia syndrome on all-cause mortality in acute heart failure patients stratified by left ventricular ejection fraction in the Middle East

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Abstract

Aims This study aims to evaluate the incidence and impact of cardiorenal anaemia syndrome (CRAS) on all-cause mortality in acute heart failure (AHF) patients stratified by left ventricular ejection fraction (LVEF) status in the Middle East.

Methods and results Data were analysed from 4934 consecutive patients admitted to 47 hospitals in seven Middle Eastern countries (Saudi Arabia, Oman, Yemen, Kuwait, United Arab Emirates, Qatar, and Bahrain) with AHF from February to November 2012. CRAS was defined as AHF with estimated glomerular filtration rate of $<$60 mL/min and low haemoglobin ($<$13 g/dL for men or $<$12 g/dL for women). Analyses were performed using univariate and multivariate statistical techniques. The overall mean age of the cohort was 59 ± 15 years, 62% (n = 3081) were men, and 27% (n = 1319) had CRAS. Co-morbid conditions were common including hypertension (n = 3014; 61%), coronary artery disease (n = 2971; 60%), and diabetes mellitus (n = 2449; 50%). A total of 79% (n = 3576) of the patients had AHF with *reduced* ejection fraction (HF*r*EF) (LVEF $<$ 50%). CRAS patients were associated with major bleeding (1.29% vs. 0.6%; P = 0.017), blood transfusion (10.1% vs. 3.0%; $P < 0.001$), higher re-admission rate for AHF at 3 months' follow-up (27.6% vs. 18.8%; $P < 0.001$) and at 12 months' follow-up (34.3% vs. 26.2%; $P < 0.001$). Multivariate logistic regression demonstrated that patients with CRAS were associated with higher odds of all-cause mortality during hospital admission [adjusted odds ratio (aOR), 2.10; 95% confidence interval (CI): 1.34–3.31; P = 0.001], at 3 months' follow-up (aOR, 1.48; 95% CI: 1.07–2.06; P = 0.018), and at 12 months' follow-up (aOR, 1.45; 95% CI: 1.12–1.87; P = 0.004). Stratified analyses showed that CRAS patients with HF*r*EF were associated with higher odds of all-cause mortality during hospital admission (aOR, 2.03; 95% CI: 1.20–3.45; P = 0.009) and at 12 months' follow-up (aOR, 1.42; 95% CI: 1.06–1.89; P = 0.019) but not at 3 months' follow-up (aOR, 1.43; 95% CI: 0.98–2.09; P = 0.063). However, in AHF patients with *preserved* ejection fraction (LVEF $\geq$ 50%), CRAS was not associated with higher odds of all-cause mortality not only during hospital admission (aOR, 2.15; 95% CI: 0.84–5.55; P = 0.113) but also at 3 months' follow-up (aOR, 1.87; 95% CI: 0.93–3.76; P = 0.078) and at 12 months' follow-up (aOR, 1.59; 95% CI: 0.91–2.76; P = 0.101).

Conclusions The incidence of CRAS was 27%. CRAS was associated with higher odds of all-cause mortality in AHF patients in the Middle East, especially in those with HF*r*EF.

Keywords Cardiorenal syndrome; Heart failure; Chronic kidney disease; Mortality; Arabian Gulf

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Introduction

In 2002, Silverberg *et al*. first described the term cardiorenal anaemia syndrome (CRAS).[1] The term CRAS is widely used in recent years after understanding the importance and association between heart failure (HF), renal failure, and anaemia. It has been demonstrated that any of the above-mentioned three conditions can contribute to the development and worsening of the other two conditions. Hence, the proper understanding of its significance and association is important in the management of CRAS patients.[2]

The role of CRAS in acute HF (AHF) is scarcely investigated as almost all the previous studies were performed on chronic HF (CHF) patients. The prevalence of CRAS in HF ranges between 19% and 62%.[3] In CHF, patients with CRAS have been associated with higher mortality than patients without CRAS.[4] There are currently no data available on AHF and CRAS in the Arabian Gulf region. Hence, the aim of this study was to evaluate the incidence and impact of CRAS on all-cause mortality in AHF patients stratified by left ventricular ejection fraction (LVEF) in the Middle East.

Methods

Gulf CARE is a prospective, multinational, multicentre registry of patients admitted with the diagnosis of AHF to 47 hospitals in seven Middle Eastern countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen). The registry design, methods, and collected clinical variables have been described elsewhere.[5] Briefly, men and women $\geq$ 18 year of age, admitted (from 14 February 2012 to 14 November 2012) to the participating hospitals with an admission diagnosis of AHF, were recruited. Baseline and admission-based variables captured data on demographic, co-morbidities, behavioural risk factors, clinical presentation, investigations, including medication history, and in-hospital outcomes. Follow-up for all-cause mortality was carried out telephonically at 3 months and either telephonically or through outpatient clinic visits at 1 year.

Data entry was carried out online using a custom-designed electronic case-record form (CRF) at the Gulf CARE website (www.gulfcare.org). The study complies with the Declaration of Helsinki. Institutional or national ethics committee or review board approvals were obtained from each of the seven participating countries. The study was registered at clinicaltrials.gov (NCT01467973).

AHF was defined on the basis of the European Society of Cardiology (ESC) criteria.[6] Definitions of data variables in the CRF were based on the 2008 ESC guidelines and the American College of Cardiology clinical data standards.[7] Khat chewing was defined as chewing khat plant/leaves (*Catha edulis* containing cathinone, an amphetamine-like stimulant that can cause euphoria, hypertension, myocardial infarction, and dilated cardiomyopathy)[8] within 1 month of the index admission. Presence of documented chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) of $<$60 mL/min/1.73 m^2 or serum creatinine levels $>$177 mmol/L (or 2 mg/dL) for at least 3 months as well as the presence of renal dysfunction (serum creatinine $>$2 mg/dL) in the setting of acute *de novo* HF or in patients with unknown history of kidney disease. Anaemia was defined as haemoglobin levels of $<$12 g/dL in women and $<$13 g/dL in men. CRAS was defined as the condition where HF, CKD, and anaemia coexist.[1] HF with *preserved* ejection fraction (HF*p*EF) was defined as those with LVEF of $\geq$50%, while HF with *reduced* ejection fraction (HF*r*EF) was defined as those patients with LVEF of $<$50%.[6]

Statistical analysis

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analysed using Pearson's χ^2 test. For continuous variables, mean and standard deviation were used to summarize the data while analysis was performed using Student's *t*-test.

Multivariable logistic regression models were performed to evaluate the impact of CRAS on all-cause mortality (primary outcome) at in-hospital and at 3 and at 12 months post-hospital discharge stratified by LVEF status. In total, there were three models for each time period: Model 1 was for all patients, and the other two models were stratified by LVEF (HF*p*EF and HF*r*EF groups) separately. Multivariate analyses were conducted using logistic regression models utilizing the simultaneous method. For the in-hospital mortality, the model was adjusted for age, gender, body mass index, smoking, khat chewing, peripheral vascular disease (PVD), hypertension, diabetes mellitus, prior stroke/transient ischaemic attack, first admission haemoglobin, systolic blood pressure (BP), diastolic BP, LVEF, serum creatinine, in-hospital percutaneous coronary intervention or coronary artery bypass graft, in-hospital course [including non-invasive ventilation, intubation/ventilation, cardiogenic shock, inotropes, intra-aortic balloon pump, acute dialysis/ultrafiltration, atrial fibrillation (AF) requiring therapy, major bleeding, blood transfusion, stroke, and systemic infection requiring therapy],

intravenous (bolus) furosemide during admission and prior medication use [diuretics, digoxin, oral nitrates, calcium channel blockers (CCBs), beta-blockers, aldosterone antagonist, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARBs), aspirin, and clopidogrel]. For the 3 and 12 months' mortality, the models were adjusted for variables just like in the in-hospital mortality model, except for the fact that instead of the prior medications, they included discharged medications (diuretics, digoxin, oral nitrates, CCBs, beta-blockers, aldosterone antagonist, ACE inhibitors, ARBs, aspirin, and clopidogrel). Furthermore, in-hospital course was also removed from the models at 3 and 12 months.

The goodness of fit of the multivariable logistic model was examined using the Hosmer and Lemeshow goodness-of-fit statistic.[9] Based on the χ^2 distribution, a Hosmer and Lemeshow statistic with a $P > 0.05$ is considered a good fit. The discriminatory power of the logistic model was assessed by the area under the receiver operating characteristic (ROC) curve, also known as the *C*-index.[10] A model with perfect discriminative ability has a *C*-index of 1.0; an index of 0.5 provides no better discrimination than chance. Models with area under the ROC curve of >0.7 are preferred. An *a priori* two-tailed level of significance was set at $P < 0.05$. Statistical analyses were conducted using STATA Version 13.1 (STATA Corporation, College Station, TX, USA).

Table 1 Demographic and clinical characteristics of the cohort stratified by cardiorenal anaemia syndrome status among patients with acute heart failure

Characteristic, n (%) unless specified otherwise	All (n = 4934)	CRAS		*P*-value
		No (n = 3615)	Yes (n = 1319)	
Demographic				
Age, mean ± SD, years	59 ± 15	57 ± 15	65 ± 14	<0.001
Male gender	3081 (62%)	2378 (66%)	703 (53%)	<0.001
BMI, mean ± SD, kg/m^2	28.1 ± 6.3	27.8 ± 6.0	29.1 ± 7.0	<0.001
Smoking	1076 (22%)	912 (25%)	164 (12%)	<0.001
Khat	886 (18%)	738 (20%)	148 (11%)	<0.001
Alcohol	175 (3.6%)	152 (4.2%)	23 (1.7%)	<0.001
Medical history				
Hyperlipidaemia	1770 (36%)	1126 (31%)	644 (49%)	<0.001
CAD	2971 (60%)	2107 (58%)	864 (66%)	<0.001
Hypertension	3014 (61%)	1992 (55%)	1022 (77%)	<0.001
Diabetes mellitus	2449 (50%)	1560 (43%)	889 (67%)	<0.001
PVD	208 (4.2%)	102 (2.8%)	106 (8.0%)	<0.001
Stroke/TIA	399 (8.1%)	231 (6.4%)	168 (13%)	<0.001
AF	594 (12%)	408 (11%)	186 (14%)	0.007
CKD/dialysis	740 (15%)	219 (6.1%)	521 (40%)	<0.001
Clinical parameters at presentation				
HR, mean ± SD, b.p.m.	78 ± 13	78 ± 12	76 ± 14	<0.001
SBP, mean ± SD, mmHg	138 ± 34	137 ± 34	141 ± 34	<0.001
DBP, mean ± SD, mmHg	81 ± 20	82 ± 20	79 ± 19	<0.001
Crea, mean ± SD, μmol/L	128 ± 110	99 ± 64	207 ± 159	<0.001
LVEF, mean ± SD, %	37 ± 14	36 ± 14	38 ± 14	0.017
Hg, mean ± SD, g/dL	12.6 ± 2.4	13.4 ± 2.2	10.4 ± 1.5	<0.001
In-hospital course				
PCI/CABG	353 (7.2%)	303 (8.4%)	50 (3.8%)	<0.001
Treatment course[a]	2224 (45%)	1519 (42%)	705 (53%)	<0.001
Admission diagnosis				
De novo AHF	2251 (46%)	1805 (50%)	446 (34%)	<0.001
ADCHF	2683 (54%)	1810 (50%)	873 (66%)	
NYHA at discharge[b]				
I	2423 (52%)	1892 (55%)	531 (44%)	
II	1837 (40%)	1261 (37%)	576 (48%)	<0.001
III	145 (3.1%)	103 (3.0%)	42 (3.5%)	
IV	221 (4.8%)	170 (5.0%)	51 (4.3%)	

ADCHF, acute decompensated chronic heart failure; AF, atrial fibrillation; AHF, acute heart failure; b.p.m., beats per minute; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; Crea, first serum creatinine; CRAS, cardiorenal anaemia syndrome; DBP, diastolic blood pressure; Hg, first haemoglobin on admission; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack.
CRAS was defined as estimated glomerular filtration rate of <60 mL/min and haemoglobin of <13 g/dL for men or <12 g/dL for women. HR was missing in 202 subjects, SBP and DBP in 155, and LVEF in 426. Percentages might not add up to 100% owing to rounding off.
[a]Treatment course included non-invasive ventilation, intubation/ventilation, cardiogenic shock, inotropes, intra-aortic balloon pump, acute dialysis/ultrafiltration, atrial fibrillation requiring therapy, major bleeding, blood transfusion, stroke, and systemic infection requiring therapy.
[b]Last NYHA classification excluded those who died in-hospital (n = 308).

Results

The analysed cohort consisted of 4934 patients, after removing 71 subjects (1.4%) who had missing anaemia and eGFR. The overall mean age of the cohort was 59 ± 15 years in which 62% (n = 3081) were men. Fifty-four per cent of the patients (n = 2683) presented with acute decompensated CHF (ADCHF) with the mean LVEF of 37 ± 14%. Co-morbid conditions were common in this cohort particularly hypertension (n = 3014; 61%), coronary artery disease (CAD; n = 2971; 60%), diabetes mellitus (n = 2449; 50%), and hyperlipidaemia (n = 1770; 36%), and 79% (n = 3576) had HF*r*EF. The rest of the demographic and clinical variables are shown in *Table 1*.

A total of 27% (n = 1319) of the AHF patients had CRAS. CRAS patients were older (65 vs. 57 years; $P < 0.001$) and more likely to be obese (29.1 vs. 27.8 kg/m^2; $P < 0.001$); presented with higher rates of hyperlipidaemia (49% vs. 31%; $P < 0.001$), CAD (66% vs. 58%; $P < 0.001$), hypertension (77% vs. 55%; $P < 0.001$), diabetes mellitus (67% vs. 43%; $P < 0.001$), stroke/transient ischaemic attack (13% vs. 6.4%; $P < 0.001$), PVD (8.0% vs. 2.8%; $P < 0.001$), AF (14% vs. 11%; P = 0.007), CKD/dialysis (40% vs. 6.1%; $P < 0.001$), and lower admission haemoglobin levels (10.4 vs. 13.4 g/dL; $P < 0.001$). The CRAS group was more likely to have treatment course during hospital admission (53% vs. 42%; $P < 0.001$). The CRAS cohort was also more likely to be associated with ADCHF than were those who did not have CRAS (66% vs. 50%; $P < 0.001$) (*Table 1*).

The majority of the patients were on standard HF therapy. Intake of digoxin prior to the admission was found almost similar in both groups (16% vs. 17%; P = 0.600). ACE inhibitors were the only medication type that the non-CRAS group used more than did the CRAS cohort (44% vs. 38%; $P < 0.001$), and this persisted even during discharge. Use of beta-blockers (72% vs. 66%; $P < 0.001$) and aldosterone antagonist (48% vs. 31%; $P < 0.001$) was more in the non-CRAS group compared with the CRAS group (*Table 2*).

The overall cumulative all-cause mortality at in-hospital, 3 months, and 1 year was 5.1% (n = 231), 11.6% (n = 521), and 19.2% (n = 867), respectively. After adjusting for demographic and clinical characteristics as well as medication use in the overall multivariate logistic regression models (*Table 3*), the CRAS group was associated with higher odds of all-cause mortality during admission [adjusted odds ratio (aOR), 2.10; 95% confidence interval (CI): 1.34–3.31;

Table 2 Medication utilization of the cohort stratified by cardiorenal anaemia syndrome status among patients with acute heart failure

Characteristic, n (%) unless specified otherwise	All (n = 4934)	CRAS		P-value
		No (n = 3615)	Yes (n = 1319)	
Prior medications				
Diuretics	2834 (57%)	1921 (53%)	913 (69%)	<0.001
Digoxin	819 (17%)	594 (16%)	225 (17%)	0.600
Oral nitrates	1265 (26%)	795 (22%)	470 (36%)	<0.001
CCBs	655 (13%)	338 (9.4%)	317 (24%)	<0.001
ACE inhibitors	2097 (43%)	1592 (44%)	505 (38%)	<0.001
ARBs	628 (13%)	403 (11%)	225 (17%)	<0.001
Statins	2519 (51%)	1687 (47%)	832 (63%)	<0.001
Aspirin	3037 (62%)	2115 (59%)	922 (70%)	<0.001
Ivabradine	115 (2.3%)	70 (1.9%)	45 (3.4%)	0.002
Beta-blockers	2155 (44%)	1500 (41%)	655 (50%)	<0.001
Aldosterone antagonists	822 (17%)	595 (16%)	227 (17%)	0.531
Intravenous (IV) medications during admission				
IV furosemide—bolus	4482 (91%)	3271 (90%)	1211 (92%)	0.152
IV furosemide—infusion	856 (17%)	559 (15%)	297 (23%)	<0.001
IV nitrates—infusion	997 (20%)	706 (20%)	291 (22%)	0.050
Discharged medications (n = 4626)[a]				
Diuretics	4340 (94%)	3213 (94%)	1127 (94%)	0.868
Digoxin	1153 (25%)	893 (26%)	260 (22%)	0.002
Oral nitrates	1757 (38%)	1185 (35%)	572 (48%)	<0.001
CCBs	727 (16%)	390 (11%)	337 (28%)	<0.001
ACE-I	2812 (61%)	2287 (67%)	525 (44%)	<0.001
ARBs	775 (17%)	562 (16%)	213 (18%)	0.283
Statins	3348 (72%)	2433 (71%)	915 (76%)	<0.001
Aspirin	3741 (81%)	2777 (81%)	964 (80%)	0.584
Ivabradine	238 (5.1%)	163 (4.8%)	75 (6.3%)	0.044
Beta-blockers	3262 (71%)	2469 (72%)	793 (66%)	<0.001
Aldosterone antagonists	2002 (43%)	1629 (48%)	373 (31%)	<0.001

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CRAS, cardiorenal anaemia syndrome.
CRAS was defined as estimated glomerular filtration rate of <60 mL/min and haemoglobin of <13 g/dL for men or <12 g/dL for women. Percentages might not add up to 100% owing to rounding off.
[a]Medications at discharged only included those who were discharged alive from the hospital and did not leave against medical advice (n = 4626).

Table 3 Impact of cardiorenal anaemia syndrome status on mortality (at in-hospital, at 3 months, and at 12 months) of the Gulf CARE cohort stratified by left ventricular ejection fraction status

	Pearson's χ^2 test				Multivariate logistic regression			
Mortality	All	No CRAS	CRAS	*P*-value	Adj. OR [95% CI]	Adj. *P*-value	HL	ROC
In-hospital								
All patients	231 (5.1%)	132 (4.0%)	99 (8.3%)	<0.001	2.10 [1.34–3.31]	0.001	0.175	0.87
HF*p*EF (LVEF ≥ 50%)	53 (5.7%)	33 (5.1%)	20 (7.1%)	0.222	2.15 [0.84–5.55]	0.113	<0.001	0.85
HF*r*EF (LVEF < 50%)	178 (5.0%)	99 (3.7%)	79 (8.7%)	<0.001	2.03 [1.20–3.45]	0.009	0.311	0.87
3 months								
All patients	521 (11.6%)	322 (9.7%)	199 (16.7%)	<0.001	1.48 [1.07–2.06]	0.018	<0.001	0.77
HF*p*EF (LVEF ≥ 50%)	115 (12.3%)	74 (11.4%)	41 (14.5%)	0.179	1.87 [0.93–3.76]	0.078	0.096	0.79
HF*r*EF (LVEF < 50%)	406 (11.4%)	248 (9.3%)	158 (17.4%)	<0.001	1.43 [0.98–2.09]	0.063	0.005	0.77
12 months								
All patients	867 (19.2%)	545 (16.4%)	322 (27.1%)	<0.001	1.45 [1.12–1.87]	0.004	0.008	0.74
HF*p*EF (LVEF ≥ 50%)	181 (19.4%)	114 (17.5%)	67 (23.8%)	0.027	1.59 [0.91–2.76]	0.101	0.742	0.74
HF*r*EF (LVEF < 50%)	686 (19.2%)	431 (16.2%)	255 (28.1%)	<0.001	1.42 [1.06–1.89]	0.019	0.022	0.74

ACE, angiotensin-converting enzyme; Adj. OR, adjusted odds ratio; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CI, confidence interval; CRAS, cardiorenal anaemia syndrome; HF*p*EF, heart failure with *preserved* ejection fraction; HF*r*EF, heart failure with *reserved* ejection fraction; HL, Hosmer and Lemeshow *P*-value; LVEF, left ventricular ejection fraction; ROC, area under the receiver operating characteristic curve, also known as *C*-statistic.
CRAS was defined as estimated glomerular filtration rate of <60 mL/min and haemoglobin of <13 g/dL for men or <12 g/dL for women. Per cents are row percentages. Multivariate analyses were conducted using logistic regression models utilizing the simultaneous method. For the in-hospital mortality, the model adjusted for age, gender, body mass index, smoking, khat chewing, peripheral vascular disease, hypertension, diabetes mellitus, prior stroke/transient ischaemic attack, systolic blood pressure, diastolic blood pressure, LVEF, serum creatinine, in-hospital percutaneous coronary intervention or coronary artery bypass graft, in-hospital course (including non-invasive ventilation, intubation/ventilation, cardiogenic shock, inotropes, intra-aortic balloon pump, acute dialysis/ultrafiltration, atrial fibrillation requiring therapy, major bleeding, blood transfusion, stroke, and systemic infection requiring therapy), prior medication use [diuretics, digoxin, oral nitrates, CCBs, beta-blockers, aldosterone antagonist, ACE inhibitors, ARBs, aspirin, I_f channel blocker (ivabradine)], intravenous (bolus) furosemide during admission, admission diagnosis (acute decompensated chronic heart failure or acute heart failure), and New York Heart Association functional class. For the 3 and 12 months' mortality, the models adjusted for variables just like in the in-hospital mortality model, except for the fact that instead of the prior medications, they included discharged medications [diuretics, digoxin, oral nitrates, CCBs, beta-blockers, aldosterone antagonist, ACE inhibitors, ARBs, aspirin, and I_f channel blocker (ivabradine)]. From an original discharged cohort of 4934 (excluding those who died in-hospital and left against medical advice), lost to follow-up reached a total of 1.5% (n = 75) at 3 months and still remained at 1.5% (n = 75) at 1 year. However, as the analysis was stratified by LVEF, this excluded those who had missing LVEF (n = 426) on admission, leaving the analysable cohort of 4508.

P = 0.001], at 3 months' follow-up (aOR, 1.48; 95% CI: 1.07–2.06; *P* = 0.018), and at 12 months' follow-up (aOR, 1.45; 95% CI: 1.12–1.87; *P* = 0.004).

It was in those patients with HF*r*EF, when stratified by LVEF, that CRAS was associated with higher odds of all-cause mortality during hospital admission (aOR, 2.03; 95% CI: 1.20–3.45; *P* = 0.009) and at 12 months' follow-up (aOR, 1.42; 95% CI: 1.06–1.89; *P* = 0.019) but not at 3 months' follow-up (aOR, 1.43; 95% CI: 0.98–2.09; *P* = 0.063). In those patients with HF*p*EF, CRAS was not associated with higher odds of all-cause mortality during hospital admission (aOR, 2.15; 95% CI: 0.84–5.55; *P* = 0.113), at 3 months' follow-up (aOR, 1.87; 95% CI: 0.93–3.76; *P* = 0.078), or at 12 months' follow-up (aOR, 1.59; 95% CI: 0.91–2.76; *P* = 0.101).

Of note, there were a total of 39 (0.8%) events of major bleeds in the cohort with the CRAS group more likely to be associated with major bleeds (1.3 vs. 0.6%; *P* = 0.017). The CRAS cohort was also more likely to be associated with the utilization of blood transfusion between the groups (10.8 vs. 3.0%; *P* < 0.001). Additionally, the CRAS group was also more likely to be associated with higher rates of hospitalization for HF at 3 months (27.6% vs. 18.8%; *P* < 0.001) and at 12 months (34.3% vs. 26.2%; *P* < 0.001).

Discussion

This is among the first cardiorenal anaemia syndrome studies in AHF patients in the Middle East. In this cohort of AHF patients, 27% had CRAS, which was also associated with worse all-cause mortality during in-hospital, at 3 months' follow-up, and at 12 months' follow-up, than in AHF patients who did not have CRAS, especially in those patients with HF*r*EF.

Incidence of CRAS varies from 3% to 44.4%.[11–14] In Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trial, 14% (371/2653) of the patients were identified to have CRAS.[11] From a Canadian population-based study of new onset HF, 3% (362/12 065) of the patients had CRAS.[12] In a small Tanzanian study, they found that 44% (202/455) of the patients had CRAS.[13] In another study, 22% (210/955) of the patients had CRAS.[14] In our study, we found that ~27% patient population comes under the CRAS category, which is almost double the results we obtained from CHARM trial. We hypothesize that this may be due to differences in ethnicity.

Over the past two decades, the medical community is curiously investigating and initiating various research

registries for the CRAS population. In the ATTEND registry, CRAS patients were considered as high-risk category relative to patients without anaemia or renal dysfunction. CRAS in patients at discharge was an independent predictor of re-admission for HF and mortality.[15,16] Review of literature shows CRAS patients were associated with higher mortality.[17] Left ventricular dysfunction and renal dysfunction are independent predictors of poor prognosis and higher mortality.[18] In a single-centred study, it was shown that, along with anaemia in AHF patients, a high red blood cell distribution width was associated with higher all-cause mortality.[19]

Literature review shows that in the European Society of Cardiology—Heart Failure (ESC-HF) pilot registry, 26% (1300/5000) of AHF patients had CKD. In Acute Decompensated Heart Failure National Registry (ADHERE), 64% (76 800/120 000) of the patients had CKD.[20,21] In our study, CKD was present in 44% patients, which comes between the ESC-HF and ADHERE results.

Anaemia was found in 31% (1550/5000) of the patients of (ESC-HF) pilot registry, 40% (48 000/120 000) of the patients in ADHERE registry, 37% (55 500/150 000) of the patients in a meta-analysis of 34 trials, and 33% of the patients in the EuroHeart Failure Survey.[22–25] In a small study of 142 CHF patients who visited the outpatient clinic, 55.6% of patients had anaemia.[26,27] In our study, 48% of the patients had anaemia, which was slightly higher than that of all the previous major studies. Higher incidence of anaemia in our study may be due to the criteria used or due to regional variation.

The Framingham study did an analysis of CHF patients' data from 1950 to 1959, which showed a 1 year mortality of 30%, and the adjusted data for mortality among CHF patients during 1990 to 1999 were 28%.[28] In a cohort of 1 136 201 patients from the Medicare database, an annual mortality of 23% (261 326/1 136 201) in patients with CRAS was shown. If you compare 2 year mortality, then the probability will rise to 300%.[29] In an Australian study, patients had greater all-cause mortality, which is 55% (411/748).[4] In our study, the overall mortality at in-hospital, 3 months, and 12 months was higher with the CRAS group.

The limitation of this study is its nature of being a registry, which may have introduced bias through confounding by variables not controlled for or measured (such as iron levels and history of chronic anaemia). This study is a subanalysis of an observational study, which is like any observational study, where the possibility for unmeasured confounding variables exists. In some countries, only a few hospitals took part in the registry; hence, the results are not entirely generalizable. Reasons for underuse of medications or procedures were not known in this study. The recording of natriuretic peptides was optional as not all countries routinely measure them. Echocardiographic interpretation was at the discretion of the person performing the study; no centralized evaluation was performed. Patients' renal function at discharge is unknown, and there are no data regarding the frequency of patients with improvement of renal function. This study did not record the cognitive status and the disability status in patients with stroke, which obviously have a major impact on morbidity and mortality and only 1 year mortality. Mortality rates at follow-up were only recorded at 1 year without the specification of the exact date of death of each patient, and hence, the Kaplan–Meier curves could not have been performed. Finally, no information was available regarding the cause of stroke. Future studies need to overcome these limitations.

Conclusions

In conclusion, the incidence of cardiorenal anaemia syndrome in AHF in the Arabian Gulf citizens was 27%. CRAS was associated with worse short-term and long-term all-cause cumulative mortality in AHF patients, especially in those with HF*r*EF.

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Conflict of interest

None declared.

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