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Prognostic factors of readmission and mortality after first heart failure hospitalization: results from EPICAL2 cohort

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Abstract

Aims We aimed to identify prognostic individual factors in patients with first acute heart failure (HF) hospitalization, considering both death and readmission as part of the natural history of HF.

Methods and results We used data from the observational, prospective, multicentre EPICAL2 cohort study from which we selected incident cases of acute HF alive at discharge. We relied on an illness-death model to identify prognostic factors on first readmission and on mortality before and after readmission. In 451 patients hospitalized for first acute HF, we observed within the year after discharge, 23 (5.1%) deaths before readmission and 270 (59.9%) first readmissions, of which 60 (22.2%) were followed by death of any cause. First, among patient characteristics, only Charlson index ≥ 8 was associated with first readmission [adjusted hazard ratio (aHR) = 1.6, 95% confidence interval (CI) (1.1–2.3), $P = 0.011$]. Second, Charlson index ≥ 8 [aHR = 4.2, 95% CI (1.2–14.8), $P = 0.025$], low blood pressure (BP) [aHR = 12.2, 95% CI (1.9–79.6), $P = 0.009$], high BP [aHR = 6.9, 95% CI (1.3–36.4), $P = 0.023$], and prescription of recommended dual or triple HF therapy at index discharge [aHR = 0.2, 95% CI (0.1–0.7), $P = 0.014$] were associated with mortality before any readmission. Third, Charlson index ≥ 8 [aHR = 2.4, 95% CI (1.1–5.6), $P = 0.037$] and the time to first readmission (per 30 days additional) [aHR = 1.2; 95% CI (1.1–1.4), $P = 0.007$] were associated with mortality after readmission.

Conclusions Regardless of the prognostic state considered, we showed that comorbidities are of critical prognostic value in a real-world cohort of incident HF cases. This argues in favour of multidisciplinary care in HF.

Keywords Heart failure (HF); First readmission; Illness-death model

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Introduction

The prevalence of heart failure (HF) is estimated between 1% and 2% of the adult population in developed countries, rising to more than 10% with age over 70 years.¹ In Europe, the mortality rate is $\sim 7\%$ per year and increases to 26.7% within the year after hospitalization for HF.² HF also represented the most frequent cause of hospitalization in patients over 65 years of age, with a high readmission rate within the year following the first hospitalization: between 20% and 25%.^{3,4} HF imposes a huge economic burden: Developed countries spend 1–2% of their total health care

expenditure on the management of this disease. Hospitalizations account for about two-thirds of the total cost of the syndrome.⁵ The first hospitalization for acute HF represents a major event in the natural course of the disease and is associated with a high risk of further hospital readmissions and a high mortality rate.⁶ Identifying prognostic factors is thus critical to target HF patients with special needs and develop tailored HF management.

Previous studies have identified prognostic factors associated with mortality and/or readmissions.^{7,8} However, by mixing both incident and prevalent HF cases, most of these studies were prone to immortal time bias.⁹ Moreover, studies

focusing on readmission as an outcome of prognostic interest considered death and readmission as independent outcomes, which might threaten the validity of both the prognostic factors identified and estimations of their prognostic value. Last, most studies focusing on HF prognosis considered readmission and death related to HF or cardiovascular causes as outcomes of main interest,¹⁰ as if cardiovascular defects were the only matter in HF patients. The aim of our study was to identify prognostic individual factors in patients with first acute HF hospitalization, considering both death and readmission as part of the natural history of HF.

Methods

Design and settings

The *Epidémiologie et Pronostic de l'Insuffisance Cardiaque Aiguë en Lorraine* (EPICAL2) study was an observational, prospective, multicentre, and population-based cohort study involving 21 volunteer hospitals spread over the Lorraine region of Northeast France.^{11,12} The cohort enrolled 2254 consecutive adult HF patients hospitalized between October 2011 and October 2012 in cardiology intensive care units, cardiology departments, or emergency departments. Patients admitted to the hospital for acute HF or developing acute HF during hospitalization were included and followed up for 3 years after discharge from the index hospitalization or until death if it happened first. The main objectives of EPICAL2 were (i) to describe morbidity and mortality at short term (0 to 6 months) and mid-term (up to 3 years), (ii) to identify the main prognostic factors, and (iii) to assess the effectiveness of various aspects of HF care.

All patients were informed about the study protocol and were free to refuse to be included in the cohort. This cohort study was conducted according to the principles of the Declaration of Helsinki and was approved by the national ethics committees (*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche* No. 10.030 and *Commission Nationale de l'Informatique et des Libertés* No. 9111069 and No. 9111069v1).

Population and sampling

For the present analyses, as part of the first and second objectives of EPICAL2, we focused on the incident HF cases, that is, patients included in EPICAL2 cohort, hospitalized for their first acute HF hospitalization, discharged alive from index hospitalization, and with successful matching with the *Programme de Médicalisation des Systèmes d'Information* (PMSI).

Data collection

Concerning index hospitalization, we collected baseline characteristics including sociodemographic characteristics, medical history, clinical characteristics, and laboratory results at admission, and treatments at discharge, from medical records using a standardized form. We calculated length of stay from admission to discharge.

Sociodemographic characteristics consisted of gender, age, and body mass index [BMI; categorized as underweight or normal (<25 kg/m²), overweight (25–30 kg/m²), and obese (>30 kg/m²)]. Medical history consisted of cardiovascular risk factors (hypertension, dyslipidaemia, and smoking), cardiovascular history (acute coronary syndrome, stroke, peripheral disease, valve disease, and arrhythmia), and chronic comorbidities [chronic obstructive pulmonary disease (COPD), diabetes mellitus, and chronic kidney disease]. The Charlson index was calculated to assess the burden of comorbidities¹³ (Supporting Information, *Appendix S1*) and then classified into three categories (i.e. ≤5, 6–7, and ≥8).

Clinical characteristics consisted of factors precipitating HF decompensation (i.e. ischaemic factors including acute coronary syndrome and/or the progression of underlying coronary artery disease, hypertensive surge, and arrhythmia), blood pressure [BP; mmHg, low BP (defined as systolic BP ≤ 110 mmHg and/or diastolic BP ≤ 90 mmHg) and high BP (defined as systolic BP > 140 mmHg and/or diastolic BP > 110 mmHg)], cardiogenic shock, acute pulmonary oedema, severe stage of HF, left bundle branch block, and left ventricular ejection fraction (LVEF). LVEF was classified into three categories according to the 2021 European Society of Cardiology (ESC) guidelines¹ (≤40%, 40–50%, and ≥50%).

Laboratory results included increased B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) (defined as BNP > 400 pg/mL or NT-proBNP > 450 pg/mL in patients < 50 years old, NT-proBNP > 900 pg/mL in patients between 50 and 75 years old, or NT-proBNP > 1800 pg/mL in patients > 75 years old—according to the state of the art at the beginning of the cohort¹⁴), anaemia (defined as haemoglobin < 10 g/dL), hyponatraemia (defined as natraemia < 135 mmol/L), hyperkalaemia (defined as kalaemia > 5 mmol/L), and estimated glomerular filtration rate [eGFR; categorized as severe or end-stage kidney disease (eGFR < 30 mL/min/1.73 m²), moderate kidney disease (eGFR ≥ 30 and <60 mL/min/1.73 m²), and no kidney disease (eGFR ≥ 60 mL/min/1.73 m²)]. We calculated eGFR using the Modification of Diet in Renal Disease (MDRD) formula.

Drug prescriptions collected at discharge included diuretics, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and beta-blockers. We also collected therapeutic education and disease management programme (defined as a multidisciplinary community-based disease management programme offered to all patients at

the discretion of the physician). Based on the 2008 ESC guidelines¹⁵ available at the time the EPICAL2 study was designed, and on the 2012 ESC guidelines,¹⁶ which were implemented during the study course, we considered HF medications that were recommended back then to define recommended HF medications. They were considered alone or in combination, that is, dual HF therapy (ACEI or ARB + beta-blocker), triple HF therapy [ACEI or ARB + beta-blocker + mineralocorticoid receptor antagonists (MRA)], or unconventional HF therapy (MRA alone or in combination with ACEI or ARB or beta-blocker).

Outcomes: first readmission and mortality

The outcomes of interest were first all-cause hospital readmission, within the year after index hospitalization discharge, and all-cause 1 year mortality.

We collected 1 year vital status for each patient and the date of death, if appropriate, through national civil registries.

We used data on readmissions that are routinely collected as part of the PMSI, which is the French national information system on hospital stays used by the national health insurance system for claims. At the time of EPICAL2 study, the use of national ID number to match data from cohorts to PMSI data was drastically restricted to studies authorized by the State Council. Accordingly, we relied on a probabilistic matching using administrative data both collected as part of our cohort and as part of PMSI routine procedures. For this matching, we used the following criteria: hospital ID number (Finess); month, year of discharge, and length of stay of index hospitalization; sex; age at index hospitalization; and residence ZIP-code. To be considered a match, a PMSI hospital stay had to match the index hospital stay in EPICAL2 on all of these criteria. In case more than one hospital stays from the PMSI database matched the index hospital stay in EPICAL2 relying on these matching criteria, we selected the one with a main diagnosis code included in I00–I99 according to the ICD-10. Due to linkage of data from the same patient in the PMSI database, once the EPICAL2 hospital stay was matched to one PMSI hospital stay, subsequent hospital stays of the same patient could be easily retrieved from the PMSI database.

We censored surviving patients at 1 year follow-up. We calculated both time to first all-cause readmission and survival time from the date of index hospital discharge.

Statistical analyses

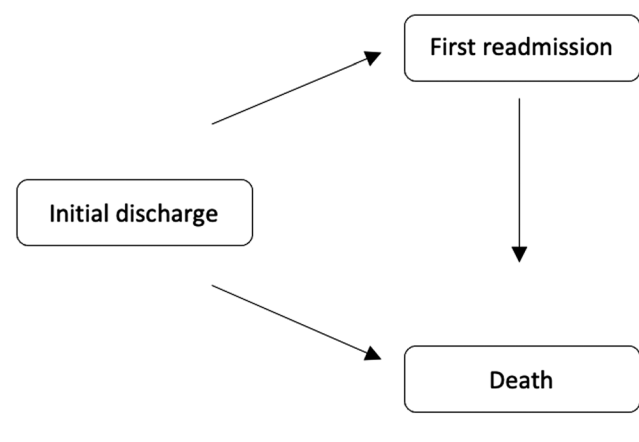
We relied on a Cox–Markov illness-death model (Supporting Information, *Appendix S1*), which fits well to semi-competing risk settings.¹⁷ Semi-competing risk refers to a setting where the primary interest lies in a non-terminal event, the occurrence of which may depend

on the occurrence of a terminal event. In our analyses, we considered first hospital readmission as the non-terminal event and death as the terminal event. In our progressive illness-death model (*Figure 1*), from hospital discharge ('initial discharge' state) to the end of the follow-up, HF patients could transition through one of the following series of state(s): (i) death before any chance of hospital readmission; (ii) first hospital readmission then followed by death; (iii) first hospital readmission not followed by death; or they could also stay in the 'initial discharge' state, that is, without any event or transition.

Baseline characteristics were described overall and stratified by the final state of occupation in the illness-death model using number and percentage for categorical variables, and mean and standard deviation (SD), or median and interquartile range (IQR) in case of non-normal distribution, for continuous variables.

Using Aalen–Johansen estimators,¹⁸ we could estimate cumulative hazards of transition between the states of interest ('initial discharge' to 'first readmission', 'first readmission' to 'death', and 'initial discharge' to 'death') and state occupation probabilities [further reported as percentage and 95% confidence interval (95% CI)]. Relying on Cox–Markov illness-death models, we could also identify prognostic factors on each transition between the states. We entered sex, age, BMI, Charlson index, COPD, diabetes mellitus, chronic kidney disease, factors precipitating HF decompensation, cardiogenic shock, LVEF, BP, increased BNP/NT-proBNP, natriuremia, hyperkalaemia, eGFR, recommended HF medications, therapeutic education, and disease management programme into bivariate models. Among these variables, we retained those with a *P* value < 0.2 in bivariate analyses for multivariable analyses. We reported the results as crude and adjusted hazard ratios (HR and aHR, respectively) and 95% CI. In order to release the Markov assumption, we used state arrival extended Markov proportional hazards model¹⁹ (Supporting In-

Figure 1 States between which hospitalized incident HF cases can transition under the semi-competing risks frameworks: the progressive illness-death model.



formation, *Appendix S1*). We handled covariates with missing data by multiple imputation, which resulted in 78 imputed datasets. For variables derived from continuous variables (i. e. BMI, BP, LVEF, anaemia, hyperkalaemia, natraemia, and eGFR), we imputed the source variable(s). To check the influence of multiple imputations on parameter estimates, we also conducted a sensitivity analysis on complete cases.

We used SAS 9.4 software (SAS Institute, Inc) for descriptive analyses and R software Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) along with the *mstate* package²⁰ for the analyses involving the state arrival extended Cox–Markov illness-death model.

Results

Baseline characteristics

Among 2254 patients included in EPICAL2 cohort, 542 patients were alive at discharge after their first hospitalization for acute HF, of which one patient was lost to follow-up. Among them, our PMSI probabilistic matching procedure failed for 90 (16.6%) patients who were excluded. Eventually, 451 patients were included in our study (*Figure 2*). Baseline characteristics are presented in *Table 1*.

Mean (SD) age of patients was 76.0 (12.38) years, and most of them were age > 80 years ($n = 213$, 47.2%). Patients were mainly female ($n = 242$, 53.7%) and most often presented with hypertension ($n = 329$, 72.9%). Almost a third of them had diabetes mellitus ($n = 122$, 27.1%), acute coronary syndrome ($n = 138$, 30.6%), and arrhythmia ($n = 138$, 30.6%). Almost a fifth had a Charlson comorbidity index ≥ 8 ($n = 96$, 21.3%). The main factors precipitating HF were ischaemic factors ($n = 105$, 23.3%), arrhythmia ($n = 86$, 19.1%), and hypertensive surge ($n = 76$, 16.9%). Concerning clinical characteristics at admission, high BP was observed in two-thirds ($n = 263$, 58.3%) of the patients, and low BP in one-tenth ($n = 56$, 12.4%). Mean (SD) LVEF was 44.0 (14.6) %. Regarding laboratory results, two-thirds of the patients had increased BNP or NT-proBNP ($n = 278$, 61.6%), and 17.3% ($n = 78$) had hyponatraemia.

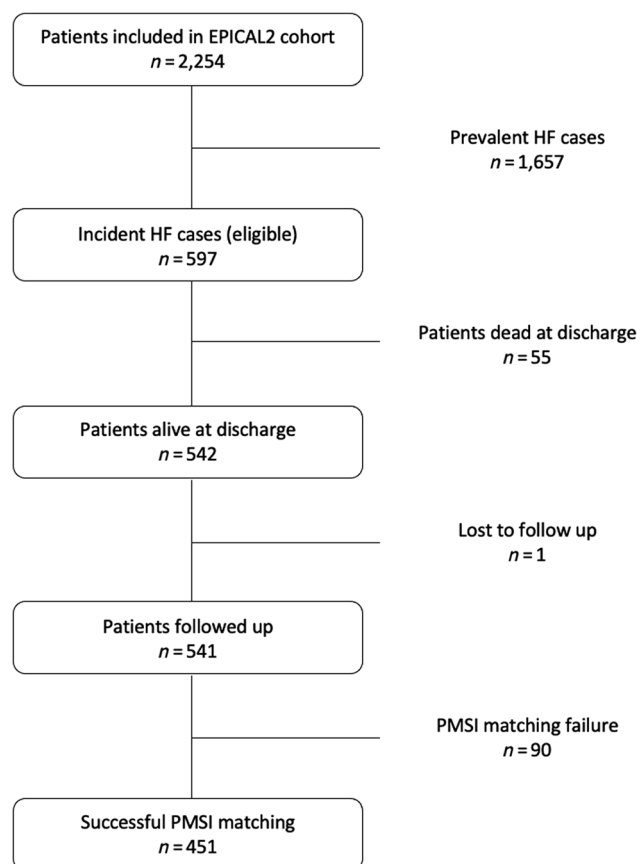
At discharge, nearly two-thirds ($n = 303$, 67.2%) of the patients were prescribed diuretics. Dual or triple HF therapy according to the ESC guidelines was prescribed to one-third ($n = 140$, 31.0%) and less than one-tenth ($n = 35$, 7.8%) of the patients, respectively.

Median (IQR) length of stay was 8.0 (5.0–14.0) days for the index hospitalization.

Follow-up: 1 year first readmission and mortality

Within the year after the index hospitalization, 23 (5.1%) deaths occurred before any readmission, and 270 (59.9%)

Figure 2 Flow chart of HF patients.



all-cause first readmissions occurred [of which, $n = 147$ (54.4%) due to cardiovascular causes]. After the first readmission, 60 (22.2%) patients died during the follow-up. Overall, 158 (35.0%) patients were censored at 1 year without any event.

Figure 3 reports the results of the Aalen–Johansen estimations: (A) estimated cumulative hazards of transition between the states of interest and (B) stacked estimated state occupation probabilities. From index hospitalization discharge, 1-year estimated probability of being already readmitted for all cause but still alive was 46.6%, 95% CI (42.2–51.5%); 1-year estimated probability of all-cause death before any readmission was 5.1%, 95% CI (3.4–7.6%); and 1-year estimated probability of all-cause death after readmission was 13.3%, 95% CI (10.5–16.9%).

Prognostic factors associated with first readmission and mortality

Baseline HF patients' characteristics according to the final state of occupation in the illness-death model during the first

Table 1 Baseline HF patients' characteristics

	N	%
Sociodemographic characteristics		
Sex		
Male	209	46.3%
Female	242	53.7%
Age (years)		
≤65	97	21.5%
66–80	141	31.3%
>80	213	47.2%
BMI		
Missing	94	
Underweight or normal	132	37.0%
Overweight	115	32.2%
Obese	110	30.8%
Length of stay (days)		
≤3	51	11.3%
4–7	172	38.1%
≥8	228	50.6%
Medical history		
Cardiovascular risk factors		
Hypertension	329	72.9%
Dyslipidaemia	185	41.0%
Smoking	169	37.5%
Cardiovascular history		
Acute coronary syndrome	138	30.6%
Stroke	59	13.1%
Peripheral disease	56	12.4%
Valve disease	86	19.1%
Arrhythmia	138	30.6%
Chronic comorbidities		
COPD	86	19.1%
Diabetes mellitus	122	27.1%
Chronic kidney disease	67	14.9%
Charlson index		
≤5	184	40.8%
6–7	171	37.9%
≥8	96	21.3%
Clinical characteristics		
Factors precipitating HF decompensation		
Ischaemic factors	105	23.3%
Hypertensive surge	76	16.9%
Arrhythmia	86	19.1%
BP		
Missing	4	
Low ^a	56	12.5%
Normal	128	28.6%
High ^b	263	58.8%
Cardiogenic shock	31	6.9%
Acute pulmonary oedema	198	43.9%
Severe stage of HF	115	25.5%
Left bundle branch block	76	16.9%
LVEF (%)		
Missing	114	
≤40	118	35.0%
40–50	127	37.7%
≥50	92	27.3%
Laboratory results		
Increased BNP/NT-proBNP ^c		
Missing	170	
No	3	1.1%
Yes	278	98.9%
Anaemia ^d		
Missing	13	
No	405	92.5%
Yes	33	7.5%
Hyponatraemia ^e		
Missing	98	

(Continues)

Table 1 (continued)

	N	%
No	349	77.9%
Yes	78	22.1%
Hyperkalaemia ^f		
Missing	102	
No	322	92.3%
Yes	27	7.7%
eGFR		
Missing	189	
Severe or end-stage kidney disease	32	12.2%
Moderate kidney disease	123	46.9%
No kidney disease	107	40.8%
Treatment at discharge		
Diuretics		
ACEI or ARB (exclusively)	156	34.6%
Beta-blocker (exclusively)	32	7.1%
Dual HF therapy ^g	140	31.0%
Triple HF therapy ^h	35	7.8%
Unconventional HF therapy ^j	18	4.0%
None	70	15.5%
Therapeutic education		
Missing	2	
No	387	86.2%
Yes	62	13.8%
Disease management programme		
Missing	28	
No	366	86.5%
Yes	57	13.5%

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

^aSystolic BP ≤ 110 mmHg and/or diastolic BP ≤ 90 mmHg.

^bSystolic BP > 140 mmHg and/or diastolic BP > 90 mmHg.

^cBNP > 400 pg/mL or (NT-proBNP > 450 pg/mL in patients < 50 years old, NT-proBNP > 900 pg/mL in patients between 50 and 75 years old, or NT-proBNP > 1800 pg/mL in patients > 75 years old).

^dHaemoglobin < 10 g/dL.

^eNatraemia < 135 mmol/L.

^fKalaemia > 5 mmol/L.

^gACEI or ARB + beta-blocker.

^hACEI or ARB + beta-blocker + mineralocorticoid receptor antagonist.

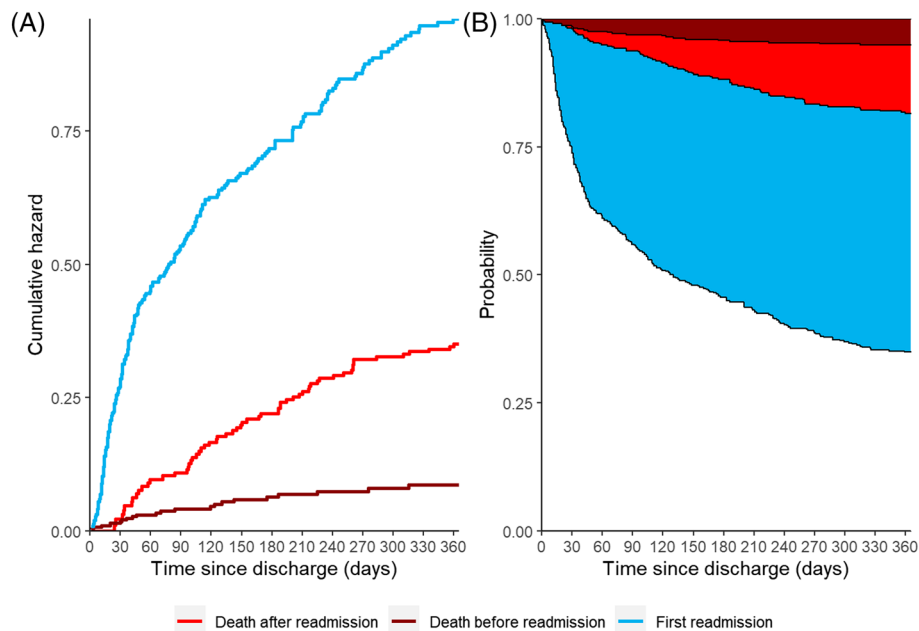
^jMineralocorticoid receptor antagonist alone or in combination with ACEI or ARB or beta-blocker.

year after index hospitalization discharge are described in Supporting Information, *Table S1*.

Patients readmitted and still alive at the end of follow-up tended to be younger ($n = 56$, 26.7% patients ≤ 65 years old) and to present more often with ischaemic factors precipitating HF decompensation ($n = 58$, 27.6%) than patients from other states.

Patients deceased before any readmission were more often women ($n = 14$, 60.9%) and had less often a Charlson index ≤ 5 ($n = 4$, 17.4%) than their counterparts from other states. They were mainly >80 years old ($n = 15$, 65.2% patients). They presented more often with hypertension ($n = 21$, 91.3%) and acute pulmonary oedema at admission ($n = 14$, 60.9%). They also had more often a reduced LVEF

Figure 3 Aalen–Johansen estimations (in illness–death framework) for first readmission and death within a year after index hospital discharge in incident HF patients: (A) estimated cumulative hazards of transition between the states and (B) stacked estimated state occupation probabilities.



($\leq 40\%$) ($n = 8$, 34.8%). More than nine-tenth of them had increased BNP or NT-proBNP. At index hospitalization discharge, nine (39.1%) of them had none of the HF medications recommended by the ESC. In addition, therapeutic education ($n = 1$, 4.3%) or disease management programme ($n = 0$, 0.0%) was barely considered in this group.

Patients readmitted and then deceased during the year of follow-up were mainly >80 years old ($n = 40$, 66.7% patients) and presented more often with arrhythmia ($n = 28$, 46.7%) and diabetes mellitus ($n = 22$, 36.7%) than their counterparts from other states. At index hospitalization discharge, despite almost nine-tenth of them being prescribed at least one of the HF medications recommended by the ESC, they were barely included in a disease management programme ($n = 3$, 5.0%).

Results from bivariate and multivariable analyses are presented in Supporting Information, *Table S2* and *Table 2*, respectively. First, only Charlson index ≥ 8 was associated with first readmission [aHR = 1.6, 95% CI (1.1–2.3), $P = 0.011$]. Second, Charlson index ≥ 8 [aHR = 4.2, 95% CI (1.2–14.8), $P = 0.025$], low BP [aHR = 12.2, 95% CI (1.9–79.6), $P = 0.009$], high BP [aHR = 6.9, 95% CI (1.3–36.4), $P = 0.023$], and prescription of recommended dual or triple HF therapy at index discharge [aHR = 0.2, 95% CI (0.1–0.7), $P = 0.014$] were associated with death before any readmission. Third, Charlson index ≥ 8 [aHR = 2.4, 95% CI (1.1–5.6), $P = 0.037$] and the time to first readmission (per 30 days additional) [aHR = 1.2, 95% CI (1.1–1.4), $P = 0.007$] were associated with death after readmission. Although results from bi-

variate analyses showed that occurrence of first readmission was associated with subsequent mortality [HR = 3.5, 95% CI (2–6.1), $P < 0.001$], this result did not resist adjustment for confounders in multivariable analyses.

Results from the sensitivity analyses on complete cases are presented in Supporting Information, *Table S3*. Characteristics at inclusion in complete cases vs. incomplete cases (i.e. cases with at least one missing value among the variables of interest) are presented in Supporting Information, *Table S4*. In complete cases ($n = 93$), we observed 58 readmissions and 9 deaths (of which 7 occurred after readmission and 2 before any readmission). Results from the multivariate analyses showed that only Charlson index between 6 and 7 was associated with first readmission [aHR = 0.4, 95% CI (0.2–0.8), $P = 0.014$].

Discussion

Our study highlighted several important findings in patients hospitalized for the first time due to HF. First, within the year after this hospitalization, 5.1% of patients died before any readmission and almost 60% were readmitted to the hospital for any cause. Among them, more than 10% died after readmission. Second, Charlson index ≥ 8 was a significant prognostic factor of first readmission and death. Third, low or high BP (and getting with HF medication guidelines at index discharge) was associated with increased (and decreased, re-

Table 2 Prognostic factors associated with first readmission and death relying on the Cox–Markov illness-death model in HF patients

Factors	First readmission		Death before readmission		Death after readmission	
	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
Age (years)						
≤65	—		—		—	
66–80	0.8 (0.6–1.2)	0.339	0.8 (0.2–3.8)	0.821	1.1 (0.4–3)	0.889
>80	0.7 (0.5–1.1)	0.090	0.9 (0.2–4.3)	0.917	2.0 (0.8–5.4)	0.154
BMI						
Overweight	—		—		—	
Underweight or normal	1.2 (0.9–1.6)	0.248	1.9 (0.5–6.6)	0.315	1.4 (0.7–2.7)	0.362
Obese	1.1 (0.8–1.5)	0.568	1.5 (0.3–6.1)	0.607	0.7 (0.3–1.6)	0.412
Charlson index						
≤5	—		—		—	
6–7	1.1 (0.8–1.6)	0.446	1.9 (0.5–6.5)	0.325	1.8 (0.8–4)	0.161
≥8	1.6 (1.1–2.3)	0.011	4.2 (1.2–14.8)	0.025	2.4 (1.1–5.6)	0.037
Ischaemic factors	1.1 (0.8–1.4)	0.687	0.7 (0.2–2.3)	0.574	0.7 (0.4–1.5)	0.422
Cardiogenic shock	1.6 (0.9–2.7)	0.087	0.3 (0–6)	0.433	1.5 (0.5–4.2)	0.480
BP						
Normal	—		—		—	
Low BP	0.8 (0.5–1.2)	0.203	12.2 (1.9–79.6)	0.009	1.6 (0.6–4.1)	0.346
High BP	0.8 (0.6–1)	0.102	6.9 (1.3–36.4)	0.023	1.2 (0.6–2.2)	0.569
Natraemia						
Normal	—		—		—	
Hyponatraemia	1 (0.7–1.4)	0.803	1.6 (0.6–4.4)	0.355	0.9 (0.4–1.9)	0.802
Hypernatraemia	0.7 (0.1–3.3)	0.632	2.4 (0.3–19.9)	0.414	1.5 (0.1–36.9)	0.791
Treatment at discharge						
None	—		—		—	
ACEI or ARB (exclusively)	0.9 (0.6–1.4)	0.783	0.4 (0.1–1.1)	0.067	1.1 (0.5–2.6)	0.817
Beta-blocker (exclusively)	0.9 (0.5–1.5)	0.655	0.2 (0–1.3)	0.099	1.4 (0.5–4.4)	0.524
Dual or triple HF therapy	0.9 (0.6–1.4)	0.704	0.2 (0.1–0.7)	0.014	1.0 (0.4–2.5)	0.919
Unconventional HF therapy	0.9 (0.4–1.8)	0.763	0.6 (0.1–4.2)	0.644	1.4 (0.2–9.1)	0.745
Readmission time (/30 days)					1.2 (1.1–1.4)	0.007
Readmission					5.4 (0.4–80)	0.223

ACEI, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; HF, heart failure.

aHR: adjusted on all other characteristics specified in the table. Bold values are used to highlight statistically significant results.

spectively) mortality before any readmission. Finally, according to this illness-death model, the risk of death was increased when the first readmission was delayed.

Different patient profiles according to the final state of occupation

We identified different clinical profiles of patients in each final state of our illness-death model. First, patients readmitted and still alive at the end of the follow-up were likely younger and had more frequent ischaemic factors precipitating HF. Chun *et al.*⁶ also showed that repeated cardiovascular admissions occurred more frequently among younger patients and those with ischaemic HF. Second, patients who died before any readmission were more likely female, older, presented more often with hypertension and significant clinical congestive signs, reduced LVEF, and were less often prescribed recommended HF medications at index discharge. This gender disparity concerning HF incident cases, with more women observed in the worst possible prognostic state, might raise concerns about gender inequity in HF management. Probably due to their older age and more frequent comorbidities, women were also more represented in the

group with higher abstinence of HF recommended medications. This gender inequity was also reported in the management of patients with myocardial infarction.²¹ Third, patients deceased after a first readmission were more likely older and presented with arrhythmia and diabetes mellitus. This clinical profile probably referred to HF with preserved LVEF, that is, a heterogeneous clinical syndrome due to cardiovascular and non-cardiovascular coexisting comorbidities, like atrial fibrillation and diabetes mellitus, which is known to lead to multiple readmissions before eventual death.²²

Comorbidities: the most important prognostic burden in HF

A higher Charlson index (≥8) was significantly associated with higher rate of first readmission. This result corroborated results from other studies.^{8,23} This association suggests that HF patients with several comorbidities have specific needs and should be paid specific attention. In addition, we observed a statistically significant association between a higher Charlson index (≥8) and mortality before or after first readmission. Disease management programmes have been developed for HF patients and have proven effective on HF

admissions^{24,25} and mortality.^{11,12} Due to the huge prognostic burden of comorbidities in HF patients whatever the final state considered, a holistic management programme including therapeutic education and management of both cardiovascular and non-cardiovascular conditions seems critical to improve HF prognosis, that is, to reduce both readmission and mortality in HF.

Recommended HF medication at index discharge: a way to prevent early mortality

Recommended HF medication according to the ESC guidelines at index discharge was associated with decreased mortality before any readmission. Based on the results of randomized controlled trials, the ESC regularly updates guidelines for HF management,¹ including recommended HF medications. Adherence to such HF medications has also proven effective to reduce mortality in real-world settings.²⁶ In some of our previous analyses of EPICAL2 cohort, we showed that adherence to guideline-recommended HF medication prescription at hospital discharge was critical because HF medication prescriptions remained quite stable over the 2 years after discharge.²⁷ We also showed that HF patients often presented with various comorbidities, such as chronic kidney disease or asthma/COPD, which importantly limited physicians' ability to prescribe the recommended drugs, leading to suboptimal adherence to guidelines.²⁷ In the same way, the present analysis emphasizes the importance of prescribing recommended HF medication at index hospitalization discharge in real-world HF incident cases to prevent early mortality.

Impact of delayed readmission on the prognosis of patients after a first acute HF

The clinical impact of readmission timing after a first acute HF has been scarcely investigated. The vulnerable period after discharge is considered to continue several months after discharge, and an early arbitrary cut-off is not supported by the pathophysiological rationale related to HF.²⁸ In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial,²⁹ 76% of readmissions occurred 30 days after discharge. Moreover, the results of our study highlight that a delayed readmission after the index hospitalization should be perceived as an alarming sign of subsequent worse prognosis in patients with HF. It could be an opportunity to implement shared decision-making (e.g. individualized decision regarding device-based therapy and advanced care planning) and multidisciplinary patient educational programmes with optimal medical therapy and strict adherence to recommended lifestyle modifications whatever their age.

Strengths of our study

We relied on a prospective, multicentre cohort of incident HF cases exposed to real-world clinical practices, illustrating the natural course of the syndrome. Most prognostic studies implemented in HF patients included highly selected and heterogeneous samples of patients, mixing incident and prevalent cases,^{7,30} which might have threatened their validity due to immortal time bias.⁹ Then, we used an appropriate statistical model. By considering risk of death, risk of readmission, and all the possible transitions between the states, the Cox–Markov illness-death model is better fit than usual logistic or Cox models to handle both right-censoring and semi-competing risks,¹⁷ to estimate mortality and readmission rates, and eventually to identify prognostic factors of each transition between the states. This model enabled to consider death and readmission concomitantly and the fact that occurrence of death hindered any chance of readmission.

Limitations

Our study had several limitations. First, PMSI matching failure led us to exclude 90 HF patients, which might have resulted in selection bias. However, the magnitude of the differences observed between included vs. excluded HF patients made this selection bias unlikely to dramatically alter our conclusions (Supporting Information, *Table S5*). In the same way, multivariate analyses conducted on complete cases relied on a smaller number of outcomes, which ruled out any attempt to study death as an outcome. However, despite the selection bias they might suffer from, our analyses on complete cases led to similar results regarding the impact of comorbidities on first readmission. Second, our sample mixed patients with reduced LVEF and patients with preserved LVEF. This might have resulted in a heterogeneous sample due to different pathophysiological profiles, preventing us to identify prognostic factors that would be specific to one of these profiles. Third, the study was conducted prior to more contemporary prognostic HF therapy known to improve 30 day readmission and both cardiovascular and all-cause mortality, such as an angiotensin receptor neprilysin inhibitor and sodium-glucose cotransporter-2 (SGLT2) inhibitors.¹

Conclusions

Using an appropriate statistical model, we showed that comorbidities were of critical prognostic value on first readmission and mortality in a real-world setting of incident HF cases. This argues in favour of multidisciplinary care in HF. In addition, recommended HF treatment at first HF hospital dis-

charge further demonstrated its favourable impact on reducing early mortality.

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Conflict of interest

None declared.

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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. Baseline HF patients' characteristics according to the final state of occupation in our progressive illness-death model.

Table S2. HF patient characteristics associated with first readmission and death relying on the Cox-Markov illness-death model: results from the bivariate analyses.

Table S3. Prognostic factors associated with first readmission in HF patients - sensitivity analyses on complete cases.

Table S4. Comparison of baseline characteristics of HF patients with incomplete cases vs. complete cases.

Table S5. Comparison of baseline characteristics of HF patient with PMSI matching failure (excluded) and with successful PMSI matching (included).

Appendix S1. Supporting information.

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