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Prognosis of the comorbid heart failure and Anemia: A systematic review and meta-analysis

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ABSTRACT

Background: Anemia is found to be an independent risk factor of morbidity, mortality and hospitalization among patients with heart failure. The prevalence, as the potential treatment options of anemia in HF has received increasing clinical interest and epidemiological studies have indicated a variation in the prevalence of anemia in patients with HF.

Method: Electronic search took place in the databases: Pubmed, Cochrane and CINAHL to locate studies in English that investigated the effect of anemia in patients with HF. The overall pooled effect (relative risk, RR) of anemia as comorbid factor compared with HF patients without anemia was estimated by using a random effects analysis (95% confidence interval (CI) for the outcomes of HF — related mortality rate, re-hospitalization and physical condition.

Results: Twenty-six studies were selected. In the overall RR of mortality, re-hospitalization and extended hospitalization was 1.70, 95% CI (1.47–1.98), p < 0.00001, for readmission rate 1.57, 95% CI (1.17, 2.10), p = 0.003 and 1.25, 95% CI (0.59–1.90), p = 0.0002 respectively in behalf of heart failure patients without anemia. Likewise, patients with anemia tend to have worse functionality according to NYHA classification 1.23, 95% (CI 0.99–1.52), p = 0.06. A meta-regression analysis conducted in an effort to explain the heterogeneity of mortality.

Conclusion: The meta-analysis gives an outline profile of patients with the co-morbidity HF and anemia in terms of clinical outcomes. The results point out worse prognosis in HF patients with anemia. Nevertheless, the available data did not allow the extraction of a conclusion in which exact Hb levels anemia becomes a negative predictor of prognosis.

1. Introduction

Heart failure is a chronic clinical syndrome that is associated with significant mortality, morbidity, and healthcare costs. Frequently, patients with HF experience hospitalizations and even though there are new therapies, the mortality rate of heart failure (HF) patients is still high [1–3]. Furthermore, HF estimates 5% and 2% of all hospital admissions and global health spending respectively [4–6].

Despite the new therapies, prognosis in HF remains poor. More specifically, the mortality rate ranges from 30 to 40% in the first year and 60–70% in the first five years. Also, this condition affects the quality of life of the patients [4,6–7]. This poor prognosis worsens even more when co-morbidities such as anemia, diabetes mellitus (DM) or chronic kidney failure co-exist [8–10], anemia is a co-morbidity of great interest. Over the last decade, the prevalence, as the potential treatment options of anemia in HF have received increasing clinical interest and epidemiological studies have indicated a wide variation in the prevalence of anemia in patients with chronic HF [8,11–13]. More specifically, the prevalence of anemia in HF patients varies in published studies from 4 to 55%, due to heterogeneous patient populations and the lack of specific definition [12,14–17].

As mentioned above, varied definitions of anemia have been used including hematocrit <30–37%, hemoglobin <12 mg/dL and the definition from the World Health organization (WHO). According to WHO, anemia is defined as hemoglobin less than 12 g/dl for women and less than 13 g/dl for men [18–21].

In addition, several projects have demonstrated that anemia with the presence of HF was a predictor of morbidity, mortality and hospitalization and also a negative impact on patient's quality of life.

1.1. Aim

The goal of the present systematic review and meta-analysis is to investigate the prognosis of anemia in patients with heart failure.

1.2. Individual objectives

To investigate the prognosis of the co-morbidity of anemia and heart failure, examining the following clinical outcomes:

- the mortality rate between patient's with and without anemia;
- the re-hospitalization frequency among patients with and without anemia;
- if there is a difference regarding the length of hospital stay among patients with and without anemia; and
- the association between the co-morbidity and the functionality of the patients according to NYHA classification.

2. Methods

2.1. Design

The present study is a systematic review and meta-analysis of studies assessing the relation of anemia and HF on outcomes of mortality frequency of hospitalization, length of stay in the hospital, and mortality. Using a meta-regression analysis, we want to estimate the heterogeneity of the studies included in the meta-analysis. In order to select the studies that would be included in the meta-analysis, we set some criteria as is referenced below. To assess the studies and to conduct the current meta-analysis, we used the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.2. Search strategy

The search of the literature was conducted from May 2014 until June 2014. The articles research took place in the electronic databases: Pubmed, Cochrane Library and CINAHL. To conduct the search, we used the combination of the words: "heart failure"," anemia", "and readmission "and" NYHA class". A combination of all words took place using the word AND.

In order to select the articles we set the following criteria: The articles should be published in the English language in the last decade (2004–2014) and should have examined clinical outcomes of the co-morbidity HF-anemia. The aim of the study, specifically, should be one or more of the following clinical outcomes: frequency of readmissions, mortality and/or length of hospital stay. The exclusion criteria where the following: articles that were in another language, except English and studies that have been published before 2004. Furthermore, we excluded studies that were examining the effectiveness of anemia treatments. Last but not least, we excluded articles that have been referred generally for cardiovascular problems and not specifically for HF. It is noticeable to highlight that we did not exclude articles that were referred in other co-morbidities that usually co-exist with HF, as HF is a complicated syndrome with a lot of co-morbidities. Although, we did include these articles in the meta-analysis only if the results of HF and anemia were separated from the rest of the co-morbidities.

2.3. Evaluation and selection of studies

Overall, from the research in the databases: PubMed, Cochrane library and CINAHL 3831 studies have come to light. After reading the studies title, 3580 were excluded and therefore 251 studies remained for further investigation. Eighteen studies were excluded, because they were published in other languages except English.

Furthermore, based on the inclusion and exclusion criteria studies, excluded after reading the abstract as they investigated: 1) effectiveness of therapy, 2) other co-morbidities of HF and the results were not separated for anemia, 3) how changes in Hb level can influence the rate of morbidity or mortality 4) they compare different subgroups of patients with heart failure and anemia between them. Also, studies excluded in

this stage; 1) were not specific for HF (they include other cardiac complications), they investigated differences for patients with HF and anemia, comparing in-patients and out-patients and finally few studies did not examine any of the clinical outcomes of our interest.

Moreover, 150 studies were reviews, systematic reviews or Scientific Integrity Reviews, two of them meta-analyses and the following two reports were not found as a full text.

Lastly, six studies were found to be the same studies from different databases or different combination of words and two of the studies were excluded after reading the whole report document. These studies were excluded because their data was in a form that we could not use them.

After the above process, twenty-six studies were found to meet the inclusion criteria and therefore, a critical appraisal applied for the completeness of information, design and implementation. Various amounts of studies were more or less methodologically good. The main features of each study are summarized in the Table 1 and the process undertaken is indicated in Fig. 1.

2.4. Statistical analyses

In order to conduct meta-analysis of the data that have been extracted from each study we used the software program Review Manger 5.3 of Cochrane Library. The primary measures of the meta-analysis were the following clinical outcomes: mortality, readmission, length of hospital stay and the correlation with the NYHA functional class if any. Firstly, we estimate the heterogeneity of the studies. According to the results, we chose to perform the random effect models by the DerSimonian and Laird. In addition this model takes into account both the between and within studies variability.

In each comparison we calculated the quantitative heterogeneity visually using Q (x^2) and I^2 statistics. We also calculated the 95% CI in each comparison. The same process has been followed for the secondary outcomes of the meta-analysis.

Funnel plot was performed to assess the publication bias. The funnel plot was not skewed or asymmetrical, which represent absent of publication bias. When the funnel plot has these two characteristics, it is due to publication bias; exclusion of small studies or exclusion of studies with "negative" results.
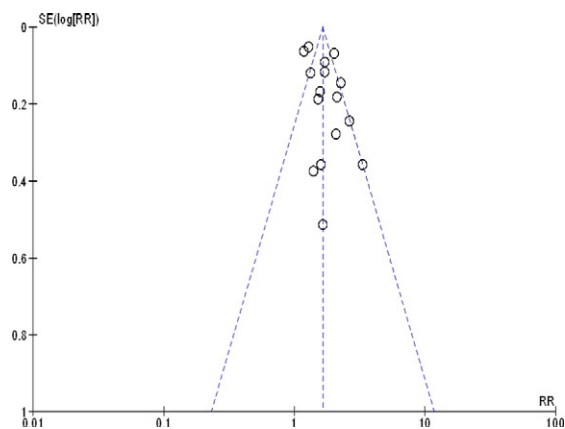
3. Results

The current search found a total of 26 studies that met the inclusion criteria for the meta-analysis. Thirteen of these studies were prospective correlation studies [3,10,22–32] ,nine were retrospective correlation [6,16,18,33–37,40] and two of them were descriptive correlation studies [41–42]. Also in one study the authors collected the data retrospectively and prospectively (two studies in one) [43]. In regards to the country that each research was conducted in, two of them were in Brazil, two