

Prognostic relevance of normocytic anemia in elderly patients affected by cardiovascular disease

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ABSTRACT

BACKGROUND Anemia associated with cardiovascular diseases (CVD) is a common condition in older persons. Prevalence and prognostic role of anemia were extensively studied in patients with myocardial infarction (MI) or congestive heart failure (CHF) whereas limited data were available on patients with atrial fibrillation (AF). This study was conducted to assess the clinical prevalence and prognostic relevance of anemia in elderly patients affected by AF and other CVDs.

METHODS A total of 866 elderly patients (430 men and 436 women, age: 65–98 years, mean age: 85 ± 10 years) were enrolled. Among these patients, 267 patients had acute non-ST-segment elevation MI (NSTEMI), 176 patients had acute CHF, 194 patients had acute AF and 229 patients were aged-matched healthy persons (CTR). All parameters were measured at the hospital admission and cardiovascular mortality was assessed during twenty-four months of follow-up.

RESULTS The prevalence of anemia was higher in NSTEMI, CHF and AF patients compared to CTR subjects (50% vs. 15%, $P < 0.05$), with normocytic anemia being the most prevalent type (90%). Adjusted mortality risk was higher in anemic patient versus non-anemic patient in all the groups of patients [NSTEMI: hazard ratio (HR) = 1.81, 95% CI: 1.06–2.13; CHF: HR = 2.49, 95% CI: 1.31–4.75; AF: HR = 1.98, 95% CI: 1.01–3.88]. Decreased hemoglobin levels ($P = 0.001$) and high reticulocyte index ($P = 0.023$) were associated with higher mortality in CVD patients.

CONCLUSIONS The significant associations between CVD and anemia and the prognostic relevance of anemia for elderly patients with CVD were confirmed in this study. The presence of anemia in AF patients is associated with a two-fold increased mortality risk compared with non-anemic AF patients. Low hemoglobin and high reticulocyte count independently predict mortality in elderly patients with CVD.

The prevalence of anemia significantly rises with advancing age in both men and women. Patients over 75 years have a 10% incidence of anemia, while those over 90 years have an incidence higher than 25%.^[1–3] Numerous causes may explain an anemic state in older persons, including macro-/micro-hemorrhages, iron deficiency, and chronic inflammation. Interestingly, the puzzling entity of unexplained anemia in the elderly represents 30% to 46% of elderly patients.^[4]

An anemic state in older individuals is associated with a number of negative outcomes, including heart disease, hospitalization, and death.^[5,6] It has been recently shown that a pre-existing state of anemia is correlated with the development and progression of acute coronary syndrome.^[7] For example, anemic patients who develop acute myocardial infarction (AMI) have an increased risk of death and in-hospital cardiovascular complications.^[8,9] In addition, the unfavorable impact of anemia has been reported

also in patients with AMI undergoing percutaneous coronary intervention.^[10] It is also widely recognized that a high prevalence of anemia is common in heart failure (HF) patients and is associated with significantly higher mortality rates.^[11,12]

Atrial fibrillation (AF) is the most common cardiac arrhythmia in older persons and it is associated with increased morbidity and mortality.^[3] AF is also a potent risk factor for ischemic stroke and reduces physical and cardiac performance as well as patient quality of life.^[13,14] However, only few reports have investigated the prevalence of anemia in patients with AF and its relevance on the clinical outcomes. It has been recently reported that anemia was associated with increased mortality and hospitalization in elderly patients with AF.^[15] However, in this previous study, anemia was defined based on hematocrit (Hct) levels and not hemoglobin (Hb) levels (< 13 g/dL in men and < 12 g/dL in women) as currently recommended by World Health Organization (WHO).^[16] The Hct value depends on plasma volume and consequently can be modulated from many different variables, including hemodynamic compensation, pharmacological treatment, hydro-electrolytic balance, hydration state, which are highly variable in patients with chronic heart disease. Thus, we aimed at investigating the association between anemia (defined by Hb level) and commonly observed heart diseases [congestive HF (CHF), AMI and AF] in a large sample of older patients. We also aimed at testing the prognostic value of anemia on mortality over time.

According to current AF management guidelines, oral anticoagulant therapy (OAT) is the cornerstone for the prevention of severe outcomes. However, OAT increases the risk of severe bleeding affecting the mortality rate, especially in elderly patients.^[17] Thus, to reduce the possible bias related to different AF pharmacological treatments, we included in the survival analysis only patients with OAT therapy.

METHODS

Study Population

The enrolment of patients started in February 2014 and ended in December 2017. Of the 3,453 patients that were consecutively admitted to the

Cardiology Unit of Italian National Research Centre on Aging Hospital in Ancona, Italy. A total of 866 elderly patients that fulfilled inclusion criteria were enrolled in the study (430 men and 436 women, age: 65–98 years, mean age: 85 ± 10 years). Among these patients, 267 patients had acute non-ST-segment elevation myocardial infarction (NSTEMI), 176 patients had acute CHF without evidence of AMI (CHF), 194 patients had acute AF without AMI and CHF (AF) and 229 patients were aged-matched healthy persons (CTR). Clinical history and information on the use of medications were collected for all patients.

Inclusion Criteria

Patients aged ≥ 65 years with evidence of acute NSTEMI, CHF decompensation, or acute AF at the time of admission to the INRCA Cardiology Department were enrolled. AF was diagnosed based on electrocardiography (ECG) analysis and clinical evaluation. Among the 194 AF patients, 68 patients exhibited a new-onset AF, and 126 patients had a recurrence of previous AF. Clinical and pharmacological management was as follows: (1) patients with new-onset acute AF were treated for 3–4 weeks with warfarin and heart rate was monitored to evaluate the need of cardioversion. Among these patients, 59 patients received pharmacological or electric cardioversion. During the subsequent follow-up, 48 subjects developed a permanent AF^[18] and, among them, 39 subjects continued to be treated with chronic OAT; and (2) 126 patients had a recurrence of AF. 39 patients of them were chronically treated with Class Ic drugs (propafenone or flecainide) and 78 patients were treated with amiodarone. In this group, 23 patients were concomitantly treated with beta-blockers. 98 of 126 patients developed a permanent AF during the follow-up, and among them, 86 patients required a chronic OAT. Anemic and non-anemic patients had similar AF treatment strategies.

In summary, among the 194 patients enrolled in our study with acute AF, 146 patients developed a permanent AF and among them, 125 patients were treated with OAT during the entire study period.

NSTEMI was diagnosed according to the European Society of Cardiology guidelines.^[19] Briefly, the diagnosis was made based on the presence of at least

two of the following criteria: (1) clinical symptoms potentially correlated to AMI, in particular, typical chest pain or sudden onset of dyspnea; (2) typical ECG alterations. ECG signs of myocardial ischemia included either transient or persistent ST-segment depression > 1 mm, persistent and definite T-wave inversion, including the pseudo-normalization of previously negative T-wave in ≥ 2 contiguous leads; and (3) significant rise and consequent fall of cardiac troponin T (cTnT) within the first 48–72 h from the Critical Care Unit admission. We have previously reported that conventional cTnT is a specific and sensitive marker for AMI diagnosis in elderly patients.^[20] Moreover, an echocardiogram was performed in all enrolled NSTEMI patients to confirm the presence of an infarcted area.

Patients with CHF and no evidence of AMI were selected among patients with a CHF exacerbation necessitating hospitalization. Only patients with CHF decompensation due to non-acute coronary syndrome etiology (such as an exacerbation of pulmonary pathologies due to infectious diseases, acute pulmonary embolism, hypertensive crisis, or valvular pathologies, i.e., aortic stenosis) were recruited for this study. In all acute CHF patients, the diagnosis was confirmed by transthoracic echocardiography and N-terminal prohormone of brain natriuretic peptide increased levels. The diagnosis of anemia was defined by a Hb concentration below the lower reference value (< 12 g/dL in women and < 13 g/dL in men) as reported by the WHO.^[16] Even if such reference values are under debate, studies have consistently acknowledged such cut-off levels to define anemia and recent epidemiological findings have confirmed such values as risk factors for mortality and functional impairment in the elderly.^[2]

CTR patients were selected among subjects participating in the cardiovascular disease (CVD) prevention program at INRCA. CTR subjects had the same median age as patients and the same percentages of men and women. All participants underwent clinical examinations from the same medical team. All subjects gave their informed consent before enrolment and the study protocol was approved by the local Ethical Committee.

Exclusion Criteria

Patients with severe hepatic or renal dysfunction,

malignancy, other diseases with a short-term prognosis (< 12 months), dialysis, blood transfusion, and acute gastric hemorrhage were excluded from the study. Patients with ST-segment elevation myocardial infarction and stable and unstable angina were also excluded. Moreover, patients with multiple cardiovascular morbidities, such as AF/CHF or AF/NSTEMI or NSTEMI/CHF were excluded from this study.

Follow-up

Over the 24-month follow-up period, 131 deaths were observed. 114 subjects that died due to CVD were included in statistical analyses, while 17 subjects that died for other causes were excluded. Moreover, to avoid possible bias on mortality rate due to the different pharmacological treatment of AF patients, only AF patients with a chronic disease in OAT were included in the survival analysis ($n = 125$).

Laboratory Assays

Blood concentrations of Hb, C-reactive protein (CRP), creatinine, albumin, and red blood cell count were measured by standard procedures. Conventional cTnT plasma levels (normal range: < 0.03 ng/mL) were determined by Electro Chemi Luminescence Immuno Assay using the Modular Analytics E170/Cobas immunoanalyzer (Roche Diagnostics) according to manufacturer's instructions.

The following hematological investigations were carried out for all patients in order to classify the type of anemia. Hb, total leucocyte count, differential leucocyte count, erythrocytic sedimentation rate, platelet count, Hct, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, packed cell volume and reticulocyte count. Reticulocyte index (RI) was calculated as reticulocyte percentage \times [(patient Hct/normal Hct)/maturation factor], with normal Hct equal to 45% for males and 42% for females, and maturation factor defined according to patient Hct (1.0: Hct $\geq 35\%$; 1.5: $25\% \geq$ Hct $> 35\%$; 2.0: $20\% \geq$ Hct $> 25\%$; and 2.5: Hct $< 20\%$).

Statistical Analysis

Baseline clinical characteristics according to study groups (CHF, NSTEMI, AF, and CTR) are reported as mean \pm SD. Differences among groups were com-



pared using general linear model analysis adjusted for age and gender. Contrast analyses were applied to compare CHF, NSTEMI, and AF patients versus CTR at baseline. When appropriate, the χ^2 test was applied for categorical variables. The correlations between parameters were calculated with Spearman's rho correlation coefficient.

Cumulative probability and survival curves were constructed using Kaplan-Meier estimates and compared using the log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) for death was calculated by using Cox regression model. We estimated the HR and 95% CI in two models for each group (CHF, NSTEMI and AF). The first model was unadjusted showing crude HR and 95% CI, whereas the second model was adjusted for the parameters that showed significant differences between anemic and non-anemic patients. Adjusted covariates included: age, sex, body mass index, red and white blood cells number, Hct, total cholesterol, high-density lipoproteins cholesterol, CRP, cTnT and creatinine. The final models were determined using a forward stepwise elimination procedure. The proportional hazard assumption was confirmed by ex-

amination of log-log survival curves and by testing of partial residual (Schoenfeld) and no relevant violation was found.

Probability values lower than 0.05 were considered statistically significant. The reported *P*-values were two-tailed in all calculations. Data were analyzed with SPSS 25.0 (SPSS Inc., IBM, Chicago, IL, USA).

RESULTS

Table 1 shows the main clinical characteristics of all participants. Interestingly, NSTEMI, CHF, and AF patients showed significantly lower Hb levels than CTR in both men and women.

There was a significant difference among numerous biochemical markers, including Hb among NSTEMI and CHF versus CTR, whereas only Hb values were found to be significantly different between AF patients and CTR.

Significant negative correlations between Hb and CRP and between Hb and creatinine were observed (Spearman's rho = -0.34 , $P < 0.001$ and Spearman's rho = -0.31 , $P < 0.001$, respectively).

Table 1 Biochemical and clinical parameters according to clinical status (n = 886).

Variables	Control subjects (n = 229)	Congestive heart failure (n = 176)	Non-ST-segment elevation myocardial infarction (n = 267)	Atrial fibrillation (n = 194)
Age, yrs	81.9 ± 10.1	83.6 ± 8.2 [†]	82.7 ± 8.5	80.7 ± 11.4
Body mass index, kg/m ²	25.2 ± 4.4	25.6 ± 5.4 ^{**}	25.1 ± 4.4 [†]	25.3 ± 4.0
White blood cells, 10 ³ /μL	7.0 ± 2.6	11.2 ± 6.0 ^{**}	10.3 ± 5.1 ^{**}	8.0 ± 3.1
Red blood cells, 10 ⁶ /μL	4.4 ± 0.6	4.0 ± 0.6	4.4 ± 4.0	4.4 ± 0.7
Hematocrit, %	39.9 ± 4.7	36.0 ± 7.0 ^{**}	36.7 ± 5.3 ^{**}	38.2 ± 5.3
Glycemia, mg/dL	108.9 ± 40.9	145.8 ± 59.1 ^{**}	151.7 ± 71.3 ^{**}	122.1 ± 47.0
Creatinine, mg/dL	1.0 ± 0.7	1.6 ± 1.1 ^{**}	1.5 ± 1.0 ^{**}	1.3 ± 0.9
Hemoglobin, g/dL				
Females	13.2 ± 1.8	11.5 ± 1.9 ^{**}	11.9 ± 1.8 ^{**}	12.0 ± 1.8 ^{**}
Males	14.5 ± 1.3	11.9 ± 2.0 ^{**}	12.5 ± 2.5 ^{**}	12.8 ± 2.2 [†]
Albumin, %	53.1 ± 6.2	50.3 ± 7.2 ^{**}	51.3 ± 6.6 ^{**}	53.9 ± 6.2
Total cholesterol, mg/dL	165.7 ± 46.9	147.9 ± 47.7	157.2 ± 45.8	165.7 ± 46.9
High-density lipoproteins cholesterol, mg/dL	52.3 ± 15.7	42.4 ± 16.6 ^{**}	45.5 ± 14.6 ^{**}	48.5 ± 16.4
Homocysteine, μmol/L	16.8 ± 7.0	18.6 ± 10.7	16.8 ± 8.0	17.7 ± 10.7
Cardiac troponin T, ng/mL	0.04 ± 0.07	0.15 ± 1.23 ^{**}	0.73 ± 0.41 ^{**}	0.08 ± 0.07
C-reactive protein, mg/dL	1.79 ± 5.28	6.97 ± 9.33 ^{**}	5.07 ± 7.48 ^{**}	1.90 ± 3.43

Data are presented as means ± SD. [†]Refers to the *P*-value was less than 0.01. ^{**}Refers to the *P*-value was less than 0.05. *P*-value was used to compare congestive heart failure, non-ST-segment elevation myocardial infarction and atrial fibrillation patients versus control subjects at baseline.



The state of anemia evaluated according to WHO current guidelines was compared between each group and CTR. The total percentage of subjects with anemia was similar (approximately 50%) in all groups of patients ($\chi^2 = 3.79$, $P = 0.150$) (Table 2). An increased number of subjects with anemia was observed in all the three groups of patients, including AF, compared with CTR [anemic patients vs. anemic CTR subjects; CHF: 93 (52.8%) vs. 34 (14.9%), $P < 0.01$; NSTEMI: 156 (58.4%) vs. 34 (14.9%), $P < 0.01$; AF: 96 (49.5%) vs. 34 (14.9%), $P < 0.01$] (Table 3). Interestingly, about 90% of anemic patients had normocytic anemia, independently of CVD (Table 2).

The Kaplan-Meier analysis revealed an increased mortality risk for anemic subjects in all three groups of patients compared to CTRs (Figure 1).

Unadjusted (crude HR) and adjusted mortality risks were calculated and showed in Table 3. As expected, anemic patients with CHF or NSTEMI showed significantly higher risk for mortality during the 24-month follow-up period, even after adjusting for age, sex, body mass index, red and white blood cell number, Hct, total cholesterol, high-density lipoproteins cholesterol, CRP, cTnT and creatinine (CHF: adjusted HR = 2.49, 95% CI: 1.31–4.75, $P =$

0.005; NSTEMI: adjusted HR = 1.81, 95% CI: 1.06–2.13, $P = 0.014$). Interestingly, also anemic patients with AF had a significantly higher mortality risk compared to AF patients without anemia, even after adjustment for above-mentioned confounding variables (AF: adjusted HR = 1.98, 95% CI: 1.01–3.88, $P = 0.046$). Among patients with CVD, decreased Hb levels predicted mortality after adjustment for age and sex (adjusted HR = 1.06, 95% CI: 1.04–1.09 for each 1 g/dL decrease in Hb, $P = 0.001$). The RI was also evaluated to assess the extent of the bone marrow compensatory response to anemia. An RI > 2 suggests the presence of a bone marrow response to blood loss or hemolysis. As expected, the median RI of elderly subjects with anemia was overall low (Table 2), suggesting the high prevalence of hypoproliferative normocytic anemia. Notably, we observed that increased RI is associated with higher mortality in CVD patients, after adjustment for age and sex (adjusted HR = 1.51, 95% CI: 1.06–2.14 for each 1-point RI increase, $P = 0.023$).

Survival analyses in AF patients were performed only in those treated with OAT. Even though we reported survival analyses in the setting of AF patients using OAT, we tested for differences among

Table 2 Number and percentage of subjects with anemia (ANEMIA+) and without anemia (ANEMIA-) in patients affected by congestive heart failure, non-ST-segment elevation myocardial infarction, or atrial fibrillation ($n = 637$), and in healthy control subjects ($n = 229$).

Group	ANEMIA-	ANEMIA+	Normocytic anemia	Reticulocyte index
Congestive heart failure	83 (47.2%)	93 (52.8%)	84 (90.3%)	0.74 (0.23–1.25)
Non-ST-segment elevation myocardial infarction	111 (41.6%)	156 (58.4%)	140 (89.7%)	0.80 (0.16–1.44)
Atrial fibrillation	98 (50.5%)	96 (49.5%)	87 (90.6%)	0.67 (0.25–1.09)
Control subjects	195 (85.1%)	34 (14.9%)	31 (91.1%)	0.75 (0.30–1.20)

Data are presented as n (%) or median (interquartile range). Congestive heart failure versus control subjects: $\chi^2 = 66$, $P < 0.01$; non-ST-segment elevation myocardial infarction versus control subjects: $\chi^2 = 99$, $P < 0.01$; atrial fibrillation versus control subjects: $\chi^2 = 59$, $P < 0.01$.

Table 3 Unadjusted and fully adjusted Cox proportional hazard regression analyses of 24-month mortality.

Group	Death rate		Unadjusted model		Adjusted model*	
	Anemia absent	Anemia present	HR (95% CI)	P-value	HR (95% CI)	P-value
Congestive heart failure	25.6%	46.1%	2.02 (1.20–3.43)	0.017	2.49 (1.31–4.75)	0.005
Non-ST-segment elevation myocardial infarction	25.0%	41.8%	1.73 (1.10–2.72)	0.008	1.81 (1.06–2.13)	0.014
Atrial fibrillation	17.0%	36.2%	2.49 (1.38–4.52)	0.003	1.98 (1.01–3.88)	0.046
Control subjects	8.2%	14.7%	1.83 (0.54–6.15)	0.232	0.46 (0.09–2.20)	0.327

*Refers to models were adjusted for age, sex, body mass index, red and white blood cells number, hematocrit, total cholesterol, high-density lipoproteins cholesterol, C-reactive protein, cardiac troponin T and creatinine. CI: confidence interval; HR: hazard ratio.



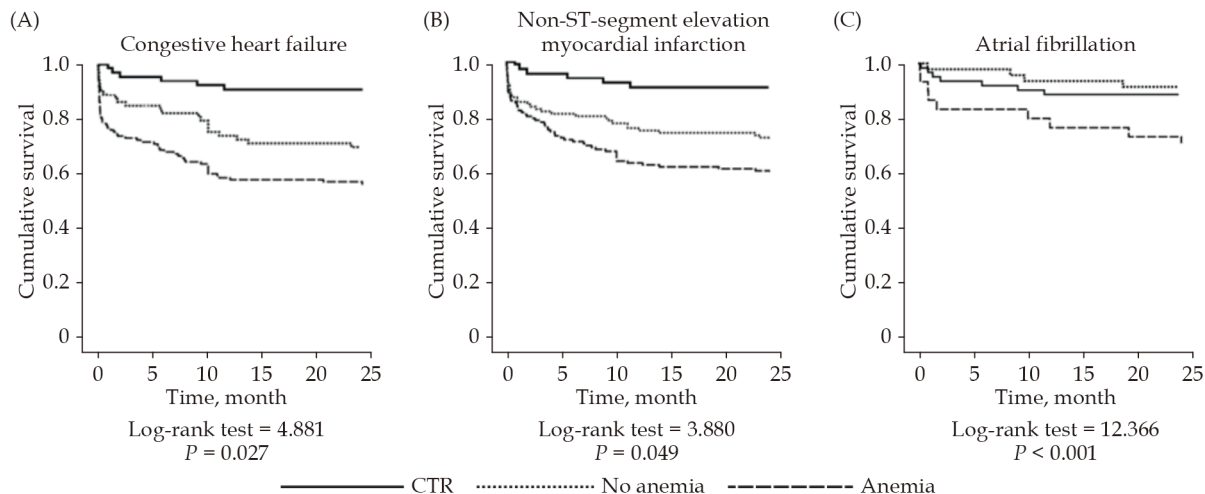


Figure 1 Kaplan-Meier curves for time to death in patients with congestive heart failure (A), non-ST-segment elevation myocardial infarction (B), and atrial fibrillation (C) grouped according to the presence or absence of anemia on admission assessed by means of hemoglobin concentration. The survival curve for CTR is displayed for comparison. CTR: control subjects.

those using digitalis, but we did not find any significant correlations with mortality (data not shown).

DISCUSSION

Anemia in older persons is associated with severe complications compared to younger adults. Older patients with anemia are considered a delicate group needing specific attention because they are at a greater risk for a wider range of complications, including increased risk for mortality, cognitive dysfunction, longer hospitalization times, co-morbid conditions, reduced bone density, and increase of falls and fractures.^[2,5,6,13] It is widely known that anemia is independently associated with poor outcomes in patients with CVD, including CHF and AMI.^[4,12] However, there is currently limited data on the association between anemia and AF in older patients.^[15] Here, we analyzed the presence of anemia in a cohort of elderly patients, including patients with NSTEMI, CHF, or AF. We found that patients with heart disease of any kind were more likely to be anemic. In fact, about 50% of the enrolled patients were anemic at the time of hospital admission, without significant differences among the three disease states. The prevalence of anemia was previously extensively studied in CHF and AMI patients, and thus we confirmed the expected results. However, this is among the first studies classifying anemic patients according to the WHO definition,^[16] and showing an association between

low Hb levels and AF in a group of elderly patients.

Due to the study design, we can only speculate on the reasons explaining the relationship between anemia and AF. Firstly, the presence of a long chronic state of anemia may trigger ventricular remodeling and cardiac dysfunction.^[21] Secondly, the Hb reduction may be associated with other risk factors for CVD, such as decreased nutritional status or increased inflammatory status. Different markers of inflammation, such as fibrinogen, white blood cell count, and CRP were reported to be related with the strength of the association between anemia and CVD.^[22] We observed a negative correlation between Hb and CRP, confirming that anemia may be a marker associated with the inflammatory process. Moreover, recent studies suggest strongly that aging is associated with the deregulation of pro-inflammatory cytokines, most notably interleukin-6, which may negatively impact hematopoiesis, either by inhibiting erythropoietin (EPO) production or by interacting with EPO receptors.^[23] At the moment, all the major clinical trials testing the impact of erythrocyte stimulating agents on anemia have failed to show any improvements in the outcomes related to CVD, stroke, and vascular thrombosis. However, moderate elevations in Hb (e.g., to 13 g/dL) using EPO have been associated with a significant increased risk of thrombotic cardiovascular events and HF.^[24] The literature has revealed that the ageing process itself affects blood production with a reduced ratio of bone marrow to fat cells and reduced marrow re-

sponse when stimulated with EPO.^[25] We found that about 90% of CVD (NSTEMI, CHF and AF) patients with anemia showed a normocytic pattern, which is commonly associated with a wide variety of chronic disorders, including inflammatory conditions, infections, and various systemic diseases.^[26] Thus, it could be hypothesized that ageing “*per se*” in association with the presence of chronic diseases could contribute to the decline of Hb and the age-related increase in the prevalence of anemia.^[27] Interestingly, we found that many variables were significantly different in NSTEMI and CHF compared to CTR, while there was no difference in AF patients compared to the CTR, except for anemia. This observation suggests that the link between anemia and AF could be different from that between CHF/NSTEMI and anemia. One may hypothesize that a relative ischemia due to the anemia could induce electrophysiological alterations, modifying the heart conductance system in particular at the level of the sinus node. Another possible mechanism may be related to tachycardia and autonomic nervous system (sympathetic) activation due to the presence of anemia and reduction of effective blood volume.

The key finding of our study is that elderly patients affected by CVD and anemia showed an increased mortality risk at 24 months of follow-up in comparison to non-anemic patients. The prognostic relevance of anemia was proven in NSTEMI, CHF and AF groups separately, independently of multiple confounders. In a previous paper, we reported that in old NSTEMI patient, Hb levels are an independent predictor of all-cause death at one year after acute event.^[28] Here, we confirm that reduced Hb levels are associated with higher 24-month mortality in a cohort of elderly CVD patients. Moreover, we showed that increased RI, which suggests chronic blood loss in elderly patients, is associated with higher mortality in CVD patients. While the extent of the bone marrow compensatory response to anemia in CHF has been previously evaluated by means of RI,^[29] this is the first study assessing the prognostic relevance of RI in CVD patients.

Although few studies have shown that anemia, determined at a single time point, was associated with worse prognosis in AMI and/or CHF patients, only few studies explored the impact of anemia in AF patients.^[15,30] Here, we showed that anemic pa-

tients with AF have an approximately two-fold risk of death compared to non-anemic AF patients. Our results are in agreement with a previous report from the Fushimi AF Registry showing that the presence of anemia in AF patients is associated with increased risk of CHF hospitalization, major bleeding, and all-cause mortality.^[30] Importantly, this result was obtained by including in the survival analysis only AF patients with chronic AF and under OAT, to avoid possible bias due to the different impact on mortality rate of pharmacological treatments.^[31]

LIMITATIONS

Some limitations of the present study must be considered. On the one hand, our study is limited by its retrospective design and the mandate to have an available complete blood count assessment at the time of the hospital admission, which could have limited the power to detect relevant association due to the relatively limited sample size. On the other hand, we were unable to identify transient versus persistent anemia. Previous reports showed that patients with transient anemia have survival rates significantly better than those with persistent anemia.^[31] Since the presence of persistent anemia confers poorest survival in patients with CVD when compared with incident or resolved anemia, it could be speculated that the largest part of the elderly patients enrolled could be affected by persistent anemia. However, it was reported that both baseline and late anemia carried prognostic significance in patients affected by coronary artery disease.^[32]

CONCLUSIONS

In conclusion, we showed that the concomitant presence of anemia in elderly CVD patients exerts an additive adverse effect on mortality. Anemia of older persons is often related to subclinical chronic inflammation, that is, inflammaging, but also malnutrition, hematological and solid malignancies should be regarded as possible causes.^[33] Given that the management of anemia largely depends on its etiology and most of the therapeutic options are feasible also at advanced ages,^[34] a comprehensive diagnostic workup to find the underlying causes is warranted to reduce the burden of mortality associated with late-life CVD. Future intervention trials



and more accurate clinical registries are needed to identify those patients who may benefit from specific therapies targeting anemia associated with AMI, CHF and AF.

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REFERENCES

- [1] Ania BJ, Suman VJ, Fairbanks VF, *et al.* Incidence of anemia in older people: an epidemiologic study in a well defined population. *J Am Geriatr Soc* 1997; 45: 825–831.
- [2] Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Curr Opin Hematol* 2005; 12: 123–128.
- [3] Davis RC, Hobbs FD, Kenkre JE, *et al.* Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. *Europace* 2012; 14: 1553–1559.
- [4] Pang WW, Schrier SL. Anemia in the elderly. *Curr Opin Hematol* 2012; 19: 133–140.
- [5] Girelli D, Marchi G, Camaschella C. Anemia in the elderly. *Hemasphere* 2018; 2: e40.
- [6] Riva E, Tettamanti M, Mosconi P, *et al.* Association of mild anemia with hospitalization and mortality in the elderly: the Health and Anemia population-based study. *Haematologica* 2009; 94: 22–28.
- [7] Sabatine MS, Morrow DA, Giugliano RP, *et al.* Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation* 2005; 111: 2042–2049.
- [8] Wong CK, White HD, Wilcox RG, *et al.* New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO-III experience. *Am Heart J* 2000; 140: 878–885.
- [9] Teng TH, Finn J, Hung J. Mild anaemia is associated with increased all-cause mortality in heart failure. *Heart Lung Circ* 2010; 19: 31–37.
- [10] McKechnie RS, Smith D, Montoye C, *et al.* Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. *Circulation* 2004; 110: 271–277.
- [11] Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation* 2018; 138: 80–98.
- [12] Horwich TB, Fonarow GC, Hamilton MA, *et al.* Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002; 39: 1780–1786.
- [13] Alkhouli M, Friedman PA. Ischemic stroke risk in patients with nonvalvular atrial fibrillation: JACC review topic of the week. *J Am Coll Cardiol* 2019; 74: 3050–3065.
- [14] Singh SN, Tang XC, Singh BN, *et al.* Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a veterans affairs cooperative studies program substudy. *J Am Coll Cardiol* 2006; 48: 721–730.
- [15] Sharma S, Gage BF, Deych E, *et al.* Anemia: an independent predictor of death and hospitalizations among elderly patients with atrial fibrillation. *Am Heart J* 2009; 157: 1057–1063.
- [16] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization, 2011. <http://www.who.int/vmnis/indicators/haemoglobin.pdf> (assessed February 3, 2021).
- [17] DiMarco JP, Flaker G, Waldo AL, *et al.* Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149: 650–656.
- [18] Kirchhof P, Benussi S, Kotecha D, *et al.* 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37: 2893–2962.
- [19] Roffi M, Patrono C, Collet JP, *et al.* 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 267–315.
- [20] Olivieri F, Galeazzi R, Giavarina D, *et al.* Aged-related increase of high sensitive troponin T and its implication in acute myocardial infarction diagnosis of elderly patients. *Mech Ageing Dev* 2012; 133: 300–305.
- [21] Silverberg DS, Wexler D, Iaina A, *et al.* The interaction between heart failure and other heart diseases, renal failure, and anemia. *Semin Nephrol* 2006; 26: 296–306.
- [22] Macciò A, Madeddu C. Management of anemia of inflammation in the elderly. *Anemia* 2012; 2012: 563251.
- [23] Franceschi C, Capri M, Monti D, *et al.* Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007; 128: 92–105.
- [24] Jeong SK, Cho YI, Duey M, *et al.* Cardiovascular risks of anemia correction with erythrocyte stimulating agents: should blood viscosity be monitored for risk assessment? *Cardiovasc Drugs Ther* 2010; 24: 151–160.
- [25] Gluba-Brzózka A, Franczyk B, Olszewski R, *et al.* The influence of inflammation on anemia in CKD patients. *Int J Mol Sci* 2020; 21: 725.
- [26] Prakash D. Anemia in the ICU: anemia of chronic disease versus anemia of acute illness. *Crit Care Clin* 2012; 28: 333–343, v.
- [27] Haslam A, Hausman DB, Johnson MA, *et al.* Prevalence and predictors of anemia in a population-based study of octogenarians and centenarians in Georgia. *J Gerontol A Biol Sci Med Sci* 2012; 67: 100–106.
- [28] Morici N, Savonitto S, Murena E, *et al.* Causes of death in patients ≥ 75 years of age with non-ST-segment elevation acute coronary syndrome. *Am J Cardiol* 2013; 112: 1–7.



- [29] Westenbrink BD, Voors AA, de Boer RA, *et al.* Bone marrow dysfunction in chronic heart failure patients. *Eur J Heart Fail* 2010; 12: 676–684.
- [30] An Y, Ogawa H, Esato M, *et al.* Cardiovascular events and mortality in patients with atrial fibrillation and anemia (from the Fushimi AF Registry). *Am J Cardiol* 2020; 134: 74–82.
- [31] Tang WH, Tong W, Jain A, *et al.* Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 2008; 51: 569–576.
- [32] Ang DS, Kao MP, Noman A, *et al.* The prognostic significance of early and late anaemia in acute coronary syndrome. *QJM* 2012; 105: 445–454.
- [33] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15: 505–522.
- [34] Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood* 2018; 131: 505–514.

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