

# Precipitating Factors for Hospitalization with Heart Failure: Prevalence and Clinical Impact Observations from the Gulf CARE (Gulf aCute heArt failuRe rEgistry)

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## Highlights of the Study

- This is the first large evaluation of the prevalence and impact of precipitating factors for hospitalization of patients with acute heart failure in the Middle East.
- It underlines the urgent need to address noncompliance with medications and ischemic heart disease with preventive and therapeutic interventions to reduce the burden and cost of hospitalizations due to heart failure in our region.

## Keywords

Heart failure · Precipitating factors · Mortality

## Abstract

**Objective:** Despite the expanding burden of heart failure (HF) worldwide, data on HF precipitating factors (PFs) in developing countries, particularly the Middle East, are very limited.

We examined PFs in patients hospitalized with acute HF in a prospective multicenter HF registry from 7 countries in the Middle East. **Method:** Data were derived from the Gulf

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CARE (Gulf aCute heArt failuRe rEgistry) for a prospective, multinational, multicenter study of consecutive patients hospitalized with HF in 47 hospitals in 7 Middle Eastern countries between February 2012 and November 2012. PFs were determined by the treating physician from a pre-defined list at the time of hospitalization. **Results:** The study included 5,005 patients hospitalized with acute HF, 2,276 of whom (45.5%) were hospitalized with acute new-onset HF (NOHF) and 2,729 of whom (54.5%) had acute decompensated chronic HF (DCHF). PFs were identified in 4,319 patients (86.3%). The most common PF in the NOHF group was acute coronary syndromes (ACS) (39.2%). In the DCHF group, it was noncompliance with medications (27.8%). Overall, noncompliance with medications was associated with a lower in-hospital mortality (OR 0.47; 95% CI 0.28–0.80;  $p = 0.005$ ) but a higher 1-year mortality (OR 1.43; 95% CI 1.1–1.85;  $p = 0.007$ ). ACS was associated with higher in-hospital mortality (OR 1.84; 95% CI 1.26–2.68;  $p = 0.002$ ) and higher 1-year mortality (OR 1.62; 95% CI 1.27–2.06;  $p = 0.001$ ). **Conclusion:** Preventive and therapeutic interventions specifically directed at noncompliance with medications and ACS are warranted in our region.

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## Introduction

Heart failure (HF) is a global pandemic affecting an estimated 26 million people worldwide and resulting in significant mortality, morbidity, and cost of care [1, 2]. The annual direct costs of HF in the USA alone are projected to increase from USD 20.9 billion in 2012 to USD 53.1 billion in 2030, with 80% of these costs of care attributable to hospitalizations [3]. Hospitalization for acute HF can be due to acute new-onset “de novo” HF (NOHF) and acute decompensated chronic HF (DCHF). A number of factors have been identified as precipitating acute HF hospitalizations [4–11]. These include: myocardial ischemia, nonadherence to medications, arrhythmias, infection, uncontrolled hypertension (HTN), anemia, renal impairment, and diet. Understanding the precipitating factors (PF) that lead to acute HF hospitalizations, particularly those that are avoidable, is of great importance in reducing the HF disease burden and improve outcomes. However, there is a limited number of studies evaluating the prevalence of PF in a real-world acute HF patient population and the implications of different types of common PF on long-term outcomes. In addition, most reported data included either DCHF or a mixture of NOHF and DCHF, but no studies comparing both in terms of PF prevalence and outcomes.

This study was carried out in a large cohort of patients enrolled in the Gulf CARE (aCute heArt failuRe rEgistry) and was designed to (1) identify the prevalence of PFs in a large real-world cohort of consecutive patients hospitalized with acute HF, (2) differentiate the frequency of different PFs according to the type of acute HF (NOHF or DCHF), and (3) evaluate the impact of PFs on the immediate and 1-year clinical outcomes.

## Methods

### Registry Design

Gulf CARE involved a multicenter, multinational, prospective, observational study that recruited patients admitted with a final diagnosis of acute HF to 47 hospitals in 7 countries in the Arabian Gulf (Oman, Saudi Arabia, UAE, Qatar, Bahrain, Yemen, and Kuwait) between February 2012 and November 2012 [12]. Data were collected on episodes of hospitalization as per a standardized case report form (CRF), beginning at the point of initial care and including each patient’s date of discharge, transfer out of hospital, or in-hospital death, and for those discharged alive at a 3- and 12-month follow-up. Each patient was given a unique ID number to prevent double counting. The study was registered at clinicaltrials.gov with the number NCT01467973. Registry design, methodology, and hospital characteristics have been previously described in detail [13].

This study included patients with acute HF of both genders who were  $\geq 18$  years old and admitted to the participating hospitals. Acute HF was defined based on the European Society of Cardiology (ESC) definition [14]. Acute HF was further classified as either DCHF or NOHF, also based on ESC guidelines [14]. DCHF was defined as worsening HF in patients with a previous diagnosis or hospitalization for HF. NOHF was defined as acute HF in patients with no prior history of HF.

Patients were excluded from the study if (1) they were discharged from the emergency room without admission, (2) they were transferred from a nonregistry hospital, (3) they could not provide informed consent, or (4) their final diagnosis was not HF. Registry organization and data collection and validation are outlined in a previous report from the Gulf CARE [12, 13]. PFs for hospitalization were entered by the treating physician from a pre-defined list in the CRF at the time of hospitalization. Each patient was assigned 1 major factor that led to hospitalization. When no factors were clearly identified, this was recorded as “unknown.”

Definitions of variables in the CRF were based on the 2008 ESC guidelines and the 2005 American College of Cardiology (ACC) clinical data standards [14, 15]. Diabetes mellitus (DM) was defined as having a history of diabetes diagnosed and treated with medication and/or insulin, or fasting blood glucose  $7.0$  mmol/L ( $126$  mg/dL), or hemoglobin (Hb) $A_{1c} \geq 6.5\%$ . HTN was defined as having a history of HTN diagnosed and treated with medication, systolic blood pressure (BP)  $>140$  mm Hg or diastolic BP  $>90$  mm Hg on at least 2 occasions, or for patients with diabetes or chronic kidney disease (CKD) systolic BP  $>130$  mm Hg or diastolic BP  $>80$  mm Hg on at least 2 occasions. Hyperlipidemia was defined as a history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol  $>5.18$  mmol/L ( $200$  mg/dL), low-density

lipoprotein cholesterol  $\geq 3.37$  mmol/L (130 mg/dL) or high-density lipoprotein cholesterol  $< 1.04$  mmol/L (40 mg/dL). Patients smoking cigarettes, a water pipe, or cigars, or chewing tobacco within 1 month of index admission were classified as current smokers. CKD was defined as a glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup> for  $\geq 3$  months, with or without kidney damage or on dialysis. If no GFR was available, serum creatinine  $> 177$  mmol/L or 2 mg/dL was marked as CKD. Obesity was defined as a body mass index (BMI)  $> 25$ . Cardiomyopathy was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal (in the absence of coronary artery disease [CAD], HTN, valvular disease, or congenital heart disease) sufficient to cause the observed myocardial abnormality. A definition of infection in the registry was any systemic infection needing antibiotics. The presence of CAD was defined according to a history of CAD, myocardial infarction, or any coronary revascularization procedure including percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG).

The primary objective of this study was to identify the rate of each PF in the acute DCHF and NOHF groups. The secondary objective was to identify the in-hospital and 1-year outcome associated with different PFs. End points assessed for in-hospital outcomes were mortality and length of stay (LOS); end points assessed at 1 year were rehospitalization rates for HF and mortality.

#### Statistical Analysis

Baseline and outcome variables were presented as *n* (%) for categorical variables, and interval variables were presented as mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for nonnormally distributed variables. The  $\chi^2$  test or Fisher exact test for  $< 5$  cells were applied to see if there were associations between the NOHF and DCHF groups regarding categorical variables. The Student *t* test was used for normally distributed-interval variables and the Wilcoxon rank sum test for nonnormally distributed interval variables. The associations between PFs and mortality (in-hospital and 1-year) and PFS and 1-year rehospitalization were examined using multivariate logistic regressions. Adjusted odds ratio (OR) and 95% confidence interval (CI) were used to quantify the association between baseline variables and mortality.  $p < 0.05$  (two-tailed) was considered statistically significant. The Statistical Package for the Social Sciences v22.0 (SPSS Inc., USA) was used for the analysis.

## Results

The study included 5,005 patients hospitalized with acute HF, 2,276 of whom (45.5%) were hospitalized with acute NOHF and 2,729 of whom (54.5%) were hospitalized with acute DCHF. Overall, PFs for HF hospitalizations were identified in 4,319 patients (86.3%) as follows: noncompliance with medications in 964 (19.3%), noncompliance with diet in 136 (2.7%), acute coronary syndromes (ACS) in 1,365 (27.3%), uncontrolled HTN in 410 (8.2%), arrhythmia in 301 (6.0%), anemia in 154 (3.1%), infection in 731 (14.6%), and worsening renal function in 221 (4.4%).

#### Baseline Characteristics

Patients with NOHF were 4 years younger and more likely to be current smokers while patients with DCHF were more likely to have prior systolic left ventricular dysfunction, CAD, valvular heart disease, atrial fibrillation, stroke/transient ischemic attacks, DM, HTN, hyperlipidemia, CKD, asthma/chronic obstructive pulmonary disease (COPD), thyroid disease, and prior revascularization procedures. Patients with NOHF had a higher heart rate, systolic and diastolic BP, and elevated troponins. Patients with DCHF had significantly lower ejection fraction on echocardiography. N-terminal pro-B-type natriuretic peptide levels were similar in the 2 groups (Table 1).

#### PFs for Hospitalization for HF

PFs for HF hospitalizations were identified in 1,894 patients in the NOHF group (83.2%) and in 2,425 in the DCHF group (88.9%). The most common PF identified in the NOHF group was ACS (39.2%), followed by infection (11.1%), and uncontrolled HTN (9.7%). The most common PF identified in the DCHF group was noncompliance with medications (27.8%), followed by infection (17.5%), and ACS (17.3%) (Table 1).

#### Outcomes and Follow-up

There were no significant differences between the 2 groups regarding in-hospital mortality and LOS. At the 1-year follow-up, mortality and rehospitalization for HF were significantly higher in the DCHF group than in the NOHF group. Revascularization procedures (PCI/CABG) were more common in the NOHF group with no significant differences in coronary angiographic findings (Table 2).

#### Outcomes according to PFs

In the NOHF group, the longest LOS was seen in patients with anemia and worsening renal function (8 days for both), followed by arrhythmia and infection (7 days for both). The shortest LOS was seen with HTN and noncompliance with diet (5 days for both).

In the DCHF group, the longest LOS was seen with arrhythmia (9 days), followed by infection (8 days). The shortest LOS was seen with HTN and noncompliance with diet (5 days for both) (Fig. 1a).

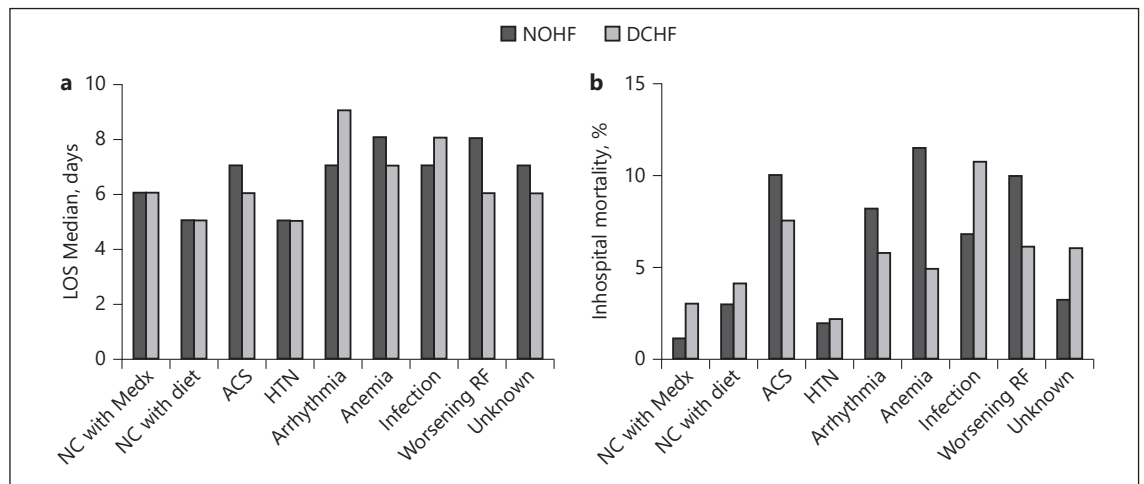
#### In-hospital Mortality

In the NOHF group, the highest mortality rate was seen with anemia (11.4%), followed by ACS and infection (9.9% for both), while the lowest rate was seen with HTN (1.8%).

**Table 1.** Baseline characteristics

	Acute NOHF ( <i>n</i> = 2,276; 45.5%)	Acute DCHF ( <i>n</i> = 2,729; 54.5%)	<i>p</i> value
Age, years	57±14.7	61±15.0	<0.001
Female sex	831 (36.5)	1,043 (38.2)	0.214
A previous CV history			
Known systolic LV dysfunction	249 (10.9)	2,033 (74.5)	<0.001
Known CAD	690 (30.3)	1,647 (60.4)	<0.001
Atrial fibrillation	145 (6.4)	462 (16.9)	<0.001
Valvular heart disease	176 (7.6)	502 (18.4)	<0.001
Congenital heart disease	18 (0.8)	23 (0.8)	0.839
PVD	89 (3.9)	134 (4.9)	0.088
Stroke/TIA	126 (5.5)	278 (10.2)	<0.001
A family history of cardiomyopathy/HF	127 (5.6)	132 (4.8)	0.237
Other comorbidities			
Current smoker	673 (29.6)	430 (15.8)	<0.001
Diabetes mellitus	1,008 (44.3)	1,484 (54.4)	<0.001
Hypertension	1,239 (54.4)	1,820 (66.7)	<0.001
Hyperlipidemia	619 (27.2)	1,180 (43.2)	<0.001
CKD/dialysis	213 (9.4)	531 (19.5)	<0.001
Sleep apnea requiring therapy	33 (1.4)	66 (2.4)	0.014
Asthma/COPD	180 (7.9)	321 (11.8)	<0.001
Thyroid disease	50 (2.2)	131 (4.8)	<0.001
Past cardiac procedures			
PCI	163 (7.2)	376 (13.8)	<0.001
CABG	90 (4.0)	276 (10.1)	<0.001
Clinical and biochemical parameters			
Heart rate, bpm	98.5±24	95.2±22.4	<0.001
Systolic BP, mm Hg	142±35.0	133.5±32.9	<0.001
Diastolic BP, mm Hg	84.6±20.3	78.4±18.8	<0.001
Respiratory rate, /min	24 (20–28)	24 (20–28)	0.124
BMI	28.0±6.0	28.3±6.5	0.037
NT pro-BNP, pg/mL	3,236 (1,404–6849)	3,127 (1,298–7,769)	0.739
Elevated troponin	1,054 (46.3)	848 (31.1)	<0.001
HbA <sub>1c</sub> , %	7.4±2.3	7.1±2.2	0.006
Total cholesterol, mmol/L	4.9±2.0	4.7±2.5	0.002
Creatinine, µmol/L	97 (75–124)	106 (80–144)	<0.001
LVEF, %	38.6±13.7	35.5±14.1	<0.001
Hemoglobin, g/dL	13.0 (12–15)	12.2 (11–14)	<0.001
Precipitating factors for developing HF			
Noncompliance with medications	205 (9.0)	759 (27.8)	<0.001
Noncompliance with diet	35 (1.5)	101 (3.7)	<0.001
Acute coronary syndromes	893 (39.2)	472 (17.3)	<0.001
Uncontrolled hypertension	220 (9.7)	190 (7.0)	0.001
Uncontrolled arrhythmia	123 (5.4)	178 (6.5)	0.097
Anemia	70 (3.1)	84 (3.1)	0.994
Infection	253 (11.1)	478 (17.5)	<0.001
Worsening renal function	71 (3.1)	150 (5.5)	<0.001
Other causes	24 (1.1)	13 (0.5)	0.017
Unknown	382 (16.8)	304 (11.1)	<0.001

Values are expressed as *n* (%), mean ± SD, or median (IQR). NOHF, new-onset heart failure; DCHF, decompensated chronic heart failure; AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; PVD, peripheral vascular disease; TIA, transient ischemic attack; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; BMI, body mass index; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; HbA<sub>1c</sub>, glycated hemoglobin; LV, left ventricular; LVEF, left ventricular ejection fraction.



**Fig. 1.** In-hospital outcomes. **a** LOS. **b** Mortality. LOS, length of stay; NC, noncompliance; Medx, medications; ACS, acute coronary syndromes; HTN, hypertension; RF, renal function.

**Table 2.** Outcomes and follow-up<sup>1</sup>

	Acute NOHF (n = 2,276; 45.5%)	Acute DCHF (n = 2,729; 54.5%)	p value
<b>In-hospital outcomes</b>			
Median LOS, days (IQR)	7 (4–10)	6 (4–11)	0.0897
Mortality	153 (6.7)	160 (5.9)	0.211
<b>1-Year follow-up</b>			
Cumulative mortality	390 (17.1)	622 (22.8)	<0.001
Rehospitalization for HF	427 (23.8)	648 (32.3)	<0.001
PCI/CABG	209 (11.6)	171 (8.5)	0.001

Values are expressed as n (%), unless otherwise indicated. NOHF, new-onset heart failure; DCHF, decompensated chronic heart failure; LOS, length of stay; HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. <sup>1</sup> There were missing observations in 75 cases and 313 patients died in hospital.

In the DCHF group, the highest mortality rate was seen with infection (10.7%), followed by ACS (7.4%), and worsening renal function (6%), while the lowest rate was seen with HTN (2.1%) (Fig. 1b).

#### One-Year Mortality

In the NOHF group, the highest mortality rate was seen with worsening renal function (33.8%), followed by ACS (20.4%), and anemia (20%), while the lowest rate was seen with HTN (9.1%).

In the DCHF group, the highest mortality rate was seen with infection (28.7%), followed by worsening renal function (28.7%), and noncompliance with diet (26.7%), while the lowest rate was seen with HTN (12.1%) (Fig. 2a).

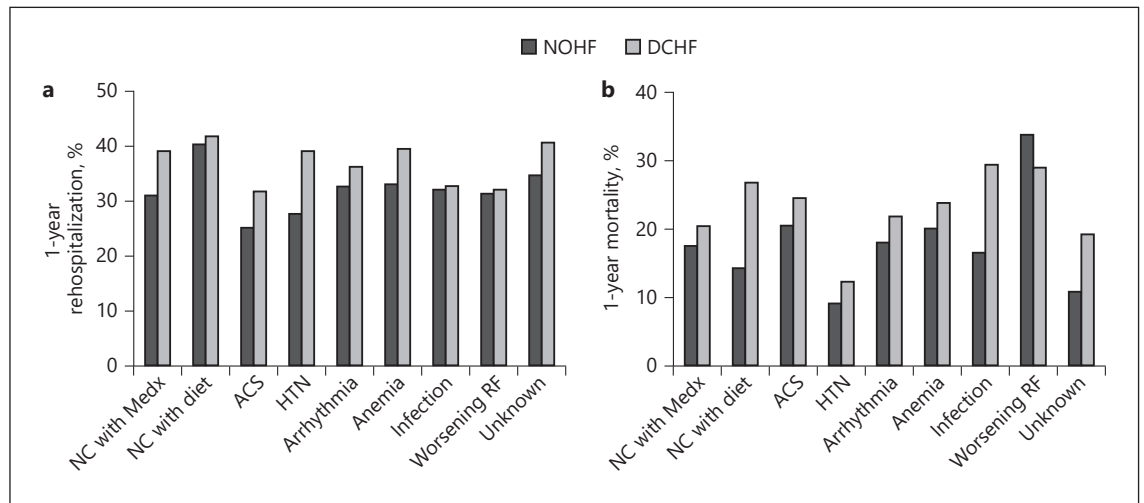
#### Rehospitalization for HF after 1 Year

In the NOHF group, the highest rehospitalization rate was seen with noncompliance with diet (40%), followed by anemia (32.9%), and arrhythmia (32.5%), while the lowest rate was seen in patients with ACS (24.7%).

In the DCHF group, the highest rehospitalization rate was seen in patients with noncompliance with diet (41.6%), followed by anemia (39.3%), and HTN (39%), while the lowest rate was seen in patients with ACS (31.6%) (Fig. 2b).

#### Multivariate Analysis

Multivariable logistic regression analyses showed that noncompliance with medications and HTN were significantly associated with lower in-hospital mortality, while



**Fig. 2.** 1-Year outcomes. **a** Rehospitalization. **b** Mortality. NC, noncompliance; Medx, medications; ACS, acute coronary syndromes; HTN, hypertension; RF, renal function.

**Table 3.** Multivariate logistic regression for inhospital and 1-year mortality and 1-year rehospitalization

	Adjusted OR	95% CI	<i>p</i> value
<b>Inhospital mortality</b>			
Noncompliance with medications	0.47	0.28–0.80	0.005
Noncompliance with diet	0.71	0.27–1.83	0.47
ACS	1.84	1.26–2.68	0.002
HTN	0.37	0.17–0.80	0.01
Arrhythmia	1.32	0.75–2.31	0.33
Anemia	1.57	0.90–3.10	0.19
Infection	1.90	1.26–2.88	0.002
Worsening RF	1.45	0.79–2.66	0.23
<b>1-Year mortality</b>			
Noncompliance with medications	1.43	1.10–1.85	0.007
Noncompliance with diet	1.80	1.15–2.80	0.01
ACS	1.62	1.27–2.06	0.001
HTN	0.68	0.47–0.99	0.05
Arrhythmia	1.56	1.04–2.09	0.03
Anemia	1.65	1.07–2.54	0.02
Infection	1.93	1.50–2.52	0.001
Worsening RF	2.53	1.80–3.60	0.001
<b>1-Year rehospitalization</b>			
Noncompliance with medications	1.05	0.86–1.28	0.66
Noncompliance with diet	1.24	0.85–1.80	0.26
ACS	0.66	0.54–0.80	0.001
HTN	0.86	0.67–1.10	0.25
Arrhythmia	0.93	0.71–1.24	0.64
Anemia	1.01	0.70–1.45	0.95
Infection	0.86	0.70–1.06	0.16
Worsening RF	0.82	0.60–1.13	0.23

OR, odds ratio; CI, confidence interval; ACS, acute coronary syndromes; HTN, hypertension; RF, renal function.

ACS, and infection were associated with higher in-hospital mortality (Table 3). Multivariable logistic regression analyses showed that factors significantly associated with increased 1-year mortality include noncompliance with medications, noncompliance with diet, ACS, arrhythmia, anemia, infection, and worsening renal function; HTN was marginally associated with a lower 1-year mortality. There was also a significant association between ACS and a lower rate of 1-year rehospitalization. There were no other significant associations.

## Discussion

This study demonstrated that in a large, prospective, multicenter registry of patients hospitalized for acute HF, PFs contributing to hospitalization were identified in most cases. The prevalence of PFs differed according to the type of acute HF, with noncompliance with medications being the most common in the acute DCHF group and ACS the most common in patients with acute NOHF. Noncompliance with medications was associated with a lower rate of in-hospital mortality but with a higher rate of 1-year mortality. In contrast, ACS was associated with higher in-hospital and 1-year mortality. Other PFs independently associated with worse outcomes included noncompliance with diet, arrhythmia, anemia, infection, and worsening renal function. On the other hand, uncontrolled HTN as the PF for hospitalization was associated with better outcomes.

Our study found that the most common PF causing decompensation and hospitalization of patients with known HF was noncompliance with medications. In addition, although the early outcome of noncompliance with medications was favorable, it was associated with higher 1-year mortality. Previous studies examining the effects of noncompliance with medications in HF reported favorable early outcomes [16], consistent with our findings. Other studies were either retrospective [17] or followed up small numbers of patients for outcomes [18, 19]. Our study expanded on previous observations in a large, real-world, consecutive patient population hospitalized with acute HF and with 1-year follow up data. The importance of our findings is that they indicate that compliance with medications might prove to be a cost-effective strategy to reduce the mortality burden and cost of HF hospitalizations [20]. In fact, a recent review and meta-analysis by Ruppert et al. [21] found that overall adherence to medication interventions significantly reduced the mortality risk among HF patients and decreased the

odds for hospital readmission. Further prospective studies are warranted that focus on which components of medication adherence interventions are most effective in specific HF populations in order to reduce mortality and rehospitalization.

The other major finding of our study is that ACS was the most common PF in patients hospitalized with acute NOHF and associated with increased odds of immediate as well as 1-year mortality. The prognostic impact of HF in patients suffering an ACS has mainly been previously reported in association with short-term mortality [22–24]. Few studies [25–27], apart from ours, have expanded the observation period to include a longer-term postdischarge phase. Additionally, in our study, ACS was associated with lower odds of rehospitalization at 1 year compared to other PFs. We hypothesize that this is due to the fact that when ACS is the reason for acute HF hospitalization, patients undergo revascularization procedures and anti-ischemic therapy that limit further ischemia and thus the need for further rehospitalization.

Worsening renal function in patients hospitalized with acute HF has previously been identified as being associated with worse in-hospital and early postdischarge outcomes [8, 28, 29]. Our findings confirm this and demonstrate that acute HF hospitalization precipitated by worsening renal function is also associated with significantly worse patient outcomes, both in-hospital as well as 1 year after discharge.

Consistent with previous studies [6, 30], infection as a PF for acute HF hospitalization was associated with a higher rate of immediate as well 1-year mortality. Although the reason for higher in-hospital mortality from infection is clear, an explanation for how this can affect long-term survival is unknown. Previous studies have shown hospitalization for pneumonia to be an independent risk factor for long-term cardiovascular events [31]. It has been hypothesized [6] that these patients have a weakened immune system, a greater comorbidity burden, and may also suffer from suboptimal medical care and thus have greater long-term morbidity and mortality. On the other hand, HTN as a PF for HF hospitalization was associated with a better prognosis, with lower LOS and lower in-hospital and 1-year mortality rates; this is also in agreement with previous studies [6, 8].

The main strength of this study is that it was performed prospectively in 47 hospitals in 7 Gulf countries using a well-defined cohort of patients. Documentation of the PFs for acute HF hospitalization was performed prospectively using a standardized approach by the study physi-

cians who had been following these patients closely. In addition, we included 1-year follow-up data on mortality and rehospitalization outcomes that extend beyond previous studies of PFs for hospitalization for HF that mainly reported inhospital and early postdischarge outcomes.

There are, however, a few limitations in this subanalysis of the Gulf CARE study. Like any observational study, the possibility for unmeasured confounding biases exists. In addition, compliance with medications and diet depended on self-reporting by patients and not on objective measures. Another limitation was that the lack of data from patients discharged directly from the emergency room could have affected the results. Nonetheless, this analysis provides new insights into the factors contributing to HF hospitalizations from a large representative dataset of patients hospitalized for HF and including patients with multiple comorbidities.

## Conclusion

PFs are common in patients hospitalized with acute HF and vary according to type. Preventive and therapeutic interventions specifically directed at preventable PFs, particularly noncompliance with medications and diet, are warranted.

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## Statement of Ethics

Ethics approval for this study was obtained from concerned authorities in the recruiting centers. Informed consent was obtained from all patients.

## Disclosure Statement

All authors declare no competing interests. The authors report no relationships that could be construed as a conflict of interest.

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