Circulation: Heart Failure

ORIGINAL ARTICLE

Infection-Related Hospitalization in Heart Failure With Reduced Ejection Fraction

A Prospective Observational Cohort Study

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BACKGROUND: Hospitalization is a common adverse event in people with heart failure and reduced ejection fraction, yet is often not primarily due to decompensated heart failure (HF). We investigated the long-term prognosis following infection-related hospitalization.

METHODS: We conducted a prospective observational cohort study of 711 people with heart failure and reduced ejection fraction recruited from 4 specialist HF clinics in the United Kingdom. All hospitalization episodes (n=1568) were recorded and categorized as primarily due to decompensated HF, other cardiovascular disease, infection-related, or other noncardiovascular disease. Survival was determined after the first hospitalization.

RESULTS: During 2900 patient-years of follow-up, there were a total of 14686 hospital days. At least one hospitalization occurred in 467 people (66%); 25% of first hospitalizations were primarily due to infection and these were not associated with typical signs including tachycardia and pyrexia. Compared with other categories of hospitalization, infection-related was associated with older age, lower serum albumin, higher blood neutrophil counts, and greater prevalence of chronic obstructive pulmonary disease at recruitment. Median survival after first infection-related hospitalization was 18.6 months, comparable to that after first decompensated HF hospitalization, even after age-sex adjustment. The burden of all-cause rehospitalization was comparable irrespective of the category of first hospitalization, but infection more commonly caused re-hospitalization after index infection hospitalization.

CONCLUSIONS: Infection is a common driver of hospitalization in heart failure and reduced ejection fraction and often presents without classical signs. It is associated with high mortality rates, comparable to decompensated HF, and a major burden of rehospitalization caused by recurrent episodes of infection.

Key Words: heart failure ■ hospitalization ■ infections ■ mortality ■ survival

The improving survival rates of people with heart failure with reduced ejection fraction (HFrEF) have been accompanied by notable changes in the mode of death, with noncardiovascular causes becoming increasingly important.[1–3] We, and others, have shown that sepsis accounts for a substantial proportion of this noncardiovascular mortality,[4,5] and that sepsis death has a distinct risk factor profile from other modes of death.[4] It is also established that infection is a common primary cause of hospitalization in people with heart failure,[5,6] yet the prognostic implications of this remain uncertain. In particular, we remain unclear about long-term survival

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WHAT IS NEW?

- Hospitalization is common in people with heart failure and reduced ejection fraction and infection accounts for approximately one quarter of these events.
- Baseline characteristics, such as comorbid chronic obstructive pulmonary disease and not having an implantable cardioverter-defibrillator/cardiac resynchronization therapy device, predict risk of infection hospitalization.
- Median survival after infection hospitalization is 18.6 months, which is comparable to that after decompensated heart failure hospitalization, and significantly worse than after other types of hospitalization.
- Infection is more commonly responsible for re-hospitalization after index infection hospitalization versus other causes of index hospitalization.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Clinicians should have a high index of suspicion for infection when hospitalizing people with heart failure and reduced ejection fraction since classical markers like heart rate and body temperature are similar irrespective of the ultimate cause of admission.
- The poor in-hospital survival of people with infection suggests intensive monitoring and treatment may be necessary, but additional research is needed to prove this.
- Infection hospitalization is more common in some people, such as those with chronic obstructive pulmonary disease, and re-hospitalization after a first infection hospital admission is more likely to be due to recurrent infection, highlighting the importance of developing effective primary and secondary prevention strategies.

Nonstandard Abbreviations and Acronyms

COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronization therapy
HF	heart failure
HFrEF	heart failure with reduced ejection fraction

and the burden of rehospitalization after an index infection-related hospitalization, versus other common causes. We set out to address this uncertainty by following up a cohort of people with stable HFrEF attending 4 specialist heart failure clinics.

METHODS

The datasets generated and/or analyzed during the current study are not publicly available due to inclusion of potentially identifying postal codes but are available from the corresponding author on reasonable request.

As described in our earlier publications,[7–9] we conducted a prospective observational cohort study with the predefined aim of studying outcomes and defining prognostic markers in patients with HFrEF. The cohort consists of 3 discretely recruited subgroups and this analysis is restricted to the most recently recruited group of 711 people, as detailed hospitalization data are available. Inclusion in the study required the presence of stable signs and symptoms of CHF for at least 3 months, age ≥18 years, and left ventricular ejection fraction ≤45% on transthoracic echocardiography. Between February 2012 and December 2014, all patients meeting these criteria and attending specialist cardiology clinics (secondary and tertiary referral) in 4 UK hospitals were approached, and 711 patients provided written informed consent. Participants received routine contemporary evidence-based care, guided by the supervising clinical team, with no study intervention; they were then observed until censorship or death, as described below. The Leeds West Research Ethics Committee gave ethical approval, all patients provided written informed consent to participate, and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Patient baseline characteristics including demographics, past medical history, functional capacity, electrocardiography, laboratory blood tests, cardiac imaging, and treatment were collected at study recruitment. Vital signs and laboratory blood tests relating to the index hospitalization were collected at the point of presentation. Two-dimensional echocardiography was performed according to the American Society of Echocardiography recommendations. Resting heart rate was measured using 12-lead ECGs. Prescribed doses of loop diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers were collected at study recruitment. Total daily doses of β-blocker, angiotensin-converting enzyme inhibitors (or angiotensin receptor blocker if used instead of angiotensin-converting enzyme inhibitors), and loop diuretic were expressed relative to the maximal licensed dose of bisoprolol, ramipril, and furosemide, respectively, as previously published.[8] Receipt of cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator implantation was assessed during the 6-month period after recruitment.

Assessment of Outcomes

All patients were registered with the UK Office of Population Censuses and Surveys, which provided details of time of death, with a final censorship date of February 18, 2019. Hospitalization data were collected from institutional clinical event databases detailing all admissions in recruiting centres. All nonelective hospital admissions experienced before death or study censorship were included and characterized by 2 investigators according to their time from study recruitment, duration, and primary cause within 4 following major categories: (1) heart failure (HF) hospitalization; (2) other cardiovascular hospitalization (eg, arrhythmia or acute coronary syndrome, without decompensated HF); (3) infection-related hospitalization; (4) other noncardiovascular hospitalization (noncardiovascular cause excluding infection-related). HF hospitalization was defined as new onset or worsening of signs and symptoms of heart failure with evidence of fluid overload requiring at least 24 hours hospitalization and the use of intravenous diuretics, as

we have previously published.[9] Infection-related hospitalization was defined as infection being the primary reason for hospitalization with documented source (or suspected source), accompanied by deteriorating symptoms, signs (eg, pyrexia, tachycardia, hypotension, tachypnea, confusion), and laboratory indices (eg, elevated inflammatory markers, with microbiological, serological, and/or imaging evidence) resulting in treatment with antimicrobial therapy, as we have previously published.[4] Sources included the following: respiratory tract, biliary/gastrointestinal, urinary tract (including cystitis, pyelonephritis etc), soft-tissue infections (eg, cellulitis, gangrene, necrotizing fasciitis), and unknown.

Statistics

All statistical analyses were performed using IBM SPSS statistics version 21 (IBM Corporation, Armonk, NY). Continuous data are presented as mean (SEM) or median (interquartile range) for normal and non-normally distributed variables, respectively, and categorical data are shown as number (percentage). Groups were compared using Student *t*-tests or ANOVA for normally distributed continuous data, Mann-Whitney *U*-tests or Kruskal-Wallis H-tests for non-normally distributed continuous data, and Pearson χ^2 tests for categorical data. Kaplan-Meier curves were used to plot survival and compared with log-rank tests; age-sex adjusted survival analyses used Cox-regression analysis. Rehospitalized time was expressed as a percentage of time in follow-up before death or censorship to account for differing survival between groups and was compared using ANOVA with post hoc Bonferroni correction. To further illustrate patterns of rehospitalized time due to infection and other classifications, patients were subdivided according to duration of follow-up. All tests were 2-sided, and statistical significance was defined as $P<0.05$.

RESULTS

Baseline characteristics of the entire cohort of 711 people are presented in Table 1. During a mean follow-up period of 48.6 months, 467 (66%) were hospitalized at least once, and 25% of first hospitalizations were primarily attributable to infection, 14% to decompensated HF, 25% to other cardiovascular causes, and 37% to other noncardiovascular causes (Figure 1A); when assessing first and recurrent hospitalizations, similar contributions were observed (Figure I in the Data Supplement). The source of infection during first hospitalization was most commonly the respiratory tract (50%), followed by soft-tissue (18%) and the urinary tract (17%; Figure 1B). The median duration of infection-related hospitalization was twice as long as noninfection related hospitalization (8 [5–16] versus 4 [2–9] days; $P=0.002$); for reference, the mean duration was 13.8 (95% CI, 10.8–16.8) days versus 7.8 (95% CI, 6.7–8.9) days.

Compared with people with a first hospitalization due to other causes, those hospitalized due to infection were older, had lower serum albumin, higher blood neutrophil counts, were more likely to have chronic obstructive pulmonary disease (COPD), and less likely to have an implantable cardioverter-defibrillator/CRT device at study recruitment (Table 1). In a multivariate logistic regression analysis including these variables, only COPD and implantable cardioverter-defibrillator/CRT device were significantly associated with risk of infection hospitalization (Table I in the Data Supplement). At the point of hospital admission, blood pressure and oxygen saturations (SpO_2) were lower, while respiratory rate and blood leukocyte counts were higher in people with infection-related hospitalization (Table 1). Core body temperature was higher in the infection-related group and heart rate was no different. Data describing people with infection-related hospitalization versus those within the 3 other major categories of hospitalization (Table 2) indicate that the prevalence of COPD is higher in the infection-related group, while baseline diuretic requirements are greater in those going on to decompensated HF hospitalization. At the point of the index hospitalization, the infection-related group had a lower diastolic blood pressure and SpO_2 than the other groups, along with higher blood leukocyte counts.

Survival

Infection-related hospitalization was associated with an age-sex adjusted 3.6-fold (95% CI, 1.6–8.1) greater risk of death during the admission versus hospitalization for any other reason. This remained the case when the binary logistic regression model also included baseline characteristics that differed between groups (odds ratio, 3.5 [95% CI, 1.4–8.4]; $P=0.005$; Table II in the Data Supplement). Importantly, these odds ratios do not account for the longer duration of infection hospitalizations.

Kaplan-Meier analysis confirms worse long-term survival in those with infection ($P=0.001$), illustrating early divergence in survival after discharge from hospital, most pronounced during the first 3 months, after which the groups remain broadly parallel (Figure 2A). In an age-sex adjusted Cox regression analysis, infection was associated with 1.4-fold greater risk of death ([95% CI, 1.1–1.8]; $P=0.012$). When age, sex, and baseline characteristics that differed between groups were added to the model, the hazard ratio reduced slightly and lost-statistical significance (hazard ratio, 1.3 [95% CI, 1.0–1.7]; $P=0.085$; Table III in the Data Supplement).

To explore the survival of patients with infection-related hospitalization versus the other 3 major subtypes of hospitalization, we plotted Kaplan-Meier survival curves (Figure 2B), which reveal that infection and decompensated HF hospitalizations are associated with significantly worse survival than other cardiovascular and noncardiovascular hospitalizations ($P<0.001$). The median survival of people with infection-related hospitalization was 18.6 months (95% CI, 9.0–28.3), which is similar to the 20.6 months (95% CI, 9.4–31.8) of people with decompensated HF hospitalization ($P=0.98$). This statistically similar adverse prognosis of infection and decompensated

Table 1. Characteristics at Recruitment and Onset of First Hospitalization for Infection-Related vs Noninfection Hospitalization

	Total Cohort (n=711)	No Hospitalization (n=244)	Infection-Related Hospitalization (n=115)	Noninfection Hospitalization (n=352)	*P* Value (Infection-Related Versus Noninfection)
Age, y	71.6 (13.0)	68.3 (12.6)	75.3 (10.1)	72.6 (13.6)	0.028
Heart rate, bpm	76.0 (17.0)	77.0 (18.2)	77.4 (16.3)	74.9 (16.5)	0.30
Systolic BP, mm Hg	125.2 (21.4)	124.6 (21.7)	124.0 (19.3)	125.9 (21.7)	0.50
Diastolic BP, mm Hg	71.0 (10.6)	72.6 (10.6)	71.1 (11.3)	70.0 (10.3)	0.44
QRS interval, ms	121.8 (30.9)	125.3 (30.4)	117.6 (30.5)	120.8 (31.2)	0.33
Hemoglobin, g/dL	13.3 (1.8)	13.8 (1.7)	13.1 (2.1)	13.0 (1.8)	0.78
WCC, $\times 10^9$/L	7.5 (2.1)	7.4 (1.9)	7.8 (2.3)	7.4 (2.2)	0.19
Lymphocytes, $\times 10^9$/L	1.6 (0.8)	1.6 (0.6)	1.5 (0.7)	1.6 (0.9)	0.17
Neutrophils, $\times 10^9$/L	5.0 (1.7)	4.9 (1.6)	5.3 (1.9)	4.9 (1.7)	0.03
Platelets, $\times 10^9$/L	236.4 (75.2)	240.1 (75.4)	229.7 (72.7)	236.1 (76.0)	0.43
Sodium, mmol/L	139.6 (3.2)	139.9 (2.8)	139.2 (3.6)	139.5 (3.4)	0.40
eGFR, mL/kg per min	61.8 (21.7)	67.1 (19.5)	58.9 (24.0)	59.2 (21.6)	0.91
Albumin, g/L	42.4 (3.6)	43.3 (3.7)	41.3 (3.3)	42.1 (3.6)	0.041
Vitamin D, nmol/L	33 (20–54)	37 (20–57)	32 (20–52)	30 (18–53)	0.43
LVEF (%)	31.8 (9.9)	31.2 (9.8)	32.2 (9.9)	32.1 (9.9)	0.93
Ramipril dose, mg/d	4.9 (3.5)	5.1 (3.5)	4.5 (3.5)	4.8 (3.6)	0.41
Bisoprolol dose, mg/d	4.3 (3.4)	4.6 (3.4)	3.7 (3.1)	4.3 (3.4)	0.10
Furosemide dose, mg/d	48.8 (47.5)	39.3 (44.0)	55.1 (44.8)	53.4 (49.8)	0.74
MRA prescription, n (%)	245 (35)	82 (34)	34 (30)	129 (37)	0.12
ICD/CRT, n (%)	153 (22)	64 (26)	9 (8)	80 (23)	<0.001
Male sex, n (%)	516 (73)	179 (73)	87 (76)	250 (71)	0.34
Diabetes mellitus, n (%)	224 (32)	61 (25)	47 (41)	116 (33)	0.12
COPD, n (%)	116 (16)	27 (11)	39 (34)	50 (14)	<0.001
Ischemic etiology, n (%)	379 (53)	110 (45)	68 (59)	201 (57)	0.70
NYHA class					0.63
I, n (%)	107 (15)	50 (21)	11 (9)	46 (13)	
II, n (%)	408 (57)	144 (59)	68 (59)	196 (56)	
III, n (%)	192 (27)	48 (20)	35 (30)	109 (31)	
IV, n (%)	4 (1)	2 (1)	1 (1)	1 (0)	
Presenting observations	(n=467)				
Heart rate, bpm	80.0 (21.9)	N/A	80.6 (21.3)	79.8 (22.2)	0.75
Systolic BP, mm Hg	124.6 (28.0)	N/A	117.7 (26.0)	126.8 (28.3)	0.011
Diastolic BP, mm Hg	70.8 (16.3)	N/A	65.4 (16.3)	72.4 (15.9)	0.001
Respiratory rate, per min	20.1 (5.0)	N/A	22.4 (6.0)	19.4 (4.4)	<0.001
Oxygen saturations, %	96.0 (4.4)	N/A	93.8 (6.1)	96.6 (3.4)	<0.001
Temperature, °C	36.4 (36.0–36.8)	N/A	36.6 (36.0–37.4)	36.3 (36.0–36.7)	0.003
WCC, $\times 10^9$/L	10.4 (5.5)	N/A	13.8 (6.6)	9.1 (4.5)	<0.001
Neutrophils, $\times 10^9$/L	8.0 (5.0)	N/A	11.7 (6.4)	6.7 (3.6)	<0.001

BP indicates blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NYHA, New York heart association; QRS, Q, R and S waves on the electrocardiogram; and WCC, white cell count.

HF hospitalization groups persisted in Cox regression analysis (Table IV in the Data Supplement) including age, sex, and the baseline characteristics differing between the 4 major subtypes of hospitalization in Table 2.

Rehospitalization

Next, we assessed re-hospitalization attributable to infection after an index hospitalization with infection versus other major categories, using data from 1101 re-hospitalization episodes. This showed that the burden

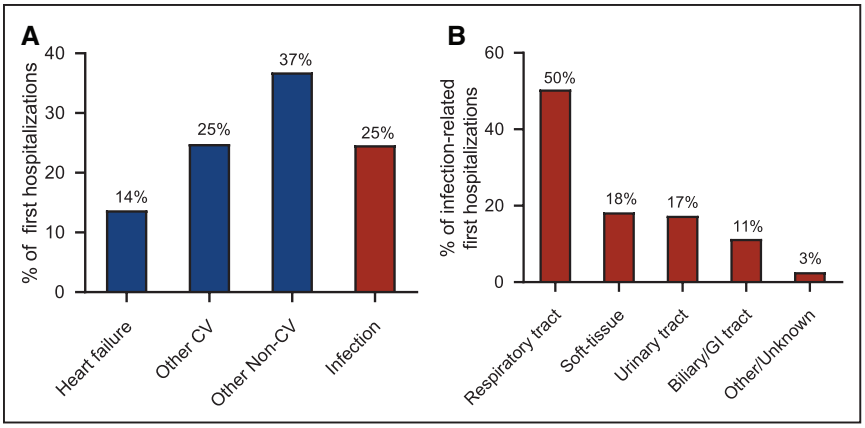

Figure 1. Classification of first hospitalizations.
Classification of (**A**) the principal cause of hospitalization and (**B**) the source of infection. CV indicates cardiovascular.

of infection re-hospitalization was greater after index infection-related hospitalization versus index decompensated HF, other cardiovascular, and other noncardiovascular admissions (P=0.004 by ANOVA; Figure 3). This observation persisted in analyses stratified by duration of follow-up (Figure II in the Data Supplement). Hence, infection accounted for the majority of rehospitalized time after index infection-related admission and this endured even over the long term, suggesting these patients form a distinct group at risk of recurrent infection-related events.

DISCUSSION

Our detailed analysis of hospitalization in people with HFrEF suggests that infection is a common cause of these events, accounting for a quarter of first hospitalization events. Baseline study characteristics identified people more likely to experience future hospitalization due to infection, versus other major causes, and at the point of hospitalization, the infection-related hospitalization group had greater physiological disturbance. Importantly, people admitted due to infection were as likely to die in the short- and long-term as people admitted with decompensated HF, a group already recognized to have poor prognosis. Furthermore, recurrent infection was a major driver of rehospitalization, particularly after index infection hospitalization. Cumulatively, these data suggest that infection is a common, serious, and distinct cause of hospitalization in people with HFrEF, which may benefit from improved prevention, early identification, and intensive management.

Infection and Adverse Events in HF Cohorts

Only a small number of other studies have explored the relationship between infection and outcomes in people with HF. Alon et al[6] found that 38% of people with HF had at least one sepsis hospitalization, with the source of infection being broadly similar to our data; they also found increased 30-day mortality after infection-associated versus other hospitalizations. Ueda et al[5] similarly reported a high short-term mortality rate in people with HF after hospitalization with infection. Our data advance the literature by showing for the first time that short- and long-term survival after infection-related hospitalization is as poor as after admission with decompensated HF, a widely acknowledged high-risk event.[10,11] Moreover, we show that after an infection hospitalization, the predominant cause of rehospitalization is infection.

Predictors of Future Infection-Related Adverse Events

Our data indicate that some patient characteristics at study recruitment are associated with future infection versus other subtypes of hospitalization, including: older age, lower serum albumin, higher blood neutrophil count, the presence of COPD, and not having an implantable cardioverter-defibrillator/CRT. While these are unlikely to allow precise identification of people who will go on to experience infection-related hospitalization, they do highlight at-risk groups and may also point to mechanisms of infection susceptibility. In particular, COPD was at least twice as common in people going on to be admitted with infection versus any other type of hospitalization and is a well-recognized substrate for respiratory tract infection.[12] Higher baseline neutrophil counts at baseline recruitment are unlikely to reflect active infection, given their modest elevation and the time lag to first hospitalization, but has been repeatedly linked with old age.[13–15] This, together with lower serum albumin, could also reflect frailty, a syndrome associated with susceptibility to infection and impaired physiological reserve.[16] Importantly, our prior work has shown that COPD and advancing age are the 2 strongest predictors of sepsis death in people with HFrEF, highlighting the importance of these factors in predicting both infection-related hospitalization and death.[4] The much lower provision of implantable cardioverter-defibrillator/CRT devices to people that subsequently experience an infection hospitalization is also notable in the context of their similar LV ejection fraction and

Table 2. Characteristics at Recruitment and Onset of First Hospitalization for Infection-Related Versus Other Subtypes of Hospitalization

	Heart Failure Hospitalization (n=64)	Other CV Hospitalization (n=116)	Other Non-CV Hospitalization (n=172)	Infection-Related Hospitalization (n=115)	*P* Value
Age, y	74.4 (11.2)	72.3 (13.7)	72.3 (14.3)	75.3 (10.1)	0.17
Heart rate, bpm	76.2 (15.0)	73.4 (15.5)	75.5 (17.4)	77.4 (16.3)	0.58
Systolic BP, mm Hg	122.5 (22.2)	127.4 (22.5)	126.0 (21.1)	124.0 (19.3)	0.59
Diastolic BP, mm Hg	68.2 (10.3)	70.5 (10.7)	70.2 (10.1)	71.1 (11.3)	0.57
QRS interval, ms	125.0 (31.9)	122.0 (31.5)	118.4 (30.7)	117.6 (30.5)	0.35
Hemoglobin, g/dL	12.8 (1.8)	13.2 (1.9)	13.0 (1.7)	13.1 (2.1)	0.54
WCC, $\times 10^9$/L	7.2 (2.0)	7.5 (2.2)	7.5 (2.3)	7.8 (2.3)	0.42
Lymphocytes, $\times 10^9$/L	1.4 (0.6)	1.6 (0.7)	1.7 (1.0)	1.5 (0.7)	0.12
Neutrophils, $\times 10^9$/L	4.7 (1.7)	4.9 (1.7)	4.9 (1.7)	5.3 (1.9)	0.15
Platelets, $\times 10^9$/L	243.7 (94.7)	222.2 (67.4)	242.6 (72.8)	229.7 (72.7)	0.09
Sodium, mmol/L	139.1 (4.5)	139.7 (3.1)	139.6 (3.1)	139.2 (3.6)	0.55
eGFR, mL/kg per min	56.3 (21.4)	57.6 (21.3)	61.3 (21.8)	58.9 (24.0)	0.36
Albumin, g/L	41.4 (4.4)	42.6 (2.8)†	42.1 (3.8)	41.3 (3.3)†	0.031
Vitamin D, nmol/L	31.0 (18.2–46.0)	35.0 (25.0–56.3)	30.0 (19.0–48.0)	30.0 (18.0–53.0)	0.17
LVEF (%)	31.9 (9.5)	31.9 (10.2)	32.3 (9.9)	32.2 (9.9)	0.98
Ramipril dose, mg/d	4.4 (3.3)	4.9 (3.6)	4.9 (3.7)	4.5 (3.5)	0.59
Bisoprolol dose, mg/d	4.0 (3.6)	4.4 (3.4)	4.3 (3.5)	3.7 (3.1)	0.32
Furosemide dose, mg/d	71.9 (44.2)§‖	48.8 (50.5)§	49.5 (49.9)‖	55.1 (44.8)	0.009
MRA prescription, n (%)	24 (38)	42 (36)	63 (37)	34 (30)	0.58
ICD/CRT, n (%)	16 (25)*	30 (26)†	34 (20)‡	9 (8)*†‡	0.002
Male sex, n (%)	46 (72)	85 (73)	119 (69)	87 (76)	0.68
Diabetes mellitus, n (%)	29 (45)‖	43 (37)	44 (26)‖‡	47 (41)‡	0.009
COPD, n (%)	11 (17)	15 (13)†	24 (14)‡	39 (34)†‡	<0.001
Ischemic etiology, n (%)	36 (56)	73 (63)	92 (54)	68 (59)	0.44
NYHA class					0.27
I, n (%)	5 (8)	18 (15)	23 (13)	11 (10)	
II, n (%)	33 (52)	59 (51)	104 (61)	68 (59)	
III, n (%)	25 (39)	39 (34)	45 (26)	35 (30)	
IV, n (%)	1 (1)	0 (0)	0 (0)	1 (1)	
Presenting observations					
Heart rate, bpm	85.1 (24.9)	79.5 (24.4)	78.1 (19.0)	80.6 (21.3)	0.36
Systolic BP, mm Hg	125.0 (32.5)	127.3 (24.5)	127.1 (29.7)	117.7 (26.0)	0.09
Diastolic BP, mm Hg	73.8 (18.6)*	72.3 (14.6)†	72.0 (16.0)‡	65.4 (16.3)*†‡	0.008
Respiratory rate, per min	21.3 (5.5)‖	19.2 (4.5)†	18.9 (3.6)‖‡	22.4 (6.0)†‡	<0.001
Oxygen saturations, %	95.8 (3.7)	96.9 (2.3)†	96.7 (4.0)‡	93.8 (6.1)†‡	<0.001
Temperature, °C	36.4 (36.0–36.7)	36.3 (36.0–36.6)	36.3 (36.0–36.8)	36.6 (36.0–37.4)	0.24
WCC, $\times 10^9$/L	8.3 (2.6)*	8.9 (3.5)†	9.6 (5.4)‡	13.8 (6.6)*†‡	<0.001
Neutrophils, $\times 10^9$/L	6.1 (2.3)*	6.5 (3.3)†	7.1 (4.0)‡	11.7 (6.4)*†‡	<0.001

BP indicates blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York heart association; QRS, Q, R and S waves on the electrocardiogram; and WCC, white cell count.

*Infection versus heart failure Bonferroni corrected $P<0.05$.

†Infection versus other cardiovascular Bonferroni corrected $P<0.05$.

‡Infection versus other noncardiovascular Bonferroni corrected $P<0.05$.

§Heart failure versus other cardiovascular Bonferroni corrected $P<0.05$.

‖Heart failure versus other noncardiovascular Bonferroni corrected $P<0.05$.

prevalence of ischemic etiology. This factor independently predicted infection hospitalization, possibly suggesting that clinicians recognized the differing prognosis of these people using factors we have not measured and used this information when making treatment recommendations.

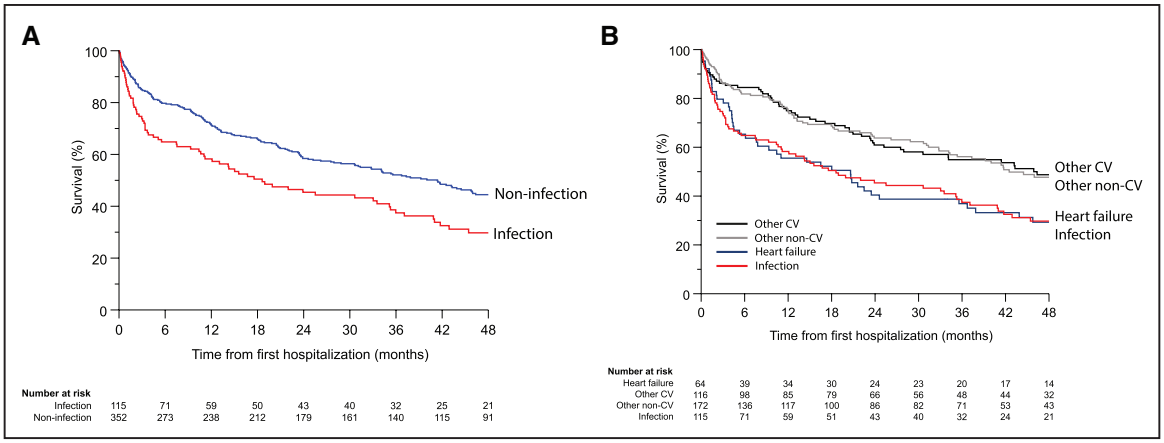

Figure 2. Survival from moment of first hospitalization.
Kaplan-Meier curves illustrating survival from the point of first hospitalization, comparing (**A**) infection-related hospitalization vs noninfection hospitalization and (**B**) infection-related hospitalization vs other major classifications of hospitalization. Numbers at risk are presented below the *x*-axis.

Presenting Features of Infection-Related Hospitalization

At the point of hospital admission, our data show that infection is associated with hypotension, particularly reflected in the diastolic blood pressure, hypoxemia, and increased circulating leukocyte counts, potentially signaling physiological compromise. Surprisingly, heart rate was similar in all groups, irrespective of the cause of admission, suggesting that tachycardia is a less reliable marker of acute infection in HFrEF, which could reflect the use of β-blockers. Moreover, a point measure of body temperature did not reliably discriminate people with and without infection, possibly reflecting its transient nature, but also potentially suggesting altered acute inflammatory responses. These data suggest that infection may be more challenging to diagnose in people with HFrEF, emphasizing the need for a high index of suspicion at the point of hospitalization.

Limitations

We recognize that hospitalizations are complex and multifactorial, meaning that classification according to the primary cause neglects other contributory factors. It is important to note that comorbid heart failure will aggravate the outcome of a primary infection, and infection is a recognized precipitant of decompensated HF.[17–20] Therefore, while our data show that people presenting primarily with infection are different from those hospitalized primarily for other reasons, identification of high-risk patients, early detection and optimal management of infection should be an important goal in HFrEF care. Importantly, our study may also underestimate rates of hospitalization as we utilized institutional data from recruiting centres, rather than nationally collected data.

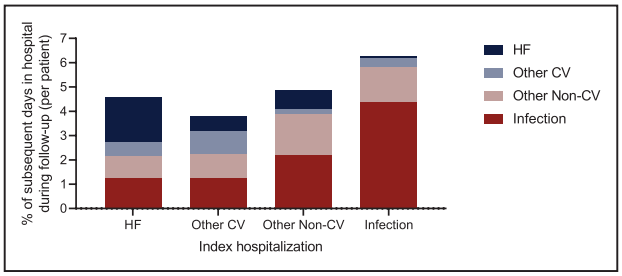

Figure 3. Contribution of infection to the burden of re-hospitalized time.
Stacked bar chart illustrating the percentage of follow-up time in hospital after discharge from the index admission due to infection and other major categories of re-hospitalization. The burden of infection re-hospitalization is greater after index infection hospitalization than other categories (*P*=0.004 by ANOVA).

Clinical Implications

Our findings have implications for patients, clinicians, and healthcare systems and also pose important questions that require further research. First, the substantial contribution to index hospitalizations suggests that greater efforts are required to prevent infection. For example, the uptake of influenza vaccination remains suboptimal in many healthcare systems, including in the United Kingdom,[21] and there may be scope to improve the efficacy of vaccination in disease states associated with impaired immune responses.[22] Second, while people with HFrEF presenting acutely with infection had somewhat different physiological parameters to other patients, their presentation often lacked typical features of infection (eg, tachycardia), suggesting a high index of suspicion is required, along with better diagnostic tests.[23] Unfortunately, we lack data to state whether this somewhat atypical presentation resulted in delayed use of antimicrobials, which is known to be associated with adverse outcomes. Moreover, the very high in hospital mortality rate associated with infection poses the question of whether more intensive monitoring, supportive care, and postdischarge care could improve survival and long-term functioning.[24] Finally, recurrent infection hospitalization

was common, highlighting a need for secondary prevention strategies.

Conclusions

Infection is a major contributor to hospitalization in people with HFrEF, yet may be difficult to identify and often presents without classical signs. It is associated with short- and long-term mortality rates as high as after hospitalization with decompensated HF and a sustained larger burden of recurrent infection-related hospitalization than after other types of index hospitalization. This suggests that new approaches to prevent, identify, and treat infection could substantially improve the outcomes of people with HFrEF.

ARTICLE INFORMATION

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