

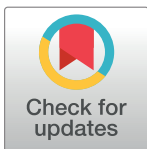
RESEARCH ARTICLE

Renal function and anemia in relation to short- and long-term prognosis of patients with acute heart failure in the period 1985–2008: A clinical cohort study

Jan C. van den Berge*, Alina A. Constantinescu, Ron T. van Domburg, Milos Brankovic, Jaap W. Deckers, K. Martijn Akkerhuis

Department of Cardiology, Thoraxcenter, Erasmus MC Rotterdam, the Netherlands

* j.vandenberge@erasmusmc.nl



Abstract

Background

Renal dysfunction and anaemia are common in patients with acute heart failure (HF). It is not known whether their combined presence has additive prognostic value. We investigated their prognostic value separately and in combination, on prognosis in acute HF patients. Furthermore, we examined whether the improvement in prognosis was comparable between patients with and without renal dysfunction.

Methods and results

This prospective registry includes 1783 patients admitted to the (Intensive) Coronary Care Unit for acute HF in the period of 1985–2008. The outcome measure was the composite of all-cause mortality, heart transplantation and left ventricular assist device implantation. In patients without renal dysfunction, anemia was associated with worse 30-day outcome (HR 2.91; [95% CI 1.69–5.00]), but not with 10-year outcome (HR 1.13 [95% CI 0.93–1.37]). On the contrary, anemia was found to influence prognosis in patients with renal dysfunction, both at 30 days (HR 1.93 [95% CI 1.33–2.80]) and at 10 years (HR 1.27 [95% CI 1.10–1.47]). Over time, the 10-year survival rate improved in patients with preserved renal function (HR 0.73 [95% CI 0.55–0.97]), but not in patients with renal dysfunction.

Conclusion

The long-term prognosis of acute HF patients with a preserved renal function was found to have improved significantly. However, the prognosis of patients with renal dysfunction did not change. Anemia was a strong prognosticator for short-term outcome in all patients. In patients with renal dysfunction, anemia was also associated with impaired long-term prognosis.

OPEN ACCESS

Citation: van den Berge JC, Constantinescu AA, van Domburg RT, Brankovic M, Deckers JW, Akkerhuis KM (2018) Renal function and anemia in relation to short- and long-term prognosis of patients with acute heart failure in the period 1985–2008: A clinical cohort study. *PLoS ONE* 13(8): e0201714. <https://doi.org/10.1371/journal.pone.0201714>

Editor: Vincenzo Lionetti, Scuola Superiore Sant'Anna, ITALY

Received: March 2, 2018

Accepted: July 21, 2018

Published: August 7, 2018

Copyright: © 2018 van den Berge et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Acute heart failure (HF) is commonly accompanied by various non-cardiovascular comorbidities. Renal dysfunction is among one of the most common although its exact prevalence has varied between studies.[1, 2] Renal dysfunction in acute HF is associated with various adverse outcomes: longer hospital stay, higher re-hospitalization rate, and higher mortality.[1, 2] Of note, the follow-up period in most of these studies is restricted to only 1 year after the initial hospitalization.

In the last decades, an improvement in long-term outcome has been observed among patients with acute HF in several cohorts.[3–5] New therapeutic options and an increased understanding of the pathophysiology of HF are most likely responsible for this trend. Importantly, renal dysfunction is a (relative) contra-indication for some of the new therapeutic modalities[6]. As of yet, it has not been established whether the improvement in prognosis over time of patients with acute HF is modified by the presence of renal dysfunction.

Anemia is another important and common comorbidity in patients with acute HF, with a prevalence up to almost 60%.[7–12] There is conflicting data regarding the prognostic impact of anemia in patients with acute HF.[10–13] Moreover, the combination of HF, renal dysfunction and anemia carries an incremental negative prognostic impact in patients with *chronic* HF.[14] However, the additive prognostic value of anemia in patients with *acute* HF with and without renal dysfunction remains scarce.

Therefore, the aims of the present study were (1) to examine the impact of renal function on short- and long-term prognosis of patients with acute HF, (2) to determine whether the improvement in prognosis of patients with acute HF and renal impairment was comparable to that of patients with normal renal function, and (3) to study the impact of anemia, alone or in combination with renal dysfunction, on prognosis of patients with acute HF.

Materials and methods

Patients

This prospective registry was carried out among patients who were admitted with acute HF at the Intensive Coronary Care Unit (ICCU) in our hospital during the period from 1985 until 2008. The study design and inclusion have been described previously.[5] Briefly, consecutive patients aged 18 years and older were included when they were diagnosed with acute HF or cardiogenic shock at admission. Both patients with de novo HF and patients with worsening symptoms of chronic HF were included. Patients could only contribute once to the database, and if patients were admitted more than once with acute HF during the inclusion period, only the first admission was included for analyses.

This was a prospective cohort registry. For analyses, we used completely anonymized data. During the enrolment of the patients, approval from the research ethics committee of the Erasmus MC to conduct this study was not required. At a later stage, the committee confirmed that we did not need their approval to conduct this study. Furthermore, there was no requirement for patients' informed consent. The study was conducted according to the Declaration of Helsinki.[15]

Endpoints

The outcome measure was the composite of all-cause mortality, heart transplantation and left ventricular assist device (LVAD) implantation at 30 days, 1 year and 10 years after the initial hospitalization.

Survival status was assessed by using the Municipal Civil Registries in January 2017 and was available for 98% of the included patients. To determine whether patients received an LVAD or underwent heart transplantation, we used prospectively collected data from our hospital information system.

Variables and definitions

Baseline variables were derived from patient records and discharge letters. We collected the following variables: age, gender, Body Mass Index (BMI), cardiac history, etiology of HF, left ventricular ejection fraction (LVEF) and treatment at the ICCU. Furthermore, the results of the following laboratory tests were collected: sodium (mmol/L), potassium (mmol/L), creatinine ($\mu\text{mol/L}$), urea (mmol/L) and hemoglobin (mmol/L).

Diabetes mellitus was considered to be present when patients received antidiabetic therapy. The LVEF was classified into the following qualitative categories: good, moderate and poor. If quantitative outcome for the LVEF was used, we applied the following cut-offs: $>45\%$, $30\text{--}44\%$ and $<30\%$ for good, moderate and poor LVEF, respectively.[5] The etiology of HF was categorized into ischemic cause versus non-ischemic cause of HF. For all laboratory tests, the first measured value during hospitalization was taken into account. The estimated glomerular filtration rate (eGFR) was estimated by using the Modification of Diet in Renal Disease (MDRD) equation for serum creatinine ($\mu\text{mol/L}$): $\text{eGFR} = 30849 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) [eGFR in mL/min/1.73 m²].[16] In line with the most recent HF guideline of the European Society of Cardiology,[6] renal function was categorized as follows: preserved renal function: $\text{eGFR} \geq 60$ mL/min/1.73 m²; moderately impaired renal function $\text{eGFR} 30\text{--}59$ mL/min/1.73 m²; severely impaired renal function $\text{eGFR} < 30$ mL/min/1.73 m². We used the definition of the World Health Organization to define anemia: hemoglobin < 7.5 mmol/L in women and < 8.2 mmol/L in men. Hyponatremia was defined as a serum sodium level ≤ 135 mmol/L. For the definition of hypo- and hyperkalemia the following cut-off values were applied: serum potassium < 3.5 mmol/L and > 5.0 mmol/L, respectively.

Statistical analysis

Categorical variables are presented as frequencies and percentages. The χ^2 test and the Fisher-Freeman-Halton exact test were used to compare categorical variables. Normally distributed, continuous data are presented as mean values with standard deviation and were compared using the one-way ANOVA. Continuous data that were not normally distributed are presented as median and interquartile range (IQR). The Mann-Whitney U test or the Kruskal-Wallis H test was used to compare these data.

Since data for LVEF and etiology were incomplete for, respectively, 28% and 12% of the patients, multiple imputation was performed by using baseline characteristics as predictors. Pooled means are given for LVEF and etiology.

The Kaplan-Meier method was used for presenting the cumulative event curves and they were compared using the log-rank test. Secondary analyses were carried out among the 30-day event-free survivors. Logistic regression for 30-day outcome and the Cox proportional hazard method for long-term outcome were applied in order to examine the independent association between renal function and the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation, as well as between anemia and the composite endpoint. Adjustments were made for age, gender, history of HF, diabetes, hypertension, etiology of HF, atrial fibrillation at admission, LVEF, renal function and anemia.

All tests were two-tailed and p-values < 0.05 were considered statistically significant. Results of logistic regression and the Cox proportional hazard model were reported as odds ratios

(ORs) and hazard ratios (HRs), respectively, with their corresponding 95% confidence interval (95% CI). All statistical analyses were carried out using SPSS software (SPSS 21.0, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

In total, 1810 patients were admitted with acute HF in the period 1985–2008. Of these, 1783 (99%) patients had at least one creatinine measurement and they constitute the present study population. Over half of the patients were found to have renal dysfunction, which was severely impaired in 18%. The proportion of patients with severe renal impairment remained stable over time, whereas the number of patients with preserved renal function increased and moderately impaired renal function became less prevalent ($p < 0.001$; Fig 1).

Compared to patients with renal dysfunction, patients with preserved renal function were on average 6 years younger (Table 1). In addition, they less often had prior myocardial infarction and coronary revascularization. With decreasing renal function, the prevalence of prior HF, diabetes and hypertension increased. Hyponatremia was also more common in patients with renal dysfunction, as was anemia.

Regarding therapy, patients with renal impairment were more frequently treated with intubation and mechanical ventilation, mechanical circulatory support and inotropic agents (Table 1). Moreover, the degree of renal impairment was associated with lower in-hospital usage of beta-blockers, ACE-inhibitors and diuretics.

Renal function and outcome

The median survival of patients with a severely impaired, moderately impaired and preserved renal function was 1.0, 2.1 and 4.4 years, respectively. The impact of renal function on outcome is shown in Fig 2 and Table 2. Patients with a severely impaired renal function had the worst prognosis both at short- and long-term. These findings remained unchanged after multivariable adjustment for other prognostic factors. Although the influence of renal function on prognosis became less prominent with longer duration of follow-up, renal function still remained a

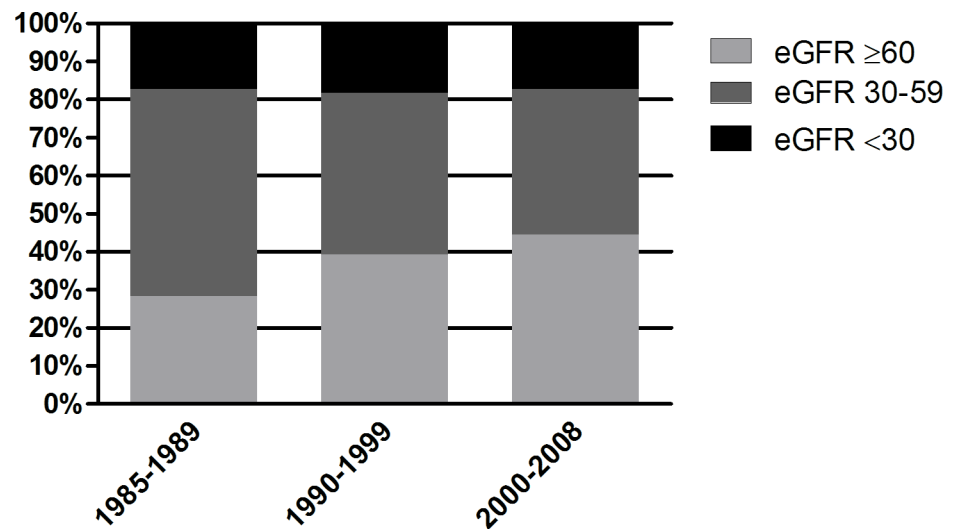


Fig 1. Distribution of the study population according to the renal function and the admission period. eGFR, estimated glomerular filtration rate in mL/min/1.73 m².

<https://doi.org/10.1371/journal.pone.0201714.g001>

Table 1. Baseline characteristics and therapy according to renal function.

| | eGFR ≥60 | eGFR 30–59 | eGFR <30 | p-value* |
|--------------------------------------------|---------------|-----------------|------------------|----------|
| No. of patients | 688 (39%) | 778 (44%) | 317 (18%) | |
| <i>Baseline</i> | | | | |
| Age (mean, y) | 59.7 ± 16.3 | 66.1 ± 13.2 | 65.9 ± 12.9 | <0.001 |
| Male | 458 (67%) | 475 (61%) | 201 (63%) | 0.09 |
| BMI | 25.4 ± 5.2 | 24.9 ± 4.8 | 25.0 ± 4.7 | 0.57 |
| <i>Medical history</i> | | | | |
| Myocardial infarction | 237 (34%) | 347 (45%) | 120 (38%) | <0.001 |
| Coronary revascularization† | 124 (18%) | 187 (24%) | 75 (24%) | 0.01 |
| Heart surgery (not CABG) | 111 (16%) | 87 (11%) | 36 (11%) | 0.01 |
| Heart transplantation | 2 (0.3%) | 1 (0.1%) | 6 (2%) | 0.002 |
| Waiting for heart transplantation | 16 (2.3%) | 11 (1.4%) | 8 (2.5%) | 0.33 |
| Heart failure | 300 (44%) | 390 (50%) | 188 (59%) | <0.001 |
| Rhythm- or conduction disorder | 157 (23%) | 210 (27%) | 73 (23%) | 0.14 |
| Diabetes | 132 (19%) | 168 (22%) | 81 (26%) | 0.07 |
| Hypertension | 194 (28%) | 257 (33%) | 133 (42%) | <0.001 |
| <i>Heart failure</i> | | | | |
| Etiology of heart failure | | | | <0.05 |
| Ischemic origin | 302 (44%) | 392 (50%) | 140 (44%) | |
| Non-ischemic origin | 386 (56%) | 386 (50%) | 177 (56%) | |
| Atrial fibrillation at admission | 159 (23%) | 178 (23%) | 49 (16%) | 0.01 |
| Left ventricular ejection fraction | | | | <0.05 |
| Good | 199 (29%) | 225 (29%) | 91 (29%) | |
| Moderate | 187 (27%) | 156 (20%) | 76 (24%) | |
| Poor | 302 (44%) | 396 (51%) | 149 (47%) | |
| <i>Laboratory values</i> | | | | |
| Sodium | 137 ± 5 | 137 ± 6 | 135 ± 6 | <0.001 |
| Potassium | 4.0 ± 0.6 | 4.2 ± 0.7 | 4.6 ± 0.9 | <0.001 |
| Urea (median, IQR) | 7.2 (5.7–9.3) | 10.6 (8.2–14.4) | 23.5 (17.5–30.8) | <0.001 |
| eGFR (median, IQR) | 75 (66–89) | 47 (39–53) | 20 (14–25) | <0.001 |
| Creatinine (median, IQR) | 80 (71–96) | 123 (109–142) | 258 (215–346) | <0.001 |
| Hemoglobin | 8.3 ± 1.3 | 8.1 ± 1.4 | 6.9 ± 1.5 | <0.001 |
| Hyponatremia | 221 (32%) | 224 (29%) | 151 (48%) | <0.001 |
| Hypokalemia | 106 (15%) | 98 (13%) | 23 (7%) | <0.001 |
| Hyperkalemia | 38 (6%) | 81 (10%) | 85 (27%) | <0.001 |
| Anemia | 262 (38%) | 334 (43%) | 244 (77%) | <0.001 |
| <i>Therapy during ICCU hospitalization</i> | | | | |
| Intubation | 69 (10%) | 117 (15%) | 57 (18%) | 0.001 |
| Resuscitation | 19 (3%) | 36 (5%) | 15 (5%) | 0.13 |
| Mechanical circulatory support‡ | 34 (5%) | 41 (5%) | 29 (9%) | 0.02 |
| Inotropics | 196 (29%) | 253 (33%) | 123 (39%) | 0.01 |
| Beta-blocker | 146 (21%) | 111 (14%) | 47 (15%) | 0.001 |
| Antiarrhythmics | 115 (17%) | 154 (20%) | 45 (14%) | 0.06 |
| Calcium antagonist | 77 (11%) | 102 (13%) | 72 (23%) | <0.001 |
| Digitalis | 300 (44%) | 347 (45%) | 87 (27%) | <0.001 |
| ACE-inhibitor or ARB | 422 (61%) | 430 (55%) | 113 (36%) | <0.001 |
| Diuretics | 640 (93%) | 718 (92%) | 257 (81%) | <0.001 |
| Nitrates | 234 (34%) | 289 (37%) | 121 (38%) | 0.24 |

(Continued)

Table 1. (Continued)

| | eGFR ≥60 | eGFR 30–59 | eGFR <30 | p-value* |
|---------------------|-----------|------------|-----------|----------|
| Nitroprusside | 46 (7%) | 74 (10%) | 39 (12%) | 0.01 |
| Antiplatelet agents | 200 (29%) | 189 (24%) | 71 (22%) | 0.04 |
| Oral anticoagulant | 351 (51%) | 406 (52%) | 136 (43%) | 0.02 |

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BMI, Body Mass Index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ICCU, intensive cardiac care unit; IQR, interquartile range

*p for any difference

†Percutaneous coronary intervention and/or CABG

‡Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

<https://doi.org/10.1371/journal.pone.0201714.t001>

strong predictor of the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation.

Over time, the 10-year outcome of patients with a preserved renal function improved significantly, both unadjusted (HR 0.70 [95% CI 0.61–0.81] for most recent period versus first period) and after adjustment for confounding variables (adjusted HR 0.73 [95% CI 0.55–0.97]; Fig 3A). This improvement was more pronounced among the 30-day survivors (adjusted HR 0.65 [95% CI 0.48–0.88]; Fig 3B). In contrast, this pattern was not present in patients with renal dysfunction. Consequently, the prognosis of these patients did not improve over time.

Anemia and outcome

Almost 50% of the patients were found to have anemia. The characteristics of these patients differed in some aspects from those without anemia (Table 3). Anemic patients more frequently had previous HF and atrial fibrillation at admission. Importantly, they more often had impaired renal function.

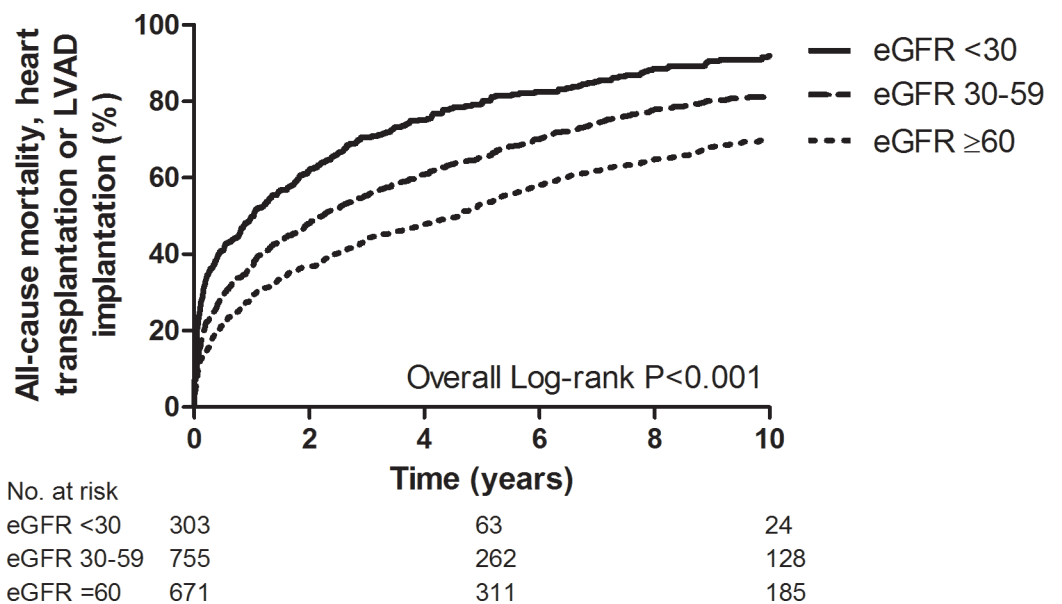


Fig 2. Kaplan-Meier curve of patients with acute heart failure according to the renal function. eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; LVAD, left ventricular assist device.

<https://doi.org/10.1371/journal.pone.0201714.g002>

Table 2. Prognosis at different follow-up moments according to renal function.

| | All-cause mortality, heart transplantation or LVAD implantation | Univariable analysis* | Multivariable analysis* |
|-----------------|-----------------------------------------------------------------|-----------------------|-------------------------|
| <i>30 days</i> | | | |
| eGFR ≥60 | 10% | Reference | Reference |
| eGFR 30–59 | 14% | 1.51 (1.10–2.08) | 1.50 (1.06–2.11) |
| eGFR <30 | 24% | 2.85 (1.99–4.08) | 2.32 (1.55–3.47) |
| <i>1 year</i> | | | |
| eGFR ≥60 | 28% | Reference | Reference |
| eGFR 30–59 | 36% | 1.41 (1.17–1.69) | 1.34 (1.11–1.62) |
| eGFR <30 | 50% | 2.21 (1.79–2.73) | 1.81 (1.44–2.28) |
| <i>10 years</i> | | | |
| eGFR ≥60 | 69% | Reference | Reference |
| eGFR 30–59 | 81% | 1.42 (1.33–1.51) | 1.24 (1.09–1.40) |
| eGFR <30 | 92% | 2.14 (1.99–2.31) | 1.68 (1.43–1.96) |

eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; LVAD, left ventricular assist device

*Odds ratio with 95% confidence interval (CI) for 30-day outcome, hazard ratio with 95% CI for 1-year and 10-year outcome

<https://doi.org/10.1371/journal.pone.0201714.t002>

The prognosis of patients with anemia was worse than of patients without anemia (Fig 4). After adjustment for confounders, anemia remained significantly associated with increased for reaching the composite endpoint of all-cause mortality, heart transplantation and LVAD implantation at 30 days, 1 year and 10 years (HR 2.23 [95% CI 1.64–3.03], HR 1.58 [95% CI 1.33–1.87] and HR 1.24 [1.11–1.39], respectively; Table 4).

Since anemia was a predictor of poor outcome in the total population of acute HF patients, we separately analyzed whether anemia had incremental prognostic value independent from renal dysfunction (Fig 5). Among patients with a preserved renal function, anemia proved to be a strong predictor for 30-day outcome, but its prognostic value decreased with longer duration of follow-up. In contrast, anemia was associated with worse outcome both during short- and long-term follow-up among patients with renal dysfunction. This relationship persisted after the exclusion of patients who died within 30 days after admission.

Discussion

In this prospective registry of patients with acute HF, we found that renal dysfunction was a strong predictor for poor outcome (i.e. the composite of all-cause mortality, heart transplantation and LVAD implantation) up to 10 years following initial hospitalization. Importantly, this study is the first to show that patients with acute HF and an impaired renal function had no improvement in prognosis that occurred in the last three decades. This contrasts findings in patients with a preserved renal function. Furthermore, we found that the prognostic impact of anemia was dependent on the presence of renal function. Anemia had no impact on the long-term prognosis of patients with a preserved renal function. On the other hand, anemia was associated with impaired prognosis among patients with renal dysfunction.

Renal function and prognosis

Renal dysfunction proved to be a strong predictor of a poor outcome: the poorer the renal function, the poorer the prognosis. Among studies that demonstrated the adverse association between renal dysfunction and poor survival,[1, 2] most only used a short follow-up period, usually up to 1 year after hospitalization. Our results support and extend these findings by

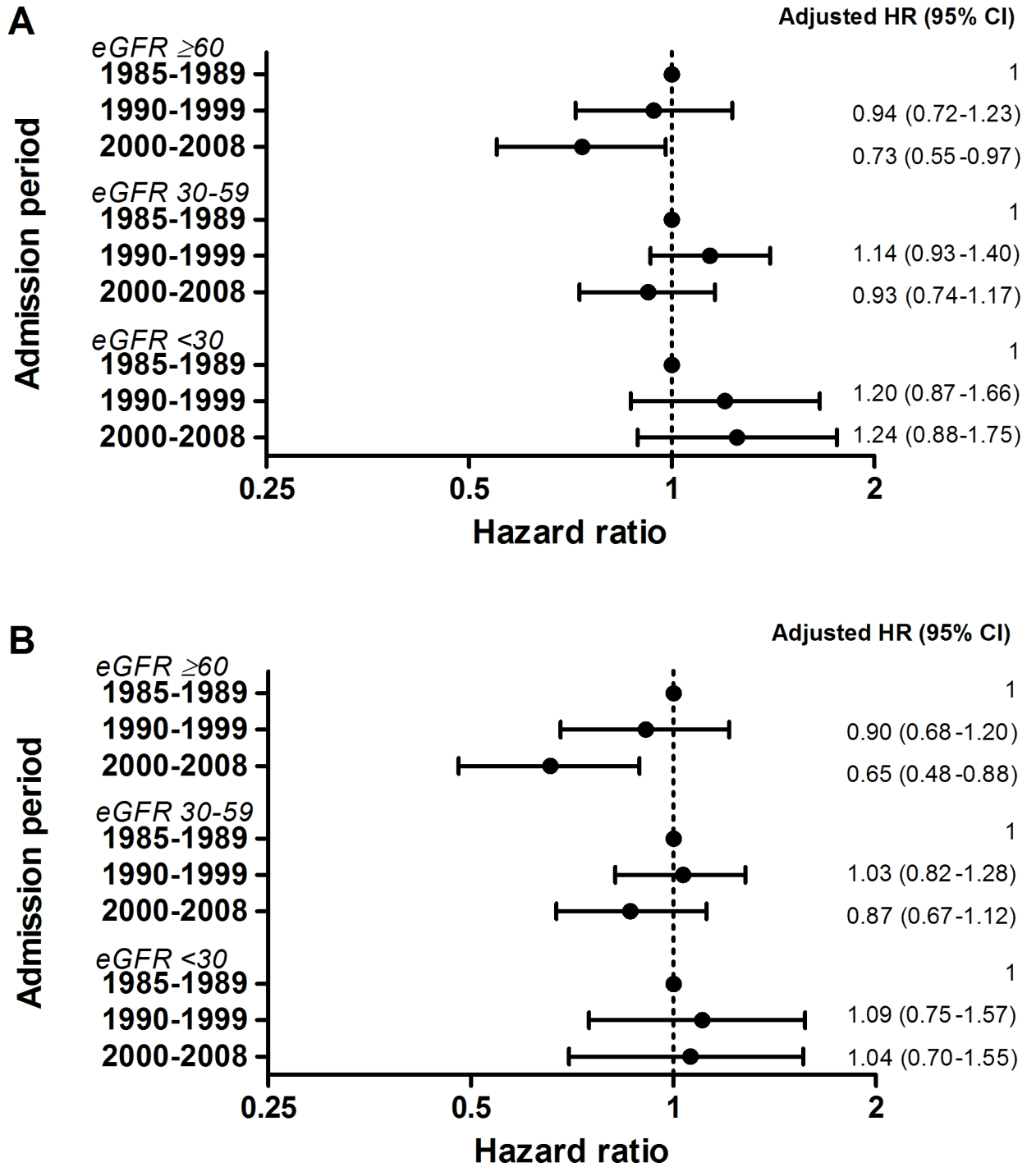


Fig 3. Prognosis over time among (A) the total population and (B) the 30-day survivors of patients with acute heart failure. Results were divided into three groups according to the renal function. CI, confidence interval; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio.

<https://doi.org/10.1371/journal.pone.0201714.g003>

demonstrating that renal dysfunction continued to be a strong predictor for long-term outcome (i.e. 10 years).

Table 3. Baseline characteristics and therapy of patients with and without anemia.

| | Anemia + | Anemia - | p-value |
|--------------------------------------------|-----------------|----------------|---------|
| No. of patients | 850 (48%) | 919 (52%) | |
| <i>Baseline</i> | | | |
| Age (mean, y) | 63.1 ± 14.5 | 64.1 ± 15.0 | 0.15 |
| Male | 565 (67%) | 560 (61%) | 0.02 |
| BMI | 24.8 ± 4.8 | 25.4 ± 5.2 | 0.20 |
| <i>Medical history</i> | | | |
| Myocardial infarction | 336 (40%) | 362 (39%) | 0.95 |
| Coronary revascularization* | 199 (23%) | 183 (20%) | 0.07 |
| Heart surgery (not CABG) | 131 (15%) | 102 (11%) | 0.01 |
| Heart transplantation | 8 (0.9%) | 1 (0.1%) | 0.02 |
| Waiting for heart transplantation | 22 (2.6%) | 12 (1.3%) | 0.05 |
| Heart failure | 440 (52%) | 425 (46%) | 0.02 |
| Rhythm- or conduction disorder | 215 (25%) | 218 (24%) | 0.44 |
| Diabetes | 199 (23%) | 181 (20%) | 0.06 |
| Hypertension | 271 (32%) | 308 (34%) | 0.47 |
| <i>Heart failure</i> | | | |
| Etiology of heart failure | | | >0.05 |
| Ischemic origin | 387 (45%) | 438 (48%) | |
| Non-ischemic origin | 463 (55%) | 481 (52%) | |
| Atrial fibrillation at admission | 141 (17%) | 243 (26%) | <0.001 |
| Left ventricular ejection fraction | | | >0.05 |
| Good | 260 (31%) | 250 (27%) | |
| Moderate | 192 (23%) | 227 (25%) | |
| Poor | 399 (47%) | 442 (48%) | |
| <i>Laboratory values</i> | | | |
| Sodium | 136 ± 6 | 138 ± 5 | <0.001 |
| Potassium | 4.3 ± 0.8 | 4.1 ± 0.7 | 0.001 |
| Urea (median, IQR) | 12.6 (8.3–20.4) | 8.4 (6.6–11.6) | <0.001 |
| eGFR (median, IQR) | 47 (26–64) | 57 (43–73) | <0.001 |
| Creatinine (median, IQR) | 123 (94–200) | 102 (82–130) | <0.001 |
| Hemoglobin | 6.7 ± 0.9 | 9.0 ± 0.8 | <0.001 |
| Hyponatremia | 359 (42%) | 233 (25%) | <0.001 |
| Hypokalemia | 100 (12%) | 125 (14%) | 0.28 |
| Hyperkalemia | 122 (14%) | 85 (9%) | 0.001 |
| <i>Therapy during ICCU hospitalization</i> | | | |
| Intubation | 151 (18%) | 92 (10%) | <0.001 |
| Resuscitation | 36 (4%) | 34 (4%) | 0.56 |
| Mechanical circulatory support† | 80 (9%) | 23 (3%) | <0.001 |
| Inotropics | 329 (39%) | 238 (26%) | <0.001 |
| Beta-blocker | 128 (15%) | 174 (19%) | 0.03 |
| Antiarrhythmics | 143 (17%) | 165 (18%) | 0.53 |
| Calcium antagonist | 130 (15%) | 123 (13%) | 0.25 |
| Digitalis | 305 (36%) | 419 (46%) | <0.001 |
| ACE-inhibitor or ARB | 417 (49%) | 540 (59%) | <0.001 |
| Diuretics | 747 (88%) | 854 (93%) | <0.001 |
| Nitrates | 295 (35%) | 342 (37%) | 0.27 |
| Nitroprusside | 73 (9%) | 86 (9%) | 0.57 |

(Continued)

Table 3. (Continued)

| | Anemia + | Anemia - | p-value |
|---------------------|-----------|-----------|---------|
| Antiplatelet agents | 238 (28%) | 224 (24%) | 0.08 |
| Oral anticoagulant | 383 (45%) | 497 (54%) | <0.001 |

ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; BMI, Body Mass Index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; ICCU, intensive cardiac care unit; IQR, interquartile range

*Percutaneous coronary intervention and/or CABG

†Intra-aortic balloon pump and/or left ventricular assist device and/or extracorporeal membrane oxygenation

<https://doi.org/10.1371/journal.pone.0201714.t003>

It is generally assumed that the new therapeutic options for the treatment of HF developed during the last decades are responsible for the prognostic improvement in the total population of patients acute HF. Our finding that only patients with a normal renal function experienced an improved long-term prognosis in the most recently study period is novel. This contrasts with the findings currently obtained among patients with renal dysfunction. Their prognosis remained stable over time. So far, the temporal trends in prognosis have not been studied separately for patients with and without renal dysfunction. Two potential mechanisms may explain this finding. First, some of the new therapeutics, like ACE inhibitors, ARBs and MRAs, that are considered to be responsible for the prognostic improvement of patients with HF over the last decades, interact with the renal function.[6] Moreover, patients with lower eGFR were also less frequently treated with diuretics during ICCU admission. Therefore, it is plausible that patients with renal dysfunction were less frequently treated with these drugs and that, in case they were treated, the optimal dose was not achieved. Indeed, we found that ACE inhibitors were less frequently prescribed during admission in patients with renal dysfunction. Although data on medical therapy during follow-up were not included in this registry, it can be assumed that this pattern of prescription continued after discharge. Another possible explanation for the disparity in temporal trends between patients with and without renal dysfunction may be the grade of their illness. Patients with renal dysfunction had more comorbidities and were

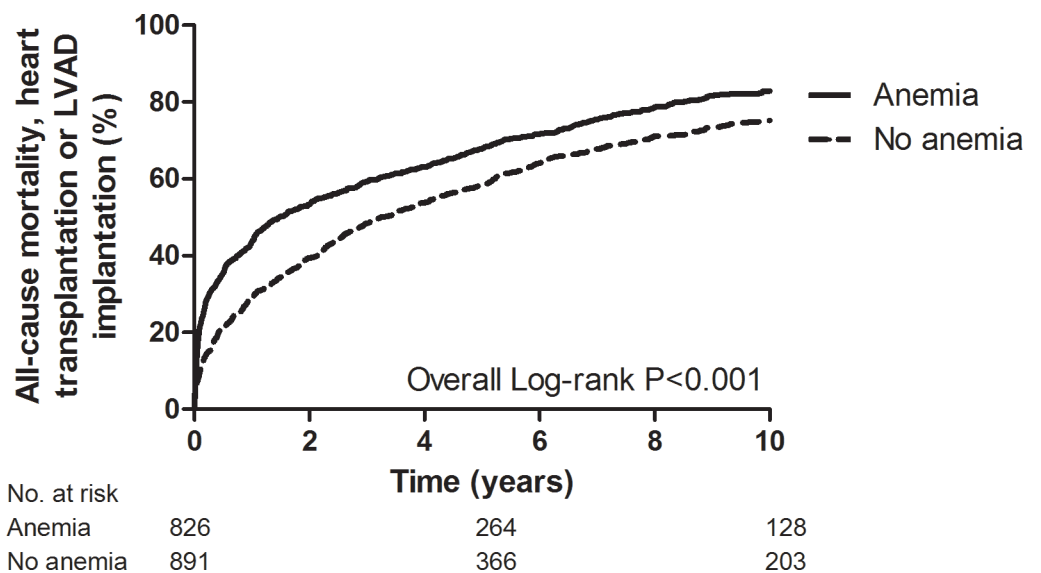


Fig 4. Kaplan-Meier curve of acute heart failure patients with and without anemia. LVAD, left ventricular assist device.

<https://doi.org/10.1371/journal.pone.0201714.g004>

Table 4. Prognosis at different follow-up moments according to the presence of anemia.

| | All-cause mortality, heart transplantation or LVAD implantation | Univariable analysis* | Multivariable analysis* |
|-----------------|-----------------------------------------------------------------|-----------------------|-------------------------|
| <i>30 days</i> | | | |
| No anemia | 9% | Reference | Reference |
| Anemia | 20% | 2.55 (1.92–3.38) | 2.23 (1.64–3.03) |
| <i>1 year</i> | | | |
| No anemia | 28% | Reference | Reference |
| Anemia | 43% | 1.75 (1.49–2.05) | 1.58 (1.33–1.87) |
| <i>10 years</i> | | | |
| No anemia | 75% | Reference | Reference |
| Anemia | 83% | 1.35 (1.28–1.43) | 1.24 (1.11–1.39) |

LVAD, left ventricular assist device

* Odds ratio with 95% confidence interval (CI) for 30-day outcome, hazard ratio with 95% CI for 1-year and 10-year outcome

<https://doi.org/10.1371/journal.pone.0201714.t004>

more frequently treated with intubation, mechanical circulatory support and inotropics than patients with preserved renal function. This suggests that patients with renal dysfunction were more critically ill as compared to those with a preserved renal function, and they might thus experience a more progressive course of their disease and, therefore, a poorer prognosis.

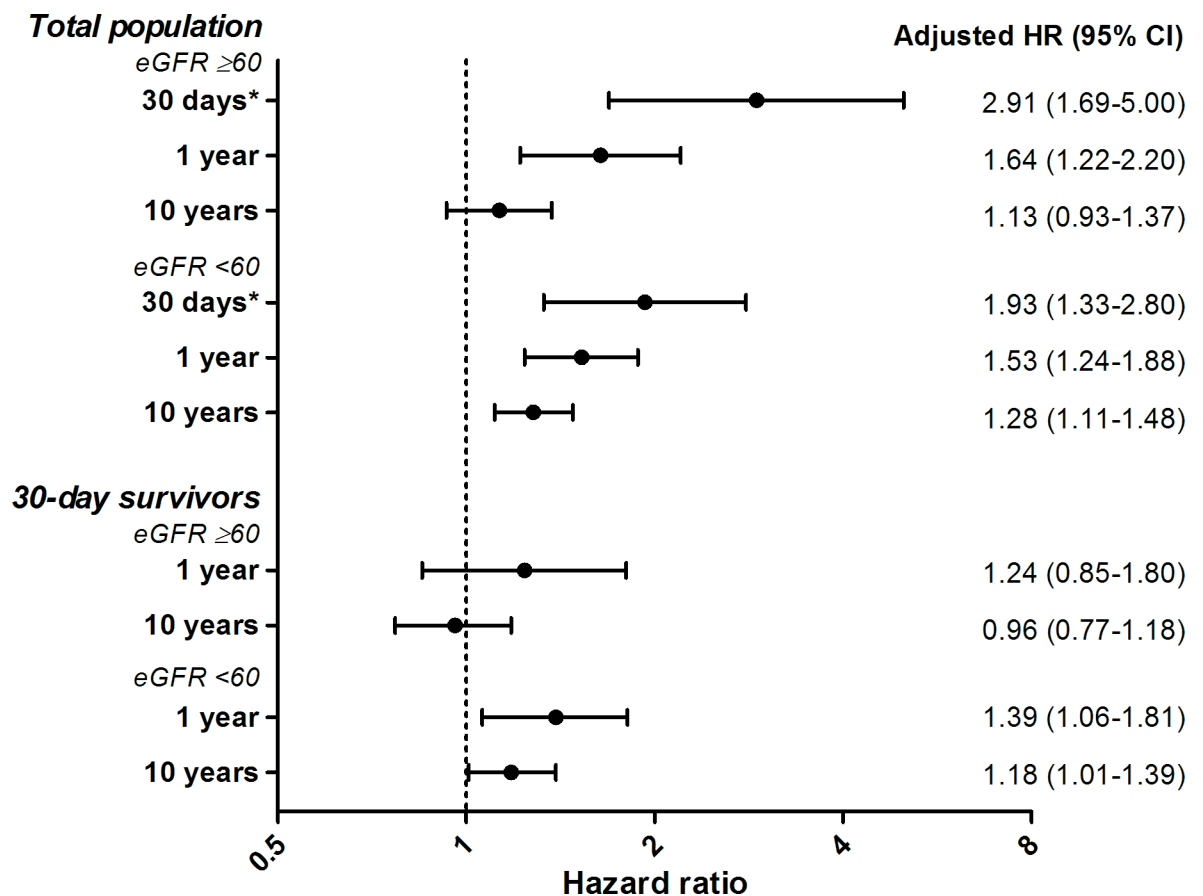


Fig 5. Prognostic impact of anemia at different follow-up moments in the total population and 30-day survivors. Analyses were separately done for renal impairment whether or not. CI, confidence interval; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; *outcome at 30 days was reported as odds ratio with 95% CI.

<https://doi.org/10.1371/journal.pone.0201714.g005>

Anemia and prognosis

The second result of our study was the finding that anemia was associated with both an impaired short- and long-term prognosis among patients with acute HF. The relation between anemia and adverse outcome in patients with acute HF has been published previously, although the data are not consistent.[10–13] Two studies that did not report anemia to be a prognosticator of poor outcome had study populations with quite different characteristics than ours.[10, 13]

When we studied the prognostic value of anemia in more detail, we found that anemia was an independent predictor of short-term outcome in all patients, irrespective of renal function. However, while anemia also was independently associated with an impaired outcome during long-term follow-up in patients with renal dysfunction, its presence had no incremental long-term prognostic impact in patients with a preserved renal function. The reasons for this difference are not totally clear. A possible explanation may be the actual cause of the anemia. However, as we were not able to assess the exact etiology of the anemia, the following hypothesis should be studied further in the future.

Anemia in patients with HF is well known, and has been attributed to multiple factors including iron deficiency, renal dysfunction, HF as a chronic disease and hemodilution.[14] The iron status was not assessed in our patients so we cannot make any conclusions as whether there was a difference in iron status between patients with and without renal dysfunction. The fact that anemia was associated with impaired long-term outcome in patients with renal dysfunction but not in patients with a preserved renal function might be due to the fact that patients with renal dysfunction more frequently had ‘true anemia’.

Hemodilution is one of the potential causes of anemia in patients with HF.[17] The causal factor in that case is a low hemoglobin level caused by an increased extracellular volume. When the extracellular volume decreases, for example by diuretic therapy, the hemoglobin level will increase and the patient will no longer be classified as having anemia. Therefore, in case of hemodilution anemia should be seen as a marker of fluid retention, just as sodium level. We hypothesize that hemodilution as the only cause of anemia was more frequent in patients without renal dysfunction than in those with renal dysfunction. Probably, patients with an impaired renal function had also anemia based on hemodilution but in addition, could also have suffered from ‘true anemia’. There are several reasons for such a phenomenon. First, it is well known that renal failure is associated with anemia.[14] Second, in our study, chronic HF was more common among patients with renal dysfunction than among those without renal dysfunction. Since chronic HF has been associated with elevated plasma levels of cytokines,[18] chronic HF can cause anemia of chronic diseases. These cytokines suppress the erythropoietic stem cells in the bone marrow and reduce the release of iron from the reticulo-endothelial system, resulting in anemia.[19]

The so-called cardiorenal anemia syndrome has not been investigated extensively in patients with acute HF. Investigators from the ATTEND registry also found anemia to be a strong predictor of in-hospital mortality both among patients with and without renal dysfunction.[20] Furthermore, their results with respect to the 1-year outcome were consistent with our data. In addition, these authors also showed that anemia had additive prognostic value for increased 1-year mortality only in the patients with renal dysfunction but not in those with a preserved renal function.[21] Because these investigators used anemia at discharge as predictor, and thus made hemodilution less likely as cause from anemia, this supports our hypothesis of ‘true anemia’ among patients with renal dysfunction. Our data provide new evidence on the very long-term prognosis of patients with acute HF since we found that anemia, even after 10

years of follow-up, continued to have additive prognostic value among patients with renal dysfunction.

Strengths and limitations

The unique strength of our study is the duration of the follow-up of 10 years after the initial hospitalization. This enabled us to investigate the prognostic impact of renal dysfunction, anemia, as well as their interrelationship on short- (very) long-term. Research covering three decades with such a long follow-up time is quite unique in this research field.

Despite these strengths, some limitations should be considered in the interpretation of the results of this study. Since our study was done in a tertiary referral hospital, external validity could have been affected. However, despite the fact that our hospital was a tertiary referral center, a significant part of our patients still were primary and secondary referrals. Therefore, our population consisted of patients within the whole, broad range of patients admitted with acute HF. Second, analyses were made on a composite outcome and therefore caution is needed when interpreting the estimates of the covariates, since these are estimates on the composite outcome only and not on the separate outcomes. Third, we were not able to identify the cause of anemia in all patients, nor were we always able to assess whether patients had chronic or acute renal dysfunction. Furthermore, while it has been suggested that changing hemoglobin and creatinine levels during admission may influence prognosis,[\[2, 22\]](#) the design of our study did not allow us to assess trends in hemoglobin and creatinine levels. Finally, since we had no data on the ethnicity of our patients, we could not multiply for black race in the MDRD formula. Therefore, the eGFR that we employed might be an underestimation of the real renal function. However, such misclassification could have only led to underestimation of the effects observed.

Conclusions

We found renal dysfunction to be a strong predictor of both short- and long-term composite endpoint of all-cause mortality, heart transplantation and LVAD implantation among patients with acute HF. In addition, we established that the long-term prognosis of patients with a preserved renal function significantly improved over the last decades. However, in patients with renal dysfunction, the prognosis did not improve over the last decades. These findings emphasize the importance of renal dysfunction as comorbidity in patients with HF and underscore the need for new therapeutic modalities, especially for patients with renal dysfunction. Furthermore, we established anemia as a prognosticator of short-term outcome both among acute HF patients with and without renal dysfunction. Among patients with renal dysfunction, the presence of anemia was also associated with impaired long-term prognosis. Anemia did not influence the long-term prognosis of patients with preserved renal function. Further research should be undertaken to investigate the pathogenesis of the prognostic impact of anemia and renal dysfunction among patients with acute HF.

Supporting information

S1 Dataset.
(SAV)

Author Contributions

Conceptualization: Alina A. Constantinescu, Ron T. van Domburg, Jaap W. Deckers, K. Martijn Akkerhuis.

Data curation: Jan C. van den Berge, Ron T. van Domburg.

Formal analysis: Jan C. van den Berge.

Funding acquisition: Jaap W. Deckers, K. Martijn Akkerhuis.

Investigation: Jan C. van den Berge, Ron T. van Domburg.

Methodology: Jan C. van den Berge, Ron T. van Domburg, Jaap W. Deckers, K. Martijn Akkerhuis.

Software: Ron T. van Domburg.

Supervision: Ron T. van Domburg, Jaap W. Deckers, K. Martijn Akkerhuis.

Visualization: Jan C. van den Berge.

Writing – original draft: Jan C. van den Berge.

Writing – review & editing: Alina A. Constantinescu, Ron T. van Domburg, Milos Brankovic, Jaap W. Deckers, K. Martijn Akkerhuis.

References

1. Butler J, Chirovsky D, Phatak H, McNeill A, Cody R. Renal function, health outcomes, and resource utilization in acute heart failure: a systematic review. *Circ Heart Fail*. 2010; 3(6):726–45. <https://doi.org/10.1161/CIRCHEARTFAILURE.109.920298> PMID: 21081740
2. Damman K, Valente MA, 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(7):455–69. <https://doi.org/10.1093/eurheartj/ehf386> PMID: 24164864
3. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009; 119(4):515–23. <https://doi.org/10.1161/CIRCULATIONAHA.108.812172> PMID: 19153268
4. Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women with heart failure of ischaemic and non-ischaemic origin: data for the period 1987–2003 from the Swedish Hospital Discharge Registry. *Eur Heart J*. 2009; 30(6):671–8. <https://doi.org/10.1093/eurheartj/ehn541> PMID: 19109351
5. van den Berge JC, Akkerhuis MK, Constantinescu AA, Kors JA, van Domburg RT, Deckers JW. Temporal trends in long-term mortality of patients with acute heart failure: Data from 1985–2008. *Int J Cardiol*. 2016; 224:456–60. Epub 2016/10/11. <https://doi.org/10.1016/j.ijcard.2016.09.062> PMID: 27723568
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016; 18(8):891–975. <https://doi.org/10.1002/ejhf.592> PMID: 27207191
7. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation*. 2003; 107(2):223–5. PMID: 12538418
8. Kajimoto K, Sato N, Takano T, investigators of the Acute Decompensated Heart Failure Syndromes r. Association between anemia, clinical features and outcome in patients hospitalized for acute heart failure syndromes. *Eur Heart J Acute Cardiovasc Care*. 2015; 4(6):568–76. <https://doi.org/10.1177/2048872614554199> PMID: 25315117
9. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J*. 2006; 27(22):2725–36. <https://doi.org/10.1093/eurheartj/ehl193> PMID: 17000631
10. Kosiborod M, Curtis JP, Wang Y, Smith GL, Masoudi FA, Foody JM, et al. Anemia and outcomes in patients with heart failure: a study from the National Heart Care Project. *Arch Intern Med*. 2005; 165(19):2237–44. <https://doi.org/10.1001/archinte.165.19.2237> PMID: 16246989

11. Tarantini L, Oliva F, Cantoni S, Cioffi G, Agnoletto V, Alunni G, et al. Prevalence and prognostic role of anaemia in patients with acute heart failure and preserved or depressed ventricular function. *Intern Emerg Med*. 2013; 8(2):147–55. <https://doi.org/10.1007/s11739-011-0601-z> PMID: 21544536
12. Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, et al. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). *Am J Cardiol*. 2008; 101(2):223–30. <https://doi.org/10.1016/j.amjcard.2007.07.067> PMID: 18178411
13. Silva RP, Barbosa PH, Kimura OS, Sobrinho CR, Sousa Neto JD, Silva FA, et al. Prevalence of anemia and its association with cardio-renal syndrome. *Int J Cardiol*. 2007; 120(2):232–6. <https://doi.org/10.1016/j.ijcard.2006.10.005> PMID: 17174420
14. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. *Eur J Heart Fail*. 2002; 4(6):681–6. PMID: 12453537
15. Goodyear MD, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. *Bmj*. 2007; 335(7621):624–5. <https://doi.org/10.1136/bmj.393339.610000.BE> PMID: 17901471
16. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007; 53(4):766–72. <https://doi.org/10.1373/clinchem.2006.077180> PMID: 17332152
17. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, et al. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J*. 2007; 28(2):166–71. <https://doi.org/10.1093/eurheartj/ehl419> PMID: 17158825
18. Torre-Amione G, Bozkurt B, Deswal A, Mann DL. An overview of tumor necrosis factor alpha and the failing human heart. *Curr Opin Cardiol*. 1999; 14(3):206–10. PMID: 10358791
19. Means RT Jr. Advances in the anemia of chronic disease. *Int J Hematol*. 1999; 70(1):7–12. PMID: 10446488
20. Kajimoto K, Sato N, Takano T, investigators of the Acute Decompensated Heart Failure Syndromes r. Association of anemia and renal dysfunction with in-hospital mortality among patients hospitalized for acute heart failure syndromes with preserved or reduced ejection fraction. *Eur Heart J Acute Cardiovasc Care*. 2016; 5(7):89–99. <https://doi.org/10.1177/2048872615593387> PMID: 26124457
21. Kajimoto K, Sato N, Keida T, Sakata Y, Takano T, Acute Decompensated Heart Failure Syndromes I. Associations of anemia and renal dysfunction with outcomes among patients hospitalized for acute decompensated heart failure with preserved or reduced ejection fraction. *Clin J Am Soc Nephrol*. 2014; 9(11):1912–21. <https://doi.org/10.2215/CJN.04400514> PMID: 25183660
22. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013; 61(19):1973–81. <https://doi.org/10.1016/j.jacc.2012.12.050> PMID: 23500313