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Original Article

Heart failure and anemia: Effects on prognostic variables☆

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ABSTRACT

Background: Anemia is frequent in heart failure (HF), and it is associated with higher mortality. The predictive power of established HF prognostic parameters in anemic HF patients is unknown.
Methods: Clinical, laboratory, echocardiographic and cardiopulmonary-exercise-test (CPET) data were analyzed in 3913 HF patients grouped according to hemoglobin (Hb) values. 248 (6%), 857 (22%), 2160 (55%) and 648

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(17%) patients had very low (<11 g/dL), low (11–12 for females, 11–13 for males), normal (12–15 for females, 13–15 for males) and high (>15) Hb, respectively.
Results: Median follow-up was 1363 days (606–1883). CPETs were always performed safely. Hb was related to prognosis (Hazard ratio (HR) = 0.864). No prognostic difference was observed between normal and high Hb groups. Peak oxygen consumption (VO_2), ventilatory efficiency (VE/VCO_2 slope), plasma sodium concentration, ejection fraction (LVEF), kidney function and Hb were independently related to prognosis in the entire population. Considering Hb groups separately, peakVO_2 (very low Hb HR = 0.549, low Hb HR = 0.613, normal Hb HR = 0.618, high Hb HR = 0.542) and LVEF (very low Hb HR = 0.49, low Hb HR = 0.692, normal Hb HR = 0.697, high Hb HR = 0.694) maintained their prognostic roles. High VE/VCO_2 slope was associated with poor prognosis only in patients with low and normal Hb.
Conclusions: Anemic HF patients have a worse prognosis, but CPET can be safely performed. PeakVO_2 and LVEF, but not VE/VCO_2 slope, maintain their prognostic power also in HF patients with Hb < 11 g/dL, suggesting CPET use and a multiparametric approach in HF patients with low Hb. However, the prognostic effect of an anemia-oriented follow-up is unknown.

1. Introduction

Anemia is frequent in heart failure (HF), although a considerable variability of its prevalence has been reported [1]. As an average, anemia is reported in 22% of HF patients with Left Ventricular Ejection Fraction (LVEF) >50%, in 20% of HF patients with LVEF from 40% to 49% and in 14% of HF patients with LVEF <40% [2–7]. The presence of anemia, as an independent risk factor, is associated with a higher all-cause mortality or hospitalization rate [2–7], and it is among the most important risk scores for HF [8,9].

However, limited data are available about the predictive power of established HF prognostic parameters in anemic HF patients. In fact, anemia is a common exclusion criterion in HF trials. Notably, exercise-derived HF prognostic parameters, such as peak oxygen consumption (peakVO_2) and ventilatory efficiency (VE/VCO_2), are rarely available in anemic HF patients due to the controversy about the safety of anemic patients performing exercise [10]. Moreover, the meaning of peakVO_2 in HF patients with anemia is questionable, as hemoglobin (Hb) is a component of VO_2.

In order to improve the risk stratification and the clinical management of the growing population of HF patients with anemia, we aimed at assessing the prognostic power of several parameters by analyzing the multicenter Italian database (MECKI score research group) [8]. This is built with several established HF prognostic parameters such as clinical, laboratory, echocardiographic and exercise measurements. In particular, we assessed the role of HF prognostic parameters in patients with different Hb values using, as a study endpoint, the composite of cardiovascular death and urgent heart transplant (HT).

2. Methods

2.1. Study population

The study cohort consisted of 3913 consecutive patients with systolic HF, recruited and prospectively followed in 19 Italian HF Centers (MECKI score research group) [8]. Inclusion criteria were: HF symptoms (NYHA functional class I-IV, stage C of ACC/AHA classification), previous documentation of left ventricular systolic dysfunction (LVEF <40%), stable clinical conditions with unchanged medications for at least three months, no major cardiovascular treatment or intervention scheduled. Exclusion criteria were: history of pulmonary embolism, moderate to

Table 1
Patients demographic, laboratory, echocardiographic data.

	All population	Very low Hb	Low Hb	Normal Hb	High Hb		
	3913	248 (6%)	857 (22%)	2160 (55%)	648 (17%)	P (Trend)	p(Class)
Age (years)	61.1 ± 12.5	65.2 ± 12.4	63.0 ± 12.9	60.8 ± 12.0	57.9 ± 12.5	<0.001	<0.001
Height (cm)	170 ± 8	168 ± 8	169 ± 8	170 ± 8	171 ± 7	<0.001	<0.001
Gender (males)	3268 (84%)	193 (78%)	755 (88%)	1689 (78%)	631 (97%)	<0.0001	<0.0001
BMI (Kg/m^2)	26.8 ± 4.4	26 ± 4.3	26.2 ± 4.1	26.9 ± 4.4	27.6 ± 4.6	<0.001	<0.001
NYHA I	574(14.7%)	17 (6.8%)	86 (10.0%)	331 (15.3%)	140 (21.6%)	<0.0001	<0.0001
NYHA II	2197(56.2%)	122 (49.2%)	464 (54.2%)	1247 (57.7%)	364 (56.3%)		
NYHA III	1091(27.9%)	103 (41.5%)	294 (34.3%)	556 (25.7%)	138 (21.3%)		
NYHA IV	49 (1.2%)	6 (2.4%)	12 (1.4%)	26 (1.2%)	5 (0.8%)		
Idiopathic etiology	1659 (42.5%)	81 (32.6%)	299 (35.0%)	964 (44.7%)	315 (48.7%)	<0.0001	<0.0001
Ischaemic etiology	1884 (48.2%)	133 (53.6%)	476 (55.7%)	986 (45.7%)	289 (44.7%)		
Valvular etiology	130 (3.3%)	19 (7.7%)	35 (4.1%)	65 (3.0%)	11 (1.7%)		
Other etiology	234 (6.0%)	15 (6.0%)	44 (5.1%)	143 (6.6%)	32 (4.9%)		
Hemoglobin (g/dL)	13.6 ± 1.6	10.3 ± 0.7	12.1 ± 0.5	13.8 ± 0.7	15.8 ± 0.6	<0.001	<0.001
K^+ (mmol/L)	4.3(4.0;4.6)	4.2 (3.9;4.6)	4.3 (4.0;4.6)	4.27 (4.0;4.6)	4.3 (4.0;4.6)	0.21	0.02
Creatinine (mg/dL)	1.10 (0.9;1.31)	1.29 (1.03;1.73)	1.16 (0.94;1.5)	1.05 (0.9;1.27)	1.08 (0.93;1.22)	<0.001	<0.001
Na^+ (mmol/L)	139.3 ± 3.3	138.6 ± 3.5	139.1 ± 3.3	139.4 ± 3.2	139.7 ± 3.2	<0.001	<0.001
MDRD (mL/min/1.73 m^2)	71.7 ± 23.3	59.0 ± 24.9	67.6 ± 25.4	73.2 ± 21.8	77.1 ± 22.0	<0.001	<0.001
LVeSV (mL)	116 (83;157)	116 (82;152)	119 (85;160)	115 (82;156)	118 (85;163)	0.11	0.06
LVeDV (mL)	174 (130;220)	168 (128;211)	176 (132;222)	172 (129;219)	180 (136;225)	0.05	0.02
LVEF (%)	31.8 ± 9.4	31.9 ± 9.8	31.4 ± 9.4	32 ± 9.4	31.8 ± 9.1	0.53	0.57
Atrial fibrillation	617(15.8%)	46 (18.5%)	132 (15.4%)	326 (15.1%)	113 (17.4%)	1	0.31

Continuous data are reported as Mean ± SD or Median (75–25 interquartile). Categorical variable are reported as frequency (%).
BMI = Body Mass Index, NYHA = New York Heart Association, Na+ = plasma sodium concentration, K + = plasma potassium concentration, MDRD = Modification of Diet in Renal Disease, LVeSV = left ventricle end-systolic volume, LVeDV = left ventricle end-diastolic volume, LVEF = Left Ventricular Ejection Fraction, LVeSV = Left Ventricular End-Systolic Volume, LVeDV = Left Ventricular End-Diastolic Volume.

Table 2
Therapy (drugs and devices) at study run-in.

	All population	Very low Hb	Low Hb	Normal Hb	High Hb		
	3913	248 (6%)	857 (22%)	2160 (55%)	648 (17%)	p(Trend)	p(Class)
ACE-inhibitors	2994 (76.6%)	174 (70.2%)	640 (74.8%)	1660 (77.1%)	520 (80.2%)	<0.01	<0.01
ARB-blockers	695 (17.8%)	51 (20.6%)	154 (18.0%)	397 (18.4%)	93 (14.4%)	0.04	0.07
Beta-blockers	3312 (84.6%)	202 (81.5%)	716 (83.5%)	1850 (85.6%)	544 (84.0%)	0.24	0.20
Diuretics	3188 (81.5%)	215 (86.7%)	736 (85.9%)	1758 (81.4%)	479 (73.9%)	<0.001	<0.001
Anti-aldosteronic drugs	2111 (54.0%)	144 (58.1%)	506 (59.1%)	1147 (53.2%)	314 (48.5%)	<0.001	<0.001
Anti-platlets drugs	2101 (53.8%)	139 (56.0%)	490 (57.2%)	1142 (53.0%)	330 (50.9%)	0.01	0.06
Anticoagulants	1139 (29.1%)	80 (32.3%)	276 (32.2%)	599 (27.8%)	184 (28.4%)	0.03	0.07
Digitalis	898 (23.0%)	53 (21.4%)	197 (23.1%)	480 (22.2%)	168 (25.9%)	0.20	0.24
Amiodarone	979 (25.1%)	62 (25.0%)	227 (26.5%)	542 (25.2%)	148 (22.8%)	0.21	0.44
PM	734 (18.8%)	69 (27.9%)	218 (25.6%)	354 (16.5%)	93 (14.4%)	<0.001	<0.001
ICD	1157 (30.0%)	82 (33.5%)	310 (36.5%)	598 (28.1%)	167 (26.5%)	<0.001	<0.001
CRT	473 (13.1%)	38 (16.4%)	140 (17.8%)	232 (11.7%)	63 (10.5%)	<0.001	<0.001

ACE = angiotensin I converting enzyme, ARB = angiotensin II receptor, PM = Pace-maker, ICD = Implantable Cardioverter-Defibrillator, CRT = Cardiac. Resynchronization Therapy.

severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina and significant electrocardiographic alterations or presence of any clinical comorbidity interfering with exercise performance.

2.2. Clinical, laboratory, echocardiographic and CPET evaluations

At enrollment, patients' clinical history, treatment, physical, laboratory, EKG, echocardiographic and cardiopulmonary exercise test (CPET) data were collected. Among the parameters recorded, we analyzed: a) patients' NYHA class, weight, height and treatment; b) HF etiology, defined as dilative ischemic and non-ischemic cardiomyopathy (on the basis of the presence or absence of relevant stenosis at coronary angiography, respectively) or cardiomyopathy secondary to valvular disease and to other causes; c) Hb, plasma sodium concentration (Na^+), plasma potassium concentration (K^+), and creatinine. We calculated glomerular filtration rate as MDRD by using the following formula: $186.3 * (\text{creatinine})^{-1154} * (\text{Age})^{-0.203} * 0{,}75$ for women [11]. Moreover, we analyzed several EKG and CPET parameters and, at echocardiography, left ventricle end-systolic (LVeSV) and end-diastolic volumes (LVeDV) and LVEF (Simpson's rule) [12]. All CPETs were performed using either an electronically braked cycle ergometer (3596 patients) or a treadmill (317 patients); for a proper comparison, the VO_2 data measured on treadmill were reduced by 10% [13]. In CPETs performed on cycle ergometer, a ramp protocol was applied, while treadmill studies were performed using a modified Bruce protocol. The exercise protocol was set to achieve peak exercise in ~10 min [14]. CPETs were interrupted when patients stated that they had reached maximal effort. We performed breath-by-breath analysis of expiratory gases and ventilation. Anaerobic threshold (AT) was measured by V-slope analysis of VO_2 and VCO_2, and it was confirmed analyzing the ventilatory equivalents and the end-tidal pressures of CO_2 and O_2. If no agreement was obtained or AT was not detected, AT was considered as not identified. Exercise-induced periodic breathing was defined as a cyclic fluctuation of ventilation [15]. VE/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Peak exercise oxygen pulse was calculated as peak VO_2/peak heart rate (HR). Predicted values of HR were calculated as: peak HR pred = (220 − Age), if male, =(210 − Age) if female [13].

2.3. Patient follow-up and prognosis

Patient follow-up was carried out according to the local HF program. Follow-up ended with the last clinical evaluation in the Center where the patient had been enrolled or with the patient's death or urgent HT.

Table 3
Patients CPET data.

	All population	Very low Hb	Low Hb	Normal Hb	High Hb		
	3913	248 (6%)	857 (22%)	2160 (55%)	648 (17%)	p(Trend)	p(Class)
Ramp protocol (Watt/min)	9.9 ± 2.3	9.5 ± 2.2	9.7 ± 2.1	9.9 ± 2.3	10.4 ± 2.6	<0.001	<0.001
Peak VO_2 (% pred)	55.5 ± 16.5	47.7 ± 15.3	49.8 ± 14.3	57.4 ± 16.5	59.6 ± 16.8	<0.001	<0.001
Peak VO_2 (mL/Kg/min)	14.3(11.6;17.4)	11.71(9.7;14.2)	13.2(10.8;15.6)	14.6(11.8;17.8)	15.9(13.2;19.3)	<0.001	<0.001
Peak HR (bpm)	121 ± 25	114 ± 25	117 ± 24	122 ± 24	127 ± 26	<0.001	<0.001
Peak HR (% pred)	77 ± 15	75 ± 17	75 ± 16	78 ± 15	78 ± 15	<0.001	<0.001
Peak Load (Watt)	83 ± 33	65 ± 24	73 ± 27	85 ± 33	97 ± 35	<0.001	<0.001
Peak pulse (mL/bpm)	9.7 ± 3.5	8.2 ± 2.9	8.9 ± 2.9	9.9 ± 3.6	10.8 ± 3.3	<0.001	<0.001
Peak VT (L)	1.5 ± 0.5	1.3 ± 0.4	1.4 ± 0.4	1.5 ± 0.5	1.7 ± 0.5	<0.001	<0.001
Peak RR (bpm)	31 ± 7	32 ± 7	31 ± 7	31 ± 7	31 ± 7	0.32	0.55
Peak VE (L/min)	44.6(36.1;54.7)	40.2(32.8;48)	42.7(34.8;50.8)	44.9(36.2;55)	49.6(39.9;59.8)	<0.001	<0.001
RQ	1.11 ± 0.13	1.14 ± 0.14	1.13 ± 0.12	1.11 ± 0.13	1.10 ± 0.12	<0.001	<0.001
VO_2 at AT (mL/Kg)	10.3 ± 3.3	8.9 ± 2.8	9.6 ± 2.7	10.5 ± 3.4	11.3 ± 3.6	<0.001	<0.001
VO_2 at AT (%)	68.3 ± 13.9	70.4 ± 15.6	69.4 ± 13.3	67.9 ± 13.8	67.5 ± 14.1	0.001	0.0066
Load at AT (Watt)	50 ± 23	39 ± 16	44 ± 18	52 ± 24	57 ± 24	<0.001	<0.001
HR at AT (bpm)	97 ± 19	93 ± 17	94 ± 18	98 ± 20	100 ± 21	<0.001	<0.001
VO_2/work slope	9.73 ± 2.13	9.42 ± 2.61	9.45 ± 2.05	9.79 ± 2.08	10.07 ± 2.14	<0.001	<0.001
VE/VCO_2 slope	32.5 ± 7.6	35.5 ± 8.1	34.2 ± 8.1	32.0 ± 7.3	30.8 ± 6.8	<0.001	<0.001
Periodic breathing	682(17.5%)	63(25.4%)	171(20%)	352(16.3%)	96(14.8%)	<0.001	<0.001

Continuous data are reported as Mean ± SD or Median (75–25 interquartile). Categorical variable are reported as frequency (%).
VO2 = Oxygen consumption, HR = Heart-rate, TV = Tidal Volume, RR = Respiratory-rate, VE = Ventilation, RER = Respiratory Exchange Ratio, AT = Anaerobic Threshold, VCO2 = Carbon Dioxide Consumption, PB = Periodic Breathing.

Table 4
Follow up, cardiovascular deaths and urgent heart transplants for the entire study population and grouped for different hemoglobin values.

	All population	Very low Hb	Low Hb	Normal Hb	High Hb	p-value
	3913	248 (6%)	857 (22%)	2160 (55%)	648 (17%)	
Median follow up (days)	1363	1250	1221	1072	946	
(interquartile range)	(606–1883)	(678–1994)	(629–1912)	(575–1736)	(439–1614)	<0.0001
Cardiovascular deaths	541	67	149	255	70	<0.0001
(CV deaths/1000 persons/years)	(37)	(85)	(49)	(31)	(27)	<0.0001
Urgent HTs	105	6	22	54	23	0.52
(Urgent HTs/1000 persons/years)	(7)	(7)	(7)	(7)	(9)	0.73
Cardiovascular Deaths + Urgent HTs	646	73	171	309	93	<0.0001
(Cardiovascular Deaths + Urgent HTs/1000 persons/years)	(44)	(92)	(56)	(38)	(36)	<0.0001

CV = cardiovascular; HT = heart transplant.

2.4. Data management

Data management was that of the MECKI score research group, as previously reported [8]. Data were analyzed for the entire study population and grouping patients according to Hb value (high Hb: >15 g/dL; normal Hb: 13–15 g/dL for males and 12–15 g/dL for females; low Hb: 11–13 g/dL for males and 11–12 g/dL for females; very low Hb: <11 g/dL [16]).

An institutional review committee approved the study, and the subjects gave informed consent.

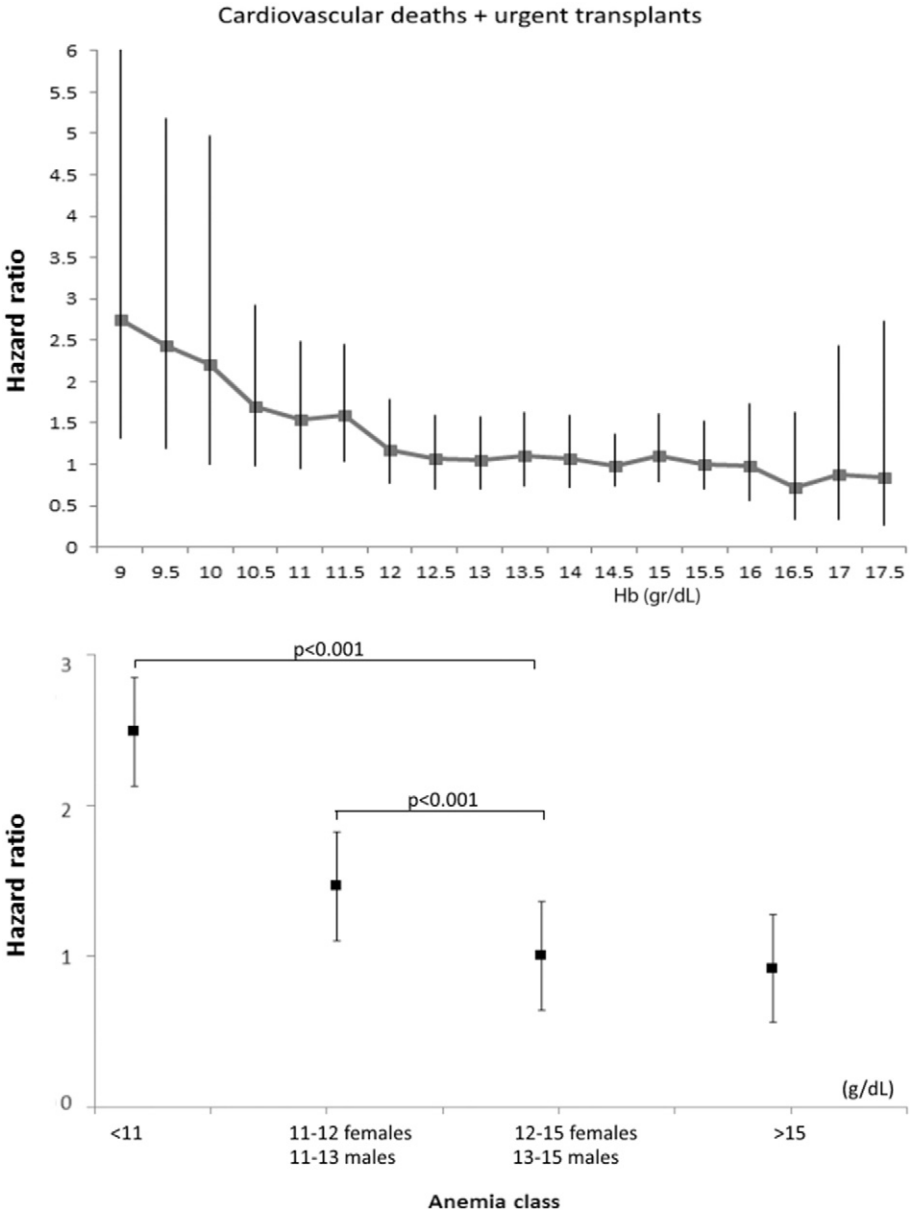

Fig. 1. Hazard ratio according to Hemoglobin levels. Hazard Ratio of cardiovascular death + heart transplant for hemoglobin (Hb) (upper panel) and for patients grouped for high Hb, normal Hb, low Hb and very low Hb (lower panel).

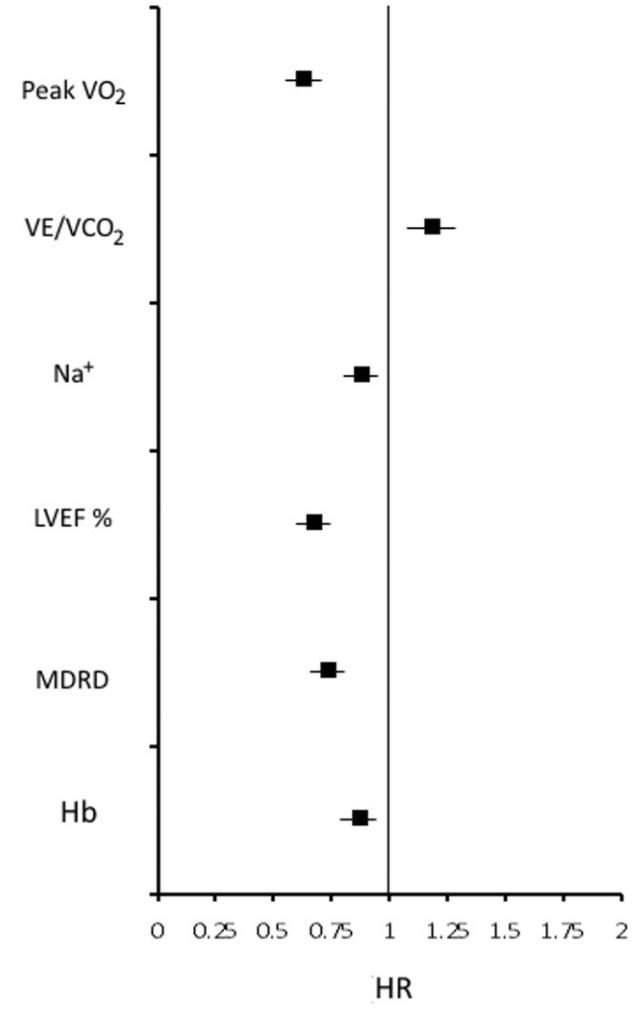

Fig. 2. Multivariable model for Hazard Ratio in the entire population. Hazard Ratio for association between peak oxygen consumption (VO_2), ventilatory efficiency (VE/VCO_2), Na^+, left ventricle ejection fraction (LVEF), renal function (MDRD), Hb and cardiovascular death + heart transplant through study follow-up in the entire study population. Each variable is adjusted for the other variables of the model (VO_2, VE/VCO_2, Na^+, LVEF, MDRD, Hb).

2.5. Statistical methods

Categorical variables were presented as frequency and percentage, and they were compared by chi-square test. Numerical variables were summarized as means ± SD or medians and interquartile range when their distribution was markedly not normal. Multivariable model for Hazard Ratio was performed when the entire population was analyzed. Each variable is adjusted for the other variables of the model (VO_2, VE/VCO_2, Na^+, LVEF, MDRD, Hb). Unpaired t-test or non-parametric Mann–Whitney test were used as appropriate for between-group comparison. Kaplan–Meier curves were constructed and analyzed by Odds Ratio (OR). A $p < 0.05$ was used to define statistical significance. All analyses were performed using SPSS 18 software and SAS statistical package v.9.2 (SAS Institute Inc., Cary, NC).

3. Results

Table 1 presents the characteristics of the entire study population (3913 HF patients) and differentiated according to Hb levels in very low (248; 6%), low (857; 22%), normal (2160; 55%), and high (648; 17%) Hb. Ischemic etiology was more frequently observed in patients with low Hb, while an opposite trend was observed in patients with HF due to idiopathic cardiomyopathy. Treatment was up to date according to guidelines (Table 2). However, ACE-inhibitors and ARB-blockers combined were similar among the Hb classes, as beta-blockers were. A non-significant trend toward more anti-coagulant and anti-platelet therapy was observed in patients with low and very low Hb level. LVEF was similar among Hb groups. CPETs were performed safely in all patients; specifically, no CPET-related death or cardiac arrest was recorded. CPET data are reported in Table 3. Peak VO_2 and VE/VCO_2 slope were progressively lower and higher as Hb decreased. The very low Hb group was characterized by the most severe patients in terms of NYHA class, laboratory (Na^+ and MDRD), CPET-derived parameters and treatment strategy (more diuretics).

Median follow-up was 1363 days (interquartile range 606–1883) in the entire population. During follow-up, 541 (37 per 1000 persons/year) cardiovascular deaths and 100 (7 per 1000 persons/year) urgent HTs were observed (Table 4). Follow-up, cardiovascular deaths and urgent HTs in the study population grouped for different Hb values are also reported in Table 4.

Anemia was related to prognosis, as shown by the Hazard Ratio of study endpoint in the entire population (Fig. 1, upper panel) and in patients grouped according to Hb level (Table 4, Fig. 1, lower panel). Notably, no differences in prognosis were observed between normal Hb and high Hb groups.

We tested for prognosis all the variables reported in Tables 1, 2 and 3 using the same statistical approach that allowed us to derive the MECKI score [8]. In the overall population, we confirmed that PeakVO_2 (% of predicted), VE/VCO_2 slope, Na^+, LVEF, MDRD and Hb were independently related to prognosis (Fig. 2). Kaplan–Meier curves of the four Hb groups and adjusted for the proven confounders, i.e. peak VO_2, VE/VCO_2 slope, MDRD, LVEF and Na^+, are reported in Fig. 3. Low Hb and very low Hb curves diverged already after 1 year. At 5 years, patients with very low Hb had a significant reduction of survival compared to patients with low Hb (OR 2.1), with normal Hb (OR 3.0), and with high Hb (OR 3.3).

The independent predictive role of PeakVO_2, VE/VCO_2 slope, Na^+, LVEF, and MDRD were also assessed in the four Hb-based groups (Fig. 4). PeakVO_2 and LVEF maintained their prognostic roles in all Hb groups. The same happened, at least as a trend, for kidney function and Na^+. Differently, a high VE/VCO_2 slope was associated with poor prognosis only in patients with normal and low Hb, but not in those with very low or high Hb.

4. Discussion

This study leads to a number of important findings. Firstly, in line with several previous reports [2–6], we confirmed that anemia influences HF prognosis. Secondly, there is a direct correlation between Hb level and prognosis below but not above Hb = 12 g/dL. Thirdly, CPET can be performed safely in anemic HF patients. Finally, among CPET parameters, peakVO_2, but not VE/VCO_2 slope, maintains its prognostic role in very low Hb HF patients.

In clinical practice, as well as in a previous position paper report [10], concerns were raised about performing exercise in patients with severe anemia, suggesting that any exercise test be postponed until anemia correction is obtained. In the present study, we showed that CPET can be safely performed even in HF patients with very low Hb. Moreover, in patients with severe anemia, peakVO_2 maintains its strong prognostic role, confirming the role of CPET in proper prognosis even in this setting of HF patients. It is of note that the prognostic role of peakVO_2 is independent of anemia although anemia is a component of VO_2, likely because several other physiological mechanisms, such as cardiac output, O_2 delivery, or muscular O_2 utilization, are involved in VO_2 determination.

The prevalence of anemia we observed in the present population of HF patients with low LVEF is similar to that previously reported [1–7].

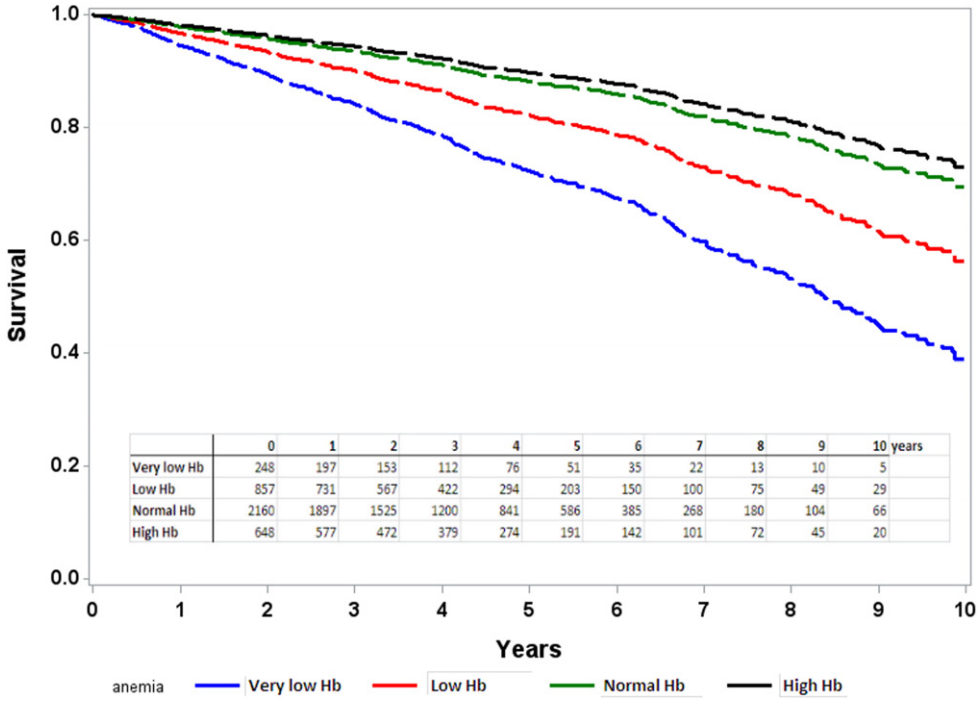

Fig. 3. Population mortality according to Hemoglobin levels. Kaplan–Meier curves for cardiovascular death + heart transplant adjusted for age, gender adjusted for the proven confounders, i.e. peak VO_2, VE/VCO_2 slope, MDRD, LVEF and Na^+ in the entire study population stratified according to Hb values: high Hb: >15 g/dL (black line); normal Hb: 13–15 g/dL for males and 12–15 g/dL for females (green line); low Hb: 11–13 g/dL for males and 11–12 g/dL for females (red line); very low Hb: <11 g/dL (blue line). The curves were arbitrarily ended at 10 years.

We also showed that, in HF patients with severe anemia, the best prognostic evaluation is a composite of different parameters, including Hb, peak VO_2, LVEF and, at least as a trend, Na^+ and kidney function. Accordingly, our findings are in line with the concept that the most powerful prognostic capacity is obtained with a multiparametric approach even in patients with combined anemia and HF [8].

The finding that VE/VCO_2 slope is not associated with prognosis in patients with Hb < 11 g/dL was unexpected, although the VE/VCO_2 slope value in patients with low Hb was the highest observed. Indeed, these patients have very severe HF with a poor prognosis, and VE/VCO_2 slope is a recognized strong HF prognosis predictor [17,18]. There are several possible explanations for this finding. However, we are intrigued by a physiological hypothesis. Indeed, a high VE/VCO_2 slope in HF is related to an increase of sympathetic activity through a CO_2-dependent stimulation of metaboreceptors and chemoreceptors. In severe anemia, the reduction of O_2 delivery due to low arterial oxygen content may per se stimulate ventilation, and therefore it may overwhelm the role of CO_2-dependent reflex hyperventilation. In patients with Hb > 15, the ones with the lowest VE/VCO_2 slope value observed, a relatively increased oxygen delivery may counterbalance the increase of sympathetic activity on ventilation, explaining why, as happens in severe anemic patients, VE/VCO_2 loses its prognostic power. It is of note that the present findings fit very well with the most recent hypothesis of ventilation regulation by O_2, which is mediated by an olfactory receptor activated by lactate [19]. This hypothesis suggests that O_2 delivery to the glomus cell of the carotid body, and not PO_2, regulates ventilation. Consequently, in the very low Hb group, an anemia-related low O_2 delivery to the carotid chemoreceptors may overwhelm the sympathetic-induced chemoreceptor and metaboreceptor hyperactivity, so that the VE/VCO_2 slope, albeit very high, loses its prognostic power. Notably, the same seems to be true for the high Hb group, albeit through an opposite mechanism. It is recognized, however, that further studies are needed to confirm the present findings that cast some doubts about the prognostic role of VE/VCO_2 slope in HF patients with very low and high Hb values.

Finally, in line with a recent analysis performed in HF patients [2], we showed that prognosis in systolic HF patients with >15 g/dL Hb value is unrelated to Hb, suggesting that Hb values between 15 and 17 are not associated with an increase of cardiovascular deaths.

4.1. Study limitations

This study has several limitations. Firstly, the follow-up was a long one, on average around 4 years, but we analyzed Hb values only at study enrollment. Moreover, patients were studied and followed up in 19 HF units, each one with its own patient follow-up program. Accordingly, we do not know whether and how often Hb level was checked and if anemia treatment was carried out and how effective the anemia treatment strategy was. It is therefore possible that patients varied their Hb during follow-up, either reducing it with HF worsening or increasing it because of proper therapeutic interventions. It is recognized that all these factors could have modified the impact of anemia on HF prognosis.

Secondly, the anemic groups, low and very low Hb and high Hb group, were arbitrarily defined. Indeed, while normal and low values of Hb are well established for men and women, both definitions of the cutoff for high Hb (>15 g/dL) and for very low Hb (<11 g/dL) are truly arbitrary.

Thirdly, patients with severe HF unable to perform CPET, either due to severe anemia or due to severe HF, were not analyzed. Therefore, our conclusions should be considered only for HF patients capable to perform CPET, regardless of Hb level. Finally, as regards CPET safety, it is recognized that minor safety issues are difficult to evaluate and, most importantly, they might have not been recorded. Consequently, only the occurrence of major (death or cardiac arrest) CPET-related events was excluded.

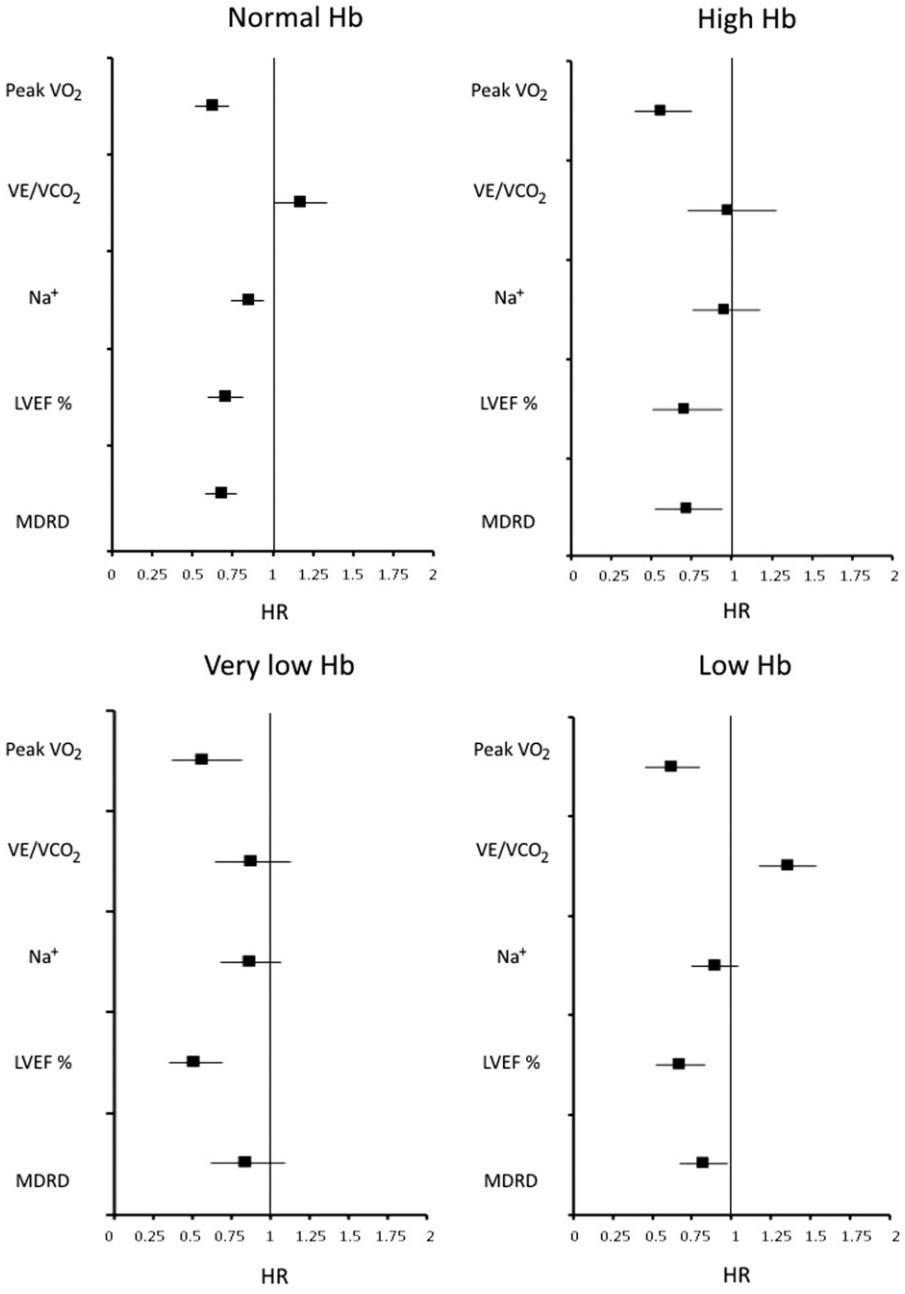

Fig. 4. Multivariable model for Hazard Ratio according to Hemoglobin group. Hazard Ratio for association between peak oxygen consumption (VO_2), ventilatory efficiency (VE/VCO_2), Na^+, left ventricle ejection fraction (LVEF), renal function (MDRD), Hb and cardiovascular death + heart transplant through study follow-up in patients with normal Hb (left upper panel), high Hb (right upper panel), very low Hb (left lower panel) and low Hb (right lower panel). Each variable is adjusted for the other variables of the model (VO_2, VE/VCO_2, Na^+, LVEF, MDRD).

5. Conclusions

Our study shows several relevant findings: a) anemic HF patients have a worse prognosis; b) CPET can be safely performed in HF patients with anemia; c) peakVO_2, but not VE/VCO_2, is a strong survival predictor in severe anemia, underlining the importance of performing CPET for prognosis evaluation in anemic HF patients; d) peakVO_2 and LVEF maintain their validity as prognostic predictors in the anemia setting, suggesting the use of a multiparametric prognostic approach also in HF patients with low Hb. However, it is unknown whether, during the prolonged follow-up, anemia status changed and whether anemia correction was done. Indeed, both spontaneous Hb values changes and anemia correction could have influenced the present findings. Indeed, an anemia-oriented follow-up of patients is desirable, but it was not standardized in the present study, and its results are, at present, unavailable.

Conflict of interest

None declared.

Appendix A

Other MECKI Score Group members are:

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- Fondazione Gabriele Monasterio, CNR-Regione Toscana, Pisa: Luigi Pastormerlo.
- S. Luca Hospital, Istituto Auxologico Italiano. Milano: Gabriella Malfatto, Elena Viganò.

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