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Parmar S, Lopez T, Shah R, Murphy D, Warrens H, Khairallah M, Anderson L, Rosano G, Chis Ster I, Banerjee D

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Research Article

Risk of hospital admissions and death in patients with heart failure and chronic kidney disease: findings from a novel multidisciplinary clinic

Simran Parmar[1, 2], Tony Lopez[1, 2], Ronak Shah[1], Daniel Murphy[3], Hilary Warrens[1, 2], Marwa Khairallah[4], Lisa Anderson[2], Giuseppe Rosano[2], Irina Chis Ster[5]*, Debasish Banerjee[1, 2]*.
*Equal contribution

[1]Renal and Transplantation Unit, St Georges University Hospitals NHS Foundation Trust, London, UK.
[2]Institute of Medical and Biomedical Allied Health Education, St Georges University of London, UK.
[3]Department of Acute Medicine, Royal Free Hospital, London, UK.
[4]Internal Medicine Department, Nephrology Division, Faculty of Medicine, Assiut University Hospital, Egypt.
[5]Infection and Immunity Institute, St George's School of Health and Medical Sciences, City St Georges University of London, UK.

Short title: Admissions in CKD and HF

Corresponding author:
Simran Parmar
Simransingh.parmar@stgeorges.nhs.uk

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Abstract

Introduction:

Patients with heart failure (HF) and chronic kidney disease (CKD) are often sub-optimally treated due to concerns of hyperkalaemia, declining kidney function, and hypotension. They commonly suffer from fluid overload which can lead to frequent hospitalisations and death. This research aims to determine the characteristics associated with hospital admissions and death in patients with CKD and HF.

Methods:

Consecutive patients with CKD stage 3 to 5 and HF (regardless of ejection fraction) attending a large, specialised CKD-HF clinic between 12/Sept/2019 and 11/Nov/2021 were identified and data were collected on demographic factors, renal and heart function, medications, hospitalisations, and death. Multinomial and Cox regressions determined the characteristics of patients requiring hospitalisation and their risk of death, respectively.

Results:

A total of 667 admissions were attributable to 318 patients, 201 admissions were for HF. Men were less likely than women to have been admitted to hospital for HF (RR 0.43, 95% CI 0.20, 0.94) and non-HF causes (RR 0.21, 95% CI 0.10, 0.47). A serum haemoglobin level greater than 100 g/L was associated with fewer HF and non-HF admissions compared to a serum haemoglobin less than 100 g/L (RR 0.26, 95% CI 0.09, 0.74; RR 0.17, 95% CI 0.06, 0.47). Compared to CKD stage 3, CKD stage 4 was associated with an increased risk of HF and non-HF admissions (RR 4.01, 95% CI 1.04, 15.5; RR 4.33, 95% CI 1.13, 16.5). Having a HF admission (HR 2.41, 95% CI 1.27, 4.60), HFrEF (HR 2.18, 95% CI 1.30, 3.63)), CKD stage 4 (HR 1.91, 95% CI 1.16, 3.16), and loop diuretic use (HR 2.24, 95% CI 1.14, 4.40) were associated with a significantly increased risk of death compared to people with no admissions, with HFpEF, CKD stage 3, and no diuretic use, respectively. The use of RAAS inhibitors halved the risk of death compared to non-prescribed patients (HR 0.44, 95% CI 0.27, 0.72).

Conclusion:

Hospital admissions among CKD-HF patients were common, particularly in those with lower serum haemoglobin levels and advanced CKD stage. The risk of death was higher in those with HF admissions, the presence of HFrEF, advanced CKD stage, loop diuretic use, and those not prescribed RAAS inhibitors.

Introduction

Heart failure (HF) and chronic kidney disease (CKD) are increasingly common comorbidities in an ageing global population [1,2]. These conditions can feature independently, each with significant risk factors for hospitalisations and death, but also frequently coexist. Approximately half of HF patients suffer from co-existing CKD, which further increases the risk of hospital admissions and mortality. [3–5].

In this comorbid population, worsening estimated glomerular filtration rates (eGFR) are associated with an increase in hospitalisations and mortality. After adjusting for demographic characteristics and cardiovascular risk factors, rates of HF admissions have been shown to be 1.7 (95% CI 1.3, 2.2) and 2.2 (95% CI 1.7, 2.9) times higher in patients with an eGFR of 30-44 ml/min/1.73 m2 and <30 ml/min/1.73 m2, respectively, compared to patients with an eGFR of ≥45 ml/min/1.73 m2 [5]. In multivariable analysis, compared to HF patients without CKD, HF patients with CKD stage 3 (HR 1.59, 95% CI 1.49, 1.69) and CKD 4 or CKD 5 (HR 2.17, 95% CI 1.95, 2.40) had an increased risk of death [4]. The relationship between ejection fraction (EF) and prognosis in patients with CKD and HF is less well defined. Chronic kidney disease is strongly associated with mortality in patients with HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [6–8]. Recent trials have shown empagliflozin to slow the decline of eGFR in patients with HFrEF and HFpEF [9,10]. This has helped inform the 2023 Focused Update of the 2021 ESC Guidelines for HF, which now include Class 1 and Level A recommendations for the use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) in HFmEF and HFpEF, alongside its already established use in HFrEF [11]. Previous work from our group has found that in patients with coexisting HF and CKD, the degree of impairment of EF was correlated with outcome: those with HFrEF were more likely to be admitted to hospital and were also 4.5 times more likely to die (adjusted odds ratio 4.5; 95% CI 1.43, 14.05) compared to patients with HF with moderately reduced EF (HFmEF) and HFpEF, after adjusting for age, sex, diabetes, and CKD severity [12].

This study aimed to build upon this previous work to identify the factors associated with an increased likelihood of hospitalisations and risk of death of patients attending our novel, multidisciplinary CKD-HF clinic.

Methods

Patients were eligible for the CKD-HF clinic if they had CKD stages 3, 4, or 5 and established HF regardless of ejection fraction [12]. The diagnosis of HF was made prior to enrolment in our clinic and was established using clinical evaluation, serum natriuretic peptide levels, and echocardiography. All consecutive patients attending the CKD-HF clinic between 12th April 2019 and 11th September 2021 were identified from hospital records. Data collected included HF and CKD status, demographics, comorbidities, blood test results, and their heart failure medication prescriptions (including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), beta-blockers, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and loop diuretics). In addition, the number, length, and cause of hospitalisations, as well as the date of death, if applicable, were collected for each patient.

Only acute admissions were considered – day-case procedures, elective procedures, and patients who attended the emergency department and were discharged without subsequent onward referral were excluded. The causes of relevant admission were determined by examining clerking notes, medical progress notes, and discharge summaries. “Heart failure” admissions were defined as a decompensation of HF or signs or symptoms of HF including pulmonary oedema or fluid overload where HF was suspected to be a contributing factor.

Descriptive statistics summarised the sample’s demographics, comorbidities, blood results, medications, and hospital admissions. We investigated two univariate outcomes (responses): a categorical outcome defined as never admitted, admitted at least once for HF, and admitted but never for HF, and a survival outcome for time since the first clinic attendance to death, with censoring at the end of the observation period (11th September 2021).

Regression techniques have been tailored to the defined outcomes, i.e., multinomial logistic regression for the outcome indicating their hospital admission status and a Cox regression for the survival setting. The associations between the outcome variables and the explanatory variables are quantified as relative risk ratios (RR for multinomial regression) and hazard ratios (HR for survival setting). An RR/HR greater (or smaller) than 1 indicates a direct (or inverse) association when comparing the levels of the categorical admission outcome and death vs. survival. A p-value less than 0.05 indicated a statistically significant result.

Univariate analyses investigated associations of these outcomes with each available potential explanatory variables whilst multivariable analyses were used to build the most parsimonious models, i.e., models with the least number of parameters yet explaining most of the variability in the outcome. A backward selection procedure guided by Akaike information criterion (AIC), in which models started with all covariates and then were sequentially removed until only statistically significant covariates remained, was used for the final multivariable model choice. Measures of goodness of fit have been applied to ensure models' adequacy; a generalised Hosmer-Lemeshow to multinomial regressions and Schoenfeld residuals for survival analyses [13]. Medication data were not included in the multinomial regression model with hospital admissions and was instead examined descriptively. This is because the medication data was collected at the end of the study period for each participant, and therefore after any recorded hospital admissions. The general assumption for all regression techniques is that the potential explanatory variables should precede the dependent variable temporally. The dates of each individual admission were sparse and inaccurate and hence difficult to provide reliable information into analyses. Medication data was included in the multivariable Cox regression analyses because the outcome variable of death was recorded after (or at the same time as) the patients' medication data would have been recorded. All data cleaning, statistical analyses and graphics were performed in R version 4.2.1 (R Foundation for Computing, Vienna, Austria).

Results

In total 318 clinic patients were identified during the study period. Their baseline demographics and medication use are in Tables 1 and 2. Stratification by sex was performed due to significant sex differences found in the subsequent regression analyses. The 318 patients contributed to a total of 443 person-years of follow up, with a median follow-up of 492 days. The 318 patients contributed to 667 hospital admissions, with 91 (28.6%) of the patients not being hospitalised during the study period. Of the 667 admissions, 201 were due to HF. This was contributed to by 110 patients (34.6%), as the remaining 208 patients did not have any admissions due to HF. During the study period 79 (24.8%) of the patients died.

The discrete distributions of the total number of admissions associated with a participant, overall and stratified by admission type, can be seen in Figure 1. The median follow-up was 492 days.

Table 1 presents baseline demographics and clinical variables overall and stratified by sex. Males were more likely to be diabetic and have HFmEF and HFrEF (compared to HFpEF). They also had a slightly higher mean eGFR and higher mean serum Hb levels. Table 2 presents the cohort's medication data, once again overall and stratified by sex. The prescription rate of ACEi/ARB/ARNi was high (overall 62.3%). When considering females this remained high at 56.0% (males 65.6%), despite the majority of female patients having HFpEF (52.3%).

Table 3 presents summary statistics for the three-categorical outcome indicating admission status (no hospital admissions, at least 1 HF admissions, and admitted but not for HF) as well as the corresponding unadjusted multinomial regression analysis and the adjusted multinomial regression analysis derived from backward selection. Post estimation of the risk ratio (RR) of at least one HF admission vs. non-HF admission were also derived. A significant interaction term between CKD and BMI was included in the multinomial regression. It means that the RR measuring the association between admission outcome and BMI varies across CKD levels and vice-a-versa, the levels of the RR measuring the association between admission outcome and CKD varies across BMI levels. Nevertheless, the effect is not statistically strong (p=0.024), and it dissipates in the observed data

analysis, namely an analysis using multiple imputation techniques under missing at random assumption. This multiple imputation and the post-estimation of the multinomial model is presented in the supplementary file.

In unadjusted analysis (Table 3) males were less likely to be admitted for non-HF admission versus no admission (RR 0.36, 95% CI 0.19, 0.67). This persisted in the multivariable analysis, which showed males to be less likely to have HF (RR 0.43, 95% CI 0.20, 0.94) and non-HF admissions (RR 0.21, 95% CI 0.10, 0.47) when compared to no admissions (Table 3). Compared to CKD stage 3, CKD stage 4 was associated with 4-times increased risk of HF and non-HF admissions (compared to no admissions) in adjusted analysis (RR 4.01, 95% CI 1.04, 15.5; RR 4.33, 95% CI 1.13, 16.5). Serum haemoglobin levels greater than 100 g/L were associated with a decreased risk of both HF and non-HF admissions (when compared to haemoglobin levels less than 100 g/L) in both unadjusted and adjusted analysis. There was no evidence to suggest any association between ejection fraction and hospital admissions in this sample. Table 3 shows 26.4% of the BMI data was missing for the non-admitted group. Therefore, we performed a multiple imputation by chained equations and repeated the multinomial regression models [14,15]. This analysis can be found in the supplementary file. Kaplan Meier curves demonstrated a significantly lower survival for patients with at least one HF admission compared to those with no admissions and non-HF admissions (Fig. 2). Adjusted Cox proportional hazards modelling showed that patients having at least one HF admission were more than twice as likely to die compared to patients with no admission (HR 2.41, 95% CI 1.27, 4.60) and almost twice as likely to die if they had at least one HF admission compared to those with non-HF admissions (HR 1.86, 95% CI 1.11, 3.14) (Table 4). Additionally, patients with HFrEF (HR 2.18, 95% CI 1.30, 3.63), patients with CKD stage 4 (HR 1.91, 95% CI 1.16, 3.16), and patients prescribed a diuretic (HR 2.24, 95% CI 1.14, 4.40) were associated with an increased risk of death compared to patients with HFpEF, CKD stage 3, and patients not prescribed a diuretic, respectively (Table 4). The use of RAAS inhibitors (ACEi/ARB/ARNi) was associated with a reduced risk of death (HR 0.44, 95% CI 0.27, 0.72).

Discussion

Summary of results

This study of patients with CKD and HF demonstrated a high frequency of hospital admission, one third of which due to heart failure. This work shows that a serum Hb level above 100 g/L is associated with a reduced risk of hospitalisations and that worsening CKD is associated with an increased risk of hospitalisations. In turn, having hospital admissions for HF, HFrEF, worsening CKD stage, diuretic use, and not being prescribed RAAS inhibitors were associated with an increased risk of death. Ejection fraction was found not to be associated with hospital admissions in this study.

Chronic kidney disease stage

This study found worsening stages of CKD to be associated with an increased risk of both HF and non-HF admissions and an increased risk of death. It is important to note that most previous research investigating the impact of eGFR on prognosis in patients with CKD and HF have compared hospitalisations and mortality between patients that have one condition with patients that have both conditions [4,7,8]. There is a paucity of studies such as ours, which have investigated the relative impacts of varying stages and subtypes of CKD and HF on prognosis in patients with both conditions. This study further adds to the literature that not only does having CKD worsen outcomes in HF patients, but in our clinic, worsening CKD stages also conferred worse outcomes. Recently published large retrospective cohort studies also support the association between lower eGFR and increased hospital admissions [16,17].

Serum haemoglobin

Serum haemoglobin levels greater than 100 g/L were associated with fewer HF and non-HF hospital admissions when compared to Hb levels below 100 g/L. Anaemia in CKD is common and is caused by decreased production of erythropoietin (EPO) and is associated with adverse outcomes including increased mortality [18]. However, previous clinical trial evidence in non-dialysis CKD patients has consistently shown no benefit in using erythropoietin stimulating agents (ESA) to achieve higher Hb targets of >130 g/L compared to lower targets of >110 g/L [19–21]. These trials also showed that

using ESAs to achieve higher targets was associated with an increased risk of death and cardiovascular disease. The findings of this study are purely observational and do not contradict these clinical trials. We simply report an association between hospital admissions and lower Hb, the latter of which may be contributed to by many other factors such as co-existing HF.

BMI

This study found that BMI had a significant interaction with CKD stage when considering hospitalisations. Descriptive analyses found that the median BMI was statistically significantly higher in those not admitted to hospital (28.4 kg/m^2) than in those admitted for HF (26.9 kg/m^2) and non-HF causes (26.3 kg/m^2). This study also found a significant proportion of missing BMI data in the never admitted group (26.4%). This was dealt with by performing a multiple imputation by chained equations, under the missing at random assumption, which can be found in the supplementary file. The average BMI of the cohort was 28.4 kg/m^2. It is possible that lower BMI may be a surrogate of disease progression in the form of cachexia and frailty, which is well established in later stages of HF and CKD [22,23]. Lower BMI may be associated with an increased risk of hospital admissions because of unmeasured confounding caused by increased disease progression or frailty. Future studies may adjust for this effect by including a frailty or mobility score.

Ejection fraction

Based on our data, there was no evidence to suggest that HFrEF was associated with hospitalisations, however, it was associated with an increased risk of death in multivariable Cox regressions. This supports previous works including the *Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)* study as well as a subsequent large Swedish retrospective cohort study, both of which found that CKD was more strongly associated with death in patients with HFrEF compared with HFpEF [6–8]. Previous work from our group has found that in patients with co-existing HF and CKD, those with reduced EF had an increased risk of death [12].

Sex differences

The multinomial regression in Table 3 shows that males were less likely to have a non-HF admission (versus not being admitted) compared to females (RR 0.36, 95% CI 0.19, 0.67). Table 1 shows the cohorts baseline demographics stratified by sex. While males were more likely to be diabetic and have HFrEF, they had a higher mean Hb and higher mean eGFR compared to females. It is possible that better kidney function and a more optimised serum Hb has contributed towards males having fewer non-HF admissions compared to females.

Additionally, the multinomial regression found that males were also less likely to have a HF admission (versus no admissions) compared to females (RR 0.43, 95% CI 0.20, 0.94). The same arguments as the ones above may apply; males had a higher eGFR and serum Hb which may have contributed to them having fewer admissions. However, Table 1 shows males were more likely to have HFrEF (40.2% vs 27.5%) and less likely to have HFpEF (34.9% vs 52.3%). This fits with the previous literature that HFpEF is more common in females than males [24]. Looking at Table 2 we can see that males were more likely to be prescribed an ACEi/ARB/ARNi, MRA, beta blocker, and SGLT2i (despite no statistical significance). There are fewer evidence-based treatments for HFpEF than for HFrEF, and because males are less likely to have HFpEF, this may explain why they were less likely to be admitted.

This analysis also showed that males were twice as likely to have a HF admission compared to non-HF admissions (RR 2.01, 95% CI 1.14, 3.55). Observational studies of just HFpEF patients have shown females to have a lower risk of death and admissions compared to males, however the results are conflicting [25–27]. More work is required to discover the many gaps that remain between the sexes of heart failure patients. This includes increasing the proportion of females in HF clinical trials which has historically been around 10-30% [28]. It is of note that there was no difference in mortality observed between the sexes in this study.

ACEi/ARB/ARNIs

This study found ACEi/ARB/ARNis were more likely to be prescribed in patients who were not admitted to hospital (through descriptive statistics in Table 2) and found them to be associated with

decreased risk of death. RAAS inhibition has been well documented to slow disease progression for each HF and CKD and as such is incorporated into guidelines for the management of both conditions. However, CKD-HF patients are less likely to be prescribed ACEi/ARB/ARNIs due to concerns over hyperkalaemia, hypotension, and short term decreases in eGFR [1,12,29,30]. Hyperkalaemia may be managed with potassium binders (Lokelma, sodium zirconium cyclosilicate and Veltassa, patiromer) to allow the use of ACEi/ARB/ARNis. Short term decreases in eGFR after initiation of RAAS inhibitors are common but should not deter clinicians as they likely reflect haemodynamic changes in the glomerulus and the evidence for the long term benefit of these medications in renal and heart disease has been well established [31]. While hypotension and its symptoms can be distressing for patients, the benefits and risks of RAASi should be considered before deciding against their use [32]. All these considerations are discussed in our multidisciplinary clinic with cardiologists and nephrologists and this clinic is effective in producing relatively high rates of ACEi/ARB/ARNI use (62.3% overall, 73.7% in CKD 3, 54.3% in CKD 4, and 51.3% in CKD 5), which in turn reduced the risks of hospitalisations and death in our cohort of CKD-HF patients. This study also provides data for ACEi/ARB/ARNi use in CKD stage 4 and 5 patients who are often excluded from large trials [33].

Loop diuretics

Loop diuretic use was associated with an increased risk of death, and patients who were admitted to hospital for HF were more likely to be taking a diuretic and had higher mean daily doses prescribed than patients not admitted to hospital (Tables 1 and 4). This effect is likely explained by both the diuretic resistance that develops with progressive CKD and congestion in higher risk patients with advanced CKD. Larger doses of loop diuretics are often needed to achieve adequate diuresis as eGFR decreases [12]. Furthermore, the use of diuretics (particularly at higher doses) and its association between death and hospitalisations is likely confounded by the severity of CKD, as increased severity of CKD is associated with both an increased risk of death and increasing diuretic doses.

Strengths, limitations, and further research

This study has many strengths. Firstly, the benefits of our joint CKD-HF clinic, which has both nephrologists and cardiologists, can be seen in the relatively high rates of GDMT for HF among our cohort. This is important in reducing the morbidity and mortality of HF in CKD patients because clinicians may struggle to initiate these medications due to concerns over hyperkalaemia and decreases in eGFR. The benefits of these medications, including RAAS inhibitors, is well established in the existing literature and is again supported by the results of this study. Secondly, few studies have investigated the relative impacts of varying stages and subtypes of CKD and HF on prognosis in patients with both conditions, as the majority of previous studies compare the effects of worsening kidney function in HF patients with controls having HF and normal kidney function. Thirdly, previous works have analysed admissions binarily (no admissions and greater than one admission) using logistic regressions and used rates per person-time and rate ratios using aggregated data. This however does not account for the cause of hospital admissions, the most common and detrimental of which being attributed to HF. This study used a more refined method of multinomial regression to capture the three distinct states a patient may have with regard to their hospital admission status. This study suggests that among CKD-HF patients, worsening CKD stages are associated with an increased risk of hospitalisations and death, and that an increased risk of death in this group is associated with worsening CKD stages, HFrEF, and not being on RAAS inhibitors, .Finally, there is limited data on the use of ACEi/ARBs in severe CKD, and while medications were not included in regression analysis examining hospital admissions due to the temporality of data collection, this study adds that RAAS inhibitors may have a role in CKD stage 4 and 5 patients, who are an understudied group of patients that are often excluded from clinical trials [28].

Limitations of this study include its observational nature and as such causality cannot be determined from correlations alone. We did not have information on the admission or discharge dates, just the number and length of each admission. We used the judgement of a single clinician to determine the cause of hospital admission – other studies have used criteria such as the Framingham criteria or had more than one person determining causes of admissions. Additionally, this study excluded

emergency department encounters for patients with fluid overload who were not subsequently admitted to hospital – this may represent lost information about the morbidity of HF. This sample represents patients with CKD stages 3-5 and may not represent patients with less severe kidney disease. Future studies may build on this work and further elucidate the characteristics associated with hospitalisations and death in order to improve the prognosis of patients with HF and moderate to severe CKD.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was not required due to the retrospective nature of the study, in accordance with local policy. All procedures followed the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualisation: DB, ICS, LA, GR, methodology: DB, ICS, data curation: SP, TL, MK, HW, DM, RS, formal analysis: SP, TL, supervision: DB, ICS, LA, GR, statistical analysis strategy and supervision: ICS, validation: DB, ICS, writing – original draft: SP, TL, MK, HW, DM, RS, writing – review and editing: DB, ICS, LA, GR.

Data Availability Statement

The data that support the findings of this study are not publicly available due to it originating from our centers electronic health record system but are available from SP upon reasonable request.

References

1 House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:1304–17. https://doi.org/10.1016/j.kint.2019.02.022.

2 Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2020;395:709–33. https://doi.org/10.1016/S0140-6736(20)30045-3.

3 Banerjee D, Rosano G, Herzog CA. Management of Heart Failure Patient with CKD. Clin J Am Soc Nephrol 2021;16:1131–9. https://doi.org/10.2215/CJN.14180920.

4 Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35:455–69. https://doi.org/10.1093/eurheartj/eht386.

5 Bansal N, Zelnick L, Bhat Z, Dobre M, He J, Lash J, et al. Burden and Outcomes of Heart Failure Hospitalizations in Adults With Chronic Kidney Disease. J Am Coll Cardiol 2019;73:2691–700. https://doi.org/10.1016/j.jacc.2019.02.071.

6 Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. European Heart Journal 2012;33:1750–7. https://doi.org/10.1093/eurheartj/ehr254.

7 McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Circ Heart Fail 2012;5:309–14. https://doi.org/10.1161/CIRCHEARTFAILURE.111.966242.

8 Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail 2017;19:1606–14. https://doi.org/10.1002/ejhf.821.

9 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. New England Journal of Medicine 2021;385:1451–61. https://doi.org/10.1056/NEJMoa2107038.

10 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. New England Journal of Medicine 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190.

11 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 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. European Heart Journal 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195.

12 Nguyen M, Rumjaun S, Lowe-Jones R, Ster IC, Rosano G, Anderson L, et al. Management and outcomes of heart failure patients with CKD: experience from an inter-disciplinary clinic. ESC Heart Fail 2020;7:3225–30. https://doi.org/10.1002/ehf2.12796.

13 Fagerland MW, Hosmer DW. A Generalized Hosmer–Lemeshow Goodness-of-Fit Test for Multinomial Logistic Regression Models. The Stata Journal 2012;12:447–53. https://doi.org/10.1177/1536867X1201200307.

14 Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393. https://doi.org/10.1136/bmj.b2393.

15 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 2011;30:377–99. https://doi.org/10.1002/sim.4067.

16 Hakopian NN, Gharibian D, Nashed MM. Prognostic Impact of Chronic Kidney Disease in Patients with Heart Failure. Perm J 2019;23:18–273. https://doi.org/10.7812/TPP/18.273.

17 de la Espriella R, Navarro J, Mollar A, D'Marco L, Palau P, Miñana G, et al. Long-Term Prognostic Impact of Estimated Glomerular Filtration Rate on Admission in Patients Hospitalized for Acute Heart Failure. Cardiorenal Med 2022;12:179–88. https://doi.org/10.1159/000526105.

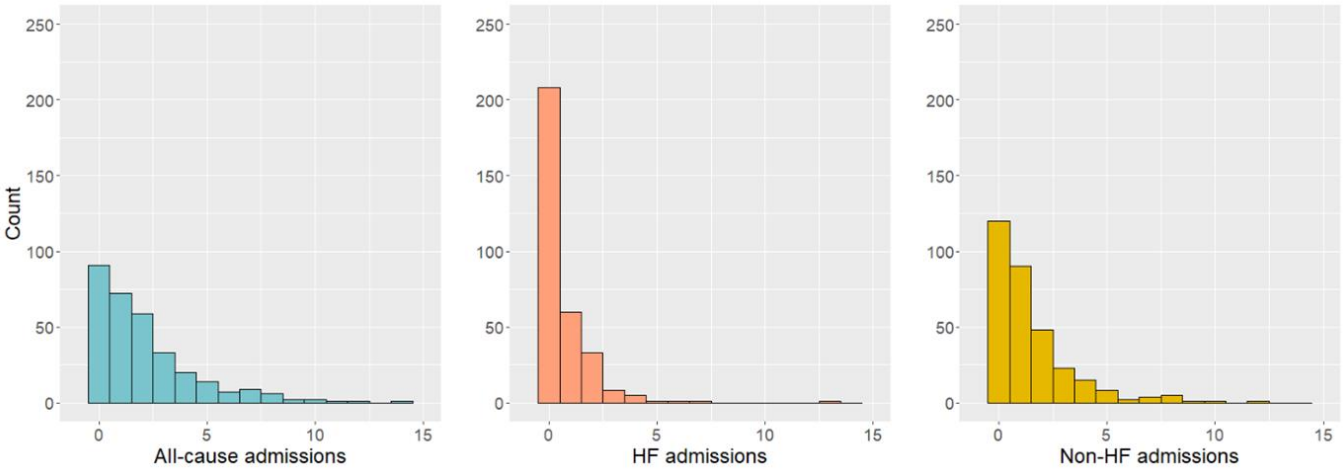
18 Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007;369:381–8. https://doi.org/10.1016/S0140-6736(07)60194-9.

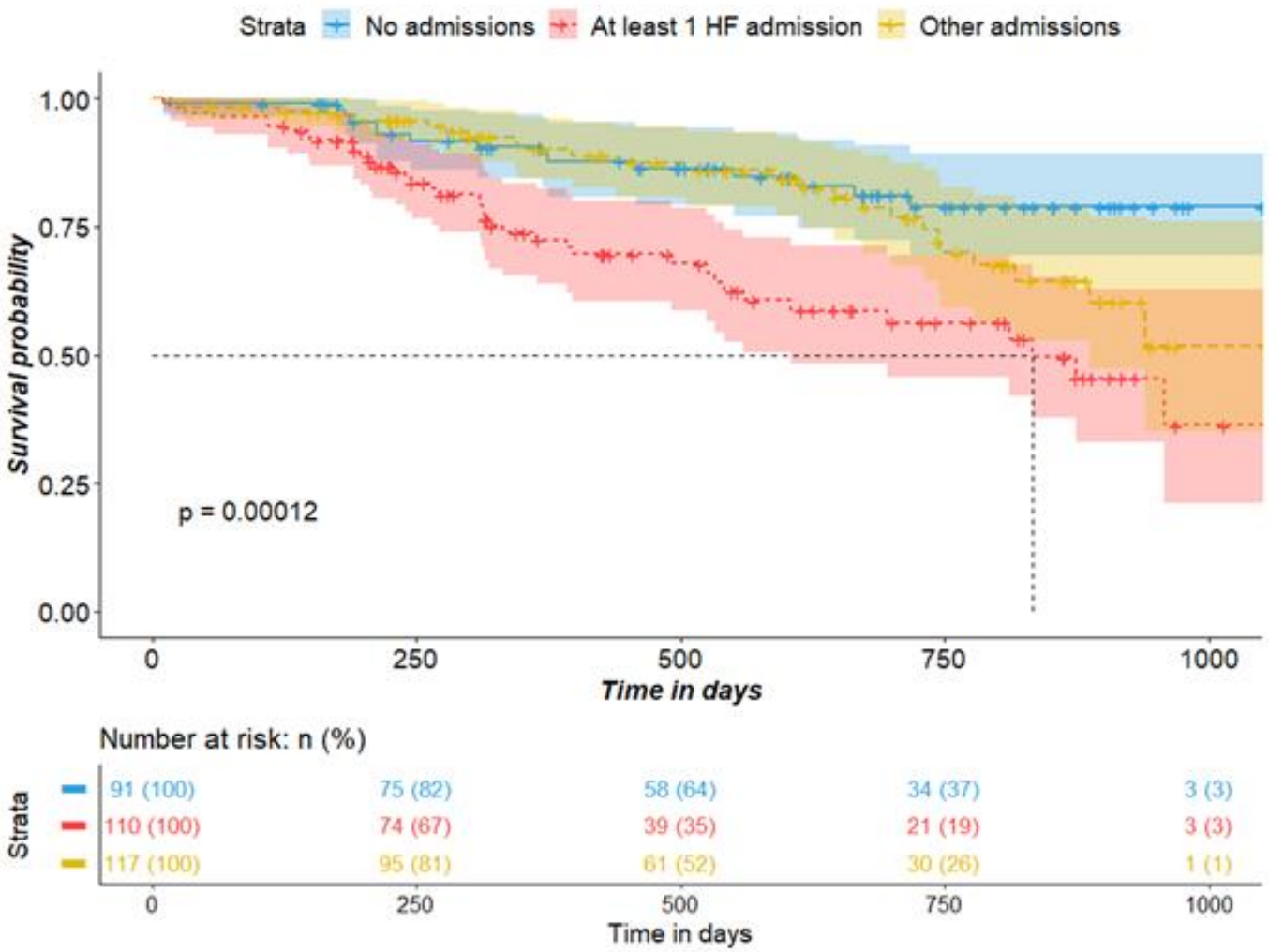
19 Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98. https://doi.org/10.1056/NEJMoa065485.
20 Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, de Zeeuw D, Eckardt K-U, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019–32. https://doi.org/10.1056/NEJMoa0907845.
21 Drüeke TB, Locatelli F, Clyne N, Eckardt K-U, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84. https://doi.org/10.1056/NEJMoa062276.
22 Oliveira EA, Zheng R, Carter CE, Mak RH. Cachexia/Protein energy wasting syndrome in CKD: Causation and treatment. Seminars in Dialysis 2019;32:493–9. https://doi.org/10.1111/sdi.12832.
23 von Haehling S, Ebner N, dos Santos MR, Springer J, Anker SD. Muscle wasting and cachexia in heart failure: mechanisms and therapies. Nat Rev Cardiol 2017;14:323–41. https://doi.org/10.1038/nrcardio.2017.51.
24 Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. European Journal of Heart Failure 2020;22:1342–56. https://doi.org/10.1002/ejhf.1858.
25 Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. Eur Heart J 2019;40:3859–3868c. https://doi.org/10.1093/eurheartj/ehz835.
26 Stolfo D, Uijl A, Vedin O, Str ömberg A, Fax én UL, Rosano GMC, et al. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum. JACC: Heart Failure 2019;7:505–15. https://doi.org/10.1016/j.jchf.2019.03.011.
27 Dewan P, Rørth R, Raparelli V, Campbell RT, Shen L, Jhund PS, et al. Sex-Related Differences in Heart Failure With Preserved Ejection Fraction. Circulation: Heart Failure 2019;12:e006539. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006539.
28 Parmar SS, Muthuppalaniappan V, Banerjee D. Gaps in Modern Heart Failure and Chronic Kidney Disease Research. Eur Cardiol 2023;18:e51. https://doi.org/10.15420/ecr.2022.64.
29 Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. American Heart Journal 2007;153:1064–73. https://doi.org/10.1016/j.ahj.2007.03.017.
30 Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. Int J Cardiol 2013;167:151–6. https://doi.org/10.1016/j.ijcard.2011.12.056.
31 Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. The Lancet 2021;398:786–802. https://doi.org/10.1016/S0140-6736(21)00519-5.
32 Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. The Lancet 2019;393:1034–44. https://doi.org/10.1016/S0140-6736(18)31808-7.
33 Damman K, Tang WHW, Felker GM, Lassus J, Zannad F, Krum H, et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. J Am Coll Cardiol 2014;63:853–71. https://doi.org/10.1016/j.jacc.2013.11.031.

Figure Legends

Fig. 1. Distributions of the total number of admissions associated with a participant, overall and stratified by admission type. People were followed up for different lengths of time and their admission dates were not recorded hence a Poisson regression to derive the mean number of admissions were difficult to derive. Given that 24.8% of patients died and the different lengths of time the patients were followed-up, the figure has just empirical value.

Fig. 2. Kaplan-Meier survival curves stratified by the type of hospital admissions in the cohort.





		Overall (n=318)	Sex	
			Females (n=109)	Males (n=209)
Sex	Females	109 (34.3%)		
	Males	209 (65.7%)	-	-
Age	Mean (SD)	74.4 (13.3)	73.7 (15.9)	74.7 (11.7)
	Median [Q1, Q3]	78 [68, 83]	79.0 [66, 84]	78.0 [68, 83]
BMI (kg/m^2)	BMI < 18.5	4 (1.3%)	4 (3.7%)	0 (0%)
	BMI 18.5-25	100 (31.4%)	34 (31.2%)	66 (31.6%)
	BMI > 25	187 (58.8%)	62 (56.9%)	125 (59.8%)
	Missing	27 (8.5%)	9 (8.3%)	18 (8.6%)
	Overall mean (SD)	28.4 (6.79)	28.9 (8.5)	28.1 (5.7)
	Overall median [Q1, Q3]	27.1 [23.5, 31.9]	27.0 [23.3, 33.25]	27.1 [23.8, 31.5]
Diabetes	No	145 (45.6%)	59 (54.1%)	86 (41.1%)
	Yes	173 (54.4%)	50 (45.9%)	123 (58.9%)
Heart Failure type	HFpEF	130 (40.9%)	57 (52.3%)	73 (34.9%)
	HFmEF	65 (20.4%)	18 (16.5%)	47 (22.5%)
	HFrEF	114 (35.8%)	30 (27.5%)	84 (40.2%)
	Missing	9 (2.8%)	4 (3.7%)	5 (2.4%)
CKD stage and eGFR ($mL/min/1.73 m^2$)	CKD 3	133 (41.8%)	49 (45.0%)	84 (40.2%)
	CKD 4	140 (44.0%)	44 (40.4%)	96 (45.9%)
	CKD 5	39 (12.3%)	14 (12.8%)	25 (12.0%)
	Missing	6 (1.9%)	2 (1.8%)	4 (1.9%)
	Overall mean (SD)	29.5 (12.0)	28.1 (10.2)	30.2 (12.8)
	Overall median [Q1, Q3]	29.0 [22, 35]	27.0 [22, 34.75]	29.0 [22, 36]
Serum haemoglobin (g/L)	Hb <100	67 (21.1%)	23 (21.1%)	44 (21.2%)
	Hb 100-150	235 (73.9%)	84 (77.1%)	151 (72.2%)
	Hb >150	9 (2.8%)	0 (0%)	9 (4.3%)
	Missing	7 (2.2%)	2 (1.8%)	5 (2.4%)
	Overall mean (SD)	115 (18.4)	110 (15.1)	117 (19.6)
	Overall median [Q1, Q3]	113 [102, 126]	111 [102, 120]	116 [103, 131.25]

Table 1: Cohort demographics and comorbidities overall and stratified by sex. Body mass index (BMI), heart failure with preserved ejection fraction (HFpEF, ejection fraction ≥50%), heart failure with moderately reduced ejection fraction (HFmEF, ejection fraction 41-49%), heart failure with reduced ejection fraction (HFrEF, ejection fraction ≤40%), estimated glomerular filtration rate

		Overall (n=318)		Sex					Hospital admission status					
				Females (n=109)		Males (n=209)		P-value	No admissions (n=91)		>=1 HF admission (n=110)		Admitted but not for HF (n=117)	
ACEi/ARB/ARNi	No	120	37.7%	48	44.0%	72	34.4%	0.121	26	28.6%	54	49.1%	40	34.2%
	Yes	198	62.3%	61	56.0%	137	65.6%		65	71.4%	56	50.9%	77	65.8%
MRA	No	232	73%	84	77.1%	148	70.8%	0.29	65	71.4%	73	66.4%	94	80.3%
	Yes	86	27%	25	22.9%	61	29.2%		26	28.6%	37	33.6%	23	19.7%
Beta blocker	No	64	20.1%	25	22.9%	39	18.7%	0.45	16	17.6%	23	20.9%	25	21.4%
	Yes	254	79.9%	84	77.1%	170	81.3%		75	82.4%	87	79.1%	92	78.6%
SGLT2i	No	233	73.3%	84	77.1%	149	71.3%	0.332	66	72.5%	80	72.7%	87	74.4%
	Yes	85	26.7%	25	22.9%	60	28.7%		25	27.5%	30	27.3%	30	25.6%
All 4 GDMT	No	289	90.9%	101	92.7%	188	90.0%	0.554	82	90.1%	99	90.0%	108	92.3%
	Yes	29	9.1%	8	7.3%	21	10.0%		9	9.9%	11	10.0%	9	7.7%
Loop diuretic	No	85	26.7%	28	25.7%	57	27.3%	0.865	27	29.7%	17	15.5%	41	35.0%
	Yes	233	73.3%	81	74.3%	152	72.7%		64	70.3%	93	84.5%	76	65.0%
Daily diuretic dose (mg of furosemide)	Mean (SD)	72.3	(77.7)	78.0	(78.3)	69.4	(77.4)	0.335	56.3	(61.3)	101	(88.8)	57.9	(70.8)
	Median [Q1, Q3]	40.0	[0, 120]	40.0	[0, 130]	40.0	[0, 95]		40	[0, 80]	80	[40, 160]	40	[0, 80]
	Missing	4	1.3%	1	0.9%	3	1.4%		1	(1.1%)	1	0.9%	2	1.7%

Table 2: Medication data stratified by the categorical admissions outcome defined as never admitted, admitted with at least one heart failure admission, and admitted but not for heart failure. Medication data was collected at the end of the observation period for each patient. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor/neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonist (MRA), sodium-glucose cotransporter-2 inhibitors (SGLT2i), guideline directed medical therapy (GDMT).

		Hospital Admissions Status						Unadjusted multinomial logistic regression									Adjusted multinomial logistic regression								
		No admissions (n=91)		>=1 HF admission (n=110)		Admitted but not for HF (n=117)		>=1 HF admission vs. No admissions			Admitted but not for HF vs. No admissions			>=1 HF admission vs. Admitted but not for HF			>=1 HF admission vs. No admissions			Admitted but not for HF vs. No admissions			>=1 HF admission vs. Admitted but not for HF		
		No.	%	No.	%	No.	%	RR	95% CI	P-value	RR	95% CI	P value	RR	95% CI	P-value	RR	95% CI	P-value	RR	95% CI	P-value	RR	95% CI	P-value
Sex	Females	21	23.1%	35	31.8%	53	45.3%	1			1			1			1						1		
	Males	70	76.9%	75	68.2%	64	54.7%	0.64	0.34, 1.21	0.170	0.36	0.19, 0.67	**0.001**	1.77	1.03, 3.05	**0.038**	0.43	0.20, 0.94	**0.035**	0.21	0.10, 0.47	**<0.001**	2.01	1.14, 3.55	**0.016**
Age	Mean (SD)	73.4	(13.8)	75.7	(12.2)	73.8	(13.8)	1.01	0.99, 1.04	0.219	1.00	0.98, 1.02	0.846	1.01	0.99, 1.03	0.270									
	Median [Q1, Q3]	77	[67, 83]	78	[72, 83]	78	[66, 83]																		
BMI kg/m²	BMI <25	22	24.2%	35	31.8%	47	40.2%	1			1			1			1			1			1		
	BMI ≥25	45	49.5%	74	67.3%	68	58.1%	1.03	0.54, 1.98	0.920	0.71	0.38, 1.33	0.282	1.46	0.84, 2.53	0.175	1.47	0.57, 3.80	0.429	1.25	0.48, 3.24	0.650	1.18	0.49, 2.80	0.711
	Missing	24	26.4%	1	0.9%	2	1.7%																		
Diabetic	No	48	52.7%	50	45.5%	47	40.2%	1			1			1											
	Yes	43	47.3%	60	54.5%	70	59.8%	1.34	0.77, 2.34	0.304	1.66	0.96, 2.89	0.072	0.81	0.48, 1.36	0.422									
Heart Failure type	HFpEF	36	39.6%	49	44.5%	45	38.5%	1			1			1											
	HFmEF	21	23.1%	17	15.5%	27	23.1%	0.60	0.28, 1.29	0.186	1.03	0.50, 2.11	0.939	0.58	0.28, 1.20	0.141									
	HFrEF	27	29.7%	44	40.0%	43	36.8%	1.20	0.63, 2.28	0.583	1.27	0.66, 2.44	0.466	0.94	0.52, 1.68	0.834									
	Missing	7	7.7%	0	0%	2	1.7%																		
CKD Stage	CKD 3	47	51.6%	35	31.8%	51	43.6%	1			1			1			1			1			1		
	CKD 4	35	38.5%	60	54.5%	45	38.5%	1.64	0.91, 2.96	0.100	1.34	0.75, 2.42	0.325	1.22	0.70, 2.12	0.482	4.01	1.04, 15.5	**0.044**	4.33	1.13, 16.5	**0.032**	0.93	0.35, 2.44	0.878
	CKD 5	5	5.5%	15	13.6%	19	16.2%	1.63	0.50, 5.35	0.418	2.96	1.01, 8.68	**0.048**	0.55	0.22, 1.41	0.213	1.48	0.27, 8.16	0.651	2.65	0.54, 13.1	0.232	0.56	0.13, 2.31	0.135
	Missing	4	4.4%	0	0%	2	1.7%																		
Serum Hb (g/L)	Hb <100	7	7.7%	26	23.6%	34	29.1%	1			1			1			1			1			1		
	Hb ≥100	80	87.9%	82	74.5%	82	70.1%	0.28	0.11, 0.67	**0.005**	0.21	0.09, 0.50	**<0.001**	1.31	0.72, 2.37	0.377	0.26	0.09, 0.74	**0.012**	0.17	0.06, 0.47	**<0.001**	1.57	0.83, 2.96	0.162
	Missing	4	4.4%	2	1.8%	1	0.9%																		
Interaction term between CKD and BMI	CKD 3*BMI≥25																1			1			1		
	CKD 4*BMI≥25																0.26	0.05, 1.26	0.096	0.16	0.04, 0.79	**0.024**	1.64	0.49, 5.49	0.425
	CKD 5*BMI≥25																0.98	0.08, 11.7	0.988	1.07	0.10, 11.1	0.954	0.91	0.13, 6.35	0.929

Table 3: Variables' summaries stratified by the multinomial outcome with three distinct categories: no hospital admissions, at least one hospital admission for HF, and at least one hospital admission but no HF admissions. Adjusted multinomial regression was performed using backward selection (AIC - Akaike Information Criterion) until only three significant covariates remained (sex, CKD

		Survival data summary				Univariate Cox regression			Multivariable Cox regression		
		Survived (n=239, 75.2%)		Died (n=79, 24.8%)		HR	95% CI	p-value	HR	95% CI	p-value
Admission status	No admissions (ref)	76	31.8%	15	19.0%	1			1		
	At least 1 HF admission	71	29.7%	39	49.4%	3.15	1.73, 5.73	**<0.001**	2.41	1.27, 4.60	**0.007**
	Admitted but not for HF	92	38.5%	25	31.6%	1.54	0.81, 2.92	0.190	1.29	0.65, 2.57	0.460
	Admitted but not for HF (ref)	92	38.5%	25	31.6%	1			1		
	At least 1 HF admission	71	29.7%	39	49.4%	2.05	1.24, 3.39	**0.005**	1.86	1.11, 3.14	**0.019**
Sex	Females	85	35.6%	24	30.4%	1					
	Males	154	64.4%	55	69.6%	1.27	0.79, 2.06	0.324			
Age	Mean (SD)	72.7	14	79.4	9.24	1.04	1.02, 1.07	**<0.001**			
	Median [Min, Max]	77	[20, 94]	81	[54, 93]						
BMI (kg/m^2)	BMI <25	75	31.4%	29	36.7%	1					
	BMI ≥ 25	139	58.2%	48	60.8%	0.86	0.54, 1.36	0.509			
	Missing	25	10.5%	2	2.5%						
Diabetic	No	106	44.4%	39	49.4%	1					
	Yes	133	55.6%	40	50.6%	0.77	0.50, 1.20	0.246			
Heart Failure type	HFpEF	101	42.3%	29	36.7%	1			1		
	HFmEF	53	22.2%	12	15.2%	0.88	0.45, 1.72	0.700	1.15	0.59, 2.27	0.682
	HFrEF	79	33.1%	35	44.3%	1.64	1.01, 2.69	**0.049**	2.18	1.30, 3.63	**0.003**
	Missing	6	2.5%	3	3.8%						
CKD Stage	CKD 3	110	46.0%	23	29.1%	1			1		
	CKD 4	96	40.2%	44	55.7%	2.20	1.36, 3.57	**0.001**	1.91	1.16, 3.16	**0.011**
	CKD 5	27	11.3%	12	15.2%	2.01	0.87, 4.65	0.102	2.07	0.86, 4.97	0.104
	Missing	6	2.5%	0	0%						
Serum Haemoglobin (g/L)	Hb <100	49	20.5%	18	22.8%	1					
	Hb ≥100	183	76.6%	61	77.2%	0.91	0.54, 1.55	0.735			
	Missing	7	2.90%	0	0%						
ACEi/ARB /ARNi	No	73	30.50%	47.0	59.50%	1					
	Yes	166	69.50%	32.0	40.50%	0.40	0.26, 0.63	**<0.001**	0.44	0.27, 0.72	**<0.001**
MRA	No	175	73.20%	57.0	72.20%	1					
	Yes	64	26.80%	22.0	27.80%	1.20	0.73, 1.96	0.477			
Beta blocker	No	44	18.40%	20.0	25.30%	1					
	Yes	195	81.60%	59.0	74.70%	0.81	0.48, 1.34	0.402			
Loop Diuretics	No	73	30.50%	12.0	15.20%	1					
	Yes	166	69.50%	67.0	84.80%	2.30	1.24, 4.24	**0.008**	2.24	1.14, 4.40	**0.019**

Table 4: Cox proportional hazards analyses for death during the follow up since diagnosis/joining the clinic. Backward selection (AIC - Akaike Information Criterion) was used until only significant covariates remained in the multivariate model (admission status, HF type, CKD stage, ACEi/ARB/ARNi use, and diuretic use). Body mass index (BMI), heart failure (HF), heart failure with preserved ejection fraction (HFpEF), heart failure with moderately reduced ejection fraction (HFmEF), heart failure with reduced ejection fraction (HFrEF), chronic kidney disease (CKD), haemoglobin (Hb), angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor/neprilysin inhibitor (ARNi), mineralocorticoid receptor antagonist (MRA).