


Sex-based differences in referral of heart failure patients to outpatient clinics: a scoping review

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Abstract

Background Guidelines recommend that hospitalized patients newly diagnosed with HF be referred to an outpatient HF clinic (HFC) within 2 weeks of discharge. Our study aims were (i) to assess the current literary landscape on the impact of patient sex on HFC referral and outcomes and (ii) to provide a qualitative overview of possible considerations for the impact of sex on referral patterns and HF characteristics including aetiology, symptom severity, investigations undertaken and pharmacologic therapy.

Methods and results We conducted a scoping review using the Arksey and O'Malley framework and searched Medline, EMBASE, PsychINFO, Cochrane Library, Ageline databases and grey literature. Eligible articles included index HF hospitalizations or presentations to the Emergency Department (ED), a description of the HFC referral of patients not previously followed by an HF specialist and sex-specific analysis. Of the 11 372 potential studies, 8 met the inclusion criteria. These studies reported on a total of 11 484 participants, with sample sizes ranging between 168 and 3909 (25.6%–50.7% female). The included studies were divided into two groups: (i) those outlining the referral process to an HFC and (ii) studies which include patients newly enrolled in an HFC. Of the studies in Group 1, males (51%–82.4%) were more frequently referred to an HFC compared with females (29%–78.1%). Studies in Group 2 enrolled a higher proportion of males (62%–74% vs. 26%–38%). One study identified independent predictors of HFC referral which included male sex, younger age, and the presence of systolic dysfunction, the latter two more often found in males. Two studies, one from each group reported a higher mortality amongst males compared with females, whereas another study from Group 2 reported a higher hospitalization rate amongst females following HFC assessment.

Conclusions Males were more likely than females to be referred to HFCs after hospitalization and visits to the Emergency Department, however heterogeneity across studies precluded a robust assessment of sex-based differences in outcomes. This highlights the need for more comprehensive longitudinal data on HF patients discharged from the acute care setting to better understand the role of sex on patient outcomes.

Keywords Heart failure; Outpatient clinic; Sex-differences

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Background

Heart failure (HF) is a highly prevalent disease, affecting over 26 million patients worldwide.¹ The growing HF epidemic is associated with significant morbidity and mortality. Mortality rates for HF have been estimated to range between 17% and

45% within 1 year of diagnosis, and the majority of deaths occur within 5 years of admission.²

Current international guidelines recommend that patients diagnosed with HF should be referred to an outpatient HF clinic (HFC) within 2 weeks of hospital or Emergency Department (ED) discharge.^{3–7} Several studies have demonstrated

that cardiologists' HF management is associated with improved guideline adherence, functional status, and composite outcome of death and cardiovascular hospitalization.^{8,9} It is however unclear whether these outcomes might differ by patient sex. In addition, sex differences in the access to community HF resources have not previously been well studied.

The objectives of this scoping review are (i) to assess the current literary landscape on the impact of patient sex on HFC referral and outcomes and (ii) to provide a qualitative overview of possible considerations for the impact of sex on referral patterns and HF characteristics including aetiology, symptom severity, investigations undertaken and pharmacologic therapy.

Methods

A scoping review was conducted to identify the evidence to date, as well as knowledge gaps related to sex differences in referral of HF patients to cardiologists, HFCs and other specialists in the community. A scoping review, rather than a systematic review, was performed to permit a broader search in order to identify and map the available evidence which addressed the study objectives.¹⁰ Our review followed the methodologic framework described by Arksey and O'Malley: (i) identification of the research question, (ii) identification of the relevant studies, (iii) study selection, (iv) data extraction and charting, and (v) collating, summarizing and reporting of results.¹¹

Inclusion criteria

A study was considered eligible for inclusion if it met all the following criteria: (i) its patient population was composed of adults (age ≥ 18 years) with a new or previously established diagnosis of HF; (ii) patients had not been followed by an HF specialist prior to HFC referral; and (iii) patients were referred to an HFC from either a hospital discharge, ED visit, or ambulatory care setting [by a general practitioner (GP), nurse practitioner or walk-in clinic]. Studies were included if they included both males and females and reported sex-specific data in both baseline characteristics and outcomes.

Study design

All experimental (RCTs and quasi-RCTs), systematic reviews, observational and cross-sectional studies published in English were included without date limitations. Conference abstracts were included for full-text screening if they provided suffi-

cient detail to meet the inclusion criteria. Case reports and opinion articles were excluded.

Search strategy

A peer-reviewed search strategy was conducted on October 12, 2016 with a search update on 15 January 2019 in Medline, EMBASE, PsycINFO, Cochrane Library and Ageline (see Supporting Information for further details).¹² A limited search update was performed through PubMed on 22 February 2022, which found no additional publications that met inclusion criteria. No limits to language or date were applied. The search strategy was created by combining index terms and keywords related to referral and health specialists involved in HF care, as well as an HF search filter developed by Damarell *et al.*, which included key words including *left ventricular dysfunction*, *cardiomyopathy* and *chronic heart failure*.¹³ Duplicates were removed using the automated duplication identification function in EndNote X7 (Thomson Reuters) and checked manually (S. V.). The remaining studies were stored using Covidence (Veritas Health Innovation Ltd, Australia) for additional duplicate identification and removal, and screening. Data extraction was done using Google Sheets (California, USA). A grey literature search was performed through national cardiovascular association websites, conference proceedings, and through manual search of included articles' reference lists.

Selection of studies and data extraction

Each title and abstract was screened independently and in duplicate (E. C. and J. R., Ji. R., N. R., S. P.). Full text screen was performed in duplicate by E. C., J. R., and Ji. R., who resolved disagreements through consensus-based discussion. L. S. adjudicated any remaining uncertainties. Data extraction was performed in duplicate by E. C. and J. R. and included information on publication details, study design, population characteristics (baseline characteristics and co-morbidities, prior investigations and HF management), HF characteristics [mean ejection fraction (EF), percentage of HF with reduced EF (HFrEF) and preserved EF (HFpEF)], New York Heart Association (NYHA) classification, referral source (ED, hospital, other) and clinical outcomes [all-cause mortality, rehospitalization and quality of life (QoL)]. There was heterogeneity in how studies reported HF referrals; some studies reported the patients being proposed to HFCs, whereas others reported number of patients enrolled to an HFC. Because these two populations are not necessarily the same, we separated the included studies into two groups: Group 1 included studies proposing patients for referral to HFCs, and Group 2 included patients newly enrolled to an HFC but did not explicitly describe the referral process.

Results

The initial search identified 9862 potentially relevant articles after deduplication, and an additional 1510 articles were added following the January 15, 2019 search update. After assessment of 751 full text articles, 10 studies met inclusion criteria. Three unique publications were found to report on outcomes from the same dataset.^{14–16} After communication with the lead author for these studies and consensus-based group discussion (E. C. and L. S.), we included only the most recent and comprehensive publication¹⁵ to avoid duplication. In the end, eight studies were included, of which two were retrospective, five were prospective, and one with combined study designs (*Table 1*).

Figure 1 provides a summary of the search process. The main reasons for exclusion were the lack of mention of sex or gender, lack of sex-stratified results and no mention of outpatient referral. Amongst the eight included studies, seven were peer-reviewed journal articles and one reference was an abstract.¹⁷

All studies were published between 1996 and 2015, continents of study origin (*Table 1*) included Europe, North America, and Australia. Study population ranged from 168 to 3909, as outlined in *Table 2*. Follow-up duration ranged from 6 to 40 ± 19 months. *Table 3* summarizes the referral data from the included studies, which were divided into two main groups.

Sex and gender

We defined sex as biological attributes that are characterized by physical and physiological features.¹⁸ Gender is defined as socially constructed roles, and individual identities that influence self-perception and interaction with others.¹⁸ All included studies reported on sex, with no gender-specific

Table 1 Study characteristics

Study characteristics	Type, n
Study design	Prospective, n = 5 <ul style="list-style-type: none"> • Registry-based study, n = 2 • Cohort, n = 3 Retrospective, n = 2 <ul style="list-style-type: none"> • Registry-based study, n = 1 • Cohort, n = 1 Combined (Retrospective and Prospective), n = 1 <ul style="list-style-type: none"> • Cohort, n = 1
Year of publication	2006–2013 n = 2 2001–2005 n = 3 1996–2000 n = 3
Geographical region	North America n = 2 (US, n = 1, Canada, n = 1) Europe n = 5 Australia n = 1

Note: The table provides an overview of the study characteristics including design, publication year and country of origin.

reported data. Many of the included studies have used the terms ‘men’ and ‘women’ interchangeably with ‘males’ and ‘females’ to describe differences in a biological context. Although we initially intended for verbatim data extraction, we have assumed that all included studies’ authors intended to describe biological sex-based differences and have employed the appropriate terminology of ‘males’ and ‘females’ when summarizing the extracted data.

Sex difference in HFC referral and enrolment

In Group 1, a significantly higher proportion of males compared with females were referred to an outpatient HFC (*Table 2*). The included study by Feldman *et al.* reported that at 6 months following an ED visit, 51% of males and 23.9% of females were referred to an HFC ($P < 0.0001$).¹⁵ Similarly, Opasich *et al.* reported 82.4% of males and 78.1% of females were referred to an HFC after HF hospitalization ($P = 0.0157$).¹⁹ Likewise, Mejhert *et al.* found that males accounted for 71% of HFC referrals and only 44% of referrals to GP, whereas females accounted for 29% of HFC referrals and 56% of referrals to GP ($P < 0.001$).²⁰

Studies in Group 2 consistently showed a higher proportion of males (62% to 74%) than females (25% to 38%) were enrolled in HFCs.^{17,21–24}

Referral source

Source of referral, specialty or sex of the referring health professionals was not consistently reported in detail in the studies. Amongst studies in Group 1, Feldman recruited patients following ED visits for a primary diagnosis of HF.

Opasich *et al.* enrolled patients who were discharged from hospital. A total of 37.1% of their population were admitted under Cardiology, whereas 62.9% were under General Internal Medicine. More females were admitted under Medicine (69.7%) than Cardiology (30.3%). females admitted under Cardiology were younger (73 ± 23 vs. 79 ± 9 years; $P < 0.0001$), had more severe symptoms (36% had NYHA class IV as compared with 28% in Medicine patients, and 26% had pulmonary oedema as compared with 23%), and were more likely to have HFrEF compared with females admitted under Medicine.¹⁹ They were also more likely to be referred to an outpatient HFC (83.5%) than females admitted to Medicine (75.7%, $P = 0.0078$). Similar disparities were not observed in male outpatient referrals (84% after Cardiology admission vs. 81.1% Medicine admission¹⁹).

Mejhert *et al.* also enrolled patients who were discharged following HF hospitalization. There was no mention of admission department, or referral source.

Figure 1 Flow diagram of literature search.

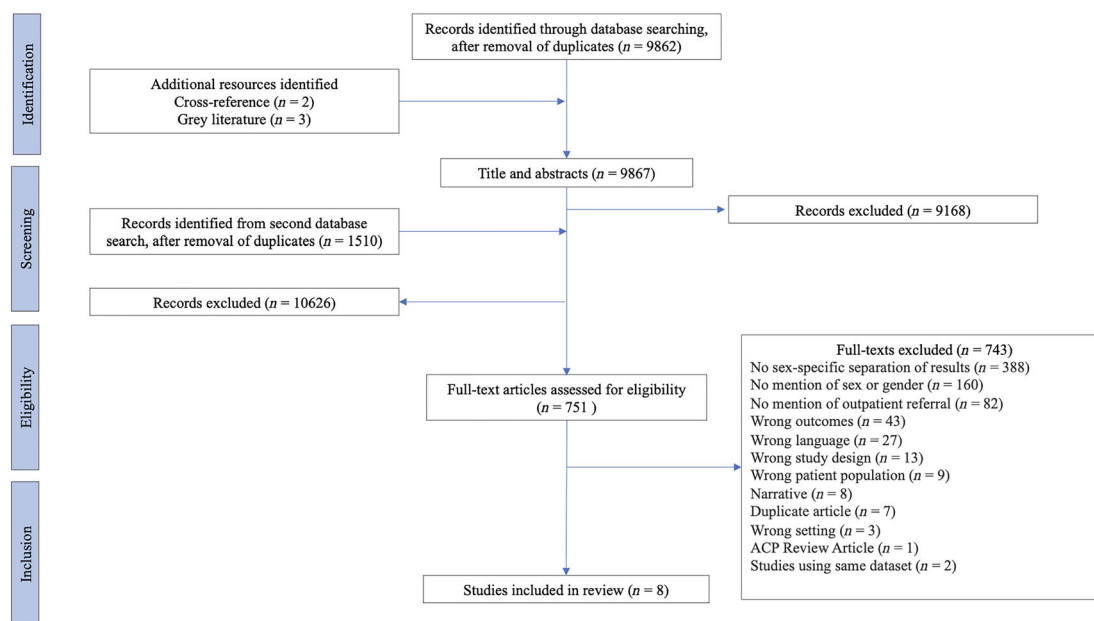


Table 2 Baseline demographics

Categories	Primary author (year)	Sample size, n	Mean age (years)			Percentage of females (%)	Duration of follow-up (months)	Referral to HFC ^b	
			Total (years)	Males (years)	Females (years)			Males (%)	Females (%)
Group 2: Studies including patients referred to HFC (n = 5)	Adams (1996)	557	51 ± 14	52 ± 0.7	49 ± 1.1	32	28.8	—	—
	Anguita Sánchez (2004)	3909	66 ± 12	65 ± 12	71 ± 13	33	13 ± 4	—	—
	Lezha (2003)	468	—	62.69	65.85	38.03	—	—	—
	Ng (2007)	168	68 ± 12	68 ± 13	69 ± 12	30.95	40 ± 19	—	—
	Opasich (2000)	3327	—	62 ± 11	65 ± 12	25.6	12	—	—
Group 1: Studies reporting on referral process (n = 3)	Feldman (2013)	549	75.5 ± 11	72.9 ± 11.2	78.2 ± 10.2	49	6	51 ^a	23.9 ^a
	Mejhert (1999)	379	—	78 (35–95)	81 (40–99)	50.66	12	71	29
	Opasich (2004)	2127	—	72 ± 12	77 ± 11	47	6	82.4	78.1

Note: The table provides a breakdown of baseline characteristics of patients, follow-up duration and HFC referral rates.

^aAt 6 months.

^bHeart Failure Clinic.

Predictors of referral

Two of the three articles in Group 1 assessed predictors of referral to an HFC.

Feldman *et al.* categorized these predictors as (i) predisposing factors (male sex, younger age, higher level of education), (ii) enabling factors (consulted a cardiologist or internist in ED, current or previous HF hospitalization from the ED, living with someone, preferring follow-up with a cardiologist), and (iii) perception of need factors (lower co-morbidity score, not on HF medications at the time of ED visit, systolic dys-

function, higher Minnesota Score). After multivariable adjustment, male sex (odds ratio (OR) 2.04; 95% CI 1.12–3.74), younger age (OR 0.95; 95% CI 0.92–0.98) and systolic dysfunction (OR 3.08; 95% CI 1.77–5.46) were independently associated with HFC referral.

Similarly, Mejhert *et al.* performed a multivariate analysis, taking into consideration age, sex, diabetes mellitus, Angiotensin-converting enzyme (ACE) inhibitor and beta-blocker therapy. They found male sex ($P < 0.01$), younger age ($P < 0.001$) and treatment with beta-blockers ($P < 0.035$) were independent predictors of HFC referral.²⁰

Table 3 Summary table

Categories	Primary author (year)	Study setting		Includes referral source	Mention of referral rate	Sex-specific referral rate	Includes outcomes	Mortality	Re-hospitalization	Predictors of HF referral	Mention of rurality
		Hospital/ED	HFC								
Group 2: Studies including patients referred to HFC (n = 5)	Adams (1996)	No	Yes	No	No	No	Yes	Yes	No	No	No
	Anguita Sánchez (2004)	No	Yes	No	No	No	Yes	Yes	No	No	Yes ^a
	Lezha (2003)	No	Yes	No	No	No	Yes	Yes	Yes	No	No
	Ng (2007)	No	Yes	No	No	No	Yes	Yes	No	No	No
Group 1: Studies reporting on referral process (n = 3)	Opasich (2000)	No	No	No	No	No	Yes	Yes	Yes	No	No
	Feldman (2013)	Yes	No	No	Yes	Yes	Yes	No	Yes ^b	Yes	No
	Mejherth (1999)	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
	Opasich (2004)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No

Note: The table provides a more detailed breakdown of the referral process described in each study.

^aCommunity hospital vs. general hospital

^bStudy mentions re-hospitalization but no sex stratification of outcomes

Time to referral

No studies reported on the impact of patient sex and gender on the timing of referral. Only Feldman *et al.* mentioned time to referral and reported that 28.5% of their population was referred to an HFC within 6 weeks of ED discharge.¹⁵ compared with females, males were consistently and more frequently referred to specialized HFC at all observed intervals following ED visit (6 weeks: 39.9% vs. 16.9%; 3 months: 45.1% vs. 21.5%; 6 months: 51.0% vs. 23.9%, $P < 0.0001$).

Impact of age

As outlined in Table 2, in all three studies in Group 1, females were significantly older than males, with Feldman *et al.* reporting mean age of 78.2 ± 10.2 years in females vs. 72.9 ± 11.2 years in males, Opasich *et al.* reporting 77 ± 11 years in females vs. 72 ± 12 years in males, and Mejherth *et al.* reporting median age of 81 years (range 40–99) in females compared with 78 years (range 35–95) in males.^{15,19,20}

In two of the above three studies, younger age was associated with a higher probability of being referred to an HFC with age in years associated with an adjusted odds ratio (aOR) of 0.95 (95% CI 0.92–0.98).¹⁵ Mejherth *et al.* also reported a significant age difference in patients referred to HFCs (Males: 70 years, Females: 73 years) compared with those referred to GPs (Males: 79 years, Females: 80 years, $P < 0.001$).²⁰

Within the studies in Group 2, while two of these studies reported females to be significantly older than males (women: 65 ± 12 to 71 ± 13 years vs. men: 62 ± 11 to 65 ± 12 years),^{23,24} two others reported no age differences between sexes^{17,22} and one study reported females to be younger than males (49 ± 11 years vs. 52 ± 0.7 years).²¹

HF phenotype and severity (NYHA class)

HF phenotype was reported in two of the three studies in Group 1 (Table 4). Feldman *et al.* found HFpEF (defined as LVEF $>40\%$) to be more prevalent in females than males (60.2% vs. 41.3%, $P < 0.0001$), while noting HFrEF to be a predictor of HFC referral (aOR 3.08 [95% CI 1.77–5.46]).¹⁵ Similarly, Opasich *et al.* found HFpEF to afflict 43.5% of females and 27.7% of males. Although they did not report predictors of HFC referral, they found that females with HFpEF tended to be admitted under Medicine rather than Cardiology (47% vs. 40%, respectively).¹⁹

Studies in Group 2 which included patients already referred to an HFC demonstrated that HFpEF was more prevalent in females than males (39.6%–60.7% vs. 20.9%–38%).^{17,23,24} Of the four studies that reported EF measure-

Table 4 Characteristics of heart failure

Categories	Primary author (year)		Type of heart failure				Mean LVEF measured				Symptom severity (NYHA class I-IV)			
	HFReF		HFpEF		Mean LVEF measured		Symptom severity (NYHA class I-IV)		Males (%)		Females (%)			
	HFReF (% males)	HFReF (% females)	HFpEF (% males)	HFpEF (% females)	Males	Females	I-II	III-IV	I-II	III-IV	I-II	III-IV		
Group 2: Studies including patients referred to HF clinics (n = 5)	Adams (1996)	—	—	—	24 ± 0.6	29 ± 1.1	32	68	33	67	—	—		
	Anguita Sanchez (2004)	73	60	27 ^a	25 ± 13	41 ± 14	62	38	46	54	—	—		
	Lezha (2003)	61.4	39.3	38 ^b	—	—	—	—	—	—	—	—		
	Ng (2007)	—	—	—	25.8 ± 10.6	30.6 ± 13.9	67	33	50	50	—	—		
	Opasich (2000)	79.1	60.4	20.9 ^c	33 ± 11	39 ± 13	69.7	30.3	64.5	35.5	—	—		
Group 1: Studies reporting on referral process (n = 3)	Feldman (2013)	—	—	41.3 ^c	—	—	—	—	—	—	—	—		
	Mejherth (1999)	—	—	—	—	—	—	—	—	—	—	—		
	Opasich (2004)	72.3	56.5	27.7 ^c	—	—	45.2 ^d	31.8	43.1 ^d	30.5	—	—		
Categories	Primary author (year)		Ischaemic (%)		Non-ischaemic (%)		Idiopathic CM (%)							
	Males	Females	Males	Females	Males	Females	Males	Females						
Group 2: Studies including patients referred to HFC (n = 5)	Adams (1996)	37	11	—	—	—	13	28						
	Anguita Sánchez (2004)	46	25	—	—	—	18	13						
	Lezha (2003)	45.9	33.7	—	—	—	7.6	1.7						
	Ng (2007)	53	56	—	—	—	—	—						
	Opasich (2000)	46.7	27.4	—	—	—	32.9	27.8						
Group 1: Studies reporting on referral process (n = 3)	Feldman (2013)	—	—	—	—	—	—	—						
	Mejherth (1999)	51	44	—	—	—	4	4						
	Opasich (2004)	49.9	32.8	—	—	—	13.8	6.9						

Note: The table describes the HF characteristics of the population of the included studies.

^aHFpEF defined as EF > 45%.

^bHFpEF not well defined, no specific EF cut-off mentioned.

^cHFpEF defined as EF > 40%.

^dIncludes class III.

Table 5 Clinical outcomes

Categories	Primary author (year)	Mortality (%)			First hospitalization or rehospitalization for HF or ED visits (%)			Survival																	
		Overall		F	Overall		F	Overall survival (%)		No admission for HF (%)		No CV events (%)													
		M	F	M	F	M	F	M	F	M	F	M	F												
Group 2: Studies including patients referred to HFC (n = 5)	Adams (1996)	36.08	41.05	25.42	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
	Anguita Sanchez (2004)	6	—	—	14	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	Lezha (2003)	—	0.69 ^a	2.2 ^a	—	—	0.69 ^a	3.37 ^a	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Ng (2007)	16.67 ^b	16.38 ^b	17.31 ^b	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Group 1: Studies reporting on referral process (n = 3)	Opasich (2000)	16.3 ^c	16.37 ^c	15.94 ^c	24.4	24.9 ^c	23 ^c	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Feldman (2013)	—	24	13	62.7	66.7	58.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Mejherth (1999)	22	24	13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Opasich (2004)	—	16.8	13.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Note: The table describes the clinical outcomes of interest, stratified by sex.

Abbreviations: F, females; M, males.

^a8 month mortality and hospitalization.

^b5 year mortality and hospitalization.

^c1 year mortality and hospitalization.

^d24 month survival.

ments, the LVEF was higher in females compared with men, ranging from 29% ± 1.1% to 41% ± 14% as compared with 24% ± 0.6% to 33% ± 11%.^{21–24}

In Group 1, only one study¹⁹ reported HF severity and found no significant sex difference (Table 4). Four of the five studies in Group 2 reported HF severity. Two of these studies found more females to have NYHA III–IV symptoms (50%–54%) than males (33%–38%),^{22,23} while no sex-based differences were reported by the other two studies (35.5%–67% females with NYHA III–IV symptoms vs. 30.3%–68% in males).^{21,24}

HF aetiology

As displayed in Table 4, males were more likely to have ischaemic HF (37%–53%) than females (11%–56%).^{17,21–24} In contrast, females were more likely to have hypertensive (51%–71% vs. 49%–61%), valvular (21%–29.2% vs. 17%–22.1%), and idiopathic (1.7%–28% vs. 7.6%–32.9%) aetiologies of HF.^{17,21–24}

Investigations

None of the studies reported on specific investigations following hospital discharge or ED, although Opasich *et al.* reported that patients admitted under Cardiology were significantly more likely to undergo further outpatient investigations compared with those admitted under Medicine, regardless of sex.¹⁹

Two of the three studies in Group 1 reported on investigations during index hospitalization. Mejherth *et al.* reported that despite a lack of sex-based differences in HF aetiology or Killip class, fewer echocardiograms were performed in hospitalized females (55%) than males (68%, $P = 0.011$).²⁰ Opasich *et al.* found that female sex was independently associated with lower use of inpatient echocardiography (OR 0.72; 95% CI 0.52–0.99), Holter monitoring, stress testing, right heart catheterization and coronary angiography.¹⁹ They attributed this finding to sex differences in HF aetiology. Specifically, HF is more likely to be attributed to ischaemia and pulmonary disease in males and to hypertension and endocrine dysfunction in females.¹⁹

Only one study in Group 2 included investigations performed at initial HFC assessment or within 6 months prior to initial HFC visit. Anguita Sánchez *et al.* found that males more frequently underwent cardiac catheterization (40% vs. 21%, $P < 0.01$) and ergometry (18% vs. 9%, $P < 0.05$) compared with females. There was no significant sex-based difference in the rate of echocardiograms, nuclear studies and Holter monitors performed.²³

HF management

The reporting of HF medication use and revascularization was inconsistent across studies. A wide range of HF therapies including ACE inhibitors, mineralocorticoid receptor antagonists, nitrates, digoxin and diuretics were reported, though no consistent sex differences in prescribing patterns were identified. Mejhert *et al.* found that treatment with beta-blockers was associated with a higher likelihood of being referred to an outpatient HFC ($P < 0.035$).²⁰ Beta-blocker use ranged from 11.4% to 64% amongst males and from 10.3% to 59.6% amongst females.^{19,20,22–24} None of the studies reported on referral rates for device therapies such as implantable cardiac defibrillators or cardiac resynchronization therapy.

Mortality and re-hospitalization

Two of the three studies in Group 1 reported on mortality. Mejhert *et al.* found a higher mortality in males (24%) compared with females (13%, $P < 0.012$) at 6 months,²⁰ whereas no sex differences were reported by Opasich *et al.* (16.8% in males vs. 13.7% in females, $P = \text{NS}$).¹⁹

Two of the studies in Group 1 did not report significant sex differences in rehospitalization rate at 6 months (Feldman *et al.*: 66.7% in males and 58.6% in females, $P = 0.05$; Opasich *et al.*: 43.7% in males and 45.9% in females, $P = \text{NS}$; Table 5)^{15,19} whereas the third study²⁰ did not stratify their rehospitalization data by sex.

Reports of mortality amongst studies in Group 2 were heterogeneous and consisted of varying intervals of follow-up. Four studies found no significant sex differences in mortality. Lezha *et al.* reported mortality rates as 2.2% (females) vs. 0.69% (males) at 8 months, Opasich *et al.* reported rates of 15.94% (females) vs. 15.37% (males) at 1 year, Anguita-Sánchez *et al.* reported rates of 14% (females) and 12% (males) at 13 months, and Ng *et al.* reported rates of 17.31% (females) vs. 16.38% (males) at 5 years.^{17,22–24} Only one study reported a significantly higher mortality rate in males (41.05% vs. 25.42%, $P < 0.001$), at 2.4 years of follow-up.²¹

Rehospitalization rate amongst those referred to outpatient clinics was reported in two of the five studies. Lezha *et al.* found that rehospitalization rate at 8 months was significantly higher amongst females (3.37% vs. 0.69%, $P = 0.025$), whereas Opasich *et al.* found no significant difference between sexes (23% vs. 24.9%) at 1 year.^{17,24}

Quality of life

Only one study reported on QoL.¹⁵ Feldman *et al.* reported a similar Minnesota Living with Heart Failure QoL score be-

tween sexes with scores of 36.1 ± 23.6 amongst males and 33.5 ± 25.8 amongst females.

Discussion

Summary of findings

This scoping review is the first, to our knowledge, to systematically examine the available literature evaluating sex-based differences in referral patterns to outpatient HFCs following an ED visit or hospitalization with a primary diagnosis of HF. This review highlights the paucity of literature assessing the referral process of HF patients and their access to specialized outpatient care. More importantly, it sheds light on the paucity of sex and gender-specific analyses in this patient group. Our review has yielded four major observations warranting further investigation: (i) males were more likely than females to be referred to HFCs after an ED visit or hospitalization. (ii) When admitted to hospital with a primary diagnosis of HF, males were more likely to be cared for by cardiologists, undergo investigations for HF and be referred to an HFC. (iii) Independent predictors of HFC referral included male sex, younger age and systolic dysfunction; the two latter factors were more often found in males. (iv) There was significant heterogeneity across the studies to assess sex-based differences in mortality or rehospitalization based on referral to HFC or lack thereof.

Risk factors and referral

Several reasons may explain the sex difference in HFC referral rates, including the different aetiologies in HF amongst females. HF in females is more likely to stem from chronic hypertension, atrial fibrillation and valvular disease^{19,25} which leads to HFpEF.²⁶ The residual beliefs amongst physicians that HF is a 'man's syndrome' may contribute to delays in referral, investigation and management of HF in females.²⁷ One included study found that younger age and male sex were independent predictors of HFC referral.¹⁵ On the contrary, females with HF tend to be older, have more co-morbidities and are more frail compared with males.^{27,28} This possibly points to the existence of referral bias and a treatment-risk paradox, whereby older patients with multiple co-morbidities who could benefit most from specialized care are not receiving it.²⁹

Amongst patients proposed for referral to an HFC, males more frequently underwent cardiac investigations than females. On the contrary, amongst patients already enrolled to an HFC, there was no difference in echocardiography use prior to or at first HFC visit. This demonstrates that in patients who are enrolled in an HFC, there does not appear to be a sex difference in the use of certain cardiac investigations such as

echocardiography, suggesting that the same implicit bias behind HFC referrals may also exist for referrals for cardiac testing.

Re-hospitalization and mortality

Our findings are consistent with other scoping reviews evaluating readmission rates following heart failure.³⁰ Hoang-Kim *et al.*, who noted that studies with shorter follow-up (<12 months) revealed that females had a higher re-admission rate than males, suggesting that early post-discharge follow-up care may be of particular benefit in this population.

Van Spall *et al.*, on the other hand, did not find a significant difference in composite outcomes of all-cause readmission, ED visits or death at 3 months when evaluating the effect of transitional care services for patients recently hospitalized for HF. However, they found that such an intervention was associated with significant improvements of patient discharge preparedness and QoL at both 6 weeks and 6 months,³¹ highlighting once again the importance of early specialist follow-up for all HF patients following hospital discharge.

Our findings of similar mortality rates between sexes in patients enrolled to an HFC were discordant with previous studies that have shown that risk of death in females diagnosed with HF is lower than in males (HR 0.86, 95% CI 0.84–0.88).³² One possible explanation for this discrepancy is that the above study population, in which similar mortality was found, comprises solely of patients already referred to and followed by an HFC, therefore self-selecting to be sick and co-morbid enough to warrant an HFC referral. This population differs from previous studies which may have included all-comers, including patients diagnosed with HF, but not necessarily referred to an HFC.

The above findings also reinforce the prognostic importance of HFpEF. Indeed, HFpEF is associated with similar rates of rehospitalization and health resource utilization as HFrEF,^{33,34} as well as similar adjusted rates of 1 year mortality.³⁵ Despite this, we have fewer therapies with proven benefits to treat HFpEF.³⁶ Given the high prevalence of HFpEF amongst females, it is therefore of particular importance to conduct further research on this topic to elucidate ways to improve the follow-up and management and thus improve the outcomes of this patient population.

Limitations

Our findings should be interpreted in the context of certain limitations. First, our report is limited by a delay in reporting our findings, as our most recent literature search was per-

formed in January 2019. Although this may have led to missed publications, it is noted that relatively few manuscripts are published in the field (all included studies were published between 1996 and 2013), and no additional pertinent studies arose from our 2019 search update as compared with our initial search in 2016. Moreover, our peer-reviewed search strategy and our thorough review of the grey literature ensured the breadth and inclusiveness of the scoping review. Second, given that this was a scoping review, with a particular focus on breadth and inclusivity in our search strategy, a critical appraisal was not performed on the included studies. While we have reported the results of the included studies, such findings should be interpreted with caution.

Third, our findings of sex-based differences in HFC referral patterns are confounded by other sex-based difference in HF, including age at presentation, HF phenotype, aetiology and inpatient specialty care. Indeed in-hospital care may have significant influence on outpatient follow-up. Despite not being to adjust for this, our objective was to provide a descriptive analysis of the existing referral process of HF patients stratified by sex and again highlights the paucity of literature on this topic.

There is also significant heterogeneity in the included studies in terms of study design and setting, referral process, patient demographics and outcomes that precluded effective synthesis of these findings in aggregate. Information on sex or specialty of referring healthcare provider, which could have provided additional insight on referral patterns and bias, was also missing. Nevertheless, our scoping review was able to identify these knowledge gaps in published and grey literature, as well as the need for further research in this domain.

Heterogeneity in referrals to HFCs may reflect the geographic variations in clinical practice guidelines. For instance, although HF management guidelines from the USA, Canadian, Australia, Europe and South Asia all recommend dedicated HF follow-up within 7–14 days post discharge, they do not specify the setting (i.e. HFC vs. primary care) where follow-up should take place.^{3–7} This likely reflects the fact that HFCs may not readily available or accessible in all regions and countries. We accounted for this through an inclusive search strategy, as well as including patients referred to internists and geriatricians.

In addition, our search was focused on patients with referrals to HFCs from the GP's office, ED or following hospitalization, and therefore may have missed some referrals originating from other specialists. However, our scope of interest was determined a priori and included patients with established rather than incident HF. Lastly, our restriction to articles published in English may have limited the scope of our findings. Specifically, the included studies capture practices and outcomes in Western countries such as Italy and Canada but not Asia, where the prevalence of HF is higher.^{37,38} Nevertheless, our scoping review was able to

identify the knowledge gaps in published literature and highlights the need for further research in this domain, both locally and internationally.

Conclusions

We identified a paucity of literature to describe sex-based differences in the referral of patients to HFCs. In addition, we found that females were reported as being less likely to be referred to outpatient HFCs than men. Our findings serve as a call to action and highlights the need for more sex-specific analyses on comprehensive longitudinal data post discharge from the acute care setting, so that we can better understand possible disparities in HF care.

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References

1. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, Younis A, Dai H. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol*. 2021; **28**: 1682–1690.
2. Ferreira JP, Kraus S, Mitchell S, Perel P, Piñeiro D, Chioncel O, Colque R, de Boer RA, Gomez-Mesa JE, Grancelli H, Lam CSP, Martinez-Rubio A, McMurray JJV, Mebazaa A, Panjra G, Piña IL, Sani M, Sim D, Walsh M, Yancy C, Zannad F, Sliwa K. World heart federation roadmap for heart failure. *Glob Heart*. 2019; **14**: 197–214.
3. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Zieroth S, al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 comprehensive update of the Canadian cardiovascular society guidelines for the Management of Heart Failure. *Can J Cardiol*. 2017; **33**: 1342–1433.
4. NHFA CSANZ Heart Failure Guidelines Working Group, Atherton JJ, Sindone A, de Pasquale CG, Driscoll A, MacDonald P, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W, Thomas L, Audehm R, Newton P, O'Loughlin J, Branagan M, Connell C. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the prevention, detection, and Management of Heart Failure in Australia 2018. *Heart Lung Circ*. 2018; **27**: 1123–1208.
5. Heidenreich PA, Fonarow GC, Brethett K, Jurgens CY, Pisani BA, Pozehl BJ, Spertus JA, Taylor KG, Thibodeau JT, Yancy CW, Ziaeian B. 2020 ACC/AHA clinical performance and quality measures for adults with heart failure. *Circ Cardiovasc Qual Outcomes*. 2020; **13**: e000099.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumgartner H, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray J, Mebazaa A, Mindham R, Murereto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the heart failure association (HFA) of the ESC. *Eur Heart J*. 2021; **42**: 3599–3726.
7. Kabbani S, al Habeeb W, Liew HB, Mohan JC, Ogola E, Sim D, Tsabedze N. Supporting the Management of Patients with heart failure within Asia-Pacific, Middle East, and African countries: A toolbox for healthcare providers. *Cardiology*. 2019; **142**: 1–10.
8. Fonarow GC, Stevenson LW, Walden JA, Livingston NA, Steimle AE, Hamilton MA, Moriguchi J, Tillisch JH, Woo MA. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol*. 1997; **30**: 725–732.
9. Ansari M, Alexander M, Tutar A, Bello D, Massie BM. Cardiology participation improves outcomes in patients with new-onset heart failure in the outpatient setting. *J Am Coll Cardiol*. 2003; **41**: 62–68.
10. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*. 2018; **18**: 143.
11. Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. *Int J Soc Res Methodol*. 2005; **8**: 19–32.
12. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.

Conflicts of interest

None declared.

Supporting information

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

Table S1. Database Details.

Table S2. Medline Search (Oct 2016).

Table S3. Embase Search (Oct 2016).

Table S4. PsycINFO Search (Oct 2016).

Table S5. Cochrane Library Search (Oct 2016).

Table S6. Ageline Search (Oct 2016).

- PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016; **75**: 40–46.
13. Damarell RA, Tieman J, Sladek RM, Davidson PM. Development of a heart failure filter for Medline: An objective approach using evidence-based clinical practice guidelines as an alternative to hand searching. *BMC Med Res Methodol*. 2011; **11**: 12.
 14. Feldman DE, Ducharme A, Giannetti N, Frenette M, Michel C, Grondin F, Sheppard R, Lauriers JD, Behloul H, Pilote L. Outcomes for women and men who attend a heart failure clinic: Results of a 12-month longitudinal study. *J Card Fail*. 2011; **17**: 540–546.
 15. Feldman DE, Huynh T, Des Lauriers J, Giannetti N, Frenette M, Grondin F, Michel C, Sheppard R, Montigny M, Lepage S, Nguyen V, Behloul H, Pilote L. Gender and other disparities in referral to specialized heart failure clinics following emergency department visits. *J Womens Health*. 2013; **22**: 526–531.
 16. Feldman DE, Huynh T, Lauriers JD, Giannetti N, Frenette M, Grondin F, Michel C, Sheppard R, Montigny M, Lepage S, Nguyen V, Behloul H, Pilote L. Access to heart failure care post emergency department visit: Do we meet established benchmarks and does it matter? *Am Heart J*. 2013; **165**: 725–732.
 17. Lezha M, Rama B. Gender differences in management of heart failure in Albania. *Eur J Heart Fail*; **16**: 5–365.
 18. Government of Canada CI of HR. What is gender? What is sex? - CIHR. Published January 10, 2014. Accessed February 12, 2021. <https://cihr-irsc.gc.ca/e/48642.html>
 19. Opasich C, de Feo S, Ambrosio GA, Bellis P, di Lenarda A, di Tano G, Fico D, Gonzini L, Lavecchia R, Tomasi C, Maggioni AP, TEMISTOCLE Investigators. The 'real' woman with heart failure. Impact of sex on current in-hospital management of heart failure by cardiologists and internists. *Eur J Heart Fail*. 2004; **6**: 769–779.
 20. Mejhert M, Holmgren J, Wändell P, Persson H, Edner M. Diagnostic tests, treatment and follow-up in heart failure patients — Is there a gender bias in the coherence to guidelines? *Eur J Heart Fail*; **1**: 407–410.
 21. Adams KF, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, Jensen LR, Tomasko L, Koch G. Relation between gender, etiology and survival in patients with symptomatic heart failure. *J Am Coll Cardiol*. 1996; **28**: 1781–1788.
 22. Ng ACC, Wong HSP, Yong ASC, Sindone AP. Impact of gender on outcomes in chronic systolic heart failure. *Int J Cardiol*. 2007; **117**: 214–221.
 23. Anguita Sánchez M, Investigadores del Registro BADAPIC. Clinical characteristics, treatment and short-term morbidity and mortality of patients with heart failure followed in heart failure clinics. Results of the BADAPIC registry. *Rev Esp Cardiol*. 2004; **57**: 1159–1169.
 24. Opasich C, Tavazzi L, Lucci D, Gorini M, Albanese MC, Cacciatore G, Maggioni AP. Comparison of one-year outcome in women versus men with chronic congestive heart failure. *Am J Cardiol*. 2000; **86**: 353–357.
 25. De Feo S, Opasich C. Comparison of the outcome in men and women with chronic heart failure. *Ital Heart J Off J Ital Fed Cardiol*. 2003; **4**: 511–513.
 26. Bogaev RC. Gender disparities across the Spectrum of advanced cardiac therapies: Real or imagined? *Curr Cardiol Rep*. 2016; **18**: 108.
 27. Eisenberg E, Palo KED, Piña IL. Sex differences in heart failure. *Clin Cardiol*. 2018; **41**: 211–216.
 28. Uchmanowicz I, Młynarska A, Lisiak M, Kałużna-Oleksy M, Wleklík M, Chudiak A, Dudek M, Migaj J, Hinterbuchner L, Gobbens R. Heart failure and problems with frailty syndrome: Why it is time to care about frailty syndrome in heart failure. *Card Fail Rev*. 2019; **5**: 37–43.
 29. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: The treatment-risk paradox. *JAMA*. 2004; **291**: 1864–1870.
 30. Hoang-Kim A, Parpia C, Freitas C, Austin PC, Ross HJ, Wijeyesundera HC, Tu K, Mak S, Farkouh ME, Sun LY, Schull MJ, Mason R, Lee DS, Rochon PA. Readmission rates following heart failure: A scoping review of sex and gender based considerations. *BMC Cardiovasc Disord*. 2020; **20**: 223.
 31. van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, Maingi M, Tjandrawidjaja MC, Heffernan M, Zia MI, Porepa L, Panju M, Thabane L, Graham ID, Haynes RB, Haughton D, Simek KD, Ko DT, Connolly SJ. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: The PACT-HF randomized clinical trial. *JAMA*. 2019; **321**: 753–761.
 32. Taylor CJ, Ordóñez-Mena JM, Jones NR, Roalfe AK, Lay-Flurrie S, Marshall T, Hobbs FDR. National trends in heart failure mortality in men and women, United Kingdom, 2000–2017. *Eur J Heart Fail*. 2021; **23**: 3–12.
 33. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghide M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF registry. *J Am Coll Cardiol*. 2007; **50**: 768–777.
 34. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I. *Circulation*. 2002; **105**: 1387–1393.
 35. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006; **355**: 260–269.
 36. Fontes-Carvalho R, Leite-Moreira A. Heart failure with preserved ejection fraction: Fighting misconceptions for a new approach. *Arq Bras Cardiol*. 2011; **96**: 504–514.
 37. Sakata Y, Miyata S, Nochioka K, Miura M, Takada T, Tadaki S, Takahashi J, Shimokawa H. Gender differences in clinical characteristics, treatment and long-term outcome in patients with stage C/D heart failure in Japan. Report from the CHART-2 study. *Circ J Off J Jpn Circ Soc*. 2014; **78**: 428–435.
 38. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G. Heart failure: Preventing disease and death worldwide. *ESC Heart Fail*. 2014; **1**: 4–25.