Anemia and chronic kidney disease are associated with poor outcomes in heart failure patients

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Research article

Anemia and chronic kidney disease are associated with poor outcomes in heart failure patients

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* Corresponding author

Abstract

Background: Chronic kidney disease (CKD) has been linked to higher heart failure (HF) risk. Anemia is a common consequence of CKD, and recent evidence suggests that anemia is a risk factor for HF. The purpose of this study was to examine among patients with HF, the association between CKD, anemia and inhospital mortality and early readmission.

Methods: We performed a retrospective cohort study in two Swiss university hospitals. Subjects were selected based on the presence of ICD-10 HF codes in 1999. We recorded demographic characteristics and risk factors for HF. CKD was defined as a serum creatinine \( \geq 124 \text{ mol/L for women and } \geq 133 \text{ µmol/L for men} \). The main outcome measures were inhospital mortality and thirty-day readmissions.

Results: Among 955 eligible patients hospitalized with heart failure, 23.0% had CKD. Twenty percent and 6.1% of individuals with and without CKD, respectively, died at the hospital \((p < 0.0001)\). Overall, after adjustment for other patient factors, creatinine and hemoglobin were associated with an increased risk of death at the hospital, and hemoglobin was related to early readmission.

Conclusion: Both CKD and anemia are frequent among older patients with heart failure and are predictors of adverse outcomes, independent of other known risk factors for heart failure.

Background

Heart failure (HF) is a common and serious condition that affects more than four million people in the United States [1]. Approximately 400,000 new cases are diagnosed each year, with mortality 6 years after diagnosis of 80% in men and 65% in women [1]. In Europe, the prevalence of symptomatic heart failure in the general population is estimated to range from 0.4% to 2% [2]. In Switzerland, approximately 210,000 people have HF [3]. Chronic kidney disease (CKD) is also a major health problem resulting in considerably increased morbidity, mortality and in high costs [4]. Furthermore, in the last decade, the prevalence of both CKD[5,6], and HF has been rising steadily [7-9]. Anemia is a frequent complica-
tion of chronic kidney disease, primarily due to failure of erythropoietin production to respond to decreased haemoglobin concentration [10,11]. Anemia has also been found to be a risk factor for cardiovascular disease and in particular for HF [12,13]. In a study conducted in one Swiss university hospital the prevalence of anemia among heart failure patients was 15% [13]. Furthermore, several studies have also shown that anemia with the presence of heart failure was a predictor of poor outcome [14-20] and greater hospital expenses [21]. Moreover, two recent studies have shown that anemia associated with CKD were independent risk factors for one year mortality among patients with HF [22,23]. One study included only patients with left ventricular systolic dysfunction [22], whereas patients with left ventricular diastolic dysfunction were also included in the other [23]. Independent associations between both CKD and anemia with increased risk of one-year mortality were found. In both studies, a 1% decrease in hematocrit was associated with a 2.5% increase in the 12 month risk of death.

The purpose of our study was to examine, among patients with HF, the combined association of CKD and anemia on adverse outcomes. To our knowledge, this is the first study using inhospital mortality and early readmission for this purpose.

Methods

Study design

This was a retrospective cohort study of patients having a diagnosis of heart failure hospitalized and discharged between January 1- December 31, 1999 from two Swiss university hospitals. All adult patients with heart failure hospitalized in all wards for any reason were included in the study. Outcome measures of interest were inhospital mortality and 30-day readmissions. Follow-up for each patient began on the date of discharge from the hospital and continued for 30 days.

Population

Using administrative data, we identified all patients hospitalized with a principal or secondary diagnosis of HF (International Classification of Disease, 10th revision:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
<th>Chronic Kidney Disease (%)</th>
<th>Mean (SD) serum creatinine µmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A 411 (43.0)</td>
<td>109 (26.5)</td>
<td>116.4 (56.2)</td>
<td></td>
</tr>
<tr>
<td>Hospital B 544 (57.0)</td>
<td>111 (20.4)**</td>
<td>112.0 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Age (N = 955)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 – 60 years 114 (11.9)</td>
<td>23 (20.2)</td>
<td>111.4 (56.2)</td>
<td></td>
</tr>
<tr>
<td>61 – 70 years 172 (18.0)</td>
<td>33 (19.2)</td>
<td>110.2 (50.7)</td>
<td></td>
</tr>
<tr>
<td>71 – 80 years 282 (29.5)</td>
<td>61 (21.6)</td>
<td>113.2 (56.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 80 years 387 (40.5)</td>
<td>103 (26.6)</td>
<td>116.7 (53.5)</td>
<td></td>
</tr>
<tr>
<td>Sex (N = 954)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male 518 (54.3)</td>
<td>131 (25.3)</td>
<td>120.1 (55.4)</td>
<td></td>
</tr>
<tr>
<td>Female 436 (45.7)</td>
<td>89 (20.4)</td>
<td>106.5 (51.5)**</td>
<td></td>
</tr>
<tr>
<td>Previous history Heart Failure (N = 876)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI (N = 945)</td>
<td>322 (34.1)</td>
<td>119.2 (50.7)**</td>
<td></td>
</tr>
<tr>
<td>COPD, bronchitis, Emphysema (N = 944)</td>
<td>188 (19.9)</td>
<td>107.3 (45.8)**</td>
<td></td>
</tr>
<tr>
<td>Hypertension (N = 950)</td>
<td>37 (19.7)</td>
<td>117.8 (57.7)**</td>
<td></td>
</tr>
<tr>
<td>Diabetes (N = 952)</td>
<td>57 (25.8)</td>
<td>122.3 (58.4)**</td>
<td></td>
</tr>
<tr>
<td>Current smoker (N = 930)</td>
<td>25 (17.7)</td>
<td>104.7 (43.0)**</td>
<td></td>
</tr>
<tr>
<td>Symptoms and findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PND (N = 608)</td>
<td>163 (26.8)</td>
<td>37 (22.7)</td>
<td>114.1 (50.1)</td>
</tr>
<tr>
<td>DOE (N = 849)</td>
<td>672 (79.2)</td>
<td>158 (23.5)</td>
<td>113.8 (50.9)</td>
</tr>
<tr>
<td>Orthopnea (N = 655)</td>
<td>92 (27.9)**</td>
<td>111.1 (56.4)</td>
<td></td>
</tr>
<tr>
<td>Leg edema (N = 791)</td>
<td>117 (26.7)**</td>
<td>118.0 (59.0)**</td>
<td></td>
</tr>
<tr>
<td>Pulmonary rales (N = 815)</td>
<td>124 (24.4)</td>
<td>115.0 (53.9)</td>
<td></td>
</tr>
<tr>
<td>S3 gallop (N = 757)</td>
<td>8 (20.5)</td>
<td>111.4 (32.6)</td>
<td></td>
</tr>
<tr>
<td>JVD (N = 700)</td>
<td>66 (28.0)**</td>
<td>118.2 (62.0)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (N = 797)</td>
<td>54 (24.4)</td>
<td>110.0 (38.9)</td>
<td></td>
</tr>
</tbody>
</table>

Mi: Myocardial Infarction; COPD: Chronic Obstructive Pulmonary Disease; PND: Paroxystal Nocturnal Dyspnea; DOE: Dyspnea On Exertion; JVD: Jugular Vein Distension

* Chronic kidney disease (CKD) was defined as a serum creatinine > = 124 µmol/L for women and > = 133 µmol/L for men

** P value < 0.05
14 g/dL, and (ECG) was recorded. Hemoglobin levels were distributed
atrial fibrillation on the admission electrocardiogram
evidence of elevated jugular vein pressure. The presence of
included pedal edema, pulmonary rales, S3-gallop and
orthopnea. Physical findings abstracted
paroxysmal nocturnal dyspnea, dyspnea on exertion
and diabetes. Clinical information included a history of
pulmonary disease, bronchitis, emphysema, hypertension
heart failure, myocardial infarction, chronic obstructive
age, sex, smoking status, recorded history of previous
hospitalization in one hospital and the scanned medical record was used
record specialists. The entire medical chart was available
in the other. Variables abstracted from the chart included
clinical information included a history of paroxysmal nocturnal dyspnea, dyspnea on exertion (DOE) and orthopnea. Physical findings abstracted
included pedal edema, pulmonary rales, S3-gallop and
evidence of elevated jugular vein pressure. The presence of
atrial fibrillation on the admission electrocardiogram (ECG) was recorded. Hemoglobin levels were distributed
in four groups: <10 g/dL, 10 g/dL to 12 g/dL, 12 g/dL to
14 g/dL, and ≥ 14 g/dL. The final serum creatinine values recorded during the hospitalization were also considered.
Chronic kidney disease (CKD) was defined as a serum creatinine ≥ 124 μmol/L for women and ≥ 133 μmol/L for
men. We choose these ranges because they were used pre-
viously in an US study, in order to be able to do comparisons of CKD prevalence between countries [23]. We did not calculate creatinine clearance because, in many
patients, the information available in our data set did not allow us to calculate it. A random replicate sample of 100
charts was abstracted to assess inter-rater reliability. The Kappa estimate was 0.91 for the determination of the ventricular function (VF) and 1.0 for inhospital mortality.

Information on inhospital mortality and readmission
within 30 days was gathered using administrative data
provided by the hospitals. We assessed all cause readmis-
son and included only patients from the index hospital. Because these hospitals are university referral centers, each for a different area, we assumed that only few patients
could have been readmitted to a different hospital. Indeed, for one provider, we could assess that none of the
patients were readmitted to another Swiss hospital using a unique identifier from the Swiss Federal Statistical
Office.

The determination of the left ventricular function was based on the chart by the presence of a value for a previ-
ously measured ejection fraction on echocardiography,
cardiac catheterization, radionuclide ventriculography or
by a narrative statement in the chart. Patients with left
ventricular systolic dysfunction (LVSD) were identified by
looking in medical charts for a current (from the index
hospitalization) or previous ejection fraction (EF) equal
or less than 40%. If no information regarding the EF was
found, we searched for a narrative description in the chart.
Specifically, the following terms were associated to LVSD:
"systolic dysfunction," "dilated cardiomyopathy," "con-
gestive cardiomyopathy," "diffuse global hypokinesis" or
"systolic-diastolic dysfunction" (patients reported to have
both systolic and diastolic dysfunction by cardiologists).
Further, angiotensin converting enzyme inhibitor (ACEI)
were identified in the medical charts through generic or
trade name, including benazapril, captopril, enalapril,
fosinopril, lisinopril, quinapril, ramipril, perindopril and
cilazapril.

The Charlson co-morbidity index, a weighted average of
selected co-morbidities, was computed at index hospitali-
ization for each patient as a measure of severity of illness
measure using the Deyo modification [24].

Statistical analysis

Bivariate analyses of the dependent and the primary expo-
sure variables were conducted. We also calculated the
crude risk ratio and 95% confidence intervals for inhospi-
tality mortality and 30-day readmission. We used chi-square
tests, Fisher’s exact tests, Student T-tests or ANOVA meth-
ods when appropriate. Dichotomous outcome variables
were inhospital mortality and readmission within 30
days. Primary exposure variables were hemoglobin and
creatinine levels. Other variables, potential confounding
factors, included in the bivariate analysis were: hospital,
age, sex, history of heart failure, diabetes mellitus, hyper-
tension, prior myocardial infarction, chronic obstructive
pulmonary disease, smoking, symptoms and findings at
admission (paroxysmal nocturnal dyspnea, dyspnea on
exertion, orthopnea, leg edema, pulmonary rales, jugu-
lar vein distension, S3-gallop), atrial fibrillation, left ven-
tricular function, ejection fraction, ACEI prescription at
discharge, Charlson co-morbidity index, as well as inhos-
pital length of stay.

We then performed multivariate analyses using logistic
regression to adjust for potential confounding factors. Logistic regression was used to calculate adjusted odds
ratio with associated 95% confidence intervals. Covariates
were initially selected using a priori considerations as well
as strength of association and statistical significance in
bivariate analyses. We included the variable "Left ven-
tricular function" in the starting model in order to control
for the heterogeneity of the study population between diastolic and systolic HF. We first looked if interaction between hemoglobin and creatinine was significant. After defining the starting model as above, we assessed, by backward elimination, which confounding factors should remain in the model. We first looked to see if the least significant variable was a confounding factor by dropping it and refitting the model. We then assessed if the odds ratio changed by more than 10% compared to odds ratio of the starting model. If the odds ratios changed by more than 10%, the variable was considered as a potential confounding factor and remained in what became the final model. If a variable did not meet these criteria, it was removed from the model and the same procedures were reapplied until the best final model was found. Fit of the models was assessed using the Hosmer-Lemeshow goodness of fit test. For all models, we checked for any potential collinearity problems between the variables. All analyses were implemented with the SAS software, version 8.02 (SAS Institute Inc. Cary, NC, USA).

### Results

#### Baseline characteristics

Our sample included 955 eligible patients with HF available for analysis. Among those 411 (43.0%) were admitted to hospital A and 544 (57.0%) in hospital B. The mean (SD) age was 75.4 years (12.8), 45.7% were female. A history of HF was present in 58.7% of the patients. A history of myocardial infarction was reported for 34.1%, hypertension for 60.7%, diabetes for 23.2%, and COPD or bronchitis or emphysema for 19.9%. At discharge, anticoagulants were prescribed in 28.7% of the patients, beta-blockers in 12.8%, calcium blockers in 13.3%, digoxin in 32.2%, diuretics in 59.9%, nitrates in 30.3%, angiotensin receptor blockers in 8.1% and spironolactone in 11.1%.

In our sample, based on a value of left ventricular ejection fraction or a narrative statement, 28.9% had their left ventricular function not determined, 28.0% had a left ventricular systolic dysfunction (LVSD), and 43.1% a left ventricular diastolic dysfunction.
ing previous or current value of left ventricular ejection fraction was found in 46.7% of the patient’s charts. The mean (SD) ejection fraction was 36.0% (15.0%) with a 25th to 75th intraquartile range from 25 to 45%. An ACEI was prescribed at discharge in 61.2% of the patients. The mean (SD) Charlson comorbidity index was 2.2 (1.4). The median length of stay was 10 days, with a 25th to 75th intraquartile range from 6 to 17 days.

Prevalence of CKD
The mean (SD) value of the last serum creatinine value reported during the hospitalization was 113.9 (54.0) µmol/L, with a range from 32 to 545 µmol/L and a 25th to 75th intraquartile range from 84 to 126 µmol/L. Chronic kidney disease was defined as a serum creatinine ≥124 µmol/L in women and ≥133 µmol/L in men. Men (25.3%) were more likely than women (20.4%) to have CKD. In total, 220 (23.0%) patients of the entire cohort had CKD. The mean serum creatinine value was statistically significantly higher in patients with a history of myocardial infarction, hypertension, diabetes or leg edema (Table 1). Higher creatinine values were also observed in patients with a Charlson comorbidity index larger than 2 (Table 2).

Prevalence of anemia
Hemoglobin level was recorded for 920 members (96%) of the cohort. The mean (SD) hemoglobin was 13.0 g/dL (2.2) with a 25th to 75th intraquartile range from 11.8 g/dL to 14.6 g/dL. On admission, an hemoglobin of ≥14 g/dL was found in 36.1% of the patients, 36.3% had an hemoglobin between 12 g/dL and 14 g/dL, 19.6% between 10 g/dL and 12 g/dL, and 8% ≤10 g/dL.

The proportion of patients with CKD was associated with increasing anemia (Table 3). The mean serum creatinine was increasing with severity of anemia (Table 3) from 102.0 µmol/L among patients with no anemia, up to 141.0 µmol/L for severe anemia (p < 0.0001). Patients with severe anemia were more likely not to be discharged with ACEI. (Table 3).

Mortality and readmission
Eighty-nine (9.3%) patients died during their hospitalization, 20% among those with CKD and 6.1% among those without CKD (p < 0.0001). Among patients who died in the hospital, 49.4% had CKD, and their mean (SD) serum creatinine value was 159.3 µmol/L (106.1) (p < 0.0001).

Anemia on admission to the hospital was associated with increased risk of death. In-hospital mortality was 5.4% for patients with a hemoglobin of ≥14 g/dL, 9.3% for a hemoglobin between 12 g/dL and 14 g/dL, 10.0% for a hemoglobin between 10 g/dL and 12 g/dL, and 18.9% for a hemoglobin < 10 g/dL (p = 0.002) (Table 3). In-hospital mortality rates were also higher in patients with COPD (Table 4) and in patients with a Charlson comorbidity index over 2. Individuals with left ventricular diastolic and systolic dysfunction, as well as those with undetermined ventricular function, had comparable risk of hospital death (Table 5).

## Table 3: Hospital Characteristics in Patients with Heart Failure According to Hemoglobin Level, N = 955

<table>
<thead>
<tr>
<th>Hemoglobin in g/dL</th>
<th>&lt;10 N (%) or Mean (SD)</th>
<th>10–12 N (%) or Mean (SD)</th>
<th>12–14 N (%) or Mean (SD)</th>
<th>≥14 N (%) or Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) (N = 920)</td>
<td>74 (8.0)</td>
<td>180 (19.6)</td>
<td>334 (36.3)</td>
<td>332 (36.1)</td>
</tr>
<tr>
<td>CKD (N = 920)*</td>
<td>28 (37.8)</td>
<td>61 (33.9)</td>
<td>78 (23.4)</td>
<td>48 (14.5)</td>
</tr>
<tr>
<td>Mean (SD) serum creatinine (N = 920)* (µmol/L)</td>
<td>141.0 (91.0)</td>
<td>131.6 (76.5)</td>
<td>110.3 (42.5)</td>
<td>102.0 (30.7)</td>
</tr>
<tr>
<td>Left ventricular function (N = 920)*</td>
<td>19 (25.7)</td>
<td>70 (38.9)</td>
<td>136 (40.7)</td>
<td>171 (51.5)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>29 (39.2)</td>
<td>58 (32.2)</td>
<td>89 (26.7)</td>
<td>80 (24.1)</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>26 (35.1)</td>
<td>52 (28.9)</td>
<td>109 (32.6)</td>
<td>81 (24.4)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>41.8 (14.7)</td>
<td>39.7 (14.7)</td>
<td>35.9 (15.5)</td>
<td>34.1 (14.3)</td>
</tr>
<tr>
<td>Mean (SD) ejection fraction in % (N = 429)*</td>
<td>31 (45.6)</td>
<td>108 (63.2)</td>
<td>196 (63.2)</td>
<td>193 (63.2)</td>
</tr>
<tr>
<td>Discharged with ACEI (N = 854)*</td>
<td>27 (6.7)</td>
<td>72 (17.7)</td>
<td>153 (37.7)</td>
<td>154 (37.9)</td>
</tr>
<tr>
<td>Hospital A (N = 406)</td>
<td>47 (9.1)</td>
<td>108 (21.0)</td>
<td>181 (35.2)</td>
<td>178 (34.6)</td>
</tr>
<tr>
<td>Hospital B (N = 514)</td>
<td>14 (18.9)</td>
<td>18 (10.0)</td>
<td>31 (9.3)</td>
<td>18 (5.4)</td>
</tr>
<tr>
<td>30 days readmissions (N = 839)</td>
<td>8 (13.3)</td>
<td>29 (17.9)</td>
<td>38 (12.5)</td>
<td>36 (11.5)</td>
</tr>
<tr>
<td>Mean (SD) length of stay (days) (N = 920)*</td>
<td>18.8 (21.3)</td>
<td>16.8 (16.4)</td>
<td>13.8 (17.0)</td>
<td>12.4 (9.5)</td>
</tr>
</tbody>
</table>

CKD: Chronic Kidney Disease; ACEI: Angiotensin Converting Enzyme Inhibitors
*p value < 0.05
dL, 17.9% for a hemoglobin between 10 g/dL and 12 g/dL and 13.3% for a hemoglobin < 10 g/dL. Patients who were current smokers and with COPD were also more likely to be readmitted (Table 4).

**Multivariate analysis**

Both hemoglobin and serum creatinine were independently associated with poor outcomes after controlling for confounding factors (Table 6). For inhospital mortality, the model controlled for length of stay and COPD. For each g/dL increase in hemoglobin, the inhospital mortality rate declined by 39% (p = 0.0008). For each one µmol/L increase in serum creatinine, inhospital mortality rate decreased by 1% (p = 0.166). Further, the interaction term between hemoglobin and serum creatinine was statistically significant (p = 0.008). At the mean creatinine level, increasing hemoglobin levels were associated with lower mortality (RR = 0.86, for each unit increase in hemoglobin). Effect modification, suggested a weaker association of hemoglobin with mortality as creatinine levels increased. Further, at the mean level hemoglobin, increasing creatinine levels were associated with higher mortality (RR = 1.015, for each unit increase in creatinine).

In the multivariate analysis using 30 days readmission as dependent variable, we controlled for age, COPD and history of heart failure. The interaction term between hemoglobin and serum creatinine was not statistically significant. Results showed that for each one g/dL increase in hemoglobin, readmission rate declined by 13% (p = 0.009). Further, for each one µmol/L increase in serum creatinine, readmission rate increased by 0.08% (p = 0.744).

After controlling for all other risk factors, the odds ratio related to inhospital mortality associated with the presence of anemia defined as hemoglobin less than 12 g/dL, was 1.47 (95% CI 0.89 to 2.42) in all heart failure patients and 4.04 (95% CI 2.46 to 6.66) in patients with additional CKD compared with HF patients who had a hemoglobin level ≥ 12 g/dL and no CKD. Similarly, the odds ratio for early readmissions were 1.60 (95% CI 1.00 to
2.58) for anemia and 1.14 (95% CI 0.67 to 1.93) for CKD. In these models, the interaction terms between anemia and CKD lacked statistical significance.

**Discussion**

In this study, both anemia and chronic kidney disease were highly prevalent among HF patients discharged from two university hospitals and independently associated with an increased risk of dying in the hospital or of being readmitted within 30 days. The association between CKD, anemia and these outcomes (in-hospital mortality and readmission) in HF patients has not been reported previously. Most studies have focused only on survival after hospital discharge as an outcome. One study, in the framework of the SOLVD study, included only patients with left ventricular dysfunction. The risk of increased mortality associated with a 1% reduction in hematocrit was 2.7% [22]. These results were comparable to another study conducted among Medicare beneficiaries in community hospitals in the US. In this latest study, patients with left ventricular diastolic dysfunction were also included as patients with left ventricular systolic dysfunction. The risk of death associated with a 1% reduction in hematocrit was 2% [23]. In a new large recent study, among HF patients, chronic kidney disease and anemia were found independently to confer a two-fold increased risk of death [25]. Silverberg et al. recently reported that, in a randomized trial of 32 ambulatory HF patients with NYHA class III and IV and an hemoglobin < 12 g/dL, the correction of anemia was associated with an improved functional status and decreased hospitalization. However, the major limitation of this study was its small sample size and the fact that the randomization was not blinded [26]. These observations suggest that anemia is a clinically important risk factor for death and readmission among heart failure patients, with or without CKD. The clinical implication of these findings for patients with HF is that failure to correct severe anemia among patients with CKD confers a preventable burden of reduced quality of life, while clinical trials have demonstrated that correction of anemia improved these measures. HF patients should be carefully examined for presence of CKD and anemia and, if present, treated according to current evidence [27]. Treating anemia among inpatients with HF and CKD may then reduce in-hospital mortality and early readmission. However, currently no large clinical trials have been conducted to evaluate the effect of erythropoietin therapy on survival or readmission among patients suffering from HF and CKD.

**Table 5: Hospital Characteristics in Patients with Heart Failure by Outcome Indicators, N = 955**

<table>
<thead>
<tr>
<th>Patients Characteristics</th>
<th>Inhospital mortality N = 955</th>
<th>30 day readmission N = 866</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction in % (N = 446)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 20</td>
<td>77</td>
<td>8 (10.4)</td>
</tr>
<tr>
<td>20–30</td>
<td>128</td>
<td>13 (10.2)</td>
</tr>
<tr>
<td>30–40</td>
<td>108</td>
<td>5 (4.6)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>133</td>
<td>14 (10.5)</td>
</tr>
<tr>
<td>Left ventricular function (N = 955)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>412</td>
<td>35 (8.5)</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>267</td>
<td>24 (9.0)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>276</td>
<td>30 (10.9)</td>
</tr>
<tr>
<td>Discharged with ACEI (N = 836)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Charlson comorbidity index (N = 955)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>398</td>
<td>26 (6.5)</td>
</tr>
<tr>
<td>2</td>
<td>216</td>
<td>20 (9.3)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>341</td>
<td>43 (12.6)*</td>
</tr>
<tr>
<td>Length of stay (days) (N = 955)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>247</td>
<td>32 (13.0)</td>
</tr>
<tr>
<td>7–12</td>
<td>321</td>
<td>17 (5.3)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>387</td>
<td>40 (10.3)*</td>
</tr>
</tbody>
</table>

ACEI: Angiotensin Converting Enzyme Inhibitor; CHF: Congestive Heart Failure; NA: not applicable because relates only to patients discharged alive.

*p value < 0.05
In our study we found that, among HF patients, the prevalence of CKD was 25% among males and 20% among females respectively. However, by using this cut-point of a serum creatinine of ≥124 µmol/L for women and ≥133 µmol/L for men for defining CKD, we underestimated the true prevalence of CKD especially among elderly people. We choose these cut-points based on previous studies implemented in the USA [23]. Reduced kidney function occurred frequently in patients with HF. Two studies have shown that creatinine clearance less than 60 ml/minute was present in 20 to 50% of HF patients [28,29]. In another study, which included Medicare beneficiaries with heart failure hospitalized in community hospitals, 38% had CKD. In this cohort, the prevalence of CKD was 33% in females and 46% in males [23]. Our results are similar to those found in these studies and show that CKD is highly prevalent among HF patients.

Interest in the relationship between HF and anemia is growing. Anemia commonly complicates HF (14–28% of patients depending on the cut off used) [30] and is a potential exacerbating factor [31]. In our study the prevalence of anemia (hemoglobin < 12 g/dL) among HF patients was 28%. In another study performed in one Swiss university hospital, the prevalence of anemia was 15% [13]. Silverberg et al. showed that the prevalence of anemia increased with the severity of HF and reached almost 80% in those patients with a NYHA class IV [26]. Anemia observed among individuals with HF is highly multi-factorial, but, a decreased renal function is a cause in numerous patients [32].

Anemic patients with chronic renal failure should receive treatment with recombinant human erythropoietin (r-HuEPO, Ééotin) to maintain hemoglobin levels over 11 g/dL with an acceptable target of 12 to 12.5 g/dL, according to recommendations from the European practice guideline for management of anemia in patients with chronic renal failure [33] and the National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease [27]. Benefits of adequate hemoglobin levels had been established in patients undergoing dialysis, and are supposed to be relevant also in CKD patients. In addition, anemic patients should receive iron supplementation in order to maintain serum ferritin levels above 100 µg/L and transferrin saturation above 20%.

This study had a number of limitations. It is an observational study based on information available in medical records. The chart abstraction process was implemented in each hospital by different persons with different education and backgrounds, although with similar training. Then, in one hospital the entire medical chart was available to the abstractors, whereas in the other only the electronic discharge letter, laboratory findings and reports from cardiology testing were available. In addition, the quality of medical records and completeness of information may also vary between centers. Incorrect information may have led to some misclassification bias. Further this study was conducted on an opportunity sample of two hospitals, making the generalisibility of results uncertain. Then, we excluded patients with valvular heart disease and acute myocardial infarction, because it was our intent to focus on a homogenous group of individuals with established heart failure. However, we agree that the issue of anemia and outcomes in both of these patient groups is important. Further, we were not able to exclude other causes of anemia, including the presence of iron, folate and vitamin B12 deficiencies, dilutional anemia, and the anemia of chronic diseases different from CKD, as explanations for anemia observed in this population and perhaps, to account for some potential confounders. Then,

### Table 6: Results of the Logistic Regression Models, N = 910

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin in g/dL</td>
<td>-0.3898</td>
<td>0.1159</td>
</tr>
<tr>
<td>Serum creatinine in µmol/L</td>
<td>-0.0122</td>
<td>0.0088</td>
</tr>
<tr>
<td>Hemoglobin in g/dL × Serum creatinine in µmol/L</td>
<td>0.0021</td>
<td>0.0008</td>
</tr>
<tr>
<td>Length of stay</td>
<td>0.0063</td>
<td>0.0060</td>
</tr>
<tr>
<td>COPD</td>
<td>0.8079</td>
<td>0.2846</td>
</tr>
</tbody>
</table>

### Model for 30 Day Readmission, N = 767

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin in g/dL</td>
<td>-0.1300</td>
<td>0.0499</td>
</tr>
<tr>
<td>Serum creatinine in µmol/L</td>
<td>-0.0008</td>
<td>0.0026</td>
</tr>
<tr>
<td>Hemoglobin in g/dL × Serum creatinine in µmol/L</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0129</td>
<td>0.0079</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>-0.4308</td>
<td>0.2187</td>
</tr>
<tr>
<td>COPD</td>
<td>0.6666</td>
<td>0.2536</td>
</tr>
</tbody>
</table>

COPD: Chronic Obstructive Pulmonary Disease; NA: not applicable because not statistically significant and therefore not in the final best model.
given the relative high number of elderly patients in the study population and that these patients may have CKD even with normal creatinine value; we underestimated the true prevalence of CKD. Finally, we acknowledge that we were not able to measure others risk factors associated with epo-resistance such as immune activation. We will consider measuring it in future studies. However, we would like to emphasize that the concerns about ACEI and anemia should not keep physicians from using ACE inhibitors in their management of heart failure.

Conclusion
In conclusion, we found further evidence that the com- plement presence of either CKD or anemia increased the risk of dying in the hospital or of being readmitted within 30 days among patients hospitalized with heart failure. The association persisted after controlling for other factors associated with adverse outcomes in these patients.

Competing interests
This study was supported by a grant from the coalition of the five Swiss University Hospitals and grants from the Fonds du 450ème anniversaire de l’Université et la Fondation Moffat. It was also sponsored by MSD Switzerland and Roche Switzerland. These sponsors were however not involved in the analysis of the results neither in writing nor in correcting the manuscript.

Authors’ contributions
JCL participated in the conception and design of the study, acquisition of data, analysis and interpretation of data, as well as drafting the manuscript. WDF participated in the design of the study, supervised the statistical analysis, and revised critically the article. MB and BB participated in the conception and design of the study, interpretation of data and revised critically the manuscript. WMM conceived of the study, participated in its design, interpretation of data and revised critically the article. All authors read and approved the final manuscript.

References

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