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Missed opportunities in the diagnosis of heart failure: a real-world assessment

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Abstract

Aims Heart failure (HF) is a leading cause of hospitalization worldwide. An early HF diagnosis is key to reducing hospitalizations. We used electronic health records (EHRs) to characterize HF pathways at the primary care physician (PCP) level prior to a first HF hospitalization (hHF). This study aimed to identify missed opportunities for HF diagnosis and management at the PCP level before a first hHF.

Methods and results This cohort study used EHRs of a large health care organization in Portugal. Patients with incident hHF between 2017 and 2020 were identified. Missed opportunities were defined by the absence of any of the following work-up in the 6 months after signs or symptoms had been recorded: lab results and electrocardiogram, natriuretic peptides, echocardiogram, referral to HF specialist, or HF medication initiation. A total of 2436 patients with a first hHF were identified. The median (interquartile range) age at the time of hospitalization was 81 (14) years, and 1361 (56%) were women. Most patients were treated with cardiovascular drugs prior or at index event. A total of 720 (30%) patients had records of HF signs or symptoms, 94% ($n = 674$) within 6 months prior to hHF. Among patients with recorded HF signs or symptoms, 410 (57%) had clinical management considered adequate before signs and symptoms were recorded. Of the 310 remaining patients, 155 (50%) had a follow-up that was considered inadequate.

Conclusions Relatively few patients with a first hHF had primary care records of signs or symptoms prior to admission. Of these, nearly half had inadequate management considering diagnosis and treatment. These data suggest the need to improve PCP HF awareness.

Keywords Electronic health records; Heart failure; Disease management; Missed opportunities; Primary care

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Introduction

Heart failure (HF) is a leading cause of hospitalization worldwide. In western societies, HF is the leading cause of hospitalization among the elderly (>65 years).¹ With an aging population, both incidence and prevalence of HF are expected to increase, providing pressure on health care systems particularly due to hospitalizations.² Thus, strategies to mitigate the burden of HF hospitalizations (hHFs) are needed.

To decrease hHFs, first, one needs to be aware, identify, and record HF signs and symptoms in electronic health records (EHRs), so that patients can be diagnosed at an early stage of the disease, allowing the implementation of adequate HF management to improve health status and decrease hospitalizations and mortality. For example, a comprehensive therapy comprising an angiotensin receptor-neprilysin inhibitor (ARNI), a sodium glucose co-transporter 2 inhibitor (SGLT2i), a mineralocorticoid receptor antagonist (MRA),

and a beta-blocker may provide a relative reduction of hHFs > 60% compared with a regimen including an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and a beta-blocker.³

Despite the progress in HF treatments, many patients living with HF will remain undiagnosed and, as consequence, poorly treated due to deficient identification and recording of HF signs and symptoms, particularly in primary care, where most health-related contacts occur.⁴

To better understand the patient's pathway within the health care system in the years preceding an hHF, we used EHRs linking primary care physician (PCP) and hospital records, allowing to trace signs, symptoms, medical exams, lab and imaging results, and medications over time in an integrated electronic system in the northern region of Portugal. Therefore, this project (eTREAT: electronic health records to TRigger EARly Treatment) aimed to identify missed opportunities for diagnosing and treating HF before hHF occurs, that is, opportunities that could potentially have prevented hHF if not missed.

Material and methods

Study design and participant selection

The eTREAT is an observational cohort study of patients followed at the *Unidade Local de Saúde de Matosinhos* (ULSM). The ULSM is a large health care organization including 14 primary care centres assisted by one hospital that provides primary, secondary, and tertiary care services to the region of Matosinhos in the north of Portugal, reflecting the activity of over a thousand medical doctors across different specialties.

We identified adult patients (aged ≥ 18 years) who had a first hHF (index event) between 1 January 2017 and 31 December 2020. hHF was defined by a primary/first ICD-9 (404.03, 404.13, 404.93, or 428) or ICD-10 (I11.0, I13.0, I13.2, or I50) code or one of these codes in any position provided that the first diagnosis included atrial fibrillation, respiratory tract infection, or renal failure in the EHR data. To be considered as a first hHF episode, the patient was required to have at least 365 days of EHRs, and no prior hHF ever recorded. Valvular heart disease and acute coronary syndromes were excluded because these are HF causes *per se* and HF may be reverted if the cause is treated.

Assessment of missed opportunities

Potential missed opportunities for HF diagnosis and management were assessed within the 5 years preceding the index date of hHF. Most patients have primary care appointments before requiring hospital appointments or treatments; there-

fore, missed opportunities for HF diagnosis and treatment focused on the PCP level. In short, we included all health care contacts within the defined time frame to build the patient journey within the health care system. Specifically, we automatically searched for PCP records of HF signs and symptoms, plus electrocardiogram (ECG) abnormalities, abnormal echocardiographic parameters, raised natriuretic peptide levels [N-terminal pro-brain natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP)], and initiation of HF medications (loop diuretics, MRAs, ACEi/ARBs, ARNIs, beta-blockers, and SGLT2is). Natural language processing and ICPC-2 codes for symptoms were used to retrieve written information in the medical registries. The search process was implemented through an automated scan of all clinical notes recorded for terms and expressions of interest described in Supporting Information, *Table S1*. Two authors (T. T. G. and M. C. P.) performed and validated this step of the analysis. An abnormal echocardiographic result was considered by any of the following: left ventricular ejection fraction (LVEF) < 50%, left atrium dilation and/or left ventricular hypertrophy (characterized by a left atrial volume indexed > 34 mL/m² or a left ventricular mass indexed ≥ 115 g/m² in men or ≥ 95 g/m² in women or relative wall thickness > 0.42 mm), or a pulmonary artery systolic pressure > 35 mmHg. An abnormal ECG was considered if recorded by the PCP as 'abnormal' (any abnormality was considered as a 'positive' result).

In Portugal, it may take some time (often >6 months) to have an echocardiogram performed and fully reported, and natriuretic peptides are not reimbursed if ordered by a PCP; thus, we considered a broad range of options for the PCP to manage HF in a way considered 'adequate' after signs and symptoms had been reported. Options for HF management by PCP included ordering basic lab results plus an ECG, referring the patient to an HF specialist, initiating HF medications, and ordering an echocardiogram or natriuretic peptides. Accordingly, we considered the following possible patient pathways for HF management:

- 1) If HF signs or symptoms had been documented/recorded, then we considered that at least one of the following should occur (be performed) within the following 6 months: (i) electrolytes, creatinine, haemogram, and ECG; (ii) NT-proBNP/BNP; (iii) transthoracic echocardiogram; (iv) hospital referral to internal medicine or cardiology appointments; or (v) HF medication initiation.
- 2) If HF signs or symptoms had been documented/recorded AND there was an abnormal ECG, then at least one of the following should occur (be performed) within 6 months: (i) NT-proBNP/BNP; (ii) echocardiogram; (iii) hospital referral to internal medicine or cardiology appointments; or (iv) HF medication initiation.
- 3) If HF signs or symptoms had been documented/recorded AND an abnormal echocardiogram was identified, then at least one of the following should occur (be performed)

within 6 months: (i) NT-proBNP/BNP; (ii) hospital referral to internal medicine or cardiology appointments; or (iii) HF medication initiation.

- 4) If HF signs or symptoms had been documented/recorded AND an abnormal NT-proBNP/BNP was present, then at least one of the following should occur (be performed) within the following 6 months: (i) echocardiogram; (ii) hospital referral to internal medicine or cardiology appointments; or (iii) HF medication initiation.
- 5) If HF signs or symptoms had been documented/recorded AND an abnormal NT-proBNP/BNP was present AND an abnormal echocardiogram was identified, then at least one of the following should occur (be performed) within 6 months: (i) hospital referral to internal medicine or cardiology appointments; or (ii) HF medication initiation.

The following scenarios were not considered for the assessment of potential missed opportunities:

- 6) abnormal NT-proBNP/BNP AND abnormal echocardiogram AND HF medication initiated prior to the reporting of signs and symptoms; and
- 7) patients followed in outpatient internal medicine or cardiology hospital appointments prior to the reporting of signs and symptoms.

Statistical analysis

Continuous variables were reported as median and interquartile range. Categorical variables were presented as absolute and relative frequencies. Baseline characteristics were compared between groups using the χ^2 test for categorical variables and the Wilcoxon test for continuous variables. Significance threshold was set at 0.05. We developed analytical programmes using VERO technology that were compiled for a target data infrastructure built upon Apache Spark Framework Version 3.2.1 and source data harmonized according to the OMOP CDM 5.4 standard. The package implements a complete data engineering pipeline to transform the source data into the final dataset as well as execution of statistical analysis and generation results reports.

Ethics approval and data processing

This study was approved by the Ethics Committee and Data Protection Officer of ULSM (translated from *Comissão de Ética para a Saúde da Unidade Local de Saúde de Matosinhos*) under approval code no. 21/CE/JAS of 12-02-2021. All data processing and analysis operations were developed using VERO technology and sent for execution at the ULSM data centre. VERO compiles analytic programmes tailored for each study centre and sends them to execution in

a fully automated fashion. No data were extracted outside the ULSM, and none of the researchers had access to patient-level data. As an additional degree of security, processed data were de-identified by the ULSM Information Technology Department prior to the analytic code execution according to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbour standard.

Results

Patient characteristics

We identified a total of 2436 patients with a first hHF in the defined time frame, 1716 (70.4%) without HF signs and symptoms recorded in the EHR, and 720 (29.6%) with HF signs and symptoms recorded prior to the index hHF. Compared with patients without HF signs and symptoms recorded, those with recorded signs and symptoms were slightly older (82 vs. 81 years), were more frequently women (62% vs. 53%), had lower serum potassium levels (4.2 vs. 4.3 mmol/L), had lower prevalence of type 2 diabetes (62% vs. 65%), had less frequent history of myocardial infarction (15% vs. 20%), had higher prevalence of arterial hypertension (91% vs. 86%), and were using loop diuretics more frequently (65% vs. 61%) ($P < 0.05$ for all). Patients with HF signs and symptoms recorded had lower left ventricular mass indexed (84 vs. 87 g/m²) and lower left atrial diameter (50 vs. 51 mm) ($P < 0.05$ for all) and had numerically lower levels of BNP (241 vs. 260 pg/mL) and NT-proBNP (3023 vs. 2340 pg/mL) than patients without HF signs and symptoms recorded. The proportion of patients with an LVEF $< 40\%$ reported was low ($< 7\%$) and similar regardless of signs and symptoms reported (Table 1).

Patient patterns prior to heart failure hospitalization

Of the 720 (30%) patients with HF signs or symptoms recorded, 674 (94%) had signs or symptoms recorded within 6 months prior to hHF, and 486 (68%) had signs or symptoms recorded within 30 days prior to hHF (Supporting Information, Table S2).

Most frequently recorded signs or symptoms included swollen limbs ($n = 190$, 26.4%), weight gain ($n = 154$, 21.4%), dyspnoea/breathlessness ($n = 152$, 21.1%), difficulty completing activities ($n = 146$, 20.3%), and rales and peripheral oedema ($n = 141$, 19.6%) (Supporting Information, Table S3).

A total of 1505 (62%) patients had a loop diuretic prescribed at any point in time before the index hHF event, with a greater proportion of loop diuretic prescription among patients with signs or symptoms recorded ($n = 467$, 65%) than

Table 1 Clinical characteristics, comorbidities, and medications of patients hospitalized for heart failure

	HF patients without signs or symptoms recorded			HF patients with signs or symptoms recorded			<i>P</i>
Eligible patients	1716			720			
Female, <i>n</i> (%)	914	53.3		447	62.1		<0.001
Age, years, P50 (P25–P75)	81	72–87		82	75–87		0.005
Clinical measurements	P50	P25–P75	% NA	P50	P25–P75	% NA	
BMI, kg/m ²	27.9	24–32	8.9	27.9	24.8–31.7	3.9	0.60
SBP, kg/m ²	136.0	124–146	5.6	136.0	122.0–147.0	1.5	0.69
DBP, kg/m ²	74.5	67–82	5.6	76.0	67.0–84.0	1.5	0.17
Laboratory measurements	P50	P25–P75	% NA	P50	P25–P75	% NA	
Haemoglobin, g/dL	12.1	10.7–13.6	0.2	12.1	10.7–13.4	0.0	0.33
Potassium, mEq/L	4.3	3.9–4.7	0.5	4.2	3.8–4.6	0.3	<0.001
HbA1c, %	6.1	5.5–7.4	1.0	6.1	5.4–7.1	0.1	0.16
BNP, pg/mL	260	105–616	49.2	240	110–576	49.6	0.65
NT-proBNP, pg/mL	2339	749–6441	79.4	3023	1113–7308	81.7	0.21
Creatinine, mg/dL	1.1	0.8–1.6	0.5	1.1	0.8–1.5	0.0	0.004
UACR, mg/g	21.2	8.1–79.5	25.3	21.5	7.8–66.5	21.1	0.63
LDL-C, mg/dL	100.0	79.2–126.0	5.9	101.0	81.0–126.9	1.3	0.45
Echocardiography measurements	P50	P25–P75	% NA	P50	P25–P75	% NA	
Left atrial volume, mL	43.0	39.0–47.0	43.2	42.0	38.0–46.0	41.0	0.24
Left atrial volume index, mL/m ²	23.9	21.4–26.7	44.9	24.2	21.4–26.1	41.8	0.62
LV mass, g	155.9	131.9–181.6	43.4	145.8	127.0–172.6	41.1	0.001
LV mass index, g/m ²	87.2	74.1–101.8	44.9	83.9	73.2–96.8	41.9	0.011
Left atrial diameter, mm	51.0	47.0–55.0	43.2	50.0	46.0–54.0	40.8	0.016
LV ejection fraction, %	58.0	48.8–63.3	51.1	59.0	53.0–64.0	46.0	0.14
LV ejection fraction < 40% ^a		116	6.8		46	6.4	0.93
LV posterior wall thickness, mL	10.0	9.0–11.0	43.7	10.0	9.0–10.0	41.1	0.013
Interventricular septum thickness, mm	11.0	10.0–12.0	43.5	11.0	10.0–12.0	40.8	0.036
Comorbidities		<i>N</i>	%		<i>N</i>	%	
Type 2 diabetes		1111	64.7		445	61.8	0.021
Chronic kidney disease		1001	58.3		405	56.3	0.131
Obesity		561	32.7		239	33.2	<0.001
Hypercholesterolaemia		473	27.6		193	26.8	<0.001
CV disease		1689	98.4		709	98.5	0.99
Arterial hypertension		1479	86.2		657	91.3	<0.001
Atrial fibrillation		865	50.4		365	50.7	0.93
Stable angina		359	20.9		128	17.8	0.086
Transient ischaemic attack		46	2.7		31	4.3	0.049
Atherosclerotic CV disease		763	44.5		302	41.9	0.27
Stroke		419	24.4		190	26.4	0.33
Myocardial infarction		344	20.1		106	14.7	0.002
Peripheral artery disease		246	14.3		94	13.1	0.44
Unstable angina		124	7.2		59	8.2	0.46
Cardiovascular medications		<i>N</i>	%		<i>N</i>	%	
Aldosterone antagonists		237	13.8		87	12.1	0.28
Anticoagulants		568	33.1		258	35.8	0.21
Antiplatelets		987	57.5		405	56.3	0.6
Beta-blockers		1018	59.3		402	55.8	0.12
SGLT2is		127	7.4		29	4.0	0.002
Calcium channel blockers		867	50.5		383	53.2	0.25
Digitalis		132	7.7		73	10.1	0.057
Direct oral anticoagulants		333	19.4		150	20.8	0.45
Diuretics		1233	71.9		562	78.1	0.002
Loop diuretics		1038	60.5		467	64.9	0.048
Low-dose aspirin		907	52.9		382	53.1	0.96
Nitrates		337	19.6		146	20.3	0.76
P2y12 antagonists		326	19		121	16.8	0.22
Renin-angiotensin-system-acting agents		1457	84.9		633	87.9	0.06
Angiotensin-converting enzyme inhibitors		1120	65.3		478	66.4	0.63
Angiotensin receptor blockers		942	54.9		421	58.5	0.12
Angiotensin receptor-neprilysin inhibitors		62	3.6		15	2.1	0.12
Thiazides		13	0.8		6	0.8	0.99
Vitamin K antagonists		310	18.1		149	20.7	0.15

BMI, body mass index; BNP, B-type natriuretic peptide; CV, cardiovascular; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HF, heart failure; LV, left ventricular; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; SGLT2is, sodium glucose co-transporter 2 inhibitors; UACR, urine albumin-creatinine ratio.

^aAbsolute numbers and percentages provided.

in those without recorded signs or symptoms ($n = 1038$, 61%, $P = 0.048$). Most patients were on stable furosemide doses of 40 mg/day, regardless of signs or symptoms being recorded ($\pm 98\%$ in each group). Few ($n = 130$) patients started a loop diuretic *de novo* within the 6 months prior to admission, with a more frequent loop diuretic initiation among patients with signs or symptoms recorded ($n = 52$ out of 253, 20.6%) than in those without recorded signs or symptoms ($n = 78$ out of 678, 11.5%, $P \leq 0.001$) (Supporting Information, *Table S4*).

Most patients ($n = 2103$, 86%) presented to the emergency room (ER) within the 24 h preceding the hospital admission. ER presentation was more common among patients with signs or symptoms recorded ($n = 467$, 90.0%) than in those without recorded signs or symptoms ($n = 1458$, 85.0%, $P = 0.003$).

Missed opportunities of heart failure diagnosis and management

Of the 720 patients with HF signs or symptoms recorded, 362 (50%) had HF management considered adequate prior to signs and symptoms being reported, and 48 (7%) were followed up in cardiology or internal medicine outpatient hospital appointments (*Figure 1*).

Of the 310 patients with documented HF signs and symptoms considered for the assessment of potential

missed opportunities, 166 (54%) patients had an abnormal ECG; among these, 137 (44%) patients had an abnormal echocardiogram; 102 (33%) patients had raised natriuretic peptides; among these, 37 (12%) patients in the study population had raised natriuretic peptides and an abnormal echocardiogram.

Among those patients with an abnormal ECG, 76 (46%) were considered to have inadequate HF management because they did not initiate HF treatment, nor were referred to cardiology or internal medicine hospital appointments, nor were ordered natriuretic peptides, nor performed an echocardiogram.

Among those patients with an abnormal echocardiogram, 62 patients (45%) were considered to have inadequate HF management because they did not initiate HF treatment, nor were referred to cardiology or internal medicine hospital appointments, nor were ordered natriuretic peptides.

Among those patients with raised natriuretic peptides, 97 (95%) were considered to have inadequate HF management because they did not initiate HF treatment, nor were referred to cardiology or internal medicine hospital appointments, nor performed an echocardiogram.

Among those patients with raised natriuretic peptides and an abnormal echocardiogram, 34 (92%) were considered to have inadequate HF management because they either did not initiate HF treatment or were referred to cardiology or internal medicine hospital appointments (*Figure 2*).

Figure 1 Study flow diagram. GP, general practitioner; HF, heart failure.

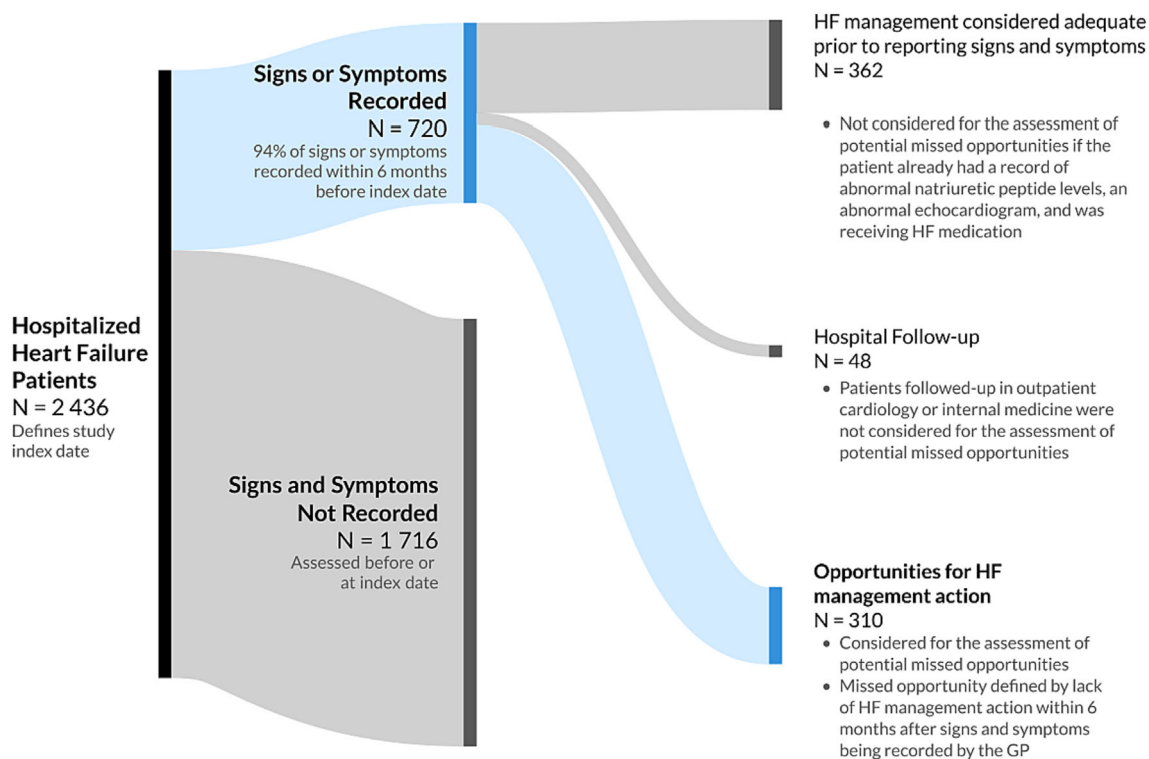


Figure 2 Action for heart failure (HF) management executed taken per clinical presentation in HF patients with signs or symptoms and opportunity for HF work-up. Management action had to be taken at most 6 months or index date after clinical presentation, whichever comes first. Not applicable (NA) indicates management actions that are not clinically relevant for a given clinical presentation. Patients contribute at most once to each clinical presentation category. Patients may contribute to more than one clinical presentation category. Management actions are not mutually exclusive. Natriuretic peptide (NP) measurements consider B-type natriuretic peptide or N-terminal pro-brain natriuretic peptide. *Started a beta-blocker, a renin-angiotensin axis inhibitor, a sodium glucose co-transporter 2 inhibitor, an aldosterone antagonist, or a diuretic. **Referred to outpatient internal medicine or cardiology. ECG, electrocardiogram.

When Clinical Presentation	Was any of the further HF management action taken within 6 months?					
	Missed Opportunity	Further action taken				
		+ ECG	NP	ECHO	Started	Referral
HF signs or symptoms N=310	155 (50%)	15 (5%)	95 (31%)	5 (2%)	77 (25%)	7 (2%)
Abnormal ECG and HF signs or symptoms • N=166	76 (46%)	NA	55 (33%)	1 (1%)	49 (30%)	5 (3%)
Abnormal ECHO and HF signs or symptoms • N=137	62 (45%)	NA	49 (36%)	NA	38 (28%)	5 (4%)
Abnormal NPs and HF signs or symptoms • N=102	97 (95%)	NA	NA	0 (0%)	5 (5%)	0 (0%)
Abnormal NPs + ECHO and HF signs or symptoms • N=37	34 (92%)	NA	NA	NA	3 (8%)	0 (0%)

Discussion

This work using ‘real-world’ EHR data allowed us to map the patient pathway in the health care system before a first hHF. The most striking finding was that <30% of the patients had any HF sign or symptom recorded in the PCP registries. Additionally, in 50% of patients with recorded HF signs or symptoms, HF management in the following 6 months was considered inadequate. These data suggest that increased awareness and documentation of HF signs and symptoms are needed at the PCP level to identify HF earlier and potentially improve outcomes.

Interestingly, compared with patients without HF signs and symptoms recorded, those with HF signs and symptoms had lower left ventricular mass, left atrial diameter, and natriuretic peptide levels, suggesting that many patients with hHF had HF that was unclassified prior to hospitalization. Still, with the exception of loop diuretics which use was slightly more frequent among patients with HF signs and symptoms recorded, the proportion of other HF treatments (e.g. ARBs/ARNIs and MRAs) was similar regardless of signs and symptoms being recorded. Two possible explanations may account for this finding: (i) PCPs correctly diagnosed HF but did not record signs and symptoms, or (ii) HF medications were used for other indications such as arterial hypertension, diabetes, atrial fibrillation, coronary artery disease, or chronic kidney disease, for example. Regardless of the reason behind

the absence of HF signs and symptoms records, the data suggest that patients with HF signs and symptoms had more pronounced volume overload due to the more frequent prescription of loop diuretics. SGLT2is were not recommended for the treatment of HF at the time this study was conducted, and differences in their use may reflect patterns of practice in the treatment of diabetes mellitus. It is also important to highlight that more than 55% of patients with HF signs and symptoms already had management that was considered adequate prior to the recording of HF signs and symptoms, because such patients had measured natriuretic peptides, performed echocardiogram, and started HF medication or had been referred to cardiology or internal medicine hospital appointments. The most likely explanation for this finding is that PCP ordered natriuretic peptides and an echocardiogram and started medication because they suspected the patient suffered from HF but only recorded signs and symptoms after receiving the results of the exams or after referring the patient to a hospital appointment.

In the group of patients with HF signs and symptoms recorded, half of these (155 of 310) had an HF management that was considered inadequate, because blood samples, ECG, natriuretic peptides, and echocardiogram were not ordered, HF medication was not started, or cardiology or internal medicine hospital referral had not been performed. It is also worth noting that most patients had HF signs and symptoms recorded within the 6 months preceding hHF,

suggesting that patients were identified late in the course of HF and were already in an advanced stage of their disease when signs and symptoms were first recorded.

The proportion of patients with an LVEF < 40% was low (<7%) and did not differ by signs and symptoms being recorded or not. Despite that LVEF assessment was missing in around 50% of the study population, these data suggest that most patients presenting with hHF had HF with mildly reduced or preserved ejection fraction (i.e. HFmrEF or HFpEF); numbers suggest a higher incidence of hospitalized HFmrEF/HFpEF than reported in other studies.^{5–8} This predominance of HFmrEF/HFpEF is likely linked to the fact that, in Portugal, most patients with HF with reduced ejection fraction (HFrEF) are followed at hospital appointments (of either cardiology or internal medicine) and no longer attend PCP appointments, thus being excluded from our study.

It is worth noting that HFpEF prevalence is increasing over time along with aging of the population and the accumulation of comorbid conditions and is currently the most frequent form of HF, despite limited treatment options even after the advent of SGLT2i.^{9–13}

Current HF guidelines are clear in the definition of HF, and such definition always requires recording of signs and symptoms regardless of HF stage, phenotype, or ejection fraction.^{14–16} The finding that, in our study, most patients with an hHF never had signs or symptoms recorded by PCP in EHR is important *per se*, highlighting the need for improving HF awareness among PCP including the importance of recording signs and symptoms, which may lead to a more personalized treatment tailored to patient's health status and will also help inform other health professionals about the evolution of HF signs and symptoms over time for each patient. Not less important is that recording signs and symptoms will also help inform the patient about his or her HF status and raise awareness to identify early hints of clinical deterioration that may potentially be handled in the outpatient setting, thus avoiding unnecessary ER visits and hospitalizations.¹⁷

Our study also showed that even after signs and symptoms had been recorded, 50% of the patients did not undergo adequate HF management because in the 6 months following the recording HF signs and symptoms, basic lab results and an ECG were not ordered, the patient was not referred to an HF specialist, HF medications were not initiated, or an echocardiogram or natriuretic peptides were not ordered. Regarding the natriuretic peptide issue, there is a need to apply a fair reimbursement strategy when natriuretic peptides are ordered by PCP in Portugal to be aligned with current HF guidelines.^{14–16}

Other external studies also showed that most patients had their first HF diagnosis upon a hospitalization and that most patients diagnosed with HF did not follow a pathway supported by guidelines for investigation, referral, and treatment of HF.¹⁸ Our study suggests that issues with HF diagnosis and

management are present across different countries and health care systems. Together, these findings strongly support the need to raise awareness about HF diagnosis, management, and treatment by PCPs.

Several limitations should be acknowledged in our study. EHR data were entered by PCPs during routine consultations and not for the purpose of research. Thus, from the data, it is apparent that many patients had performed an echocardiogram and natriuretic peptides and started HF medication even in the absence of signs and symptoms records, suggesting that PCPs might have thought about the possibility of HF diagnosis, but they did not register in the EHRs. The study period encompassed the initial COVID-19 lockdown from March to December 2020. EHR data density for the population included in this study was similar before and during COVID-19 lockdown, and thus, we consider the impact of COVID-19 in our data due to be minimal. As is typical of EHR studies, we cannot establish causality between a given exam or treatment and HF, because such exams and treatments might have been ordered/prescribed for other reasons (both cardiovascular and non-cardiovascular). In Portugal, most patients with an ejection fraction < 40% are followed exclusively at hospital appointments; therefore, our study is biased towards including mostly patients with higher ejection fractions, which limits the generalizability of our results to patients with HFrEF. Our study only includes survivors with an hHF; thus, we did not capture patients with signs and symptoms who died before the first hHF.

Conclusions

Using 'real-world' EHR data, this study mapped patients' pathway before a first hHF. The most striking finding was that only around one-third of the patients had any HF sign or symptom recorded before the first hHF and that nearly half had an HF management that was considered inadequate even after HF signs or symptoms had been recorded. These data suggest that there is a need to improve patient and PCP awareness to identify and record HF signs and symptoms for an earlier guideline-directed management, potentially improving outcomes.

Conflict of interest

J.P.F. has received research support from AstraZeneca. T.T.G. declares speaker and consulting fees from AstraZeneca, BIAL, Daiichi-Sankyo, MSD, and Medinfa. T.T.G. and M.C.P. are employees of MTG. P.P., F.B., K.A.S., M.A., and H.M. are employees of AstraZeneca. C.G. declares speaker and consulting fees from AstraZeneca, Bayer, BIAL, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, MSD, Novartis, and Novo Nordisk.

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Supporting information

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

Table S1. Data elements considered for identification of HF signs and symptoms.

Table S2. Time-based stratification of HF signs or symptoms in HF patients with signs or symptoms recorded.

Table S3. Frequency of signs and symptoms in HF patients.

Table S4. Time-based stratification of first-time prescription of loop diuretics in HF patients with no signs or symptoms recorded and HF patients with signs and symptoms recorded.

References

- Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, *et al.* Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol* 2021;**28**: 1682-1690. doi:10.1093/eurjpc/zwaa147
- Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, *et al.* Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. *Lancet* 2017;**391**: 572-580. doi:10.1016/s0140-6736(17)32520-5
- Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, *et al.* Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. *Lancet* 2020;**396**:121-128. doi:10.1016/s0140-6736(20)30748-0
- Taylor CJ. Diagnosing heart failure: Challenges in primary care. *Heart England* 2019;**105**:663-664. doi:10.1136/heartjnl-2018-314396
- Nanayakkara S, Patel HC, Kaye DM. Hospitalisation in patients with heart failure with preserved ejection fraction. *Clin Med Insights Cardiol* 2018;**12**:1179546817751609. doi:10.1177/1179546817751609
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;**14**:591-602. doi:10.1038/nrcardio.201765
- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. In: *The New England Journal of Medicine*. United States: 2006 Massachusetts Medical Society; 2006:251-259. doi:10.1056/NEJMoa052256
- Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghide M, Greenberg BH, *et al.* 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. doi:10.1016/j.jacc.2007.04.064
- Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep* 2013;**10**:401-410. doi:10.1007/s11897-013-0155-7
- Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342-1356. doi:10.1002/ejhf.1858
- Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, *et al.* SGLT-2 inhibitors in patients with heart failure: A comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;**400**:757-767. doi:10.1016/s0140-6736(22)01429-5
- Clark KAA, Reinhardt SW, Chouairi F, Miller PE, Kay B, Fuery M, *et al.* Trends in heart failure hospitalizations in the US from 2008 to 2018. *J Card Fail* 2022;**28**:171-180. doi:10.1016/j.cardfail.2021.08.020
- Norhammar A, Bodegard J, Vanderheyden M, Tangri N, Karasik A, Maggioni AP, *et al.* Prevalence, outcomes and costs of a contemporary, multinational population with heart failure. *Heart* 2023;**109**:548-556. doi:10.1136/heartjnl-2022-321702
- Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, *et al.* Clinical practice update on heart failure 2019: Pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169-1186. doi:10.1002/ejhf.1531
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891-975. doi:10.1002/ejhf.592
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, *et al.* 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: An update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2016;**68**: 1476-1488. doi:10.1016/j.jacc.2016.05.011
- Girerd N, Newton N, Tartièrre JM, Guijarro D, Jourdain P, Damy T, *et al.* Practical outpatient management of worsening chronic heart failure. *Eur J Heart Fail* 2022;**24**:750-761. doi:10.1002/ejhf.2503
- Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: Observational study using linked data in England. *Heart* 2018;**104**:600-605. doi:10.1136/heartjnl-2017-312183