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The Prognostic Impact of Renal Function Decline during Hospitalization for Heart Failure

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Keywords
Glomerular filtration · Worsening of renal function · Mortality risk · Acute decompensated heart failure

Abstract
Introduction: We aimed to evaluate the prognostic impact of renal insufficiency and fluctuation of glomerular filtration observed during hospitalization for heart failure (HF). ***Methods:*** We followed 3,639 patients hospitalized for acute HF and assessed the mortality risk associated with moderate or severe renal insufficiency, either permanent or transient. ***Results:*** After adjustment, severe renal failure defined as estimated glomerular filtration (eGFR) <30 mL/min indicates ≈60% increase in 5-year mortality risk. Similar risk also had patients with only transient decline of eGFR to this range. In contrast, we did not observe any apparent mortality risk attributable to mild/moderate renal insufficiency (eGFR 30–59.9 mL/min), regardless of whether it was transient or permanent. ***Conclusion:*** Even transient severe renal failure during hospitalization indicates poor long-term prognosis of patients with manifested HF. In contrast, only moderate renal insufficiency observed during hospitalization has no additive long-term mortality impact.

Introduction

Renal insufficiency is a common phenomenon in heart failure (HF) patients, and the relationship between both these pathophysiological conditions is reciprocal. One of these phenomena affects the others in terms of clinical course, and its coincidence leads to increased mortality and morbidity risk. Patients with chronic kidney disease (CKD) show an excessive cardiovascular risk manifesting not only as HF but also as an increased incidence of atherosclerotic vascular disease and sudden cardiac death [1, 2]. Patients with CKD die rather from cardiac events or malignancies than from uremia [3]. From the opposite point of view, HF represents a precipitating factor for CKD. Even in patients with still normal renal function, HF incidence increases the risk of rapid estimated glomerular filtration (eGFR) decline and future CKD [4]. The pathophysiology of interaction between the cardiovascular system and kidney is very complex, involving the renin-angiotensin system (RAS), natriuretic peptides, inflammatory processes, oxidative stress, accelerated atherosclerosis, etc. [5]. The clinical manifestation of this interaction is commonly known as cardiorenal syndrome [6] and is associated with a substantial mortality increase [7, 8]. Adverse heart-kidney interaction may also occur

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relatively subclinically. A transient worsening of renal function (WRF) (decrease in glomerular filtration) is a common phenomenon in all hospitalized patients, but it is particularly strongly expressed during hospitalization for acute HF. The most common interpretation is that it is caused by rapid decongestion by diuretics during the initial phase of acute HF treatment [9, 10]. However, the phenomenon also probably involves other mechanisms of cardiorenal interaction and may potentially have clinical significance.

The coincidence of HF and renal insufficiency not only represents an adverse pathophysiological situation but also negatively affects the long-term therapeutic management of chronic HF. For example, patients with renal insufficiency are typically less likely to be appropriately treated with guideline-determined medical therapy, or at least these drugs have lower doses [11]. The reasons are not only the safety concerns (typical in mineralocorticoid receptor antagonists). Subjects with severe renal impairment are also often excluded from early studies with the new drugs [12]. Consequently, these patients do not meet the prescription criteria of these innovative drugs and, therefore, cannot profit from them.

Clinical interpretation of a patient's actual glomerular filtration during hospitalization for acute HF is further complicated by two parallel problems. The first is that probably many measurements will be done during hospitalization. Although a steady-state condition is assumed to determine glomerular filtration, in the "real world," we have to make decisions based on several highly variable values. The second question is to what extent the mere fact of fluctuating glomerular filtration during hospitalization represents a prognostic indicator. In the present study, we established renal function by either the lowest or the highest glomerular filtration observed during hospitalization and compared the attributable mortality risk of renal insufficiency by these two approaches. We also aimed to assess whether fluctuation across glomerular filtration categories during hospitalization (toward severe or toward moderate renal insufficiency) leads to an impaired long-term prognosis of chronic HF patients.

Materials and Methods

Design and Study Population

The analysis represents a prospective follow-up study in patients hospitalized for acute cardiac decompensation as the first manifestation of chronic HF failure or worsening of this preexisting condition requiring hospitalization. This main qualifying criterion was based on diagnosis, formally stated in the discharge report as the primary cause leading to hospitalization (details of the selection process are shown in Fig. 1). In the first step, we identified 16,436 hospitalizations in University Hospital Pilsen between January 1, 2000, and September 29, 2020, in 10,792 individual patients (we used the data from the first hospitalization during the period 2000–2020; therefore, recurrent hospitalizations for HF were excluded). In the second step, we excluded 4,988 patients hospitalized for HF before January 1, 2010 (in our or any other hospital). In this way, we created a sample of 5,804 individual patients without a history of HF hospitalization in the previous 10 years. From this initial pool, 1,140 were older than 85 years, 138 subjects were excluded after a review of their documentation (usually because the HF was not found to be the primary cause of their hospitalization), 429 patients died during hospitalization, and other 458 subjects were excluded because of insufficient number of eGFR estimations during hospitalization (a minimum of at least three measurements during hospitalization was required). The final sample consisted of 3,639 subjects, aged ≤85 years, with the first manifestation of HF requiring hospitalization (being not hospitalized for at least 10 years for HF) and surviving the qualifying hospitalization. The date of admission to the hospital was used as a baseline point for the follow-up analysis.

Data Collection

Only data contained in the hospital information system were used, and no formal examination was done in conjunction with this analysis. We registered the following information: history of cardiovascular diseases, coronary revascularizations, diabetes mellitus, hypertension, known malignancies, and history of smoking. The presumed etiology of HF (i.e., mainly if related to coronary artery disease [CAD] or not) was critically assessed based on available information. The value of ejection fraction (EF) was derived from echocardiography realized during hospitalization (in the vast majority of patients), or if this was not recognized, we used the most recent echocardiography available or the ejection fraction value formally stated in medical records. The presence of atrial fibrillation or flutter was derived from the ECG realized during hospitalization or this information stated in medical history. Finally, recommended pharmacotherapy (including dosage) in the discharge report was also registered in drugs of special interest (such as β-blockers, RAS blockers, aldosterone antagonists, and statins).

Essential laboratory examination (glycemia, serum lipids, creatinine, and natriuretic peptides) was done as a part of the routine clinical management of patients and derived from the hospital information system. The central hospital laboratory (Department of Clinical Biochemistry and Hematology, University Hospital Pilsen) is involved in the system of regular quality control of all procedures (instruments, laboratory estimations, etc.), and only standard commercial kits and analytical platforms (namely, COBAS 8000 analytical platform; Roche Diagnostics, Basel, Switzerland) were used for laboratory estimations.

By use of the National Registry of the Institute of Health Information and Statistics of the Czech Ministry of Health, the individual vital status of all patients was ascertained. If the patient died between the discharge and December 30, 2020, the date of death was registered. We also reviewed death certificates and available documentation in hospital information systems to specify the cause of death.

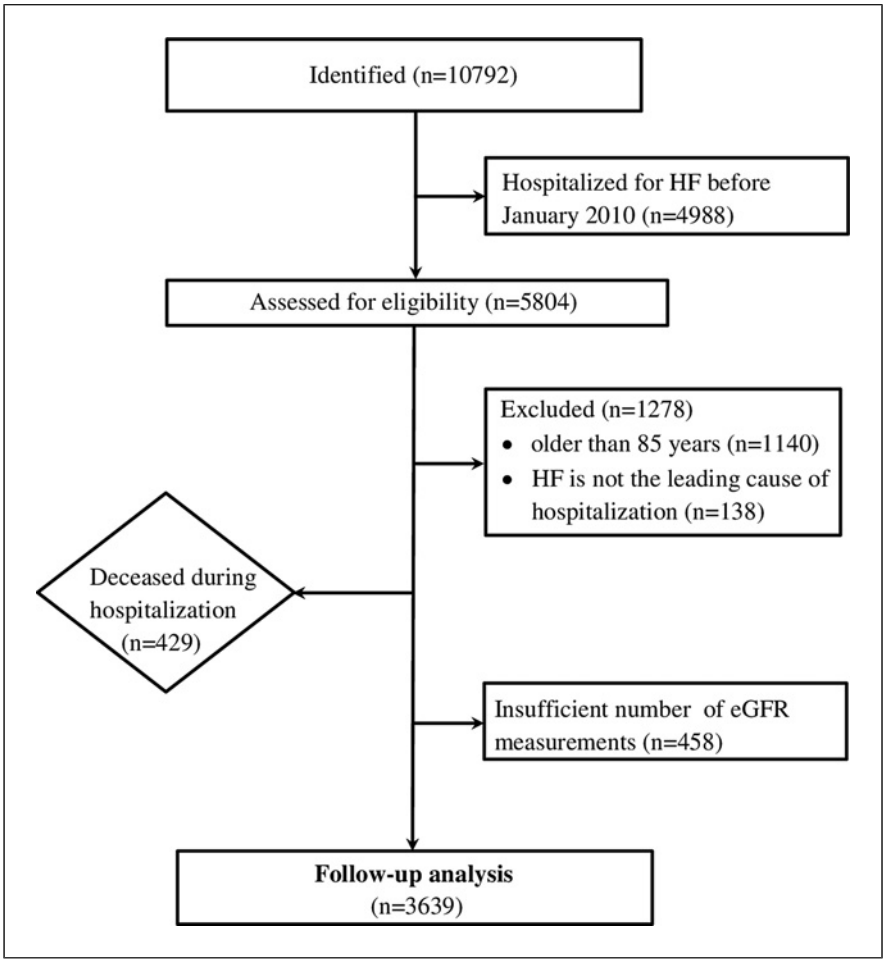

Fig. 1. Study sample selection process.

Data Management

As exposure, we used renal functions ascertained during hospitalization. We calculated eGFR by individual creatinine values and using the CKD-EPI formula [13]. The analysis was generally realized from two perspectives, using the lowest and highest eGFR value detected during hospitalization (repeated creatinine measurements are a regular part of medical care in all hospitalized patients, but only these subjects having at least three measurements were included in the study). The eGFR values were initially dichotomized concerning the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) [14] grading (grades 1–5), but for the principal analysis, the sample was finally divided only into three groups as follows: group A, normal or only mild decrease of renal function (grade 1 + 2 by KDOQI), eGFR ≥60 mL/min; group B, moderate renal insufficiency (grade 3), eGFR 30–59.9 mL/min; group C, severe renal insufficiency (grade 4 + 5), eGFR <30 mL/min. For consequent analysis, we further split the sample in another way, namely, group a – all individual eGFR values ≥60 mL/min; group b – transiently moderate renal insufficiency (the lowest individual eGFR 30–59.9 but the highest ≥60 mL/min; the mutual sequence of high and low values was not taken into account); group c – a permanently moderate renal insufficiency (both, the highest and lowest eGFR 30–59.9 mL/min); group d – transiently severe renal insufficiency (the lowest individual eGFR <30 but the highest ≥30 mL/min; group e – permanently severe renal insufficiency (any individual eGFR <30 mL/min).

As outcomes, we used all-cause death for 5 years. Censored data were used for those subjects with only partial follow-up.

We used the following definitions for covariates: we dichotomized EF into three usual categories ≤40%, 41–50%, and ≥51%. Regarding the primary etiology of HF, all cases with a history of myocardial infarction (MI), myocardial revascularization, or angiographically proven stenosis of coronary artery greater than 50% were considered as "CAD-related HF." Patients, in whom a diagnosis of dilated cardiomyopathy (CMP), tachycardia-induced CMP, post-inflammatory CMP, or other apparent secondary etiology was mentioned in the discharge summary or other available documentation, were collectively considered as non-CAD-related HF. Patients with hypertension who did not fall into any of the above categories were considered CAD-related HF.

Other comorbidities and conditions were defined as follows: hypertension, if this diagnosis was explicitly mentioned in the documentation or if the patient was treated with antihypertensives beyond those used in the treatment of HF; diabetes mellitus if the highest fasting glucose during hospitalization was ≥7 or non-fasting

glucose ≥11.1 mmol/L or HbA1c ≥70 mmol/mol, as well as treatment with antidiabetics or history of diabetes mentioned in the documentation. Hypercholesterolemia was defined as LDL cholesterol ≥1.8 mmol/L, while markedly increased brain natriuretic peptide (BNP) was defined as peak concentration ≥10 times higher than the upper limit of normal (ULN), i.e., BNP ≥1,000 or N-terminal proBNP ≥3,000 ng/L. History of malignancy means that this diagnosis was stated anywhere in the available patient's documentation, irrespective of current staging or grading.

Pharmacotherapy of particular interest was categorized by roughly equipotent daily dose into 3 groups (reduced, standard, and target dose; how individual drugs were assigned to these groups can be found elsewhere [15]). Statistical analyses were performed using STATISTICA 8 (StatSoft Inc, Tulsa, OK, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA). Conventional descriptive (i.e., the mean and standard deviation for continuous variables, the frequency for categorical ones) and statistical (multiple linear step-wise regression) methods were applied. Cox proportional hazard model was performed to identify the relative role of potential covariates on defined outcomes. Power calculations revealed that our population of patients was sufficiently large to estimate the expected incidence of the defined outcomes with a 5% relative precision level. Statistical significance was considered present at the p value of 0.05.

Results

Baseline Cross-Sectional Data and Renal Function Covariates

In this study, we followed 3,639 initially stabilized chronic HF patients – their baseline characteristics are listed in Table 1 (cohort 1). Cohort 2 (Table 1, second column) consisted of the same subjects but excluded patients with malignancy, either in medical history or as the declared cause of death. In the same manner, we excluded subjects who were deceased from an external cause (any accidents or suicides proclaimed as the primary cause of death in the death certificate) from cohort 2.

We tested the multivariate association between eGFR and a large set of characteristics by a step-wise regression model (Table 2). If the lowest eGFR observed during hospitalization was used as a dependent variable (model 1), the following independent variables entered the regression model significantly: male gender, year of hospitalization, treatment with β-blockers, and mineralocorticoid receptor antagonists as positive covariates, while age, duration of hospitalization, hypertension, diabetes, increased BNP, therapy with furosemide and with statins as inverse covariates. A similar regression analysis was performed with the highest observed eGFR (model 2), with roughly equivalent results (Table 2, second column). We also repeated both these regressions with cohort 2, with confirmatory results (*not* in table).

During the median 928 days (interquartile range 333–1,780) of follow-up, 2,094 patients (57.5% of the sample) deceased in the total sample (cohort 1), while 1,644 (53.7%) were in cohort 2. Corresponding 5-year all-cause mortalities were 49.2% and 45.1% (cohorts 1 and 2, respectively). Table 3 shows the Cox proportional hazard model, a mortality risk associated with each potential predictor of fatal outcome. Two separate regressions we performed again, one with the lowest (model 1) and the other with the highest eGFR (model 2). The following characteristics were independently associated with increased 5-year mortality risk: age over 65 years, male gender, CAD-related HF, history of malignancy, peak BNP during hospitalization ≥10 times higher than ULN, and treatment with furosemide. Decreased mortality risk was associated with the year of hospitalization, LDL ≥1.8 mmol/L, treatment with RAS blockers, statins as well as implanted cardioverter-defibrillator. Significantly increased mortality risk was associated with the eGFR category (grades 1–5 by KDOQI), and the corresponding hazard risk ratios (HRRs) were roughly similar if the lowest or highest eGFR (model 1 or 2) was used. We also repeated both regressions in cohort 2 (*not* in table). The eGFR category independently predicted 5-year mortality risk nearly similarly using the lowest or highest eGFR value (HRR 1.24 [95% CIs: 1.13–1.36], $p < 0.0001$ and 1.16 [95% CIs: 1.06–1.28], $p = 0.001$, in models 1 and 2, respectively). We also confirmed an inverse independent and significant, again nearly similarly by using the lowest or highest eGFR value (in both, cohorts 1 and 2) (*not* in table).

eGFR Categories and Mortality Risk

In the first step, we divided the sample into five subgroups by KDOQI grades (again in two ways, by the lowest and the highest eGFR). The frequencies of patients in these subgroups are shown at the end of Table 1, while the corresponding survival curves are in Figure 2. We observed the lowest survival in severe renal insufficiency subjects. KDOQI grades 4 and 5 showed almost parallel survival curves if the lowest or highest eGFR was used. Grade 1 and grade 2 patients show somewhat different characteristics depending on whether the lowest or highest eGFR was used. The mortality of grade 3 patients was roughly midway between these two positions (i.e., grades 1 and 2 vs. grades 4 and 5). For that reason, we carried out the consequent analyses across three wider subgroups: eGFR ≥60 mL/min (grades 1 and 2) (A), eGFR 30–59 mL/min (grade 3) (B), and

Table 1. Baseline characteristics of study sample [mean (standard deviation) or percentual factor proportion]

	Cohort 1	Cohort 2
n	3,639	3,063
Age, years	71.4 (10.2)	71.0 (10.5)
Age >65 years, %	77.7	76.2
Male gender, %	58.7	58.0
Length of hospitalization, days	10.7 (7.7)	10.5 (7.7)
Hospitalization ≥10 days, %	46.4	45.6
Coronary revascularization, %	28.8	28.6
History of smoking[a], %	20.8	21.0
Hypertension, %	90.6	90.5
LDL cholesterol, mmol/L	2.28 (0.97)	2.29 (0.95)
LDL ≥1.8 mmol/L, %	62.9	63.7
Fasting glycemia, mmol/L	7.32 (2.54)	7.36 (2.58)
Diabetes mellitus,[b] %	70.2	70.3
Peak BNP ≥10 times ULN,[c] %	56.4	45.7
Atrial fibrillation or flutter, %	51.2	55.6
Known history of malignancy, %	10.7	0
ICD, %	13.6	14.5
Ejection fraction ≤40%, %	47.9	49.3
CAD or hypertension,[d] %	58.2	59.2
Pharmacotherapy, %		
Antiplatelets or oral anticoagulants	78.3	78.8
Furosemide	89.5	89.5
Beta-blockers	77.4	78.3
RAS blockers	78.3	79.8
Mineralocorticoid receptor antagonists	45.8	46.9
Statins	46.7	47.4
Antidiabetics	34.6	35.1
Lowest eGFR,[e] mL/min	48.0 (22.5)	48.1 (22.5)
Highest eGFR,[e] mL/min	60.0 (24.0)	60.0 (23.9)
eGFR categories* by the lowest observed value (model 1), %		
≥90 mL/min	4.2	4.2
60–89.9 mL/min	24.4	26.4
30–59.9 mL/min	49.4	49.2
15–29.9 mL/min	14.5	14.6
<15 mL/min	7.5	7.4
eGFR categories* by the highest observed value (model 2), %		
≥90 mL/min	11.9	11.9
60–89.9 mL/min	36.9	36.6
30–59.9 mL/min	40.0	40.4
15–29.9 mL/min	8.0	7.9
<15 mL/min	3.2	3.2

LDL, low-density lipoprotein; ULN, upper limit of normal; ICD, implanted cardioverter-defibrillator. Cohort 1: all subjects; cohort 2: patients with malignancy either in medical history or as a declared cause of death plus those with the external cause of death (accidents, suicides, etc.) were excluded. eGFR, [a]past or current smoking. [b]The highest fasting glucose ≥7 or non-fasting ≥11.1 mmol/L, history of diabetes, and/or treatment with antidiabetics. [c]BNP ≥1,000 ng/L or NT-proBNP ≥3,000 ng/L. [d]As presumed primary etiology of HF. [e]Estimated glomerular filtration (eGFR) by CKD-EPI standard; highest or lowest creatinine value during hospitalization was used. *Grades 1–5 by KDOQI.

eGFR <30 mL/min (grades 4 and 5) (C). The right panels show the same survival curves for cohort 2, with a similar pattern (Fig. 1).

Table 4 shows the mortality risk associated with renal function among these more comprehensive limits, and we used subgroup A (eGFR ≥60 mL/min) as

Table 2. Covariates of renal functions (lowest and highest eGFR value observed during hospitalization)

Dependent variable	Model 1, lowest eGFR		Model 2, highest GFR	
	beta coefficient (standard errors)	*p* value	beta coefficient (standard errors)	*p* value
Age	−0.608 (0.044)	<0.0001	−0.754 (0.047)	<0.0001
Gender	6.720 (0.878)	<0.0001	6.341 (0.939)	<0.0001
Year of hospitalization	0.910 (0.143)	<0.0001	1.328 (0.153)	<0.0001
Duration of hospitalization	−0.437 (0.053)	<0.0001	0.180 (0.057)	0.002
Hypertension	−5.804 (1.561)	<0.0001	−6.548 (1.706)	<0.0001
LDL	−0.818 (0.432)	0.078	−1.316 (0.495)	0.008
Diabetes mellitus	−5.321 (0.947)	<0.0001	−3.741 (1.016)	<0.0001
BNP ≥10 times ULN	−7.856 (0.879)	<0.0001	−7.964 (0.941)	<0.0001
Furosemide[a]	−3.423 (0.428)	<0.0001	−4.161 (0.458)	<0.0001
Beta-blockers[a]	2.652 (1.024)	0.010	2.021 (1.096)	0.065
RAS blockers[a]	not entered		−0.768 (0.442)	0.083
Mineralocorticoid receptor antagonists[a]	0.844 (0.380)	0.026	2.290 (0.406)	<0.0001
Statins[a]	−0.911 (0.380)	<0.0001	−1.134 (0.406)	0.005
Constant	*−1,720.492 (288.578)*	*<0.0001*	*−2,543.173 (308.672)*	*<0.0001*

ULN, upper limit of normal; ICD, implanted cardioverter-defibrillator. Multiple linear step-wise regression; the following variables were included initially (but rejected by the model): CAD as primary etiology coronary revascularization, history of malignancy, atrial fibrillation or flutter, ejection fraction category, current or ex-smoking, antiplatelets or anticoagulants, and ICD. [a]Stratified by dose; see Methods for definitions.

the reference. Regardless of whether the highest or the lowest eGFR value was used for the decision, severe renal insufficiency patients (group C) showed significantly higher 5-year mortality risk compared to preserved renal function subjects (A) or those with moderate renal insufficiency (B). In contrast, we noted a significantly increased risk of moderate renal insufficiency (B) only if the highest value was used for definition. A nearly similar pattern was observed in cohort 2 again (not in table).

The Predictive Power of Transient Decrease of eGFR

Only transient decrease during hospitalization into KDOQI grade 3 (eGFR 30–59 mL/min, group b) was observed in 677 (18.6%) patients, while the transient decrease of eGFR into grades 4 and 5 (<30 mL/min, group d) was observed in other 394 (10.8%) subjects. The mortality risk of this only transient decrease of renal function is analyzed in Table 5. In the fully adjusted model, we observed a significant increase in 5-year mortality associated with the transient decrease of eGFR to severe renal insufficiency (group d) but not with the transient decrease to only moderate renal insufficiency (group b). As in previous analyses, we repeated all regressions with cohort 2, with confirmatory results (not in table); transient decrease to severe renal insufficiency range was associated with about twofold higher mortality risk (HRR 2.01 [95% CIs: 1.50–2.71], $p < 0.0001$, fully adjusted model).

Discussion

In the present observational study, we found that nearly all patients showed at least minor signs of renal insufficiency during hospitalization for acute HF. Using conventional KDOQI renal function grading [14], preserved renal functions (eGFR ≥90 mL/min) had only 5–12% of hospitalized patients (depending on whether we used the lowest or highest eGFR recorded during hospitalization). Obviously, the usual concept of renal function grading is not practical for the decision in this kind of patient. On the other hand, severely decreased renal functions (eGFR <30 mL/min) showed only 8–15% of patients, and among them, ≈3–8% were indeed in the renal failure zone (eGFR <15 mL/min). The problem remains how to clinically assess patients in the "gray zone" in the moderate decrease of eGFR category (30–59 mL/min, grade 3 by KDOQI classification). In the present study, we found that patients with severely decreased renal functions (eGFR <30 mL/min) showed about a 60–70% higher risk of death during the first year

Table 3. Predictors of 5-year all-cause mortality (Cox proportional hazard model)

	Model 1, lowest eGFR value used		Model 2, highest eGFR value used	
	HRR (95% CIs)	*p* value	HRR (95% CIs)	*p* value
Age >65 years	1.79 (1.48–2.17)	<0.0001	1.79 (1.48–2.17)	<0.0001
Male gender	1.21 (1.06–1.39)	0.006	1.20 (1.04–1.37)	0.011
Year of hospitalization[a]	0.98 (0.95–0.99)	0.042	0.98 (0.95–1.00)	0.042
Hospitalization ≥10 days	1.13 (0.99–1.29)	0.071	1.19 (1.04–1.35)	0.012
CAD as primary etiology	1.17 (1.00–1.37)	0.049	1.19 (1.02–1.35)	0.032
Coronary revascularization	1.01 (0.85–1.20)	0.870	1.01 (0.85–1.20)	0.891
History of malignancy	1.49 (1.23–1.81)	<0.0001	1.49 (1.23–1.81)	<0.001
Atrial fibrillation or flutter	0.96 (0.84–1.09)	0.509	0.95 (0.83–1.09)	0.475
Ejection fraction category[b]	1.04 (1.00–1.08)	0.087	1.04 (0.85–1.08]	0.089
Current or ex-smoking	1.01 (0.85–1.21)	0.881	1.02 (0.85–1.22)	0.817
Hypertension	1.20 (0.92–1.57)	0.174	1.22 (0.94–1.59)	0.137
LDL ≥1.8 mmol/L	0.86 (0.75–0.98)	0.029	0.86 (0.75–0.98)	0.027
Diabetes mellitus	1.07 (0.93–1.24)	0.361	1.10 (0.95–1.23)	0.218
BNP ≥10 times ULN	1.35 (1.18–1.55)	<0.0001	1.38 (1.20–1.58)	<0.0001
Antiplatelets or anticoagulants	1.07 (0.91–1.27)	0.412	1.07 (0.90–1.26)	0.465
Furosemide[c]	1.16 (1.09–1.24)	<0.0001	1.17 (1.10–1.25)	<0.0001
Beta-blockers[c]	0.88 (0.76–1.02)	0.086	0.87 (0.75–1.01)	0.066
RAS blockers[c]	0.87 (0.82–0.92)	<0.0001	0.87 (0.81–0.92)	<0.0001
Mineralocorticoid receptor antagonists[c]	0.98 (0.93–1.04)	0.575	0.98 (0.93–1.04)	0.542
Statins[c]	0.92 (0.87–0.98)	0.010	0.92 (0.84–0.98)	0.008
ICD	0.53 (0.39–0.71)	<0.0001	0.52 (0.39–0.71)	<0.0001
eGFR category[d]	1.19 (1.10–1.29)	<0.0001	1.13 (1.04–1.23)	0.003

HRR, hazard risk ratio; CIs, confidence intervals; ULN, upper limit of normal; ICD, implanted cardioverter-defibrillator. [a]2010, 2011 up to 2019. [b]≤40%, 41–50% or ≥51%. [c]Stratified by dose; see Methods for definitions. [d]Grades 1–5 by KDQI; for definitions of all other variables, see Methods or Table 1.

or up to 5 years of follow-up than those with eGFR ≥60 mL/min. However, patients with moderate renal insufficiency (eGFR 30–59 mL/min) showed only marginally higher mortality risk (5–11%) and statically significant only for 5-year mortality as outcomes. We have the opportunity to compare this study sample with another, very similarly designed study on patients hospitalized for acute MI [16]. In this cohort, post-MI patients with eGFR during hospitalization in the range 30–59 mL/min showed more than twofold higher 5-year mortality risk, while patients with eGFR <30 mL/min showed more than 6 times higher risk (compared to eGFR ≥60 mL/min); so, the relative impact of renal insufficiency was apparently higher in these different cardiovascular patients. The reason for the relatively small additive effect of renal insufficiency on patient mortality in our cohort may be the rather extensive adjustment we made in our analysis. A large meta-analysis by Damman et al. [1] on about 1.1 million subjects with HF showed that the unadjusted HRR associated with renal impairment (defined as eGFR <60 mL/min) was 2.28 (95% CIs: 2.10–2.47), while only 1.59 (95% CIs: 1.49–1.69) after fundamental adjustment (i.e., not so far from our results). However, the main reason is probably that our study sample (and generally all overt HF subjects) carries a very high mortality risk (≈14% of our patients died per year). Therefore, the role of any moderately strong additive factor might be potentially "dissolved" in this background risk.

A substantial number of patients (up to 40%) showed fluctuations across eGFR categories during hospitalization. It is questionable how to interpret it concerning the grading of renal functions (and attributable mortality risk, too). We assessed the renal function in two ways, based on the highest and lowest detected eGFR value. Observed mortality risk attributable to renal insufficiency was virtually similar by both these methods. The only exception was grade 1 patients, who showed a slightly more favorable survival curve when we used the highest eGFR for the decision (Fig. 1). On the other hand, using the lowest eGFR value understandably identifies more exposed patients (71.4 vs. 51.2%).

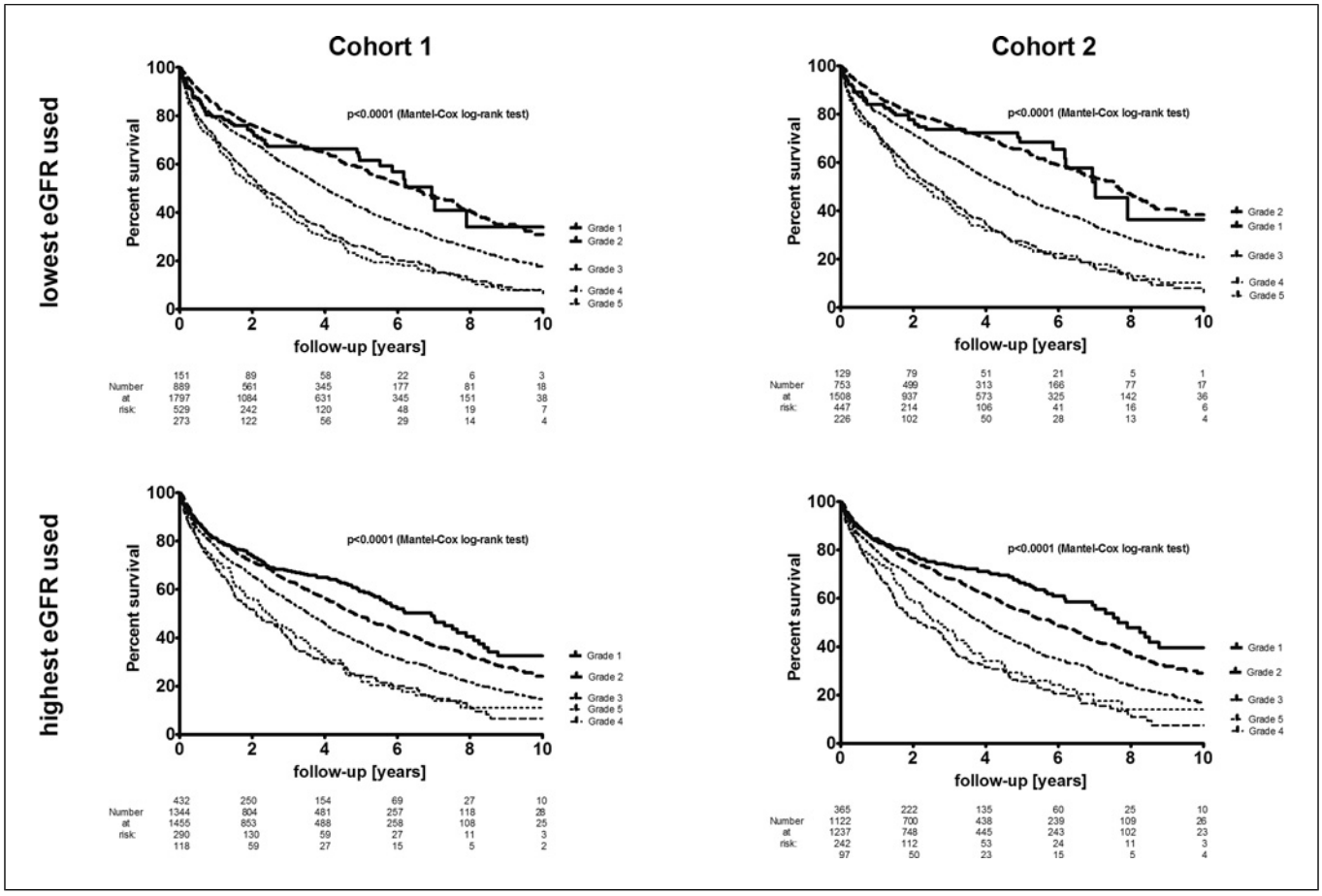

Fig. 2. Kaplan-Meier survival curves according to renal functions (grades 1–5 by KDOQI classification). Cohort 1: all subjects; cohort 2: patients with malignancy either in medical history or as a declared cause of death plus those with the external cause of death excluded.

Therefore, if the predictive value of both approaches (the highest vs. the lowest eGFR value) is roughly the same, it is probably more correct to use the lowest (worst) detected value for deciding on the actual staging of renal insufficiency.

Indeed, the remaining problem is the prognostic impact and clinical interpretation of these only transient WRFs and the inconsistency of the definitions used [17]. In our subjects, we observed a considerable rise in 5-year mortality risk (by ≈60%), but only in the patients showing an eGFR decrease to grade 4 or less (<30 mL/min) but not in patients whose eGFR fell only to a grade 3 level (30–59 mL/min). Several studies dealt with the prognostic impact of WRF during hospitalization for HF. Klein et al. [18] reported that every 5 mg/dL increase in blood urea nitrogen leads to ≈8% increase in 60-day mortality. In the study by Metra et al. [19], WRF, defined as a creatinine increase of ≥0.3 mg/dL, was associated not only with a more extended hospital stay but also with ≈a 3.5 times higher risk of 30-day mortality or recurrent HF.

In the present study, we defined the WRF in the maximally simplified way, i.e., if the highest and lowest eGFR values fall into the same KDOQI grade or not (the mutual order of the highest and the lowest eGFR values was not taken into account). The reason for this simplification was that there are several possible trajectory patterns of renal function during HF. For example, Belthuis et al. [20] identified in this context eight different trajectories (bump, dip, sustained decrease or increase, bump followed by a dip, etc.), but without any significant impact in terms of prognosis [20]. We also exploratorily repeated the analysis in such a way that the relative order of the lowest and highest eGFR values was taken into account in the regression models, with virtually similar results.

Table 4. Five-year all-cause mortality risk by the categories of renal functions (partially and fully adjusted)

	Compared groups	Model 1 (lowest eGFR value used)		Model 2 (highest eGFR value used)	
		HRR (95% CIs)	*p* value	HRR (95% CIs)	*p* value
Partially adjusted[a]					
eGFR ≥60 mL/min (A)	–	1	–	1	–
eGFR 30–59 mL/min (B)	B versus A	1.09 (1.08–1.11)	<0.0001	1.27 (1.14–1.41)	<0.0001
eGFR <30 mL/min (C)	C versus A	2.21 (1.92–2.55)	<0.0001	1.91 (1.66–2.20)	<0.0001
eGFR 30–59 mL/min (B)	–	1	–	1	–
eGFR <30 mL/min (C)	C versus B	1.69 (1.52–1.88)	<0.0001	1.57 (1.36–1.80)	<0.0001
Fully adjusted[b]					
eGFR ≥60 mL/min (A)	–	1	–	1	–
eGFR 30–59 mL/min (B)	B versus A	1.11 (0.93–1.33)	0.252	1.20 (1.03–1.39)	0.016
eGFR <30 mL/min (C)	C versus A	1.58 (1.28–1.96)	<0.0001	1.42 (1.13–1.77)	0.002
eGFR 30–59 mL/min (B)	–	1	–	1	–
eGFR <30 mL/min (C)	C versus B	1.44 (1.23–1.68)	<0.0001	1.26 (1.02–1.55)	0.030

HRR, hazard risk ratio; Cox proportional hazard model; ULN, upper limit of normal; ICD, implanted cardioverter-defibrillator. [a]Adjusted for age ≥65 years and gender. [b]Adjusted for age ≥65 years, gender, year of hospitalization, hospitalization ≥10 days, CAD as primary etiology, history of malignancy, ejection fraction category, current or ex-smoking, LDL ≥1.8 mmol/L, BNP ≥10 times ULN, dose strata of furosemide, β-blockers, RAS blockers or statins, as well as ICD.

Table 5. Five-year all-cause mortality risk associated with either transient or permanent decline of renal functions (partially and fully adjusted models)

	Compared groups	HRR (95% CIs)	*p* value
Partially adjusted[a]			
eGFR ≥60 mL/min (a)	–	1	–
eGFR 30–59 mL/min transiently (b)	b versus a	1.41 (1.21–1.64)	<0.0001
eGFR 30–59 mL/min permanently (c)	c versus a	1.39 (1.21–1.60)	<0.0001
eGFR <30 mL/min transiently (d)	d versus a	2.19 (1.85–2.61)	<0.0001
eGFR <30 mL/min permanently (e)	e versus a	2.25 (1.91–2.66)	<0.0001
eGFR 30–59 mL/min transiently (b)	–	1	–
eGFR 30–59 mL/min permanently (c)	c versus b	0.96 (0.84–1.10)	0.537
eGFR <30 mL/min transiently (d)	–	1	–
eGFR <30 mL/min permanently (e)	d versus e	1.06 (0.90–1.27)	0.440
Fully adjusted[b]			
eGFR ≥60 mL/min (a)	–	1	–
eGFR 30–59 mL/min transiently (b)	b versus a	1.06 (0.86–1.31)	0.578
eGFR 30–59 mL/min permanently (c)	c versus a	1.13 (0.92–1.39)	0.238
eGFR <30 mL/min transiently (d)	d versus a	1.62 (1.26–2.08)	<0.0001
eGFR <30 mL/min permanently (e)	e versus a	1.46 (1.12–1.91)	0.006
eGFR 30–59 mL/min transiently (b)	–	1	–
eGFR 30–59 mL/min permanently (c)	c versus b	1.05 (0.86–1.28)	0.625
eGFR <30 mL/min transiently (d)	–	1	–
eGFR <30 mL/min permanently (e)	d versus e	1.08 (0.84–1.38)	0.550

HRR, hazard risk ratio; Cox proportional hazard model; ULN, upper limit of normal; ICD, implanted cardioverter-defibrillator. [a]Adjusted for age ≥65 years and gender. [b]Adjusted for age ≥65 years, gender, year of hospitalization, hospitalization ≥10 days, CAD as primary etiology, history of malignancy, ejection fraction category, current or ex-smoking, LDL ≥1.8 mmol/L, BNP ≥10 times ULN, dose strata of furosemide, RAS blockers or statins, as well as ICD.

The modest impact of WRF observed in the present study contrasted again with post-MI patients in our other study, where even a transient decline to grade 3 was already associated with a more than twofold higher risk, while the transient decline to grade 4 or less to ≈6 times higher risk of death within 5 years [16]. A possible explanation is the specificity of patients with acute HF. A slight decrease in eGFR does not always mean the "true" WRF, but, for example, followed by rapid decongestion by diuretic treatment. A possibility to verify "true" renal functions improved urinary biomarkers, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and cystatin C [21, 22]. Sokolski et al. [23] serially assessed these urinary biomarkers in 132 hospitalized acute HF patients. They reported that only about half of the subjects with an eGFR decrease >25% were the "true" WRF and not only the "pseudo"-WRF (10 vs. 11%). The study by Shirakabe et al. [24] on 281 patients hospitalized for acute HF compared the mortality among "true" and "pseudo"-WRF; the "true/pseudo"-status of WRF again correlated with the above-mentioned urinary biomarkers. Only "true WRF" patients showed significantly increased mortality risk (more than four times), while the survival in the "pseudo-WRF" was only marginally lower than in non-WRF patients [24].

We also exploratorily repeated the regression models in Table 5 but using the individual decrease of eGFR (a difference between the highest and the lowest values). The eGFR decrease by 25% or more (one of the alternative definitions of WRF [17]) was associated with significantly higher 5-year mortality (HRR 1.27 [95% CIs: 1.5–1.54], p = 0.013). In contrast, fluctuation of eGFR by 10–24.9% followed only non-significantly increased mortality risk. We may speculate that at least part of eGFR fluctuation lower than 25% can be attributed to rapid decongestion by diuretics as the initial treatment of HF. In the study by Testani et al. [10], about a 14% decrease in eGFR was observed during hospitalization, followed by an improvement in 6-month mortality. Indeed, the majority of patients in our sample (85%) with individual eGFR decrease ≥25% fell into our category "decrease to grade 4 or less" (and the predictive potential of our straightforward method used in the present study was higher). In the same way, we compared the exploratory mortality risk associated with the first versus the last eGFR and with the first versus the highest eGFR value observed during hospitalization, with confirmatory results again. Therefore, if we have several eGFR values available during hospitalization for worsening of HF, we can only consider a fairly reliable clinical indicator of increased mortality risk associated with renal insufficiency if at least one of the values falls below 30 mL/min.

A substantial part of our patients had a history of malignancy (≈11%) or died from it (6.5%); the history of malignancy was the 2nd most potent predictor of 5-year mortality. The relationship between malignancy and HF is again bidirectional in terms of mortality risk. A patient with malignancy often dies from HF (for example, due to cardiotoxicity of oncologic treatment) [25], but vice versa, HF patients showed an increased risk of incident malignancy [26]. To exclude potential bias regarding mortality risk, we repeated all analyses, excluding patients with malignancy either in medical history or as the declared cause of death (cohort 2). For similar reasons, we excluded patients who died from external causes from this cohort. Both survival characteristics by renal function categories (Fig. 1) and all multivariate models were very similar to those realized on the whole sample (i.e., cohort 1)

Study Limitations

Our study has many limitations, mainly because virtually all the data used are exclusively from the period of hospitalization. The study sample consisted of relatively advanced HF patients, which is indicated by the mere fact that these patients need to be hospitalized for acute decompensation.

We registered all our data from the first hospitalization during 2010–2020, and we have a 10-year "look-back" (2000–2009) available regarding the previous hospitalization for HF. Thus, most cases probably represent the first HF event requiring hospitalization. On the other hand, we do not know precisely the duration of HF (which is also an essential prognostic indicator). We have no data about HF hospitalization before 2000 or individual cases of worsening HF addressed only in the outpatient setting.

The data regarding pharmacotherapy represent only one that was recommended at discharge from hospitalization. Therefore, we do not know the actual compliance and to what extent the treatment was further adjusted in outpatient care. We also do not have reliable data regarding the dose of furosemide used during hospitalization as part of the initial management of acute HF and, in particular, how it affected the trajectory of eGFR during hospitalization. Similarly, we have no information on the patient's functional status (NYHA classification) and other clinical circumstances at admission to the hospital or during follow-up. As mentioned above, our analysis also did not take into account the trajectory of renal functions during hospitalization (mutual sequence of the lowest and highest values) and its relation to patient prognosis (for the sake of maximum simplification).

Finally, due to newly adopted GDPR rules, obtaining data from the National Register of Hospitalizations is no longer possible. Therefore, we could not analyze the incidence of rehospitalization for HF or other non-fatal outcomes.

Conclusions

Most patients hospitalized for HF showed at least a mild degree of renal insufficiency. After full adjustment for potential covariates, we found a significantly increased long-term risk associated only with severe renal insufficiency (<30 mL/mL). A fluctuation of eGFR across renal function categories was often seen, but the mortality impact was evident only if at least one of the eGFR values detected during hospitalization fell below 30 mL/min. In contrast, we believe that the drop into the range of moderate renal insufficiency (eGFR 30–59 mL/min) will be, in many cases, somewhat secondary and with little importance in terms of prognosis. On the other hand, we cannot exclude that the transient decrease of eGFR during hospitalization signals future renal insufficiency, and it would certainly be interesting to know the trajectory of the renal functions of HF patients after discharge from hospitalization, mainly after they have fully stabilized. In every case, for immediate clinical decision-making, it is probably more appropriate to use the lowest seen eGFR value.

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Statement of Ethics

The Ethical Committee of the University Hospital in Pilsen approved the study protocol (on 6FEB2020). All procedures performed in the study were realized concerning the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. All subjects signed a written informed consent at admission to the hospital (used as the baseline of our follow-up analysis). The data were stored and evaluated under the provisions of the GDPR direction of the European Committee.

Conflict of Interest Statement

There are no conflicts of interest to disclose.

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Author Contributions

O.M. participated in the conception and design of the study, data collection, analysis, interpretation of data, and drafting the article; J.B. and S.B. participated in the data collection. J.F. participated in interpreting data and critically revising the article for important intellectual content. The manuscript has been seen and approved by all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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