Prognostic value of degree and types of anaemia on clinical outcomes for hospitalised older patients

Emma Riva[a,*], Riccardo Colombo[b], Guido Moreo[c], Sara Mandelli[a], Carlotta Franchi[a], Luca Pasina[a], Mauro Tettamanti[a], Ugo Lucca[a], Pier Mannuccio Mannucci[d], Alessandro Nobili[a], REPOSI Investigators

[a] *IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy*
[b] *Medicine Intensive Care and Accident & Emergency Department, Niguarda Hospital, Milan, Italy*
[c] *Internal Medicine Unit, San Carlo Clinic, Paderno Dugnano Milan, Italy*
[d] *A. Bianchi Bonomi Hemophilia and Thrombosis Centre, IRCCS Ca' Granda Maggiore Hospital Foundation and University of Milan, Italy*

ARTICLE INFO

Accepted 10 November 2016

Keywords:
Older in-patients
Anaemia
Clinical outcomes

ABSTRACT

Study objective: This study investigated in a large sample of in-patients the impact of mild-moderate-severe anaemia on clinical outcomes such as in-hospital mortality, re-admission, and death within three months after discharge.
Methods: A prospective multicentre observational study, involving older people admitted to 87 internal medicine and geriatric wards, was done in Italy between 2010 and 2012. The main clinical/laboratory data were obtained on admission and discharge. Based on haemoglobin (Hb), subjects were classified in three groups: group 1 with normal Hb, (reference group), group 2 with mildly reduced Hb (10.0–11.9 g/dL in women; 10.0–12.9 g/dL in men) and group 3 with moderately-severely reduced Hb (<10 g/dL in women and men).
Results: Patients (2678; mean age 79.2 ± 7.4 y) with anaemia (54.7%) were older, with greater functional impairment and more comorbidity. Multivariable analysis showed that mild but not moderate-severe anaemia was associated with a higher risk of hospital re-admission within three months (group 2: OR = 1.62; 95%CI 1.21–2.17). Anaemia failed to predict in-hospital mortality, while a higher risk of dying within three months was associated with the degree of Hb reduction on admission (group 2: OR = 1.82;95%CI 1.25–2.67; group 3: OR = 2.78;95%CI 1.82–4.26) and discharge (group 2: OR = 2.37;95% CI 1.48–3.93; group 3: OR = 3.70;95%CI 2.14–6.52). Normocytic and macrocytic, but not microcytic anaemia, were associated with adverse clinical outcomes.
Conclusions: Mild anaemia predicted hospital re-admission of older in-patients, while three-month mortality risk increased proportionally with anaemia severity. Type and severity of anaemia affected hospital re-admission and mortality, the worst prognosis being associated with normocytic and macrocytic anaemia.

1. Introduction

In elderly, anaemia prevalence rates rise constantly to a rate greater than 20% at age 85 and older; overall, 11.0% of men and 10.2% of women 65 years and older have been reported to be anaemic (Guralnik, Eisenstaedt, Ferrucci, Klein, & Woodman, 2004). Haemoglobin (Hb) decreases and the incidence and prevalence of mild anaemia steadily rises with age affecting more than 20% of people older than 85 years in the general population (Riva et al., 2009). In older people anaemia contributes to higher mortality and hospitalization (Culleton et al., 2006; Penninx, Pahor, Woodman, & Guralnik, 2006). A prevalence of anaemia of approximately 12% (Gaskell, Derry, Moore, & McQuay, 2008; Tettamanti et al., 2010) and an incidence of 22.5 per 1000 person-year (Tettamanti et al., 2010) was found in community-dwelling older people. In older people admitted to hospital a higher prevalence of anaemia, with a large proportion of moderate-severe cases, was associated with various chronic and acute conditions (Bhasin & Rao, 2011; Geisel et al., 2014; Joosten & Lioen, 2014; Migone De Amicis et al., 2015; Nathavitharana et al., 2012;

* Corresponding author at: Geriatric Neuropsychiatry Laboratory, Department of Neuroscience, IRCCS Istituto di Ricerche Farmacologiche "Mario Negri" Via Giuseppe La Masa 19, 20156 Milan, Italy.
E-mail address: emma.riva@marionegri.it (E. Riva).

Petroysan, Blaison, Andrès, & Federici, 2012; Rachoin, Cerceo, Milcarek, Hunter, & Gerber, 2013; Ramel, Jonsson, Bjornsson, Bjornsson, & Thorsdottir, 2008). For instance, a majority of studies reported a negative association of anaemia with morbidity or mortality in patients admitted for myocardial infarction or congestive heart failure (Biagi et al., 2011; Mentz et al., 2014), and critical renal (Locatelli et al., 2004) or respiratory conditions (Martinez-Rivera et al., 2012).

The predictive value of anaemia and its severity as a prognostic marker has not been investigated widely in older people with multimorbidity and polypharmacy in internal medicine and geriatric wards. Published data come mostly from retrospective studies conducted by single centers in small samples of in-patients.

Thus, this study investigated a large cohort of older people acutely admitted to internal and geriatric wards in Italy in order to establish whether or not low Hb measured at admission and again at discharge were independently associated with a higher risk of clinically important outcomes such as in-hospital mortality, hospital readmissions and mortality at three months after discharge.

2. Methods

2.1. Study setting, design and patients

This study was conducted in 87 hospital wards representative of the Italian internal medicine and geriatric wards participating in the 'REgistro POliterapie SIMI' (REPOSI), a collaborative and independent registry set up by the Italian Society of Internal Medicine (SIMI), the Milan IRCCS Mario Negri Institute of Pharmacological Research and the Ca' Granda Maggiore Policlinico Hospital Foundation. Briefly, the registry was designed to create a network of internal medicine and geriatric wards to evaluate older patients with multiple diseases, prescribed polypharmacy (Nobili et al., 2011). All patients 65 years or older were consecutively recruited after they were prospectively admitted to the participating wards during four seasonal one-week periods with intervals of three months. A standardized web-based case-report form was computed by the attending physicians, covering socio-demographic details, clinical parameters, diagnoses and medications prescribed at admission and discharge, plus events during the hospital stay. Three months after discharge a physician interviewed the patient or his/her relative by telephone to collect data on mortality or any hospital re-admission. All the data were reviewed by a central monitor at the IRCCS-Mario Negri Institute. The study was approved by the ethical committees of each participating hospital.

All patients enrolled in the registry were included provided they had Hb measured on hospital admission and at discharge. Anaemia was defined in accordance with World Health Organization (WHO) criteria (World Health Organization, 1968) as haemoglobin (Hb) less than 12.0 g/dL in women and less than 13.0 g/dL in men. On admission patients were classified into three groups according to their Hb: group 1 with normal Hb ($\geq$12 g/dL in women and $\geq$13 g/dL in men, taken as the reference group), group 2 with mildly reduced Hb (10.0–11.9 g/dL in women and 10.0–12.9 g/dL in men) and group 3 with moderate-severely reduced Hb $<$10 g/dL in women and men). Hb >16 g/L in women and >18 g/L in men were considered above the reference limits. The flow-chart of the study is illustrated in Fig. 1.

2.2. Outcomes

The study outcomes were in-hospital mortality, re-hospitalization and death risk within three months from discharge. Patients transferred to other wards (226), discharged in critical conditions or lost to recording (122), deceased (91), or with Hb values not available (76) were not included in the analysis. Hospital re-admissions and deaths within three months from discharge were calculated only for those patients whose case report form was filled in the section dealing with the three-month follow-up (2163).

Baseline characteristics were compared across the different Hb groups. The variables analysed on admission were: demographic data (age, sex, education, marital status, caregiver and body mass index), clinical variables including cognitive status (according to the Short Blessed Test-SBT) (Katzman et al., 1983), functional status (according to the Barthel Index) (Shah, Vanclay, & Cooper, 1989), systolic blood pressure, kidney function (defined as glomerular filtration rate estimated using the formula CKD-EPI) (Levey, Stevens, Schmid, Zhang, & Feldman, 2009) and polypharmacy (defined as concomitant exposure to five or more different medications) (Viktil, Blix, Moger, & Reikvam, 2007). Diagnoses on admission of cardiovascular diseases (hypertension, diabetes, hypercholesterolaemia, ischaemic heart disease, congestive heart failure, stroke and atrial fibrillation) and other diseases were coded according to the International Classification of Disease, Ninth Revision ICD-9 (WHO, 1987). Comorbidity index, according to the Cumulative Illness Rating Scale (CIRS) (Parmelee, Thuras, Katz, & Lawton, 1995) was calculated excluding anaemia ($<$12 g/dL in women and $<$13 g/dL in men). The CIRS comorbidity index was computed by counting the number of items for which moderate to severe illness was reported (scores 3, 4 or 5), the overall illness severity being represented by the mean of the 13 CIRS items.

2.3. Statistical analysis

Continuous variables were described using means and standard deviations (SD), medians and upper and lower quartiles in order to give a comprehensive view of the distributions; categorical variables were counted. To test whether patient characteristics in the three Hb classes were different, numerical variables were compared using the Kruskall-Wallis test and categorical variables were analysed by the chi-square test. Analyses were done using Hb values on admission and at discharge separately. Multivariable logistic regression analyses were conducted to assess whether the degree of anaemia predicted in-hospital mortality, hospital readmission or three-month mortality. For each outcome a univariable model was used, followed by three multivariate models: in the first the Hb effect was adjusted for demographic variables (age and sex), in the second for all the conditions associated with low Hb in the univariable model, in the third for the CIRS comorbidity index on admission. Robust standard errors were used to take account of the non-independence of data within the same ward. All statistical analyses were done with JMP Pro 12.0.1 (SAS Institute Inc.) and Stata IC 13.1 (Stata Inc.) software.

3. Results

3.1. Patients

Of the original population of 2703 patients in the registry, Hb values were not available for 25, so 2678 were included in the analysis (1213 in group 1, 987 in group 2 and 478 in group 3). Of these 2163 were discharged alive. In the three months after hospital discharge, 547 were lost to follow-up, so the 612 patients in group 1, 744 in group 2 and 260 in group 3 who completed the three months follow-up were included in the analysis of post-discharge outcomes (Fig. 1).

At hospital admission the characteristics of the whole population, with and without anaemia and according to severity, are listed in Table 1. Patients with anaemia were nearly one year older ($p < 0.0001$) and more likely to be men ($p = 0.0003$). After adjusting

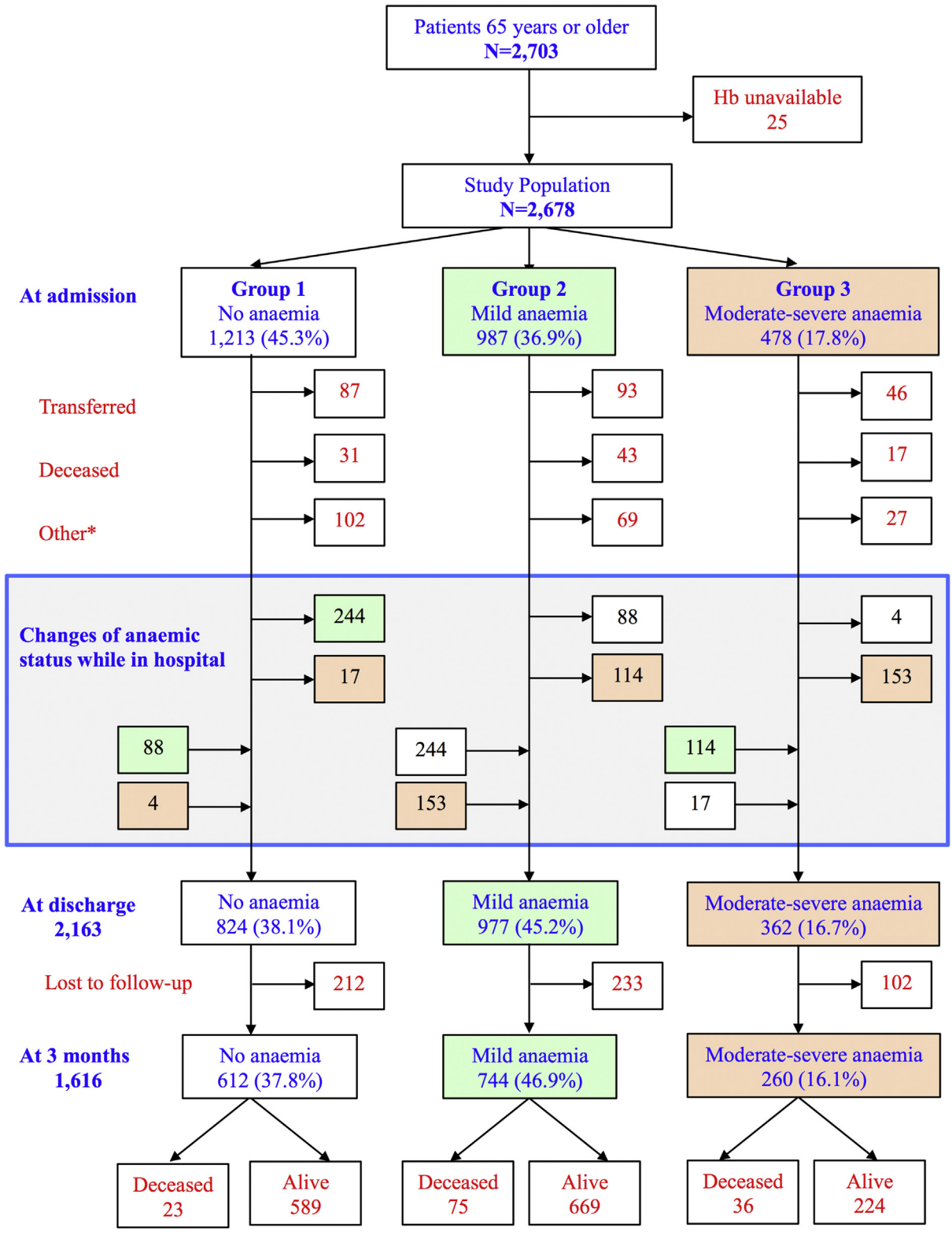

Fig. 1. Flow-chart of the REPOSI study in older hospitalized patients.

for age and sex, low Hb was associated with smoking and lower body mass index. Patients with low Hb had a higher prevalence of depression, were more likely to be dependent for daily activities, and polypharmacy was more prevalent. The proportion of patients with comorbidity on admission increased with decreasing Hb. The characteristics of group 2 and 3 were similar, with the exception

Table 1
Socio-demographic and clinical characteristics of the study population on admission to hospital.

	All Patients	Group 1	Patients with anaemia	P-Value[a]	P-Value[b]	Group 2	Group 3	P-Value[c]	P-Value[d]
Patients, % (n)[e]	2678	46.0 (1213)	54.7 (1465)			36.9 (987)	17.8 (478)		
Female, % (n)	50.7 (1358)	53.8 (653)	48.1 (705)	**0.0033**	**0.0003**	45.2 (446)	54.2 (259)	**0.0012**	**0.0024**
Age, years, mean (SD)	79.2 ± 7.4	78.5 ± 7.3	79.7 ± 7.4	<**0.0001**	<**0.0001**	79.5 ± 7.3	80.1 ± 7.4	0.1108	0.2462
Age groups, % (n)									
65–74	30.8 (824)	33.4 (405)	28.6 (419)	**0.0031**	**0.0007**	29.4 (290)	27.0 (129)	0.1131	0.2638
75–84	45.6 (1220)	45.6 (553)	45.5 (667)			46.4 (458)	43.7 (209)		
≥85	23.6 (634)	21.0 (255)	25.9 (379)			24.2 (239)	29.3 (140)		
Education, years, mean (SD)[f]	7.0 ± 3.9	7.1 ± 3.8	7.0 ± 4.0	0.3648	0.3343	7.1 ± 4.1	6.7 ± 3.7	0.0972	0.3098
Married, % (n)[g]	53.9 (1409)	54.5 (645)	53.4 (764)	0.5759	0.4514	54.3 (526)	51.6 (238)	0.3467	0.4603
BMI, Kg/m^2, mean (SD)[h]	25.8 ± 4.9	26.2 ± 5.0	25.5 ± 4.8	**0.0001**		25.7 ± 4.9	25.0 ± 4.5	**0.0252**	**0.0223**
BMI Classes, % (n)[h]									
< 18.5	3.8 (93)	3.4 (38)	4.1 (55)	**0.0016**	**0.0023**	4.0 (36)	4.5 (19)	0.1358	0.1361
18.5–24.9	42.9 (1053)	39.3 (443)	45.8 (610)			44.0 (399)	49.5 (21)		
≥25	53.3 (1314)	57.3 (647)	50.1 (667)			52.0 (471)	46.0 (196)		
Smoker, % (n)[i]	8.2 (218)	10.0 (120)	6.8 (98)	**0.0034**	**0.0073**	7.2 (70)	6.0 (28)	0.3792	0.5562
Number of diagnosis, mean (SD)[j]	5.7 ± 2.8	5.3 ± 2.7	6.0 ± 2.8	<**0.0001**	<**0.0001**	5.9 ± 2.8	6.2 ± 2.8	0.0824	0.0740
Number of diagnosis ≥5, % (n)[j]	63.6 (1699)	57.8 (699)	68.4 (1000)	<**0.0001**	<**0.0001**	66.7 (658)	72.0 (342)	**0.0399**	**0.0308**
Number of drugs, mean (SD)	5.4 ± 2.9	4.8 ± 2.8	5.8 ± 3.0	<**0.0001**	<**0.0001**	5.8 ± 3.0	5.9 ± 2.9	0.5058	0.3728
Number of drugs ≥ 5, % (n)	58.5 (1568)	50.6 (614)	65.1 (954)	<**0.0001**	<**0.0001**	64.5 (637)	66.31 (317)	0.5030	0.4316
Severity index, mean (SD)[k]	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	<**0.0001**	<**0.0001**	1.7 ± 0.3	1.7 ± 0.3	0.4887	0.6869
Comorbidity index, mean (SD)[l]	2.9 ± 1.8	2.7 ± 1.7	3.1 ± 1.8	<**0.0001**	<**0.0001**	3.1 ± 1.8	3.1 ± 1.8	0.6209	0.5002
SBT, mean (SD)[m]	9.6 (8.0)	9.5 ± 8.0	9.6 ± 8.0	0.6025	0.6280	9.4 ± 7.9	10.1 ± 8.3	0.1733	0.4370
SBT, classes									
Normal (0–4), % (n)	35.4 (898)	36.1 (418)	34.9 (480)	0.7966	0.8099	35.2 (326)	34.5 (154)	0.5859	0.7175
Moderate (5–9), % (n)	18.4 (466)	18.1 (209)	18.7 (257)			19.2 (178)	17.5 (79)		
Severe (10–28), % (n)	46.2 (1171)	45.9 (531)	46.5 (640)			45.6 (422)	48.3 (218)		
GDS, mean (SD)[n]	1.4 ± 1.2	1.3 ± 1.2	1.5 ± 1.2	**0.0067**	**0.0050**	1.5 ± 1.2	1.4 ± 1.2	0.5727	0.3756
Probably not depressed (=0), % (n)	28.0 (670)	30.2 (324)	26.1 (346)	**0.0491**	**0.0393**	26.5 (238)	25.4 (108)	0.5898	0.5318
Minor depression (1–2)	53.7 (1286)	52.9 (568)	54.3 (718)			53.3 (479)	56.2 (239)		
Probably depressed (≥2)	18.3 (440)	16.9 (181)	19.6 (259)			20.2 (181)	18.3 (78)		
Barthel Index, mean (SD)[o]	74.7 ± 31.6	77.6 ± 30.7	72.2 ± 32.2	<**0.0001**	**0.0004**	72.1 ± 32.5	72.3 ± 31.6	0.8967	0.3923
Barthel Index, dependence classes				<**0.0001**	**0.0009**				
Complete (0–24), % (n)	12.4 (323)	11.1 (131)	13.5 (192)			14.1 (135)	12.2 (57)	0.7313	0.5369
Severe (25–49), % (n)	9.0 (235)	7.6 (90)	10.2 (145)			9.8 (94)	10.9 (51)		
Moderate (50–74), % (n)	12.4 (324)	10.9 (128)	13.7 (196)			13.1 (126)	15.0 (70)		
Mild (75–90), % (n)	17.6 (458)	16.5 (194)	18.5 (264)			18.7 (179)	18.2 (85)		
No or negligible (91–100), % (n)	48.6 (1265)	53.9 (636)	44.1 (629)			44.3 (424)	43.8 (205)		

Group 1, No anaemia; Group 2, Mild anaemia; group 3, Moderate-severe anaemia.
BMI = Body Mass Index; SBT = Short Blessed Test; GDS = Geriatric Depression Scale.
The exponential refers to the number of patients with details available.
[a] Univariate P value for anaemia vs no anaemia.
[b] adjusted for age and sex.
[c] Univariate P value for mild anaemia vs moderate-severe anaemia.
[d] adjusted for age and sex.
[e] Number of patients with haemoglobin on admission.
[f] N = 2537 (1165; 1372; 932; 440).
[g] N = 2613 (1183; 1430; 969; 461).
[h] N = 2460 (1128; 1332; 906; 426).
[i] N = 2639 (1203; 1436; 968; 468).
[j] N = 2671 (1209; 1462; 987; 475).
[k] N = 2672 (1211; 1461; 984; 477).
[l] N = 2672 (1211; 1461; 984; 477).
[m] N = 2535 (1158; 1377; 926; 451).
[n] N = 2396 (1073; 1323; 898; 425).
[o] N = 2605 (1179; 1426; 958; 468).

that patients in group 3 were more often women and had more diagnoses than those in group 2 (Table 1).

Reduced Hb was significantly associated with a variety of diseases (coronary artery disease, diabetes, kidney failure, gastro-intestinal and liver disorders and cancer, also after adjusting for age, sex and comorbidity (Table 2). In addition, the prevalence of these diseases was associated with the severity of anaemia. Hospital stay was on average three days longer in patients with low Hb (12.5 ± 11.4 vs 9.9 ± 11.8 days; $p < 0.0001$), but was not influenced by the severity of anaemia.

3.2. Haematological and laboratory findings

The distribution curve of Hb in the 2678 patients with available data (Fig. 2) is shifted to the right in men, and in older patients (males and females) it is skewed to the left, a substantial proportion having Hb lower than 10 g/dL (approximately 10% and 15%, respectively). About one third of patients in group 3 (138) had Hb lower than 8.0 g/dL.

Complete blood count and laboratory findings for the entire population (anaemic plus non anaemic cases) are listed in Table 3. Women had mean Hb lower than men, and anaemia was mostly normocytic in group 2 and, to a lesser degree, in group 3 (83.0% *vs.* 58.2%). Microcytosis (MCV less than 80 fL) was less frequent in patients with mild anaemia (12.5% in group 2 vs. 31.8% in group 3), and macrocytosis (MCV > 100 fL) was more than double in those with moderate-severe anaemia (4.5% group 2 vs. 10.0% group 3).

The proportion of patients with severely reduced kidney function (eGFR <30 mL/min/1.73 m^2) was double in those with low Hb (15.0% vs. 6.3% in group 1).

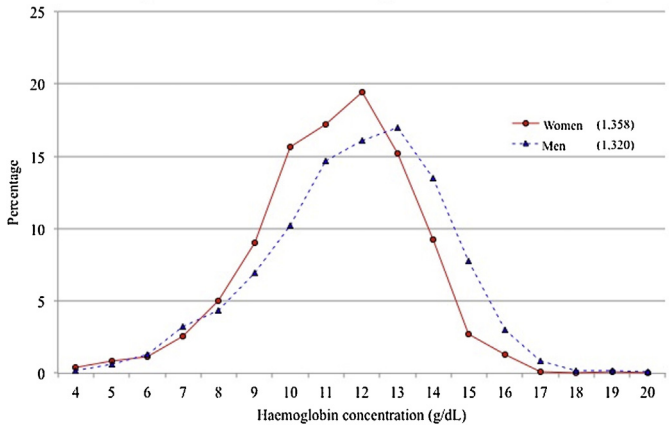

Fig. 2. Frequency distribution of haemoglobin concentration in older patients on admission to hospital.

During hospitalization Hb values changed in a large proportion of patients and the shift from anaemic to non-anaemic or *viceversa* is shown in Fig. 1.

Hb above the reference limit was not associated with in-hospital mortality (n = 0), risk of hospital re-admission (n = 13; OR = 1.33; 95% CI 0.29–4.45), or mortality at 3 month (n = 0).

3.3. Outcomes

3.3.1. In-hospital mortality

Using the group with normal Hb as reference, multivariable analysis of the three groups adjusted for age, sex and comorbidity showed that reduced Hb did not increase the risk of death during hospitalization (OR = 1.46; 95% CI 0.90–2.37 group 2 and OR = 1.19; 95% CI 0.63–2.16 group 3).

3.3.2. Hospital re-admission

Hb on admission in groups 2 and 3 was not associated with a higher risk of re-hospitalization, by multivariable analysis (Table 4); mildly reduced Hb on discharge significantly predicted the risk for older patients to be re-admitted within three months after discharge (OR = 1.62; 95% CI 1.21–2.17). Older patients with mild macrocytic anaemia had a three times higher risk of being re-hospitalized. Similarly risk of re-hospitalization was double in group 3 with moderate-severe anaemia, but there were too few older patients in this group (8/27) to reach statistical significance.

3.3.3. Mortality at three months

After adjusting for confounders, anaemia at admission and discharge was a strong predictor of mortality (OR = 2.11; 95% CI 1.50–3.01 at admission and OR = 2.69; 95% CI 1.71–4.38 at discharge). The risk of death within three months rose proportionally with the severity of anaemia (Table 4 ex 2). Normocytic (group 2 and 3) and macrocytic anaemia (group 2) was associated with the highest risk.

3.3.4. Sensitivity analysis

Results for in-hospital and three-month mortality and hospital re-admission were similar after adjusting for the diagnoses of diabetes, coronary artery disease, heart failure, liver and kidney disease, cancer, cerebrovascular disease, gastrointestinal disorders, haemolymphopoietic diseases (model 2) or the comorbidity index (model 3).

4. Discussion

We analysed a large cohort of patients, aged 65 years and older acutely hospitalized in the frame of the REPOSI hospital network (Nobili et al., 2011) in order to investigate the impact of mild and moderate-severe anaemia on major clinical outcomes, including

Table 2
Clinical conditions of patients with and without anaemia on admission.

Clinical conditions	All Patients N = 2678	Group 1	Patients with anaemia	P-Value[a]	P-Value[b]	Group 2	Group 3	P-Value[c]	P-Value[d]
Diabetes, % (no.)	27.9 (748)	24.6 (299)	30.6 (449)	0.0006	**0.0004**	30.4 (300)	31.2 (149)	0.7625	0.5092
Hypertension, % (no.)	76.5 (2050)	76.6 (929)	76.5 (1121)	0.9669	0.6975	78.4 (774)	72.6 (347)	**0.0137**	**0.0075**
Coronary artery diseases, % (no.)	24.2 (647)	21.2 (257)	26.6 (390)	**0.0011**	**0.0126**	28.8 (284)	22.2 (106)	**0.0074**	**0.0124**
Heart failure, % (no.)	15.1 (403)	13.0 (158)	16.7 (245)	**0.0077**	0.0567	17.6 (174)	14.8 (71)	0.1820	0.1351
Other cardiac diseases, % (no.)	42.6 (1140)	41.6 (505)	43.3 (635)	0.3723	0.7055	42.5 (420)	45.0 (215)	0.3797	0.5164
Kidney diseases, % (no.)	21.9 (586)	15.8 (192)	26.9 (394)	**<0.0001**	**<0.0001**	23.6 (233)	33.7 (161)	**<0.0001**	**<0.0001**
Cancer, % (no.)	18.3 (489)	14.8 (180)	21.1 (309)	**<0.0001**	**<0.0001**	20.7 (204)	22.0 (105)	0.5681	0.2866
Cerebrovascular diseases, % (no.)	19.9 (534)	21.8 (264)	18.4 (270)	**0.0316**	**0.0073**	17.6 (174)	20.1 (96)	0.2559	0.3646
Gastrointestinal disorders, % (no.)	37.9 (1015)	33.4 (405)	41.6 (610)	**<0.0001**	**<0.0001**	39.2 (387)	46.6 (223)	**0.0067**	**0.0092**
Pulmonary diseases, % (no.)	29.5 (789)	30.5 (370)	28.6 (419)	0.2824	0.0679	31.0 (306)	23.6 (113)	**0.0035**	**0.0064**
Liver diseases, % (no.)	12.6 (337)	10.3 (125)	14.5 (212)	**0.0012**	**0.0002**	14.6 (144)	14.2 (68)	0.8528	0.9592
Osteo-arthro-muscle diseases, % (no.)	23.9 (640)	24.1 (293)	23.7 (347)	0.7770	0.9602	22.9 (226)	25.3 (121)	0.3078	0.7024
Arterial diseases, % (no.)	14.2 (381)	12.5 (152)	15.6 (229)	**0.0222**	**0.0889**	17.1 (169)	12.5 (60)	**0.0239**	**0.0356**
Autoimmune diseases, % (no.)	2.9 (79)	2.5 (30)	3.3 (49)	0.1846	0.1162	3.8 (38)	2.30 (11)	0.1222	0.1115
Haemolymphopoietic diseases, % (no.)	6.6 (177)	3.7 (45)	9.0 (132)	**<0.0001**	**<0.0001**	7.8 (77)	11.5 (55)	**0.0202**	**0.0084**
Endocrine diseases, % (no.)	21.6 (579)	23.2 (282)	20.3 (297)	0.0626	0.1874	20.0 (197)	20.9 (100)	0.6679	0.9385
Infective diseases, % (no.)	13.3 (357)	13.3 (161)	13.4 (196)	0.9360	0.7838	14.1 (139)	11.9 (57)	0.2552	0.2815
Lympho-venous diseases, % (no.)	7.7 (207)	6.5 (79)	8.7 (128)	**0.0319**	**0.0113**	9.0 (89)	8.2 (39)	0.5855	0.4181
Malnutrition, % (no.)	0.6 (15)	0.7 (8)	0.5 (7)	0.5305	0.4073	0.5 (5)	0.4 (2)	0.8185	0.8679
CNS diseases, % (no.)	10.6 (284)	10.5 (127)	10.7 (157)	0.8364	0.8840	10.7 (106)	10.7 (51)	0.9675	0.9444
PNS diseases, % (no.)	0.4 (12)	0.6 (7)	0.3 (5)	0.3631	0.4453	0.4 (4)	0.2 (1)	0.5463	0.5455
Neuropsychiatric diseases, % (no.)	23.9 (641)	24.1 (292)	23.8 (349)	0.8800	0.7813	22.8 (225)	25.9 (124)	0.1852	0.3179
Urogenital diseases, % (no.)	20.3 (544)	18.4 (223)	21.9 (321)	**0.0239**	0.2956	23.5 (232)	18.6 (89)	**0.0340**	0.1717
Other, % (no.)	23.9 (640)	24.1 (293)	23.7 (347)	0.7770	0.6730	23.0 (227)	25.1 (120)	0.3741	0.4422

Group 1, No anaemia; Group 2, Mild anaemia; group 3, Moderate-severe anaemia; CNS, Central Nervous System; PNS, Peripheral nervous system.
[a] Univariate P value for anaemia vs. no anaemia.
[b] Adjusted for age and sex.
[c] Univariate P value for mild anaemia vs. moderate-severe anaemia.
[d] Adjusted for age and sex.

Table 3
Laboratory variables of patients on admission.

Variable	All Patients[c] N = 2678	Group 1 N = 1213	Patients with anaemia N = 1465	P-Value[a]	Group 2 N = 987	Group 3 N = 478	P-Value[b]
Red blood cells (10^6/mm^3)[d]	4.1 ± 0.8	4.6 ± 0.5	3.7 ± 0.7	<**0.0001**	4.0 ± 0.6	3.2 ± 0.7	<**0.0001**
Haemoglobin (g/dL)	12.0 ± 2.3	13.9 ± 1.2	10.4 ± 1.6	<**0.0001**	11.3 ± 0.8	8.5 ± 1.3	<**0.0001**
Female	11.7 ± 2.1	13.4 ± 1.1	10.1 ± 1.5	<**0.0001**	11.0 ± 0.6	8.5 ± 1.3	<**0.0001**
Male	12.3 ± 2.4	14.4 ± 1.1	10.7 ± 1.7	<**0.0001**	11.6 ± 0.8	8.4 ± 1.2	<**0.0001**
Haematocrit (%)[e]	36.4 ± 6.7	41.6 ± 4.0	32.1 ± 5.3	<**0.0001**	34.8 ± 3.4	26.6 ± 4.2	<**0.0001**
MCV(fL)[f]	88.7 ± 8.7	90.3 ± 5.9	87.4 ± 10.3	<**0.0001**	88.5 ± 8.7	85.3 ± 12.7	<**0.0001**
<80, % (no.)	11.8 (314)	3.4 (41)	18.7 (273)	<**0.0001**	12.5 (123)	31.8 (150)	<**0.0001**
80–100, % (no.)	83.0 (2209)	92.7 (1117)	74.9 (1092)		83.0 (818)	58.2 (274)	
>100, % (no.)	5.2 (139)	3.9 (47)	6.3 (92)		4.5 (45)	10.0 (47)	
MCH (pg) [g]	29.2 ± 3.6	30.2 ± 2.5	28.4 ± 4.2	<**0.0001**	28.9 ± 3.5	27.2 ± 5.1	<**0.0001**
MCHC (g/dL)[h]	32.9 ± 2.2	33.4 ± 1.8	32.4 ± 2.4	<**0.0001**	32.7 ± 2.2	31.8 ± 2.6	<**0.0001**
Leukocytes (10^3/mm^3)[i]	8.9 ± 5.3	9.2 ± 4.3	8.6 ± 6.0	**0.0072**	8.8 ± 5.4	8.4 ± 6.9	0.2647
Platelet (10^3/mm^3)[j]	231.4 ± 101.8	225.7 ± 83.3	236.1 ± 114.7	**0.0088**	231.6 ± 105.8	245.4 ± 130.9	**0.0306**
Creatinine (μmol/L)[k]	106.1 ± 70.7	97.2 ± 44.2	114.9 ± 79.6	<**0.0001**	114.9 ± 70.7	132.6 ± 97.2	<**0.0001**
eGFR (ml/min/1.73 m^2)	60.4 ± 25.7	65.1 ± 24.1	56.5 ± 26.4	<**0.0001**	57.9 ± 26.3	53.6 ± 26.2	**0.0039**
≥60 (no.)	50.4 (1343)	57.5 (695)	44.5 (648)	<**0.0001**	46.2 (454)	40.9 (194)	**0.0456**
30–59 (no.)	35.3 (941)	33.6 (406)	36.7 (535)		36.6 (360)	36.9 (175)	
<30 (no.)	14.3 (382)	8.9 (108)	18.8 (274)		17.2 (169)	22.1 (105)	
s-Glucose (mmol/L)[l]	7.0 ± 3.5	7.1 ± 3.3	7.0 ± 3.7	0.4946	7.1 ± 3.9	6.7 ± 3.1	0.0694
s-Cholesterol (mmol/L)[m]	4.19 ± 1.2	4.5 ± 1.1	3.9 ± 1.1	<**0.0001**	4.1 ± 1.1	3.7 ± 1.2	<**0.0001**
s-Albumin (g/dL)[n]	3.4 ± 0.6	3.6 ± 0.6	3.3 ± 0.6	<**0.0001**	3.3 ± 0.6	3.3 ± 0.6	0.2526

Group 1, No anaemia; Group 2, Mild anaemia defined as haemoglobin of 10.0-11.9 g/dL in women and 10.0-12.9 g/dL in men; Group 3, moderate-severe anaemia as haemoglobin <10 g/dL in women and men.
MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Haemoglobin; MCHC, Mean Corpuscular Haemoglobin Concentration; eGFR, estimated Glomerular Filtration Rate according to the CKD EPI formula (Levey AS, & al. 2009. A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604-612).
The exponential refers to the number of patients with details available.
[a] P Aneamia vs. no anaemia.
[b] P mild anaemia vs. moderate-severe anaemia.
[c] Number of patients with haemoglobin available on admission.
[d] N = 2660 (1204;1456; 983; 473).
[e] N = 2648 (1197;1451;982;469).
[f] N = 2662 (1205;1457; 986;471).
[g] N = 2660 (1204;1456;983;473).
[h] N = 2648 (1197;1451;982;469).
[i] N = 2675 (1213;1462;987;475).
[j] N = 2672 (1209;1463;987;476).
[k] N = 2666 (1209;1457;983;474).
[l] N = 2647 (1207;1440;974;466).
[m] N = 2168 (982;1186;806;380).
[n] N = 1036 (455;581;393;188).

in-hospital mortality, re-hospitalization and mortality within three months after discharge. The population in the present study differs considerably from those reported in the literature because we focused on a large sample of acutely hospitalized elderly patients with multiple and chronic diseases, requiring polypharmacy. Although in our study anaemia was not the main cause of hospital admission, low Hb was highly prevalent in patients with an array of chronic disorders, even also when comparisons were adjusted for age and sex.

4.1. Anaemia as predictors of clinical outcomes

In the recent past very few studies have investigated the association of anaemia with clinical outcomes among internal medicine patients and whether anaemia severity and type are useful predictors of in-hospital and post-discharge mortality (Nathavitharana et al., 2012; Rachoin et al., 2013; Ayaz, Sahin, Sahin, Bilir, & Rakici, 2014). Nathavitharana et al., in a retrospective observational study of a cohort of unselected medical in-patients of different ethnicities, found that anaemia was more prevalent in cases admitted for malignancy, endocrine/metabolic disorders, infections, acute coronary syndrome or congestive heart failure (Nathavitharana et al., 2012). They also found that anaemia was associated with increased mortality, earlier readmission and longer hospital stay. The rate of in-hospital mortality among elderly patients varied between 12% and 16% in various studies (Ayaz, Sahin, Sahin, Bilir & Rakici, 2014). In the present series the rate was similar and was associated with the severity of Hb reduction. We also found that low Hb negatively affected clinically relevant outcomes, even after adjusting for a large number of potential confounders. Mortality hazard ratios three months from discharge were significantly higher in people with low Hb. Finally, we found that patients anaemic at discharge but not on admission were more likely than non-anaemic ones to be re-admitted to hospital.

The type of anaemia did affect mortality at three months, the worst prognosis being associated with normocytic anaemia, independently of its severity, and macrocytic anaemia. One possible explanation for the negative role of normocytic anaemia is related to the underlying chronic diseases. Autoimmune disorder, cancer, chronic kidney disease and other chronic inflammatory states are a major cause of normocytic anaemia in older patients so it is not surprising that normocytic anaemia is a predictor of poor clinical outcome.

High mean corpuscular volume (MCV) has been reported as an independent predictor of all causes of death in patients with severe clinical conditions such as heart failure and severe renal insufficiency (Ueda et al., 2013). Savage and colleagues found that in hospitalized older patients the most common cause of macrocytosis was medications (37%), followed by alcoholism (26%). Serum B12 and/or folate deficiency, bone marrow dysplasia and non-alcoholic liver disease each accounted for only 6% of cases (Savage, Ogundipe, Allen, Stabler, & Lindenbaum, 2000). Medications known to cause macrocytic anaemia are very common and

Table 4
Adjusted risk of 3-month re-hospitalization and mortality in elderly in-patients by severity and type of anaemia.

	Re-hospitalization			Mortality		
On admission	n (%)	OR (95% CI)	P[a]	n (%)	OR (95% CI)	P[a]
Group 1 (n = 1213)	123 (10.1)	1		36 (3.0)	1	
Group 2 (n = 987)	120 (12.2)	0.83 (0.64–1.07)	0.1611	60 (6.1)	**1.82 (1.25–2.67)**	**0.0019**
Microcytic (n = 123)	14 (11.4)	1.00 (0.52–1.79)	0.9938	7 (5.7)	1.98 (0.77–4.44)	0.1445
Normocytic (n = 812)	92 (11.3)	1.14 (0.84–1.54)	0.3981	50 (6.2)	**1.95 (1.24–3.08)**	**0.0035**
Macrocytic (n = 51)	14 (27.5)	**3.81 (1.80–7.92)**	**0.0006**	3 (5.9)	1.68 (0.38–5.16)	0.4429
Group 3 (n = 478)	48 (10.0)	1.03 (0.74–1.45)	0.8493	38 (7.9)	**2.78 (1.82–4.26)**	**<0.0001**
Microcytic (n = 150)	12 (8.0)	0.70 (0.35–1.28)	0.2546	8 (5.3)	1.92 (0.79–4.15)	0.1387
Normocytic (n = 273)	26 (9.5)	0.92 (0.56–1.47)	0.7446	25 (9.2)	**3.30 (1.86–5.81)**	**<0.0001**
Macrocytic (n = 48)	10 (20.8)	**2.33 (1.03–4.94)**	**0.0427**	5 (10.4)	**3.19 (1.02–8.31)**	**0.0460**
	Re-hospitalisation			Mortality at 3 months		
On discharge	n (%)	OR (95% CI)	P[a]	n (%)	OR (95% CI)	P[a]
Group 1 (n = 612)	90 (14.7)	1		23 (3.8)	1	
Group 2 (n = 744)	159 (21.4)	**1.62 (1.21–2.17)**	**0.0010**	75 (10.1)	**2.37 (1.48–3.93)**	**0.0003**
Microcytic (n = 87)	15 (17.2)	1.15 (0.61–2.06)	0.6445	7 (8.0)	2.19 (0.84–5.11)	0.1042
Normocytic (n = 620)	131 (21.1)	**1.55 (1.15–2.11)**	**0.0043**	63 (10.2)	**2.26 (1.38–3.80)**	**0.0009**
Macrocytic (n = 37)	13 (35.1)	**3.25 (1.54–6.58)**	**0.0025**	5 (13.5)	**3.41 (1.06–9.21)**	**0.0398**
Group 3 (n = 260)	42 (16.1)	1.06 (0.70–1.58)	0.7773	36 (13.8)	**3.70 (2.14–6.52)**	**<0.0001**
Microcytic (n = 63)	9 (14.3)	0.88 (0.39–1.78)	0.7311	5 (7.9)	2.21 (0.71–5.69)	0.1561
Normocytic (n = 170)	25 (14.7)	0.96 (0.58–1.55)	0.8637	29 (17.1)	**4.71 (2.61–8.58)**	**<0.0001**
Macrocytic (n = 27)	8 (29.6)	2.35 (0.89–5.61)	0.0822	2 (7.4)	1.88 (0.29–6.99)	0.4458

OR = Odds ratio (95% confidence interval).
Group 1, No anaemia; Group 2, Mild anaemia defined as haemoglobin concentration of 10.0–11.9 g/dL in women and 10.0-12.9 g/dL in men; Group 3, Moderate-severe anaemia defined as haemoglobin concentration <10 g/dL both in women and men.
Microcytic anaemia = MCV <80 fL; normocytic anaemia = MCV 80–100 fL; macrocytic anaemia = MCV >100 fL.
[a] P = adjusted for age, sex and CIRS (Cumulative Illness Rating Scale).

include anti-diabetic drugs (metformin, biguanides), gastric acid-blocking agents (proton pump inhibitors, histamine H2-receptor blockers), and antibiotics (trimethoprim) (Bridgen, 1995). In our study nearly two-third (65%) of patients with low Hb were receiving more than five drugs. MCV is also a possible marker of bone marrow malfunction and high values are seen in myelofibrosis, and the myelodysplastic syndromes.

4.2. Strengths and limitations

Strength of this study based on REPOSI is its multicentre, pragmatic design, resulting in a large, representative sample of hospitalized older people in Italian internal medicine and geriatric wards. The inclusion of patients during four-weeks periods (one per season) balanced the effect of seasons on acute disease and hospitalization. Collection of patient data by physicians meant that the analysis includes some variables often omitted in epidemiological studies, such as illness severity, functional and cognitive status, physical and social characteristics of the patients. Furthermore, registries provide real-time and real-world information, with wide ranges of ages and comorbidities and nearly equal proportions of men and women. In addition, REPOSI included a large number of cases, which enabled us to do several statistical analyses in order to take account of the effect of multiple confounding factors. In addition, the registry data were matched by means of a propensity score.

A limitation of this study is that it was not specifically designed to assess Hb as a predictor of mortality and hospital readmission. Therefore we did not measure serum concentrations of iron, vitamin B12 and folate, which contribute to the diagnosis of the type of anaemia. However, this study was not designed to identify the distribution of anaemia types, but rather to predict short-term clinical outcomes on the basis oh Hb, a simple measurement, routinely available. Yet nevertheless found that the classification of anaemia on the basis of red cell volume is a useful predictor of clinical outcomes in older in-patients.

Another limitation of this study is the short follow-up and the large number of patients lost at the three months follow-up. As this was an observational study, the associations found cannot be interpreted as indicative of a causal role of Hb on mortality.

Finally, a number of patients classified according to Hb in one of the three groups as non-anaemic, mildly or moderately anaemic on admission were classified differently at discharge. While in hospital therapeutic interventions on the one hand and the severity of the clinical picture on the other may have influenced the change in status.

5. Conclusions

One of the major consequences of current demographic changes leading to population ageing is the increased co-occurrence of multiple diseases, which results in an increasing number of patients with polypharmacy admitted to internal and geriatric wards. Therefore clinicians, patients and caregivers badly need prognostic markers for older people that help in clinical management and long-term health care plans, since these become particularly complex in patients who not only have the acute diseases leading to hospitalization but also multiple concomitant chronic conditions.

What do our findings add to the growing evidence of the deleterious effects of low Hb? After controlling for many potential confounders, mild but not moderate-severe anaemia in older in-patients was a strong predictor of their risk of hospital readmission, while any level of low Hb raised the risk of three-month mortality. The type of anaemia rather than the severity affected mortality at three months, the worst prognosis being associated with normocytic and macrocytic anaemias.

Conflict of interest

There are no conflicts of interest or financial interest of the authors.

Funding/Support

None.

The REPOSI study is a network of Italian Internal Medicine and Geriatric hospital wards that on a voluntary basis and without any financial support agreed to participate in data collection during the four index weeks.

Author contributions

RC, GM, MT, AN, ER conceived and designed the clinical investigation; REPOSI Investigators conducted the study; CF, LP, PMM critically reviewed the manuscript, ER, SM, MT analysed data; ER wrote the paper.

Acknowledgements:

Sara Mandelli is the recipient of a Fellowship from the "Via di Natale" association, Aviano, Pordenone, Italy. The authors are grateful to Italo Monzino Foundation, Milan, Italy. We thank J. D. Baggott for kindly editing the paper.

Appendix A. Investigators and co-authors of the REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) Study Group are as follows:

Steering Committee

Pier Mannuccio Mannucci *(Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano)*, Alessandro Nobili *(co-chair, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano),* Mauro Tettamanti, Luca Pasina, Carlotta Franchi *(IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano),* Francesco Perticone *(Presidente SIMI),* Francesco Salerno *(IRCCS Policlinico San Donato Milanese, Milano),* Salvatore Corrao *(ARNAS Civico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo),* Alessandra Marengoni *(Spedali Civili di Brescia, Brescia),* Giuseppe Licata *(Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia),* Francesco Violi *(Policlinico Umberto I, Roma, Prima Clinica Medica),* Gino Roberto Corazza, *(Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I),* Maura Marcucci *(Unità di Geriatria, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico & Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italia).*

Clincal data monitoring and revision

Tarek Kamal Eldin, Maria Pia Donatella Di Blanca *(IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano).*

Database Management and Statistics:

Mauro Tettamanti, Codjo Djignefa Djade, Ilaria Ardoino, Laura Cortesi *(IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano).*

Investigators:

Italian Hospitals

Domenico Prisco, Elena Silvestri, Caterina Cenci, Giacomo Emmi *(Azienda Ospedaliero Universitaria Careggi Firenze, Medicina Interna Interdisciplinare);*Gianni Biolo, Gianfranco Guarnieri, Michela Zanetti, Giovanni Fernandes *(Azienda Ospedaliera Universitaria Ospedali Riuniti di Trieste, Trieste, Clinica Medica Generale e Terapia Medica);* Massimo Vanoli, Giulia Grignani, Gianluca Casella, *(Azienda Ospedaliera della Provincia di Lecco, Ospedale di Merate, Lecco, Medicina Interna);* Mauro Bernardi, Silvia Li Bassi, Luca Santi, Giacomo Zaccherini *(Azienda Ospedaliera Policlinico Sant'Orsola-Malpighi, Bologna, Semeiotica Medica Bernardi);* Elmo Mannarino, Graziana Lupattelli, Vanessa Bianconi, Francesco Paciullo *(Azienda Ospedaliera Santa Maria della Misericordia, Perugia, Medicina Interna, Angiologia, Malattie da Arteriosclerosi);*Ranuccio Nuti, Roberto Valenti, Martina Ruvio, Silvia Cappelli, Alberto Palazzuoli *(Azienda Ospedaliera Università Senese, Siena, Medicina Interna I);* Teresa Salvatore, Ferdinando Carlo Sasso *(Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli, Napoli, Medicina Interna e Malattie Epato-Bilio Metaboliche Avanzate);* Domenico Girelli, Oliviero Olivieri, Thomas Matteazzi *(Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Medicina Generale a indirizzo Immuno-Ematologico e Emocoagulativo);* Mario Barbagallo, Lidia Plances, Roberta Alcamo *(Azienda Ospedaliera Universitaria Policlinico Giaccone Policlinico di Palermo, Palermo, Unità Operativa di Geriatria e Lungodegenza);* Giuseppe Licata, Luigi Calvo, Maria Valenti *(Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia);* Marco Zoli, Raffaella Arnò *(Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna Zoli);* Franco Laghi Pasini, Pier Leopoldo Capecchi, Maurizio Bicchi *(Azienda Ospedaliera Universitaria Senese, Siena, Unità Operativa Complessa Medicina 2);* Giuseppe Palasciano, Maria Ester Modeo, Maria Peragine, Fabrizio Pappagallo, Stefania Pugliese, Carla Di Gennaro *(Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Medicina Interna Ospedaliera "L. D'Agostino", Medicina Interna Universitaria "A. Murri");* Alfredo Postiglione, Maria Rosaria Barbella, Francesco De Stefano *(Azienda Ospedaliera Universitaria Policlinico Federico II di Napoli, Medicina Geriatrica Dipartimento di Clinica Medica);* Maria Domenica Cappellini, Giovanna Fabio, Sonia Seghezzi, Margherita Migone De Amicis *(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Unità Operativa Medicina Interna IA);* Daniela Mari, Paolo Dionigi Rossi, Sarah Damanti, Barbara Brignolo Ottolini, Sarah Damanti *(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Geriatria);* Gino Roberto Corazza, Emanuela Miceli, Marco Vincenzo Lenti, Donatella Padula *(Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I);* Giovanni Murialdo, Alessio Marra, Federico Cattaneo *(IRCS Azienda Ospedaliera Universitaria San Martino-IST di Genova, Genova, Clinica di Medicina Interna 2);* Maria Beatrice Secchi, Davide Ghelfi *(Ospedale Bassini di Cinisello Balsamo, Milano, Divisione Medicina);* Luigi Anastasio, Lucia Sofia, Maria Carbone *(Ospedale Civile Jazzolino di Vibo Valentia, Vibo Valentia, Medicina interna);* Giovanni Davì, Maria Teresa Guagnano, Simona Sestili *(Ospedale Clinicizzato SS. Annunziata, Chieti, Clinica Medica);* Gerardo Mancuso, Daniela Calipari, Mosè Bartone *(Ospedale Giovanni Paolo II Lamezia Terme, Catanzaro, Unità Operativa Complessa Medicina Interna);* Maria Rachele Meroni *(Ospedale Luigi Sacco, Milano, Medicina 3°);* Paolo Cavallo Perin, Bartolomeo Lorenzati, Gabriella Gruden, Graziella Bruno, Cristina Amione, Paolo Fornengo *(Dipartimento di Scienze Mediche, Università di Torino, Città della Scienza e della Salute, Torino, Medicina 3);* Rodolfo Tassara, Deborah Melis, Lara Rebella *(Ospedale San Paolo, Savona, Medicina I);* Giuseppe Delitala, Vincenzo Pretti, Maristella Salvatora Masala *(Ospedale Universitario Policlinico di Sassari, Sassari, Clinica Medica);* Luigi Bolondi, Leonardo Rasciti, Ilaria Serio *(Policlinico Sant'Orsola-Malpighi, Bologna, Unità Operativa Complessa Medicina Interna);* Filippo Rossi Fanelli, Antonio Amoroso, Alessio Molfino, Enrico Petrillo *(Policlinico Umberto I, Sapienza Università di Roma, Roma, Medicina Interna H);* Giuseppe Zuccalà, Francesco Franceschi, Guido De Marco, Cordischi Chiara, Sabbatini Marta *(Policlinico Universitario A. Gemelli, Roma, Roma, Unità Operativa Complessa Medicina d'Urgenza e Pronto Soccorso);* Giuseppe Romanelli, Claudia Amolini, Deborah Chiesa, Alessandra

Marengoni *(Spedali Civili di Brescia, Brescia, Geriatria);* Antonio Picardi, Umberto Vespasiani Gentilucci, Paolo Gallo *(Università Campus Bio-Medico, Roma, Medicina Clinica-Epatologia);* Giorgio Annoni, Maurizio Corsi, Sara Zazzetta, Giuseppe Bellelli *(Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza, Unità Operativa di Geriatria);* Franco Arturi, Elena Succurro, Mariangela Rubino, Giorgio Sesti *(Università degli Studi Magna Grecia, Policlinico Mater Domini, Catanzaro, Unità Operativa Complessa di Medicina Interna);* Paola Loria, Maria Angela Becchi, Gianfranco Martucci, Alessandra Fantuzzi, Mauro Maurantonio *(Università di Modena e Reggio Emilia, Medicina Metabolica-NOCSAE, Baggiovara, Modena);* Giuseppe Delitala, Stefano Carta, Sebastiana Atzori *(Azienda Mista Ospedaliera Universitaria, Sassari, Clinica Medica);* Maria Grazia Serra, Maria Antonietta Bleve *(Azienda Ospedaliera "Cardinale Panico" Tricase, Lecce, Unità Operativa Complessa Medicina);* Laura Gasbarrone, Maria Rosaria Sajeva *(Azienda Ospedaliera Ospedale San Camillo Forlanini, Roma, Medicina Interna 1);* Antonio Brucato, Silvia Ghidoni, Paola Di Corato *(Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Medicina 1);* Giancarlo Agnelli, Emanuela Marchesini *(Azienda Ospedaliera Santa Maria della Misericordia, Perugia, Medicina Interna e Cardiovascolare);* Fabrizio Fabris, Michela Carlon, Francesca Turatto, Aldo Baritusso, Francesca Turatto *(Azienda Ospedaliera Università di Padova, Padova, Clinica Medica I);* Roberto Manfredini, Christian Molino, Marco Pala, Fabio Fabbian, Benedetta Boari, Alfredo De Giorgi *(Azienda Ospedaliera – Universitaria Sant'Anna, Ferrara, Unità Operativa Clinica Medica);* Giuseppe Paolisso, Maria Rosaria Rizzo, Maria Teresa Laieta *(Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli, Napoli, VI Divisione di Medicina Interna e Malattie Nutrizionali dell'Invecchiamento);* Giovanbattista Rini, Pasquale Mansueto, Ilenia Pepe *(Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Malattie Metaboliche);* Claudio Borghi, Enrico Strocchi, Valeria De Sando *(Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna Borghi);* Carlo Sabbà, Francesco Saverio Vella, Patrizia Suppressa, Raffaella Valerio *(Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Medicina Interna Universitaria C. Frugoni);* Stefania Pugliese, Caterina Capobianco *(Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Clinica Medica I Augusto Murri);* Luigi Fenoglio, Christian Bracco, Alessia Valentina Giraudo, Elisa Testa, Cristina Serraino *(Azienda Sanitaria Ospedaliera Santa Croce e Carle di Cuneo, Cuneo, S. C. Medicina Interna);* Silvia Fargion, Paola Bonara, Giulia Periti, Marianna Porzio *(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 1B);* Flora Peyvandi, Alberto Tedeschi, Raffaella Rossio *(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 2);* Valter Monzani, Valeria Savojardo, Christian Folli, Maria Magnini *(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna Alta Intensità di Cura);* Francesco Salerno, Alessio Conca, Giulia Gobbo, Alessio Conca *(IRCCS Policlinico San Donato e Università di Milano, San Donato Milanese, Medicina Interna);* Carlo L. Balduini, Giampiera Bertolino, Stella Provini, Federica Quaglia *(IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica III);* Franco Dallegri, Luciano Ottonello, Luca Liberale *(Università di Genova, Genova, Medicina Interna 1);* Wu Sheng Chin, Laura Carassale, Silvia Caporotundo *(Ospedale Bassini, Cinisello Balsamo, Milano, Unità Operativa di Geriatria);* Giancarlo Traisci, Lucrezia De Feudis, Silvia Di Carlo *(Ospedale Civile Santo Spirito di Pescara, Pescara, Medicina Interna 2);* Nicola Lucio Liberato, Alberto Buratti, Tiziana Tognin *(Azienda Ospedaliera della Provincia di Pavia, Ospedale di Casorate Primo, Pavia, Medicina Interna);* Giovanni Battista Bianchi, Sabrina Giaquinto (*Ospedale "SS Gerosa e Capitanio" di Lovere, Bergamo, Unità Operativa Complessa di Medicina Generale, Azienda Ospedaliera "Bolognini" di Seriate, Bergamo);* Francesco Purrello, Antonino Di Pino, Salvatore Piro *(Ospedale Garibaldi Nesima, Catania, Unità Operativa Complessa di Medicina Interna);* Renzo Rozzini, Lina Falanga *(Ospedale Poliambulanza, Brescia, Medicina Interna e Geriatria);* Giuseppe Montrucchio, Elisabetta Greco, Pietro Tizzani, Paolo Petitti *(Dipartimento di Scienze Mediche, Università di Torino, Città della Scienza e della Salute, Torino, Medicina Interna 2 U. Indirizzo d'Urgenza);* Antonio Perciccante, Alessia Coralli *(Ospedale San Giovanni-Decollato-Andisilla, Civita Castellana Medicina);* Raffaella Salmi, Piergiorgio Gaudenzi, Susanna Gamberini *(Azienda Ospedaliera-Universitaria S. Anna, Ferrara, Unità Operativa di Medicina Ospedaliera II);* Andrea Semplicini, Lucia Gottardo *(Ospedale SS. Giovanni e Paolo, Venezia, Medicina Interna 1);* Gianluigi Vendemiale, Gaetano Serviddio, Roberta Forlano *(Ospedali Riuniti di Foggia, Foggia, Medicina Interna Universitaria);* Cesare Masala, Antonio Mammarella, Valeria Raparelli *(Policlinico Umberto I, Roma, Medicina Interna D);* Francesco Violi, Stefania Basili, Ludovica Perri *(Policlinico Umberto I, Roma, Prima Clinica Medica);* Raffaele Landolfi, Massimo Montalto, Antonio Mirijello, Carla Vallone *(Policlinico Universitario A. Gemelli, Roma, Clinica Medica);* Martino Bellusci, Donatella Setti, Filippo Pedrazzoli *(Presidio Ospedaliero Alto Garda e Ledro, Ospedale di Arco, Trento, Unità Operativa di Medicina Interna Urgenza/Emergenza);* Luigina Guasti, Luana Castiglioni, Andrea Maresca, Alessandro Squizzato, Marta Molaro *(Università degli Studi dell'Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Medicina Interna I);* Marco Bertolotti, Chiara Mussi, Maria Vittoria Libbra, Andrea Miceli, Elisa Pellegrini, Lucia Carulli *(Università di Modena e Reggio Emilia, AUSL di Modena, Modena, Nuovo Ospedale Civile, Unità Operativa di Geriatria e U.O. di Medicina a indirizzo Metabolico Nutrizionistico);* Francesco Perticone, Angela Sciacqua, Michele Quero, Chiara Bagnato *(Università Magna Grecia Policlinico Mater Domini, Catanzaro, Unità Operativa Malattie Cardiovascolari Geriatriche);* Roberto Corinaldesi, Roberto De Giorgio, Mauro Serra, Valentina Grasso, Eugenio Ruggeri *(Dipartimento di Scienze Mediche e Chirurgiche, Unità Operativa di Medicina Interna, Università degli Studi di Bologna/Azienda Ospedaliero-Universitaria S.Orsola-Malpighi, Bologna);* Andrea Salvi, Roberto Leonardi, Chiara Grassini, Ilenia Mascherona, Giorgio Minelli, Francesca Maltese *(Spedali Civili di Brescia, U.O. 3a Medicina Generale);* Armando Gabrielli, Massimo Mattioli, William Capeci, Giuseppe Pio Martino *(Azienda Ospedaliera Universitaria – Ospedali Riuniti di Ancona, Clinica Medica);* Salvatore Corrao, Silvia Messina *(ARNAS Civico-Di Cristina-Benfratelli – Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S.), Palermo);* Riccardi Ghio, Serena Favorini, Anna Dal Col *(Azienda Ospedaliera Università San Martino, Genova, Medicina III);*Salvatore Minisola, Luciano Colangelo *(Policlinico Umberto I, Roma, Medicina Interna F e Malattie Metaboliche dell'osso);*Antonella Afeltra, Pamela Alemanno, Benedetta Marigliano *(Policlinico Campus Biomedico Roma, Roma, Medicina Clinica);* Pietro Castellino, Julien Blanco, Luca Zanoli *(Azienda Ospedaliera Universitaria Policlinico Vittorio Emanuele Ferrarotto, Santa Marta, S. Bambino, Catania, Dipartimento di Medicina);* Marco Cattaneo, Paola Fracasso, Maria Valentina Amoruso *(Azienda Ospedaliera San Paolo, Milano, Medicina III);* Valter Saracco, Marisa Fogliati, Carlo Bussolino *(Ospedale Cardinal Massaia Asti, Medicina A);*Vittorio Durante, Giovanna Eusebi, Daniela Tirotta *(Ospedale di Cattolica, Rimini, Medicina Interna);* Francesca Mete, Miriam Gino *(Ospedale degli Infermi di Rivoli, Torino, Medicina Interna);* Antonio Cittadini, Michele Arcopinto, Andrea Salzano, Emanuele Bobbio, Alberto Maria Marra, Domenico Sirico *(Azienda Policlinico Universitario Federico II di Napoli, Napoli,*

Medicina Interna e Riabilitazione Cardiologica); Guido Moreo, Francesco Scopelliti, Francesca Gasparini, Melissa Cocca *(Clinica San Carlo Casa di Cura Polispecialistica, Paderno Dugnano, Milano, Unità Operativa di Medicina Interna).*

Spanish Hospitals

Ramirez Duque Nieves *(Hospital Universitario Virgen del Rocio, Sevilla);* Muela Molinero Alberto *(Hospital de Leon);* Abad Requejo Pedro, Lopez Pelaez Vanessa, Tamargo Lara *(Hospital del Oriente de Asturias, Arriondas);* Corbella Viros Xavier, Formiga Francesc *(Hospital Universitario de Bellvitge);* Diez Manglano Jesus, Bejarano Tello Esperanza, Del Corral Behamonte Esther, Sevil Puras Maria *(Hospital Royo Villanova, Zaragoza);* Manuel Romero *(Hospital Infanta Elena Huelva);*Pinilla Llorente Blanca, Lopez Gonzalez-Cobos Cristina, Villalba Garcia M. Victoria *(Hospital Gregorio Marañon Madrid*); Lopez Saez, Juan Bosco *(Hospital Universitario de Puerto Real, Cadiz);* Sanz Baena Susana, Arroyo Gallego Marta *(Hospital Del Henares De Coslada, Madrid);* Gonzalez Becerra Concepcion, Fernandez Moyano Antonio, Mercedes Gomez Hernandez, Manuel Poyato Borrego *(Hospital San Juan De Dios Del Aljarafe, Sevilla);* Pacheco Cuadros Raquel, Perez Rojas Florencia, Garcia Olid Beatriz, Carrascosa Garcia Sara *(Hospital Virgen De La Torre De Madrid);* Gonzalez-Cruz Cervellera Alfonso, Peinado Martinez Marta *(Hospital General Universitario De Valencia);* Ruiz Cantero Alberto, Albarracín Arraigosa Antonio, Godoy Guerrero Montserrat, Barón Ramos Miguel Ángel *(Hospital De La Serrania De Ronda);* Machin Jose Manuel *(Hospital Universitario De Guadalajara);* Novo Veleiro Ignacio, Alvela Suarez Lucía *(Hospital Universitario De Santiago De Compostela);* Lopez Alfonso, Rubal Bran David, Iñiguez Vazquez Iria *(Hospital Lucus Augusti De Lugo);* Rios Prego Monica *(Hospital Universitario De Ponteve).*

References

Ayaz, T., Sahin, B. S., Sahin, O. Z., Bilir, O., & Rakici, H. (2014). Factors affecting mortality in elderly patients hospitalized for nonmalignant reasons. *Journal of Aging Research*7. http://dx.doi.org/10.1155/2014/584315 Article ID 584315.

Bhasin, A., & Rao, M. J. (2011). Characteristics of anemia in elderly: A hospital based study in South India. *Indian Journal of Hematology & Blood Transfusion*, *27*(1), 26–32. http://dx.doi.org/10.1007/s12288-011-0056-4.

Biagi, P., Gussoni, G., Iori, I., Nardi, R., Mathieu, G., Mazzone, A., et al. (2011). Clinical profile and predictors of in-hospital outcome in patients with heart failure: The FADOI CONFINE Study. *International Journal of Cardiology*, *152*(1), 88–94. http://dx.doi.org/10.1016/j.ijcard.2011.02.025.

Bridgen, M. L. (1995). A systematic approach to macrocytosis. Sorting out the causes. *Postgraduate Medicine*, *97*(5), 171–172 175-177, 181-4 passim.

Culleton, B. F., Manns, B. J., Zhang, J., Tonelli, M., Klarenbach, S., & Hemmelgarn, B. R. (2006). Impact of anemia on hospitalization and mortality in older adults. *Blood*, *107*(10), 3841–3846. http://dx.doi.org/10.1182/blood-2005-10-4308.

Gaskell, H., Derry, S., Moore, R. A., & McQuay, H. J. (2008). Prevalence of anaemia in older persons: Systematic review. *BioMed Central Geriatrics*, *8*(January (14)), 1. http://dx.doi.org/10.1186/1471-2318-8-1.

Geisel, T., Martin, J., Schulze, B., Schaefer, R., Bach, M., Virgin, G., et al. (2014). An etiologic profile of anemia in 405 geriatric patients. *Anemia*932486. http://dx.doi.org/10.1155/2014/932486.

Guralnik, J. M., Eisenstaedt, R. S., Ferrucci, L., Klein, H. G., & Woodman, R. C. (2004). Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. *Blood*, *104*(8), 2263–2268. http://dx.doi.org/10.1182/blood-2004-05-1812.

Joosten, E., & Lioen, P. (2014). Iron deficiency anaemia and anaemia of chronic disease in geriatric hospitalized patients: How frequent are comorbidities as an additional explanation for the anaemia? *Geriatrics & Gerontology International*, *15*(8), 931–935. http://dx.doi.org/10.1111/ggi.12371.

Katzman, R., Brown, T., Fuld, P., Peck, A., Schechter, R., & Schimmel, H. (1983). Validation of a short orientation-memory-concentration test of cognitive impairment. *The American Journal of Psychiatry*, *140*(6), 734–739. http://dx.doi.org/10.1176/ajp.140.6.734.

Levey, A. S., Stevens, L. A., Schmid, C., Zhang, Y. L., Castro, A. F. 3rd, Feldman, H. I., et al. (2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, *150*(9), 604–612. http://dx.doi.org/10.7326/0003-4819-150-9-200905050-00006 Erratum (2011) in Annals of Internal Medicine, Sep 20, 155 (6), 408.

Locatelli, F., Pisoni, R. L., Combe, C., Bommer, J., Andreucci, V. E., Piera, L., et al. (2004). Anaemia in haemodialysis patients of five European countries: Association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrology Dialisys Transplantation*, *19*(1), 121–132. http://dx.doi.org/10.1093/ndt/gfg458 Erratum in: Nehrology Dialisys Translantation, 19(6), 1666.

Martinez-Rivera, C., Portillo, K., Muñoz-Ferrer, A., Martnez-Ortiz, M. L., Molins, E., Serra, P., et al. (2012). Anemia is a mortality predictor in hospitalized patients for COPD exacerbation. *Journal of Chronic Obstructive Pulmonary Disease*, *9*(3), 243–250. http://dx.doi.org/10.3109/15412555.2011.647131.

Mentz, R. J., Greene, S. J., Ambrosy, A. P., Vaduganathan, M., Subacius, H. P., Swedberg, K., et al. (2014). 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. *Circulation. Heart Failure*, *7*(3), 401–408. http://dx.doi.org/10.1161/CIRCHEARTFAILURE.113.000840.

Migone De Amicis, M., Poggiali, E., Motta, I., Minonzio, F., Fabio, G., Hu, C., et al. (2015). Anemia in elderly hospitalized patients: Prevalence and clinical impact. *Internal and Emergency Medicine*, *10*(5), 581–586. http://dx.doi.org/10.1007/s11739-015-1197-5.

Nathavitharana, R. L., Murray, J. A., D'sousa, N., Sheehan, T., Frampton, C. M., & Baker, B. W. (2012). Anaemia is highly prevalent among unselected internal medicine inpatients and is associated with increased mortality, earlier readmission and more prolonged hospital stay: An observational retrospective cohort study. *Internal Medicine Journal*, *42*(6), 669–683. http://dx.doi.org/10.1111/j.1445-5994.2011.02566.xi.mj_2566 68.

Nobili, A., Licata, G., Salerno, F., Pasina, L., Tettamanti, M., Franchi, C., et al. (2011). Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *European Journal of Clinical Pharmacology*, *67*(5), 507–519. http://dx.doi.org/10.1007/s00228-010-0977-0.

Parmelee, P. A., Thuras, P. D., Katz, I. R., & Lawton, M. P. (1995). Validation of a measure of physical burden at autopsy: The cumulative illness rating scale. *Journal of the American Geriatric Society*, *43*(2), 130–137. http://dx.doi.org/10.1111/j.1532-5415.1993.tb05945.x.

Penninx, B. W. J. H., Pahor, M., Woodman, R. C., & Guralnik, J. M. (2006). Anemia in old age is associated with increased mortality and hospitalization. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*(5), 474–479. http://dx.doi.org/10.1093/gerona/61.5.474.

Petroysan, I., Blaison, G., Andrès, E., & Federici, L. (2012). Anaemia in the elderly: An aetiologic profile of a prospective cohort of 95 hospitalised patients. *European Journal of Internal Medicine*, *23*(6), 524–528. http://dx.doi.org/10.1016/j.ejim.2012.03.013.

Rachoin, J. S., Cerceo, E., Milcarek, B., Hunter, K., & Gerber, D. R. (2013). Prevalence and impact of anemia in hospitalized patients. *Southern Medical Journal*, *106*(3), 202–206. http://dx.doi.org/10.1097/SMJ.0b013e318287fcd9.

Ramel, A., Jonsson, P. V., Bjornsson, S., Bjornsson, S., & Thorsdottir, I. (2008). Anemia, nutritional status, and inflammation in hospitalized elderly. *Nutrition*, *24*(11–12), 1116–1122. http://dx.doi.org/10.1016/j.nut.2008.05.025.

Riva, E., Tettamanti, M., Mosconi, P., Apolone, G., Gandini, F., Nobili, A., et al. (2009). Association of mild anaemia with hospitalization and mortality in the Elderly: The Health and Anaemia Population-based Study. *Haematologica*, *94*(1), 22–28 0.3324/haematol.13449.

Savage, D. G., Ogundipe, A., Allen, R. H., Stabler, S. P., & Lindenbaum, J. (2000). Etiology and diagnostic evaluation of macrocytosis. *The American Journal of the Medical Science*, *319*(6), 343–352. http://dx.doi.org/10.1016/S0002-9629(15)40772-4.

Shah, S., Vanclay, F., & Cooper, B. (1989). Improving the sensitivity of the Barthel index for stroke rehabilitation. *Journal of Clinical Epidemiology*, *42*(8), 703–709. http://dx.doi.org/10.1016/0895-4356(89)90065-6.

Tettamanti, M., Lucca, U., Gandini, F., Recchia, A., Mosconi, P., Apolone, G., et al. (2010). Prevalence, incidence and types of mild anaemia in the elderly: The Health and Anaemia population-based study. *Haematologica*, *95*(11), 1849–1856. http://dx.doi.org/10.3324/haematol.2010.023101.

Ueda, T., Kawakami, R., Horii, M., Sugawara, Y., Matsumoto, T., Okada, S., et al. (2013). High mean corpuscular volume is a new indicator of prognosis in acute decompensated heart failure. *Circulation Journal*, *77*(11), 2766–2771.

Viktil, K. K., Blix, H. S., Moger, T. A., & Reikvam, A. (2007). Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug related problems. *British Journal of Clinical Pharmacology*, *63*(2), 187–195. http://dx.doi.org/10.1111/j.1365-2125.2006.02744.x.

World Health Organization, Geneva (1987). *International classification of diseases, injuries, and causes of death. ninth revision (ICD-9)*. World Health Organization. http://dx.doi.org/10.7326/0003-4819-88-3-424.

World Health Organization (1968). *Nutritional anaemia: Report of a WHO scientific group*, *405*, World Health Organization Technical Report Series1–40.