RESEARCH NOTE

REVISED The prevalence and clinical significance of anemia in patients hospitalized with acute heart failure [version 2; peer review: 2 approved, 1 not approved]

Attila Frigy¹, Zoltán Fogarasi¹, Ildikó Kocsis¹, Lehel Máthé¹, Előd Nagy²

¹Department of Internal Medicine IV, University of Medicine and Pharmacy Tîrgu-Mures, Târgu Mureş, Romania

²Department of Pharmaceutical Biochemistry, University of Medicine and Pharmacy Tîrgu-Mures, Târgu Mureş, Romania

V2 First published: 26 May 2016, 5:1006
<https://doi.org/10.12688/f1000research.7872.1>

Latest published: 18 Aug 2017, 5:1006
<https://doi.org/10.12688/f1000research.7872.2>

Abstract

Abstract: In a cohort of patients hospitalized with acute heart failure (AHF) the prevalence of anemia and the existence of a correlation between anemia and the severity of the clinical picture were assessed.

Methods: 50 consecutive patients (34 men, 16 women, mean age 67.5 years) hospitalized with AHF were enrolled. Statistical analysis was performed for studying correlations between anemia and the presence/levels of diverse parameters (clinical, laboratory, echocardiographic, treatment related) reflecting the severity and prognosis of AHF ($\alpha=0.05$).

Results: 21 patients (14 men, 7 women, mean age 69.6 years), representing 42%, had anemia at admission. Comparing patients with and without anemia there were no significant differences regarding age, gender, presence of atrial fibrillation ($p=0.75$), diabetes ($p=1$), ischemic heart disease ($p=0.9$), left ventricular ejection fraction (EF) ($p=1$), hypotension ($p=0.34$) and tachycardia >100 b/min at admission ($p=0.75$), level of eGFR ($p=0.72$), and need of high dose (>80 mg/day) loop diuretic ($p=0.23$). However, EF showed a significant positive correlation with eGFR only in AHF patients with anemia ($r=0.65$, $p=0.001$). In a multiple regression model, EF had a significant effect on the eGFR quartiles ($p=0.004$).

Conclusions: Anemia is a frequent finding in patients hospitalized with AHF. The presence of anemia was not correlated with other factors related to AHF severity and prognosis. However, a low EF associated with low eGFR was characteristic for patients with anemia, suggesting that the decrease of renal perfusion by low cardiac output further aggravates anemia on the background of chronic kidney disease.

Keywords

acute heart failure , prognosis , anemia

Open Peer Review

Approval Status

	1	2	3
version 2			
(revision)			
18 Aug 2017			
version 1			
26 May 2016			

1. **José Machado**, University of Minho, Braga, Portugal

2. **Manfred Seeberger** , Klinik Hirslanden, Zürich, Switzerland

3. **Norbert Jost**, University of Szeged, Szeged, Hungary

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Lehel Máthé (lehelmathe@gmail.com)

Author roles: **Frigy A:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Fogarasi Z:** Data Curation, Investigation, Methodology, Resources; **Kocsis I:** Data Curation, Investigation, Methodology, Resources, Writing – Original Draft Preparation; **Máthé L:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Writing – Original Draft Preparation; **Nagy E:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 Frigy A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

How to cite this article: Frigy A, Fogarasi Z, Kocsis I *et al.* **The prevalence and clinical significance of anemia in patients hospitalized with acute heart failure [version 2; peer review: 2 approved, 1 not approved]** F1000Research 2017, 5:1006
<https://doi.org/10.12688/f1000research.7872.2>

First published: 26 May 2016, 5:1006 <https://doi.org/10.12688/f1000research.7872.1>

REVISED Amendments from Version 1

Statistical analysis was reconsidered and more emphasis was placed on correlations with renal function. The main message of the article remained the same.

See referee reports

Anemia is relatively frequent in patients with heart failure (HF). In a population of patients with newly diagnosed HF the prevalence of anemia was 17%¹. The presence of anemia is related to the severity of functional class (from 9% in NYHA class I to 79% in class IV)². In acute heart failure (AHF) anemia, regardless of its etiology, could be an important extracardiac factor of decompensation; its diagnosis, evaluation and treatment being an important part of management. Also, the presence of anemia proved to be an important prognostic factor during the in-hospital and post-discharge period³.

The aim of this study was to assess a cohort of patients hospitalized with AHF for (1) the prevalence of anemia and (2) the existence of correlations parameters reflecting the severity of heart failure and the grade of anemia, with special accent on decreased renal function.

Methods

We collected data from 50 consecutive patients (34 men, 16 women, mean age 67.5 years) hospitalized with AHF (acute decompensated heart failure in 36 cases). At admission, all the patients signed the general consent form used at our institution, agreeing with anonymous data collection and usage for scientific purposes. Approval of the hospital ethical committee (permit number: 3865/01.03.2016) was obtained for data processing and publication. Exclusion criteria were: recent (<1 month) acute coronary syndrome, and advanced renal disease on hemodialysis. At admission and during hospital stay routine (part of usual care) clinical and paraclinical data were recorded in a dedicated database: demographic data, clinical diagnosis, triggering factors of decompensation, signs and symptoms at admission, ECG data, echocardiographic data, laboratory parameters at admission, and in-hospital treatment data. Anemia was defined as Hb<12 g/dL for women and Hb <13 g/dL for men. eGFR was estimated by the CKD-EPI equation.

Statistical analysis was performed with STATISTICA 5.0, using Fisher's exact test for the comparison of discrete data, the Mann-Whitney U test for continuous parameters and the Spearman rank correlation for comparison analysis and multiple linear regression, to determine parameters influencing eGFR ($\alpha=0.05$).

Results

Dataset 1. Patient data

<http://dx.doi.org/10.5256/f1000research.7872.d122902>

Please see legend.csv for a description of the data

21 patients (14 men, 7 women, mean age 69.6 years), representing 42% of the cohort, had anemia at admission. The most common form was renal anemia (10 patients), while 8 patients suffered of iron deficiency anemia. We did not find significant differences between the two groups of patients, with and without anemia, with regards to gender ($p=1$) and age ($p=0.57$). Also, there were no significant differences regarding the presence of atrial fibrillation ($p=0.75$), diabetes ($p=1$), ischemic heart disease ($p=1$), hypotension (systolic blood pressure <90 mmHg) at admission ($p=0.34$), tachycardia >100 b/min at admission ($p=0.75$), severe aortic stenosis (0.12), pulmonary hypertension (0.13), the level of eGFR ($p=0.33$), left ventricular ejection fraction (EF) ($p=0.95$) and need of high dose (>80 mg/day) loop diuretic ($p=0.23$) (Table 1).

Table 1. The comparison of diverse parameters in patients with and without anemia.

Parameter	Anemia		P
	No (n=29)	Yes (n=21)	
Age (years)	66,06 ± 2,07	69,62 ± 2,48	0,45
Gender (male/female)	20/9	14/7	1
Hemoglobin (g/L)	14,06 ± 0,19	10,76 ± 0,25	<0,001
eGFR (mL/min)	66,36 ± 4,55	60,21 ± 6,12	0,33
LV ejection fraction (%)	40 ± 3,10	40,71 ± 3,81	0,95
Ischemic heart disease	15 (51,7%)	11 (52,4%)	1
Diabetes	19 (65,5%)	13 (61,9%)	1
Atrial fibrillation	15 (52,3%)	11 (51,7%)	1
Systolic blood pressure <90 mmHg	6 (20,7%)	7 (33,3%)	0,34
Tachycardia (>100 b/min)	9 (31%)	5 (23,8%)	0,75
Severe aorta stenosis	6 (20,7%)	9 (42,8%)	0,12
Pulmonary hypertension	7 (26,9%)	11 (52,4%)	0,13
Antiaggregant treatment	2 (6,9%)	0 (0%)	0,5
Anticoagulant treatment	27 (93%)	19 (90,4%)	1
Daily ≥ 80 mg furosemid	21 (72,4%)	11 (52,4%)	0,23

We observed a significant positive correlation between eGFR and the ejection fraction ($r=0.65$, $p=0.001$) in patients with anemia, but not in those with normal hemoglobin levels ($r=-0.13$, $p=0.48$). In a multiple regression model, determining the eGFR quartiles, we found a significant effect of EF on eGFR ($p=0.004$).

Discussion and conclusions

There is general agreement that anemia is a good predictor of prognosis in patients with acute and chronic HF. Anemia is associated with increased mortality, however there are conflicted data whether this is an independent predictor or reflects the progression of HF and/or is related to the presence of more frequent comorbidities^{1,4,5}. In the setting of AHF, anemia could also serve as a precipitating factor of decompensation.

In our cohort of patients the presence of anemia was not correlated with other factors related to AHF severity and prognosis. This fact suggests its independent role in influencing the clinical picture and prognosis. On the other hand, almost half of anemia patients suffered of chronic kidney disease, and this subgroup showed a significant association of low EF with low eGFR. Moreover, ejection fraction proved to have a significant effect on estimated glomerular filtration rate in a multiple regression model, suggesting that low EF in heart failure might cause the decrease of GFR, aggravating

the chronic kidney disease and, consequently contributing to the development of renal anemia.

Data availability

F1000Research: Dataset 1. Patient data, [10.5256/f1000research.7872.d122902](https://doi.org/10.5256/f1000research.7872.d122902)⁶

Consent

Written informed consent for publication of their clinical details was obtained from the patients.

Author contributions

AF and ZF: study design, data collection, data processing and statistical analysis, manuscript preparation; IK: study design, data collection; LM: data processing and statistical analysis; EN: data processing and statistical analysis, manuscript preparation.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. 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.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Silverberg DS, Wexler D, Blum M, *et al.*: **The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations.** *J Am Coll Cardiol*. 2000; **35**(7): 1737–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Felker GM, Gattis WA, Leimberger JD, *et al.*: **Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure.** *Am J Cardiol*. 2003; **92**(5): 625–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Mentz RJ, Greene SJ, Ambrosy AP, *et al.*: **Clinical profile and prognostic value of anemia at the time of admission and discharge among patients hospitalized for heart failure with reduced ejection fraction: findings from the EVEREST trial.** *Circ Heart Fail*. 2014; **7**(3): 401–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Kosiborod M, Curtis JP, Wang Y, *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.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Frigy A, Fogarasi Z, Kocsis I, *et al.*: **Dataset 1 in: The prevalence and clinical significance of anemia in patients hospitalized with acute heart failure.** *F1000Research*. 2016.
[Data Source](#)

Open Peer Review

Current Peer Review Status:

Version 2

Reviewer Report 13 September 2017

<https://doi.org/10.5256/f1000research.13480.r25177>

© 2017 Machado J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

José Machado

Computer Science and Technology Center, University of Minho, Braga, Portugal

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 11 September 2017

<https://doi.org/10.5256/f1000research.13480.r25175>

© 2017 Seeberger M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Manfred Seeberger

Department of Anaesthesiology and Intensive Care Medicine, Klinik Hirslanden, Zürich, Switzerland

As described by the authors, they have reconsidered their statistical analysis but the main message of the article remained the same. These changes do not address my concerns expressed regarding the first version of the article.

"The authors have raised an interesting question. However, they need to define a more specific study hypothesis and calculate the sample size needed for analyzing that hypothesis. The current study design and sample size does not allow for drawing any reliable conclusions."

Therefore, I am sorry to renew my concerns. I consider this study as valuable hypothesis-

generating work. However, there are several reasons that should keep the authors from drawing the conclusions stated in the article:

1. The current work was not hypothesis-driven research
2. Consequently, no sample size / power calculation was made
3. Making multiple statistical analyses based on 21 patients with anemia will result in some positive findings/correlations (maybe just by chance) and many negative findings (maybe just because the sample size is dramatically inadequate).

At its current state, I cannot recommend to publish the revised version of the article. I could support publication if the findings were presented as hypothesis-generating but with the clear statement that the study lacks power for drawing valid conclusions.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 23 August 2017

<https://doi.org/10.5256/f1000research.13480.r25176>

© 2017 Jost N. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Norbert Jost

Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary

The authors for the revised paper from "A Frigy *et al*: The prevalence and clinical significance of anaemia in patients hospitalized with acute heart failure" have answered my original concerns. They have now included the required data from the patients included in the cohort for the study. I suggest the acceptance of the paper.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cardiovascular pharmacology, cardiac electrophysiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 November 2016

<https://doi.org/10.5256/f1000research.8473.r17358>

© 2016 Jost N. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Norbert Jost

Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary

◦ **Title and Abstract:**

More or less acceptable. I would suggest adding some details about the general life quality of the patients.

◦ **Article content:**

Please give details about the general conditions of the patients including: i) data about other diseases (cardiac and not cardiac as well); ii) status when they arrived at the hospital and how was their status when leaving the hospital; was there post hospitalization care or not, and if yes what were the results.

◦ **Conclusions:**

Insufficiently short. Please supplement with information and comments about some comparative details of other studies in this field.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 July 2016

<https://doi.org/10.5256/f1000research.8473.r14766>

© 2016 Seeberger M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Manfred Seeberger

Department of Anaesthesiology and Intensive Care Medicine, Klinik Hirslanden, Zürich, Switzerland

The authors have assessed the prevalence of anemia in a cohort of 50 patients hospitalized with acute heart failure (AHF), and also assessed the existence of a correlation between anemia and the severity of the clinical picture. They found anemia in 21/50 patients but no correlation of anemia with other factors related to severity and prognosis of AHF. They conclude that this finding is

suggestive of an independent role of anemia in influencing the clinical picture and prognosis of AHF.

The study by Frigy *et al* may serve as an interesting pilot study for a larger prospective study. However, the current sample size is insufficient for drawing any reliable conclusion on the prevalence of anemia in patients with AHF, and on the influence of anemia on course and outcome of AHF. Given the small sample size, it is not meaningful to perform multiple statistical analyses. And the small sample size should keep the authors from rejecting a possible correlation between anemia and other factors related to severity and prognosis of AHF. And the final conclusion remains unclear to me: why does the lack of statistical correlation between anemia and other factors related to severity and prognosis of AHF suggest an independent role of anemia in influencing prognosis of the disease? The authors have not studied prognosis and outcome at all.

The authors need to define the study question more specifically: what is (are) the outcome(s) they are looking for in the population of patients with acute heart failure? Based on a specific study question and hypothesis, the authors need to perform a sample size calculation. It will be interesting to read the results of that adequately sized study.

The authors have raised an interesting question. However, they need to define a more specific study hypothesis and calculate the sample size needed for analyzing that hypothesis. The current study design and sample size does not allow for drawing any reliable conclusions.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 07 June 2016

<https://doi.org/10.5256/f1000research.8473.r14212>

© 2016 Machado J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

José Machado

Computer Science and Technology Center, University of Minho, Braga, Portugal

This article addresses the prevalence of anemia amongst patients hospitalized with acute heart failure (AHF) and the existence of a correlation between anemia and the severity of the clinical picture. The manuscript is well written, but I have some concerns on certain points. Below are more specific comments by section:

- Introduction: More information about the purpose of the topic addressed would provide welcome context, i.e. the relevance of the study conducted. A bit more detail about anemia and acute heart failure would also be helpful in order to understand better the relevance of the potential correlation addressed;

- Methods: They may be some reservations concerning the data size: a small sample of data was used in order to conduct this study. On the other hand, more information regarding the methods used and how the study was specifically conducted would also be insightful;
- Discussion and conclusions: A poor discussion and conclusions are presented. Thereby, the results should be discussed in more detail, i.e. the results presented in Table 1. For instance, a more specific discussion could be done regarding the most relevant parameters presented in Table 1, i.e. parameters in patients with and without anemia.

Overall, I consider this study interesting but more information regarding certain topics seems undoubtedly needed in order to complete and clarify some crucial points addressed throughout this paper.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research