ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 3164–3173
Published online 30 August 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14506

ORIGINAL ARTICLE

Hospitalization for acute heart failure during non-working hours impacts on long-term mortality: the REPORT-HF registry

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Abstract

Aims Hospital admission during nighttime and off hours may affect the outcome of patients with various cardiovascular conditions due to suboptimal resources and personnel availability, but data for acute heart failure remain controversial. Therefore, we studied outcomes of acute heart failure patients according to their time of admission from the global International Registry to assess medical practice with lOngitudinal obseRvation for Treatment of Heart Failure.

Methods and results Overall, 18 553 acute heart failure patients were divided according to time of admission into 'morning' (7:00–14:59), 'evening' (15:00–22:59), and 'night' (23:00–06:59) shift groups. Patients were also dichotomized to admission during 'working hours' (9:00–16:59 during standard working days) and 'non-working hours' (any other time). Clinical characteristics, treatments, and outcomes were compared across groups. The hospital length of stay was longer for morning (odds ratio: 1.08; 95% confidence interval: 1.06–1.10, $P < 0.001$) and evening shift (odds ratio: 1.10; 95% confidence interval: 1.07–1.12, $P < 0.001$) as compared with night shift. The length of stay was also longer for working vs. non-working hours (odds ratio: 1.03; 95% confidence interval: 1.02–1.05, $P < 0.001$). There were no significant differences in in-hospital mortality among the groups. Admission during working hours, compared with non-working hours, was associated with significantly lower mortality at 1 year (hazard ratio: 0.88; 95% confidence interval: 0.80–0.96, $P = 0.003$).

Conclusions Acute heart failure patients admitted during the night shift and non-working hours had shorter length of stay but similar in-hospital mortality. However, patients admitted during non-working hours were at a higher risk for 1 year mortality. These findings may have implications for the health policies and heart failure trials.

Keywords Heart failure; Hospitalization; Prognosis; Mortality

Received: 5 July 2023; Accepted: 10 August 2023
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Introduction

The time of hospital presentation affects outcomes of patients with cardiac conditions such as myocardial infarction, arrhythmias, pulmonary embolism, aortic aneurysm rupture, and others.[1–6] Several factors may influence nighttime clinical presentation and management of patients, including circadian rhythm, delayed time to diagnosis and treatment, suboptimal nighttime physician staffing, and hospital resource availability.

In acute heart failure (AHF), data remain controversial. AHF patients admitted to hospital during night hours (vs. morning hours) and during non-working (vs. working hours) tend to be more dyspnoeic, with more severe pulmonary congestion and less peripheral oedema.[7–11] They are also more commonly classified in a lower New York Heart Association (NYHA) class on the days preceding their hospitalization.[7–11] Although their clinical profile in studies is similar, information on evidence-based treatment is scarce, and the influence of time of presentation on short- and long-term survival is inconclusive. For instance, an analysis from the US Nationwide Health Care Utilization Project Inpatient Sample (NIS) registry showed a shorter length of stay (LOS) and higher in-hospital mortality for weekend vs. weekday admissions. In contrast, the Get With The Guidelines-Heart Failure (GWTG-HF) national registry reported longer LOS and reduced in-hospital mortality for a similar population.[9,12] Many other studies show contradictory results.[7,11,13] So far, only the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) and the international Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trials have reported 180 day mortality according to time of admission. However, results were inconclusive.[7,8] Inconsistencies of earlier studies may be partly attributed to variations in their design and overall differences in patient populations between clinical trials and registries. Moreover, prior analyses have used a broad 12 h definition of nighttime presentation. We postulated that this 12 h definition does not mirror the reduced hospital staff and resource availability of the actual night shift (23:00–06:59). Previous studies have not evaluated the impact of rotating morning, evening, and night shifts on patient outcomes nor reported on the long-term survival of patients.

The association of AHF patients' admission time with LOS and mortality risk remains unclear. This may impact optimal planning and calculation of power in HF clinical trials. Also, in-hospital management information may be particularly interesting to healthcare providers. Policy actions could improve the quality of care and subsequently improve the survival of patients.

In the present analysis of the International Registry to assess medical practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF), we sought to gain more insights into the association of time of admission of HF patients and their clinical characteristics, hospital treatment, and long-term survival.

Methods

REPORT-HF (ClinicalTrials.gov NCT02595814) was a prospective observational cohort study that has been described in detail previously.[14] Overall, 18 553 patients were enrolled in 385 sites in 44 countries in 6 continents between July 2014 and March 2017. The number of enrolled patients reflected the country's size and the region's population. The study was in line with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or a legal representative.

The registry included adult patients hospitalized with a primary diagnosis of AHF, according to clinical judgement of the clinician-investigator. When possible, consecutive enrolment took place. However, in some large-volume centres, patients were enrolled in prespecified periods with a focus on even distribution across days of the week and seasons of the year. Demographics, medical history, signs and symptoms, and previous medication were reported at admission (*Table 1* and Supporting Information, *Table S1*). Information about vital signs, in-hospital acute treatment, and complications were documented during hospitalization. Data on patients' hospital pathway, discharge medication, and outcomes were captured at discharge (*Table 1* and Supporting Information, *Table S1*). Finally, follow-up was accomplished via telephone interviews unless a regular visit was planned at the inclusion centre. Countries were organized in geographic regions using a modification of the World Health Organization classification.[14] Income level was specified according to the World Bank classification using the 2017 national gross reference as previously reported.[15] The effect of income inequality was studied using the Gini coefficient. Zero (0%) represented absolute income equality and one (100%) absolute income inequality as previously described.[16] Door to treatment time was determined as the difference between the time of drug administration and the time of arrival. LOS was considered the number of days from admission to discharge; in-hospital deaths were excluded. There was no independent adjudication of outcomes. The study was approved by local ethics committees or institutional review boards.

Definitions of admission time according to shifts and working hours

The exact time of admission to the hospital was documented in the case report form of the study for all patients. For the current analysis, time of admission was defined as 'morning'

DOI: 10.1002/ehf2.14506

Table 1 Patients' characteristics according to time of admission

Patients	Morning	Evening	Night	*P*-value	Working hours	Non-working hours	*P*-value
Number	9665	6389	2487		9205	9348	
Age, median (IQR)	68 (58, 77)	67 (57, 77)	66 (56, 76)	<0.001	67 (57, 77)	67 (57, 77)	0.93
Sex (male)	5997 (62%)	3878 (61%)	1489 (60%)	0.14	5749 (62%)	5623 (60%)	0.001
Predominant race				<0.001			<0.001
Caucasian	5351 (55%)	3140 (49%)	1155 (46%)		4903 (53%)	4753 (51%)	
Black	393 (4%)	301 (5%)	171 (7%)		372 (4%)	495 (5%)	
Asian	2853 (30%)	2075 (32%)	810 (33%)		2920 (32%)	2818 (30%)	
Native American	156 (2%)	167 (3%)	52 (2%)		156 (2%)	219 (2%)	
Pacific Islander	4 (<1%)	2 (<1%)	1 (<1%)		4 (<1%)	3 (<1%)	
Other	908 (9%)	704 (11%)	298 (12%)		850 (9%)	1060 (11%)	
Region				<0.001			<0.001
Central and South America	1226 (13%)	1068 (17%)	347 (14%)		1159 (13%)	1482 (16%)	
Eastern Europe	1808 (19%)	755 (12%)	239 (10%)		1712 (19%)	1090 (12%)	
Eastern Mediterranean Region and Africa	1122 (12%)	730 (11%)	389 (16%)		1019 (11%)	1222 (13%)	
North America	731 (8%)	607 (10%)	247 (10%)		737 (8%)	855 (9%)	
South East Asia	987 (10%)	912 (14%)	430 (17%)		1020 (11%)	1309 (14%)	
Western Europe	1953 (20%)	1187 (19%)	449 (18%)		1689 (18%)	1905 (20%)	
Western Pacific	1838 (19%)	1130 (18%)	386 (16%)		1869 (20%)	1485 (16%)	
Income inequality				<0.001			<0.001
Lower middle income	1335 (14%)	1132 (18%)	618 (25%)		1338 (15%)	1747 (19%)	
Upper middle income	4484 (46%)	2479 (39%)	763 (31%)		4235 (46%)	3491 (37%)	
High income	3846 (40%)	2778 (43%)	1106 (44%)		3632 (39%)	4110 (44%)	
Time since diagnosis (years), mean (SD)	5 (6)	5 (5)	4 (6)	0.31	5 (6)	5 (6)	0.47
Time since diagnosis (years), median (IQR)	3 (1, 6)	3 (1, 6)	2 (1, 6)	0.17	3 (1, 6)	3 (1, 6)	0.41
NYHA class at admission				<0.001			<0.001
I	427 (4%)	270 (4%)	153 (6%)		377 (4%)	474 (5%)	
II	1765 (18%)	1070 (17%)	445 (18%)		1596 (17%)	1684 (18%)	
III	2877 (30%)	1663 (26%)	542 (22%)		2787 (30%)	2296 (25%)	
IV	1114 (12%)	765 (12%)	273 (11%)		1109 (12%)	1043 (11%)	
Missing/unknown	3482 (36%)	2621 (41%)	1074 (43%)		3336 (36%)	3851 (41%)	
LVEF, mean (SD)	40 (16)	39 (16)	39 (15)	<0.001	40 (16)	39 (16)	0.002
LVEF, median (IQR)	39 (26, 54)	36 (25, 53)	35 (25, 50)	<0.001	38 (26, 54)	36 (25, 52)	0.002
Medication at admission							
ACE-Is/ARBs	4942 (53%)	3091 (50%)	1198 (50%)	0.001	4648 (52%)	4587 (51%)	0.048
Beta-blockers	5186 (55%)	3158 (51%)	1233 (51%)	<0.001	4851 (54%)	4734 (52%)	0.004
MRAs	2662 (28%)	1525 (25%)	485 (20%)	<0.001	2576 (29%)	2097 (23%)	<0.001
Statins	3686 (39%)	2347 (38%)	1008 (42%)	0.007			
How did the patient arrive to the hosp.				<0.001			<0.001
Own transport	6817 (71%)	4176 (65%)	1407 (57%)		6542 (71%)	5861 (63%)	
Ambulance	2058 (21%)	1746 (27%)	978 (39%)		1819 (20%)	2969 (32%)	
Other	790 (8%)	467 (7%)	102 (4%)		844 (9%)	518 (6%)	
Where was patient first evaluated upon hosp. arrival				<0.001			<0.001
Emergency room	5421 (56%)	4211 (66%)	1996 (80%)		4897 (53%)	6739 (72%)	
Heart failure facilities	609 (6%)	259 (4%)	54 (2%)		631 (7%)	292 (3%)	
Cardiac ward	2235 (23%)	952 (15%)	159 (6%)		2216 (24%)	1132 (12%)	
Cardiac/coronary ICU	767 (8%)	491 (8%)	196 (8%)		747 (8%)	707 (8%)	
General/medical/surgical ICU	246 (3%)	187 (3%)	49 (2%)		253 (3%)	229 (2%)	

(*Continues*)

Table 1 (continued)

Patients	Morning	Evening	Night	*P*-value	Working hours	Non-working hours	*P*-value
Other	381 (4%)	287 (4%)	29 (1%)		456 (5%)	242 (3%)	
Signs and symptoms							
Dyspnoea rest (at admission)	7069 (82%)	4642 (83%)	1895 (88%)	<0.001	6647 (81%)	6962 (85%)	<0.001
Orthopnoea (at admission)	6083 (77%)	4005 (79%)	1543 (80%)	0.003	5793 (77%)	5841 (79%)	<0.001
PND (at admission)	4819 (63%)	3100 (64%)	1183 (65%)	0.095	4589 (63%)	4513 (64%)	0.20
Chest pain (at admission)	4259 (49%)	2684 (48%)	1125 (51%)	0.022	3981 (48%)	4090 (50%)	0.074
Peripheral oedema (at admission)	6067 (70%)	4035 (70%)	1298 (60%)	<0.001	5942 (72%)	5463 (66%)	<0.001
Pulmonary rales (at admission)	5232 (65%)	3600 (69%)	1451 (73%)	<0.001	4935 (65%)	5348 (70%)	<0.001
JVP (at admission)	3070 (55%)	2357 (63%)	886 (60%)	<0.001	3038 (57%)	3275 (60%)	0.010
Low urine (at admission)	1311 (19%)	936 (21%)	310 (18%)	0.026	1310 (20%)	1247 (19%)	0.19
S3 gallop (at admission)	1060 (15%)	828 (18%)	302 (17%)	<0.001	1053 (16%)	1138 (17%)	0.029
Pleural effusion (at admission)	2512 (32%)	1667 (33%)	608 (31%)	0.68	2430 (33%)	2358 (32%)	0.15
Hepatomegaly (at admission)	1767 (24%)	954 (20%)	265 (14%)	<0.001	1716 (25%)	1270 (18%)	<0.001
Heart rate (minimum), median (IQR)	84 (72, 100)	87 (74, 102)	92 (78, 109)	<0.001	84 (72, 100)	89 (75, 104)	<0.001
SBP admission, median (IQR)	130 (110, 150)	130 (110, 150)	139 (119, 160)	<0.001	130 (110, 148)	130 (113, 152)	<0.001
DBP admission, median (IQR)	79 (69, 90)	80 (68, 90)	80 (70, 94)	<0.001	78 (68, 90)	80 (70, 90)	<0.001
Pulse pressure admission, median (IQR)	50 (40, 65)	50 (40, 65)	54 (40, 71)	<0.001	50 (40, 63)	50 (40, 70)	<0.001
SBP discharge, median (IQR)	120 (107, 130)	118 (105, 130)	120 (110, 130)	<0.001	120 (106, 130)	120 (107, 130)	0.027
DBP discharge, median (IQR)	70 (60, 80)	70 (60, 80)	70 (61, 80)	<0.001	70 (60, 80)	70 (60, 80)	0.57
Rhythm				<0.001			<0.001
Sinus rhythm	4889 (60%)	3202 (61%)	1381 (67%)		4555 (59%)	4923 (63%)	
Atrial fibrillation/flutter	2363 (29%)	1414 (27%)	445 (21%)		2278 (29%)	1944 (25%)	
Pacemaker rhythm	423 (5%)	259 (5%)	87 (4%)		419 (5%)	350 (4%)	
Bradyarrhythmias/AV block	95 (1%)	59 (1%)	22 (1%)		88 (1%)	88 (1%)	
Other	430 (5%)	356 (7%)	138 (7%)		442 (6%)	483 (6%)	
Treatment: Diuretics–vasodilators							
i.v. diuretics all	8417 (87%)	5641 (88%)	2254 (91%)	<0.001	8019 (87%)	8298 (89%)	<0.001
Diuretic total dose, mg, median (IQR)	40 (40, 80)	40 (40, 80)	60 (40, 80)	<0.001	40 (40, 80)	40 (40, 80)	<0.001
Vasodilators i.v. all	1703 (18%)	1182 (19%)	567 (23%)	<0.001	1583 (17%)	1870 (20%)	<0.001
Inotropes i.v. all	1479 (15%)	945 (15%)	300 (12%)	<0.001	1424 (15%)	1302 (14%)	0.003
Time to any, min, median (IQR)	60 (11, 187)	55 (10, 168)	40 (6, 155)	<0.001	60 (12, 189)	50 (9, 165)	<0.001
Time to vasodilators, min, median (IQR)	78 (21, 261)	60 (15, 203)	35 (10, 161)	<0.001	80 (25, 262)	51 (10, 194)	<0.001
Time to inotropic, min, median (IQR)	240 (49, 2321)	210 (40, 2224)	206 (25, 1884)	0.15	229 (40, 2167)	234 (47, 2094)	0.61
Time to diuretics, min, median (IQR)	79 (20, 235)	72 (20, 207)	60 (14, 207)	<0.001	82 (20, 238)	66 (15, 207)	<0.001
Mechanical ventilation	129 (1.3%)	121 (1.9%)	54 (2.2%)	0.005	122 (1.3%)	182 (1.9%)	<0.001
Treatment: Other interventions							
Non-invasive ventilation	130 (1.3%)	105 (1.6%)	66 (2.7%)	<0.001	111 (1.2%)	190 (2.0%)	<0.001
Ultrafiltration	9 (0.1%)	8 (0.1%)	2 (0.1%)	<0.001	11 (0.1%)	9 (0.1%)	0.63
Haemodialysis	98 (1.0%)	79 (1.2%)	30 (1.2%)	0.56	97 (1.1%)	110 (1.2%)	0.42
Haemofiltration	8 (0.1%)	4 (0.1%)	2 (0.1%)	0.97	5 (0.1%)	9 (0.1%)	0.30
Peritoneal dialysis	7 (0.1%)	13 (0.2%)	4 (0.2%)	0.15	11 (0.1%)	13 (0.1%)	0.71
Intra-aortic balloon pump placement	22 (0.2%)	13 (0.2%)	6 (0.2%)	0.98	19 (0.2%)	22 (0.2%)	0.67
LVAD implantation	12 (0.1%)	11 (0.2%)	5 (0.2%)	<0.001	16 (0.2%)	13 (0.1%)	0.55
Right heart cath. or Swan-Ganz catheter placement	173 (1.8%)	86 (1.3%)	25 (1.0%)	0.003	167 (1.8%)	118 (1.3%)	0.002
Natriuretic peptides							
NT-proBNP admission (pg/mL), median (IQR)	4198.5 (2014, 8814.5)	4574 (2143.5, 9636.5)	5013 (2166, 10 264)	0.019	4080 (2001, 8864.5)	4868 (2151, 9851)	<0.001
BNP admission (pg/mL), median (IQR)	942 (414, 1860)	903 (409, 1956)	872 (407, 1790)	0.77	933 (405, 1832)	910 (414, 1945)	0.61

(*Continues*)

Table 1 (continued)

Patients	Morning	Evening	Night	*P*-value	Working hours	Non-working hours	*P*-value
Outcomes							
Length of index hosp. stay (discharge population), days, median (IQR)	8 (5, 12)	8 (5, 12)	7 (4, 11)	<0.001	8 (5, 13)	8 (5, 12)	<0.001
In-hospital mortality	222 (2%)	181 (3%)	48 (2%)	0.046	227 (2%)	224 (2%)	0.76
Death at 1 year, censored at 365 days	1722 (19%)	1280 (21%)	456 (19%)	0.001	1648 (19%)	1813 (20%)	0.006
HF hospitalizations within 0–12 months	2113 (23%)	1305 (22%)	518 (22%)	0.22	1978 (23%)	1962 (22%)	0.47
Hospitalizations at 1 year	3544 (38%)	2235 (37%)	889 (38%)	0.32	3326 (38%)	3348 (38%)	0.77

ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AV, atrioventricular; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; i.v., intravenous; ICU, intensive care unit; IQR, interquartile range; JVP, jugular venous pressure; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT, N-terminal; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP, systolic blood pressure; SD, standard deviation.

shift (7:00–14:59), 'evening' shift (15:00–22:59), and 'night' shift (23:00–06:59) to mirror the common hospital work schedule. Also, time was divided in 'working hours' between 9:00 and 16:59 during typical days of the work week per country and 'non-working hours' for any other time, including weekends and bank holidays in each country, in line with previous studies.[7] For most countries, a Saturday to Sunday weekend was considered to capture weekend days (except for a few weekend working days in China and Vietnam). Also, during the study period, Egypt, Jordan, Saudi Arabia, United Arab Emirates, and Israel had a Friday to Saturday weekend, and Algeria had a Thursday to Friday weekend. Sunday was the only weekend day off for the Philippines and India.

Statistical analysis

Comparisons of shift groups were made with one-way analysis of variance (ANOVA) or Kruskal–Wallis test depending on the distribution (*Table 1* and Supporting Information, *Table S1*). For the working and non-working hours groups, *t*-tests and Wilcoxon's rank-sum tests were used. Categorical parameters were evaluated using χ^2 tests. We investigated the impact of time of admission on LOS in univariable and multivariable logistic regression analyses. LOS was based on a cut-off corresponding to the median LOS ($\leq$8 or $>$8 days). In the multivariable analyses, we included variables known to impact LOS and mortality based on previous reports and expert clinical opinion (*Table 2*).[14,16–18] Outcome analyses on 1 year mortality were performed using univariable, multivariate Cox proportional hazards models and competing risks analyses for mortality. Cox proportional hazards assumption was checked using the Schoenfeld residuals and the cox.zph function and was not violated. Missing data were imputed five times using Multivariate Imputation by Chained Equations and pooled using Rubin's rule. We performed interaction analysis for the univariable models for region, Gini coefficient, and country income level. Interaction was tested by comparing the goodness of fit between models with and without the interaction term to determine the overall *P*-value for interaction. All statistical analyses were performed in STATA, Version 15.0, or R, Version 3.4.2. A two-sided *P*-value $<$ 0.05 was considered statistically significant.

Results

Data on the time of admission were available for 18 541 (99.9%) patients in the registry. More than half of them (52%) presented in the morning shift, 34% in the afternoon, and 14% during the night shift (*Table 1*). The patients were evenly admitted during working and non-working hours. Patients with AHF in the Eastern Mediterranean Region and Africa and South East Asia tended to be admitted later in

Table 2 Patient outcomes

Presentation according to working or non-working hours				
Length of stay[a]				
Working hours (ref. non-working hours)	Univariate	OR: 1.19	CI: 1.12–1.26	$P < 0.001$
Working hours (ref. non-working hours)	Multivariate[b]	OR: 1.03	CI: 1.02–1.05	$P < 0.001$
In-hospital mortality				
Working hours (ref. non-working hours)	Univariate	HR: 1.01	CI: 1.00–1.01	$P = 0.76$
Working hours (ref. non-working hours)	Multivariate[c]	HR: 0.97	CI: 0.80–1.17	$P = 0.73$
1 year mortality				
Working hours (ref. non-working hours)	Univariate	HR: 0.91	CI: 0.85–0.97	$P = 0.006$
Working hours (ref. non-working hours)	Multivariate[d]	HR: 0.87	CI: 0.81–0.93	$P < 0.001$
Working hours (ref. non-working hours)	Multivariate[be]	HR: 0.88	CI: 0.80–0.96	$P = 0.003$
Presentation according to morning, evening, or night shift				
Length of stay[a]				
Morning shift (ref. night shift)	Univariate	OR: 1.49	CI: 1.36–1.63	$P < 0.001$
Morning shift (ref. night shift)	Multivariate[b]	OR: 1.08	CI: 1.06–1.10	$P < 0.001$
Evening shift (ref. night shift)	Univariate	OR: 1.54	CI: 1.40–1.70	$P < 0.001$
Evening shift (ref. night shift)	Multivariate[b]	OR: 1.10	CI: 1.07–1.12	$P < 0.001$
In-hospital mortality				
Morning shift (ref. night shift)	Univariate	HR: 1.000	CI: 1.01–1.00	$P = 0.29$
Morning shift (ref. night shift)	Multivariate[c]	HR: 1.040	CI: 0.76–1.43	$P = 0.80$
Evening shift (ref. night shift)	Univariate	HR: 1.010	CI: 1.00–1.02	$P = 0.01$
Evening shift (ref. night shift)	Multivariate[c]	HR: 1.260	CI: 0.91–1.75	$P = 0.16$
1 year mortality				
Morning shift (ref. night shift)	Univariate	HR: 0.963	CI: 0.87–1.07	$P = 0.49$
Morning shift (ref. night shift)	Multivariate[d]	HR: 0.865	CI: 0.78–0.96	$P = 0.006$
Morning shift (ref. night shift)	Multivariate[de]	HR: 0.937	CI: 0.82–1.08	$P = 0.36$
Evening shift (ref. night shift)	Univariate	HR: 1.116	CI: 1.00–1.24	$P = 0.04$
Evening shift (ref. night shift)	Multivariate[d]	HR: 1.004	CI: 0.90–1.12	$P = 0.93$
Evening shift (ref. night shift)	Multivariate[de]	HR: 1.066	CI: 0.93–1.23	$P = 0.38$

CI, confidence interval; HR, hazard ratio; OR, odds ratio.
[a]Length of stay analysis is based on a cut-off of >8 days (median value).
[b]Adjusted model controls for age, sex, region, systolic blood pressure, body mass index, heart rate, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, orthopnoea at admission, and elevated jugular venous pressure at admission.
[c]Adjusted model controls for age, sex, region, systolic blood pressure, New York Heart Association class, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, anaemia, valvular heart disease, and country income.
[d]Adjusted model controls for age, sex, region, systolic blood pressure, New York Heart Association class, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, anaemia, valvular heart disease, country income, beta-blocker at discharge, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at discharge, length of stay, and intravenous inotropes.
[e]Competitive risk analysis including cardiovascular mortality and all-cause mortality.

the day and more during non-working hours. An opposite pattern was seen in Western Pacific. In addition, patients in Western Europe presented more frequently in non-working than working hours, whereas Eastern European patients showed an opposite trend. Patients in lower-middle-income countries tended to be admitted during the evening and night rather than the morning phase of the day and non-working vs. working hours. A similar trend was observed in high-income countries but not upper-middle-income ones (*Table 1*).

Patient characteristics

Patients admitted during the morning or evening shifts were older than those admitted during the night shift. There was no significant difference in age between working and non-working hours (*Table 1*). Also, AHF patients hospitalized later in the day and during non-working hours were more likely to be diabetic and have lower left ventricular ejection fraction. There was also a difference in medication prescription, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists both on admission and at discharge, with the difference between the night and morning shifts and working vs. non-working hours being the most striking (*Table 1* and Supporting Information, *Table S1*). Compared with morning and evening shifts, patients admitted at night more frequently had higher systolic blood pressure, higher pulse pressure, and more dyspnoea and orthopnoea. They had more severe pulmonary congestion but less commonly peripheral oedema. Similar signs and symptoms were observed for working vs. non-working hours. Interestingly, NT-pro-brain natriuretic peptide (BNP) was higher in night shift admissions and non-working hour admissions.

In-hospital management

Patients admitted during night (vs. day and evening) shifts and during non-working (vs. working hours) were treated more commonly with diuretics and vasodilators, and door to treatment time was shorter for both medications. Non-invasive and invasive mechanical ventilation was correspondingly more frequent (*Table 1*).

Length of stay and mortality

LOS was significantly shorter in patients admitted during the night shift compared with morning and afternoon shifts, after correction for major confounders (*Table 2*). Similarly, LOS was shorter for non-working vs. working hour admissions. In-hospital mortality appeared to be higher in patients presenting in the afternoon compared with the night shift. However, this association was not statistically significant after adjustment of other major confounders. One-year mortality was significantly higher in patients admitted during non-working compared with working hours in both the univariate and comprehensive multivariate analyses (*Table 2*). There was no interaction of income class and Gini index with working hours for 1 year mortality; however, there was an interaction for region; Easter Europe had significantly lower 1 year mortality during working hours compared with Central and South America [working hours: Eastern Europe hazard ratio (1 year mortality) 0.77, 95% confidence interval 0.601–0.997, $P = 0.047$].

Discussion

In the REPORT-HF global registry, the time of AHF admission was evaluated according to common 8 h working shifts and according to working vs. non-working hours. There was some time-based variation in the clinical presentation and the phenotype of patients, including income-related differences. However, in-hospital management appeared to be similar between times of presentation and most often was based on phenotype. LOS was shorter in patients admitted during the night shift compared with morning and afternoon shifts and in patients presenting at non-working vs. working time even after adjustment for major confounders. Finally, 1 year mortality was significantly higher in patients admitted during non-working vs. working hours.

In this study, Western European patients were admitted more frequently during non-working vs. working hours than Eastern European patients. This was also shown in the ASCEND-HF but not RELAX-AHF sub-analysis.[7,8] Regional discrepancies with previous studies may be principally related to the variation of countries included in each region. Patients in lower-middle-income countries tended to be hospitalized during the evening and night and non-working hours. Health systems in lower-middle-income countries may be more difficult to navigate, and patients might avoid hospitals unless they are severely ill. A reverse pattern of time-related AHF admission was observed in upper-middle-income countries as citizens may be more familiarized with the function of their health systems and have primary care providers who they can visit during working hours who may refer them to the hospital. However, it was unexpected that high-income countries expressed a similar trend to lower-middle-income countries. This may require further analyses beyond the scope of this paper.

Clinical presentation

This study also confirms previous reports of more acutely ill patients during nighttime and off hours as evidenced by high heart rate, dyspnoea, orthopnoea, pulmonary congestion, and elevated blood pressure.[7–11] The findings align with a previously proposed predominant pathophysiological model of fluid redistribution. Adding to this hypothesis, systolic blood pulse pressure was higher in the population admitted during afternoon and night shifts and off hours. In contrast, patients were more likely to present with peripheral congestion in the morning and during regular hours. These less symptomatic patients may experience decompensation within the previous days or weeks and seek medical attention in a more programmed and orderly manner (e.g. wait for working hours or morning). Likewise, patients admitted in the morning and off hours are likely to arrive with their transport and be firstly evaluated in heart failure facilities or the cardiac ward rather than the emergency. Patients admitted during the night shift and off hours were more commonly treated with diuretics, vasodilators, and non-invasive ventilation. Our results align with the ASCEND-HF analysis and show that treatment was administrated promptly and in a clinically appropriate fashion.[7]

Length of stay

The influence of daytime vs. nighttime presentation on hospital LOS is, to date, controversial.[7,8,11] There was no difference in the LOS for nighttime vs. daytime admission in the Japan nationwide Acute Decompensated Heart Failure Syndromes (ATTEND) registry, but LOS was shorter for nighttime admissions in the ASCEND-HF trial.[7,11] Matsushita *et al*. report a similar shorter LOS for AHF patients admitted to intensive care unit during the night.[10] As for the weekend/weekday division of patients, GWTG-HF registry reports longer LOS for presenting during weekends, whereas the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with

Heart Failure (OPTIMIZE-HF) registry did not report significant differences.[9,13] Our analysis illustrates shorter LOS for patients admitted during the night shift compared with morning and evening shifts and during non-working vs. working hours, even after adjustment for potential confounders. A possible explanation is the higher percentage of clinical improvement observed for patients presenting later in the day and during off hours due to symptoms more consistent with fluid redistribution rather than weight gain. However, patients admitted to the hospital during the 'non-working' hours and night are more acute and those admitted during working hours are more elective. Longer LOS for morning and working hours hospitalizations may be also related to admissions for elective workout, which takes time. Although many known confounders were taken under account, it is still possible that if more variables were available, the further adjustment could have led to non-significant associations with LOS.

In-hospital mortality

Studies so far are also inconsistent concerning short-term mortality of HF patients according to presentation time. Daytime vs. nighttime hospitalization did not affect short-term mortality in the ATTEND registry and the RELAX-AHF trial.[7,8] The current study has additionally divided time according to 8 h shifts and has confirmed a neutral effect of the night shift for in-hospital mortality.

The weekend/weekday dichotomous administrative data from the GWTG-HF registry and other smaller studies showed higher adjusted short-term mortality for weekend vs. weekday patients.[9] In contrast, mortality was lower in the ASCEND-HF trial and RELAX-AHF analysis.[7–9] In the OPTIMIZE-HF trial, nevertheless, there were no significant differences.[13] In the current study, time of admission had a neutral effect. However, we should acknowledge considerable differences with previous studies, mainly in time cut-offs and definitions of short-term mortality. For example, the sub-analysis of the ASCEND-HF trial defined working hours as 9 AM to 5 PM from Monday to Friday, whereas analyses of the GWTG-HF and the OPTIMIZE-HF registries used a broader weekend/weekday dichotomous.[7,9,13] Similarly, the ASCEND-HF analysis reports 30 day mortality. In contrast, the GWTG-HF registry and the OPTIMIZE-HF registry mention only in-hospital mortality outcome.[7,9,13]

One-year mortality

Although in-hospital mortality could have been affected by substandard diagnostic and therapeutic procedures during the nighttime and off hours, the longer term mortality of AHF patients depends mainly on their risk profile. So far, few studies have investigated the influence of time of HF presentation only on mid-term mortality. The RELAX-AHF trial showed lower 180 day cardiovascular mortality for night and day admissions, which was no longer apparent when patients were reassigned to non-working vs. working hours.[8] An analogous analysis of the ASCEND-HF trial showed lower 180 day cardiovascular mortality among non-working vs. working hour admission. Still, there were no differences when patients were divided in line with RELAX-AHF nighttime vs. daytime admission criteria.[7] For the first time, the current analysis from REPORT-HF showed higher mortality at 1 year follow-up for patients presenting during non-working vs. working hours. It is worth noting that these results were consistent worldwide across regions and income levels.

There are some possible explanations for our findings. Non-working hour patients in the REPORT-HF registry were severely dyspnoeic upon presentation, previously linked to higher mid-term mortality.[19] This has been attributed to a possible later presentation of these patients and alternative causes of dyspnoea, such as malignancy, ischaemia, and lung disease. We should also appreciate that compared with previous studies, the REPORT-HF global registry matches real-world practice more accurately. Hypotension, acute coronary syndromes, valvular heart disease, and anaemia were not excluded as in the RELAX-AHF and ASCEND-HF trials, which may have led to a higher risk population. Moreover, for patients presenting to the emergency department, Kim *et al*. observed a higher threshold for admission at weekend vs. weekdays.[20] This could ultimately result in a population with a higher risk profile during non-working hours and can offer an additional explanation for our results. In line with this hypothesis, NT-proBNP, a relevant marker of disease severity that is also related to prognosis, was elevated in non-working hour as compared with working hour admissions. Of course, other parameters such as medication adherence, non-cardiac comorbidity, social background, employment status, medical illiteracy, or unknown confounders that have not been recorded in this registry and thus controlled for may have influenced long-term survival. Finally, the current analysis has the longest so far follow-up.

This study offers a different clinical perspective on the influence of patients' presentation time with AHF. There is a seeming paradox between a shorter LOS and long-term outcomes for patients admitted during off hours, which suggests that there may be trade-offs in efficiency and long-term outcomes. Subsequent studies should closely evaluate management strategies as an opportunity for improvement. Off-hour patients experience more acute dyspnoea relief, which is not clearly translated into better long-term outcomes. Symptom relief may not serve as the primary reason for early hospital discharge. Instead, the focus may move to in-hospital blood pressure control, training optimization of medical treatment, follow-up visits, social support, and more.

It has also been shown that patient enrolment volume and region may affect the generalizability of the results of previous HF trials.[21,22] Non-working hours are not suitable for the enrolment of patients as this may require more staff. A definite relation between non-working hour admission with long-term mortality may impact the execution and calculation of the power of future trials, especially those requiring long-term follow-up. Considering the inconsistent results of earlier studies, there is a definite demand for more research.

Limitations

Patients in lower income countries are less likely to be referred to a hospital, which may have caused a bias in the overall inclusion of patients. Likewise, rural areas may not be adequately represented, especially in sub-Saharan Africa. The overall proportion of Black patients is relatively low. Ethnicity was not included in multivariate models because of its collinearity with region. Although all banking holidays were included in off hours, some local holidays may not have been accounted for. Natriuretic peptides were not included in multivariate models as these biomarkers were more extensively recorded in specific countries.

The exact day of the week regarding outcomes was not evaluated because the weekend definition is not standardized globally. The need for written informed consent may have precluded the participation of more unstable and less collaborative patients and could explain the low in-hospital mortality. Similarly, some early deaths of patients before their consent may have been missed. We should, however, recognize that our 1 year mortality of 20% is still relatively high. Also, older frail patients with more comorbidities may not have been considered appropriate for inclusion as their follow-up may have been problematic. Finally, there were no available data on medical and nursing staff and diagnostic facilities during the investigation, which could give more clinical insights into this open issue.

Conclusions

This analysis of the global REPORT-HF registry showed variations in patients' demographics according to their time of admission, including region and income-related differences. There were also significant differences in AHF patients' phenotype and clinical management. Nighttime and non-working hour admissions were associated with shorter LOS. However, there were no differences in in-hospital mortality. Admission during non-working hours was associated with increased 1 year mortality even after adjustment for major confounders. These findings may have important implications for the clinical management of patients, the health policies and logistics, and the design and conduction of future heart failure trials.

Conflict of interest

D.F. reports consulting fees from Abbott, Bayer, Boehringer Ingelheim, and Leo. S.P.C. is supported by grants from the National Institute of Health and Patient-Centered Outcomes Research Institute and as a consultant for Siemens, Reprieve, Abbott, and Aiphia. C.E.A. reports grant support, personal fees, and/or non-financial support from Abbott, AstraZeneca, Boehringer Ingelheim, Biotronik, Novartis, Novo Nordisk, Oruen Ltd, Radcliffe Group Ltd, and Vifor. K.D. has received honoraria and/or research support from Medtronic, Boston Scientific, St Jude, Biotronik, Sorin, Merck, Novartis, Amgen, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, GlaxoSmithKline, Roche, Sanofi, Abbott, Otsuka, Leo, Servier, and Bristol-Meyers Squibb. J.T. is supported by the National University of Singapore Start-up grant, the Tier 1 grant from the Ministry of Education, and the CS-IRG New Investigator Grant from the National Medical Research Council; has received consulting or speaker fees from Daiichi-Sankyo, Boehringer Ingelheim, Roche Diagnostics, and Us2.ai; and owns patent US-10702247-B2 unrelated to the present work. G.E. reports personal fees from AstraZeneca, Abbott, Boehringer Ingelheim, Novartis, and Vifor. J.C. reports grants and speaker honoraria from Amgen, Medtronic, and Novartis. S.D.A. has received research support from Vifor International and Abbott Vascular and consultancy and/or speaking fees from AstraZeneca, Bayer, Boehringer Ingelheim, Respicardia, Impulse Dynamics, Janssen, Novartis, Servier, and Vifor International. U. D. reports research support from AstraZeneca, Pfizer, Boehringer Ingelheim, Vifor, Roche Diagnostics, and Boston Scientific and speaker's honoraria and consultancies from AstraZeneca, Novartis, and Amgen. A.O. is employed by Novartis. M.G. was formerly Novartis employee. M.H. received honoraria as a lecturer from Novartis, Aventis, and Amgen. J.P. reports honoraria for lectures and advisory boards from Novartis, Pfizer, Servier, OrionPharma, and Roche Diagnostics. C.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, ProSciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, and Us2.ai; and serves as co-founder and non-executive director of Us2.ai. G.F. reports research grants from the European Union, committee fees from Novartis related to REPORT-HF, and lecture fees and/or committee member in trials and/or registries sponsored by Servier, Boehringer Ingelheim, Medtronic, Vifor, Amgen, and Bayer. All other authors have nothing to disclose.

Funding

REPORT-HF was funded by Novartis.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patients' characteristics according to time of admission.

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