International Journal of Cardiology 169 (2013) 349–353

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Hemoglobin nonrecovery following acute myocardial infarction is a biomarker of poor outcome: A retrospective database study

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ARTICLE INFO

Article history:
Received 26 February 2012
Received in revised form 4 September 2013
Accepted 27 September 2013
Available online 3 October 2013

Keywords:
Hemoglobin
Anemia
Acute myocardial infarction

ABSTRACT

Background: Anemia on admission and during hospitalization is associated with poor short and long term prognosis among patients with acute coronary syndrome (ACS). Our objective was to examine the prognostic implications of longitudinal hemoglobin (Hb) levels following a first acute myocardial infarction (AMI).
Methods: We utilized data obtained from the computerized database of a large community based health care maintenance organization to identify patients who survived for at least 6 months following a first AMI, during the years 2003–2010. Hazard ratios were calculated using Cox proportional regression models with various Hb measurements as dependent variables, and net reclassification improvement (NRI) was applied to evaluate the prognostic usefulness of these Hb measurements.
Results: Last Hb measurement during a 6–24 month follow-up period was found to have the highest prognostic power. In males, Hb levels below 13 g/dL were gradually associated with a higher risk of events, reaching a HR of 4.13 at Hb levels <11 g/dL. In females, only Hb levels lower than 11 g/dL were significantly associated with a higher event rate (HR = 2.42, p = 0.003). Hb decrease was significantly associated with an increased risk in both genders, even among non-anemic patients at baseline.
Conclusions: Anemia and Hb decrement following a first AMI are associated with worse prognosis and elevated risk of combined all cause mortality and recurrent cardiac events.

1. Introduction

Patients with acute coronary syndromes (ACS) frequently present with anemia or relatively low levels of hemoglobin (Hb) [1–3], and anemia is a known negative prognostic predictor in ACS and in other various cardiac conditions including heart failure and congenital heart disorders [4–7]. Among patients suffering from an acute coronary event, anemia on admission and during hospitalization for acute myocardial infarction (AMI) is a predictor of a poor outcome in both short and long terms [1,4,5], although most previous studies were limited by analyzing the impact of Hb measurements taken only during the acute event and subsequent hospitalization. Other studies were limited to a single Hb measurement after hospital discharge, reporting that persistent or developing anemia indicates an elevated risk for heart failure, hospitalization and mortality [8,9]. Long term longitudinal Hb determinations and its prognostic implications were studied in heart failure patients [6] but not in relatively large scale studies of patients following AMI.

We presently evaluated longitudinal Hb levels following a first AMI in order to assess their prognostic implications during the two years following the event.

2. Methods

2.1. Settings

We conducted a retrospective cohort study using the database of Maccabi Healthcare Services (MHS), Israel's second largest healthcare maintenance organization (HMO), described in detail elsewhere [10–12]. Briefly, the MHS database is a community based database, operating since 1996 and currently includes medical history and laboratory data for ~2 million members. Under the Israel National Health Insurance Act, all Israeli citizens are enrolled in one of the four HMO's. The HMO's may not bar any citizen from membership, and citizens may switch from one HMO to another, although these movements are summed up to only 1–2% of the population in reality.

All data was obtained from MHS computerized database and used to elicit information on all community consultations, diagnoses by hospital and community physicians, dispensed medications, laboratory results, and other treatments and interventions. Event dates are drawn automatically from hospital reports. The study complies with the declaration of Helsinki and was approved by the institutional review board (IRB) of Assuta Medical Center, Tel-Aviv. The authors of this manuscript have certified that they comply with the principles of ethical publishing in the "International Journal of Cardiology".

Abbreviations: ACS, acute coronary syndromes; Hb, hemoglobin; AMI, acute myocardial infarction; HMO, health care maintenance organization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HR, hazard ratios; CI, confidence intervals; NRI, net reclassification index.

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0167-5273/$ – see front matter
http://dx.doi.org/10.1016/j.ijcard.2013.09.004

2.2. Study population

Included in the study were 5290 males and 1732 female MHS members aged 26 or above who had a record of having a first AMI between 2003 through 2010. Cancer patients (n = 595; 383 males, 212 females) and pregnant women (n = 6) were excluded. In addition, individuals with many (20 or more) Hb determinations during a two year post event were also excluded (n = 68) since these multiple measurements may have obscured an alternative medical problem. In order to calculate an Hb trend, individuals with only one Hb determination during a two year post event period (n = 674; 555 males, 119 females) and less than 30 days between first and last Hb determination (n = 43) were excluded. Additional exclusion criteria applied included absence of estimated glomerular filtration rate (eGFR) as impairment of renal function has implications on Hb status, and follow-up time shorter than six months, as our goal was to assess longitudinal Hb level influence on long term prognosis, leaving 4155 males and 1325 females eligible for analyses. Fig. 1 presents detailed flowchart of the study population.

The index date for each patient was defined as the date of first AMI. Follow-up was conducted for each patient until the date of a second AMI, a PCI or CABG procedure, death, leaving MHS or after two complete years from index, whichever came first.

2.3. Hemoglobin measurements

The mean number of Hb determinations per patient was 4.6 (SD = 2.9), and 19% of the patients had only two Hb measures. For each subject, the following Hb determinations were reviewed: first Hb level after the index date and last Hb level during follow-up. In order to assess the relative change in Hb levels during follow-up, we calculated the mean yearly Hb difference (Hb change divided by the time difference in days/365), accounting for the lag time difference between the first and last measurements. Anemia status for each Hb measurement was defined as Hb levels <12 g/dL in women and <13 g/dL in men, in accordance with the World Health Organization's criteria [13].

2.4. Study outcomes

The study outcome was defined as a recurrent AMI, additional coronary intervention (PCI, or CABG) or death from any reason, occurring at least six months and up to 24 months following the first myocardial infarction.

2.5. Statistical analysis

All analyses were stratified by gender. Cox proportional hazard regression models were used, with various Hb measures as dependent variables. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. The proportional hazard assumption was tested based on Schoenfeld residuals regressed on follow-up time [14]. To control for possible confounding, factors which are known to be of prognostic value after coronary events or to affect Hb levels, and are available at the database, were included as covariates in multivariable models: age, eGFR – using the simplified MDRD (Modification of Diet in Renal Disease) formula taking into account only gender, age and serum creatinine – then classified as above 60 ml/min, moderately impaired between 60 and 30 ml/min, and severely impaired <30 ml/min [15]; diabetes, hypertension, chronic obstructive pulmonary disease (COPD), rheumatic disease and inflammatory bowel disease (IBD). Exposures to chronic medication such as statins, warfarin, clopidogrel, enoxaparin, heparin, beta blockers, ACE inhibitors, ARB's, nitrates or proton pump inhibitors (PPI) (defined as at least one purchase during 6 months from the index date) were also included.

In order to explore the predictive value of various Hb measures, different multivariate models, each with a different Hb measure, were performed. In addition, net reclassification improvement (NRI) measure was applied in order to evaluate the prognostic usefulness of these Hb measures as biomarkers [16].

Finally, in order not to assume linear association with Hb, we analyzed last Hb categories and their association with prognosis. All analyses were adjusted for age. A p value lower than 0.05 (two-tailed) was considered statistically significant. The analyses were done using the IBM SPSS statistical package version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

The cohort included a total of 4155 males and 1325 females eligible for analyses. The mean age was 58.2 years (SD = 12.2, range 27–98) for men and 69.8 years (SD = 12.7, range 27–98) for women. Forty six male patients (1.1%) and sixteen female patients (1.2%) left MHS during the follow-up period. Table 1 presents the basic characteristics, comorbidities and relevant medications used by study population. An outcome event, defined as all-cause mortality, an additional myocardial infarction or coronary intervention, occurred within 6–24 months from the index event in 573 males (13.8%) and 212 females (16.0%): 98 deaths, 321 interventions and 154 cases of recurrent MI in males, and 76 deaths, 61 interventions and 75 cases of recurrent MI in females.

In both genders, lower first Hb levels after the index event and anemia at this measurement were associated with a higher risk for an additional myocardial infarction, coronary intervention or death during the study period (Table 2). It is noteworthy that the last Hb measurement had stronger prognostic power compared to the first Hb measurements, with an age- and sex-adjusted HR of 1.33 (95% CI 1.27–1.39, p < 0.001) per 1 g/dL Hb decrease. Hb decrement in the two years following a first AMI predicted a significantly elevated risk for death, recurrent infarction

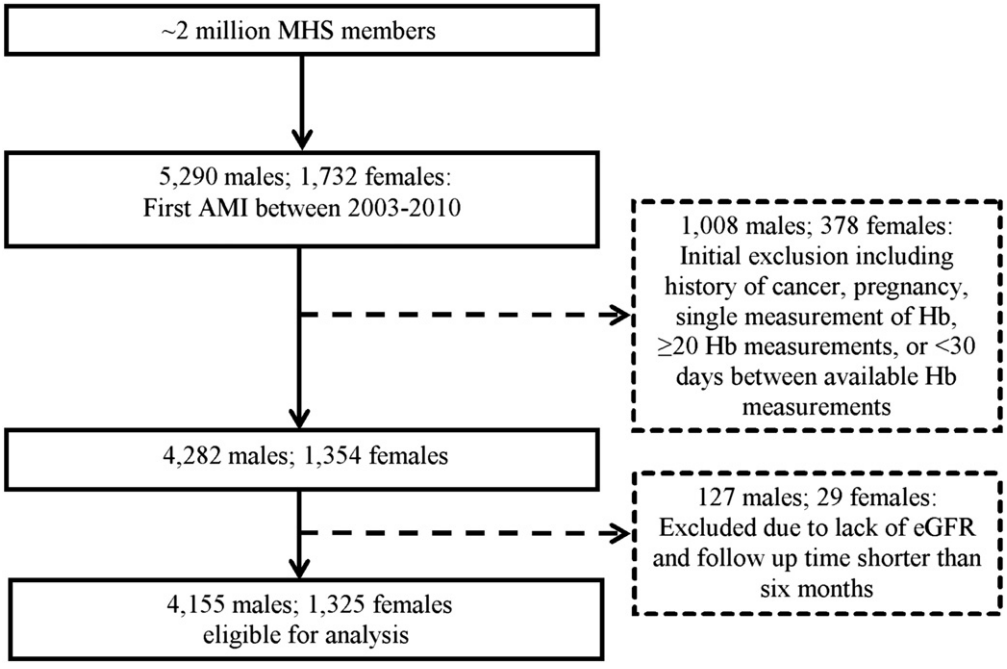

Fig. 1. Study flow chart. Primarily 5290 males and 1732 females MHS members aged 26 or above who had a record of having a first AMI from 2003 through 2010 were included. Individuals with multiple (20 or more) Hb determinations during a two year post event were excluded since these measurements may have obscured an alternative medical problem. Additional exclusion criteria applied included absence of estimated glomerular filtration rate (eGFR) and follow-up time shorter than six months.