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Hemoglobin levels above anemia thresholds are maximally predictive for long-term survival in COPD with chronic respiratory failure

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ABSTRACT

Background: In patients with COPD, chronic anemia is known as an unfavorable prognostic factor. Whether the association between hemoglobin (Hb) levels and long-term survival is restricted to anemia, or extends to higher Hb levels has not yet been systematically assessed.

Methods: We determined Hb levels in 309 patients with COPD and chronic respiratory failure (CRF) prior to initiation of non-invasive ventilation (NIV), accounting for confounders that might affect Hb. Patients were categorized as anemic (Hb<12g/dl (f); Hb<13g/dl (m)), polycythemic (Hb≥15g/dl (f); Hb≥17g/dl (m)), or normocythemic. In addition, percentiles of Hb values were analyzed with regard to mortality from any cause.

Results: Two-hundred-seven patients (67.0%) showed normal Hb levels, 46 (14.9%) anemia, and 56 (18.1%) polycythemia. Polycythemic patients showed a higher survival rate than anemic (p=0.01) and normocythemic patients (p=0.043). In a univariate Cox hazards model, Hb was associated with long-term survival (HR 0.855; 95%-CI 0.783-0.934; p<0.001). The 58th percentiles of Hb (14.3g/dl (f); 15.1g/dl (m)) yielded the highest discriminative value for predicting survival (HR 0.462; 95%-CI 0.324-0.661; p<0.001). In the multivariate analysis this cut-off was an independent predictor for survival (HR 0.627; 95%-CI 0.414-0.949; p=0.027), in addition to age and body mass index.

Conclusion: In patients with COPD and CRF undergoing treatment with NIV and LTOT, high Hb levels are associated with better long-term survival. The optimal cut-off level for prediction was above the established threshold defining anemia. Thus, predicting survival only on the basis of anemia does not fully utilize the prognostic potential of Hb values in COPD.

Keywords: COPD; chronic respiratory failure; long-term survival; hemoglobin; anemia; non-invasive ventilation; polycythemia

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, inflammation and lung remodelling (1) and associated with extra-pulmonary systemic manifestations, e.g. cardiovascular diseases, malnutrition, osteoporosis, renal failure, depression and anxiety (2-4). Anemia, most likely of multifactorial origin, is also a common co-morbidity (5-8). In a large cohort of patients with severe COPD receiving long-term oxygen therapy (LTOT), Chambellan and co-workers found, that a low hematocrit (Hc) was not uncommon and associated with higher mortality and morbidity (7). Also in stable COPD of widely ranging disease severity the prevalence of anemia was high (17%) and related to a reduction of functional capacity and survival time (8). Recent data showed anemia in 18% of COPD patients treated for acute respiratory failure, and a link between anemia and 90-day mortality (9).

However, hypoxia-induced "secondary" polycythemia is also common in severe COPD. In contrast to anemia, polycythemia may reflect that an adequate compensatory physiologic response to hypoxemia is still present despite the systemic inflammation. Historically, phlebotomy has been used in patients with high hemoglobin (Hb)/Hc levels. Moreover, in numerous studies functional benefits of phlebotomy in hypoxic pulmonary disease have been described (10-16). Conversely, polycythemia contributes to the development of cor pulmonale and pulmonary hypertension, which are linked to a poor prognosis (17). However, most of these studies were performed prior to the widespread use of LTOT and domiciliary non-invasive ventilation (NIV), and large systematic trials on phlebotomy in polycythemic patients are lacking. For patients with polycythemia due to hypoxic lung diseases, guidelines primarily recommend the evaluation for LTOT or positive pressure ventilation by a respiratory physician (18). Phlebotomy is suggested only in patients with symptoms of hyperviscosity or Hc above 56% (18).

In the study by Cote et al. the prevalence of polycythemia (Hb>17 g/dl) was low

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(5.9%), and not associated with worsened outcomes in COPD patients (8). Chambellan et al. found the longest survival in polycythemic patients receiving LTOT. However, their analysis based on Hc levels did not exclude patients with co-morbidities or conditions that might interfere with red blood cell count. Accordingly, it was claimed, that more studies would be desirable to explore the impact of red cell mass on clinical outcomes, in particular survival (7, 8).

Based on these considerations we investigated the prognostic impact of Hb levels in a large cohort of COPD patients with chronic respiratory failure (CRF), who were under optimized therapy including LTOT and domiciliary NIV, while accounting for major confounders of Hb levels. The aim was to assess whether the association of Hb and mortality is linear or not, and whether the optimal Hb cut-off levels for the prediction of long-term survival are similar to, or different from the common clinically used cut-off values of anemia or polycythemia.

METHODS

Study subjects

Patients were identified from an electronic database of the Donaustauf Hospital, Center for Pneumology, in which all patients treated with domiciliary NIV are registered. The decision for NIV was made on the basis of international recommendations (19), pronounced nocturnal hypercapnia or clinical criteria. Demographic and anthropometric data as well as diagnoses, concomitant diseases (coronary heart disease, left heart failure, arterial hypertension, diabetes mellitus, cardiac arrhythmia), medication (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, beta-2 agonists, parasympatholytica, theophylline, systemic steroids), blood gas values, parameters of lung function and exercise testing, and laboratory parameters were documented. Since January 2002 data were entered

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prospectively. In the present analysis, only patients with COPD stage III/IV (GOLD, Global initiative for Chronic Obstructive Lung Disease) who received NIV between April 1992 and March 2007 were included. The diagnosis was based on clinical history and a ratio of forced expiratory volume in one second (FEV_1) to inspiratory vital capacity (VC) of <70%, and FEV_1 being <30%predicted or <50%predicted plus chronic respiratory failure (CRF) (1).

We included only patients in whom blood count data were obtained at admission prior to the initiation of NIV. Moreover, based on the medical records, patients with the following confounders of Hb levels not causatively related to COPD were excluded: i) previous invasive ventilation; ii) renal failure with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m²; iii) malignancies/hematological disorders within the last 5 years; iv) surgeries, interventions, accidents or hemorrhage within the last 3 months; v) additional chronic inflammatory, autoimmune or infectious disease; vi) previous gastrointestinal resection; vii) substitution of iron, folate or vitamin B_{12}; viii) phlebotomy due to polycythemia or blood transfusion.

Measurements

Demographic, anthropometric and laboratory data (Hb, leukocytes, C-reactive protein (CRP), creatinine) were assessed upon admission. Patients were categorized as anemic (Hb <12g/dl in females; Hb<13g/dl in males) (20), polycythemic (Hb 15≥g/dl in females; Hb≥17g/dl in males) (8), or normocythemic. The eGFR was calculated by the Modification of Diet in Renal Diseases (MDRD) equation, which is known to be particularly accurate in elderly patients (21).

Spirometry and body plethysmography (MasterScreen, CardinalHealth Inc., Höchberg, Germany) were performed according to the guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) (22), using ERS reference values (23). 6-minute walk distance (6MWD) was determined according to the ATS statement (24) using

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reference values by Enright and Sherrill (25). Blood gases were assessed from the hyperemic earlobe after incision, using a capillary tube and blood gas analyzer (Rapidlab; Bayer Inc; East Walpole, MA, USA). Only values obtained without oxygen supply were included.

Follow-up

Vital status was determined through telephone contact to the patients' relatives or family physicians and by review of medical records. Informed written consent of the patients or their relatives was obtained. All patients underwent a follow-up period of at least 5 months, until July the 1st 2007 or death. Mortality was documented as overall mortality including all causes of death. The study approach was approved by the local Ethics Committee of the University of Regensburg.

Statistical analysis

Normality of data distribution was checked by the Kolmogorov-Smirnov-Test. Data are shown as median and quartiles. For the comparison of subgroups the non-parametric Kruskal-Wallis test was used, for categorical variables the Chi-squared test. Univariate Cox proportional hazards regression models were run to assess the impact of single predictors on survival. Predictors with $p<0.05$ were included in a multivariate Cox proportional hazards regression model to adjust for other prognostic factors than Hb.

To identify the optimal cut-off values for Hb and to compare them with the standard cut-off values, the following analyses were conducted. For each individual, the probability of death within 1 year was obtained from the multivariate Cox proportional hazards model as described above. The relationship between Hb level and these probabilities was visualized in a scatter plot, together with a non-linear loess (locally-weighted polynomial regression) smoother. Each percentile of Hb, taken separately for females and males, was used to define two subgroups with low and high Hb level. Univariate Cox proportional hazards models were fitted for each of these levels and the one with the smallest p-value yielded the optimal cut-off

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for Hb. Survival probabilities of the commonly used Hb categories and the ones identified by us were plotted as Kaplan-Meier curves which were compared by the log rank test. To compare the prognostic impact of the newly found Hb cut-off values and the standard Hb categories, univariate Cox proportional hazards regression models were employed.

RESULTS

Patients' characteristics

A total of 534 patients with COPD GOLD III/IV were analysed. After exclusion of patients with co-morbidities, or conditions potentially contributing to abnormalities in red blood cell count, and patients with a lack of follow-up, 309 patients remained. Their median (quartiles) Hb was 14.5 (15.9; 13.1) g/dl, and 207 patients (67.0%) were categorized as normocythemic, 102 (33.0%) as abnormal. Among the latter, 46 patients (14.9%) were anemic and 56 (18.1%) polycythemic. There were differences in the distributions of sex ($p=0.002$), age ($p<0.001$), survival time ($p=0.008$), and co-morbidities between anemic, normocythemic and polycythemic patients **(Table 1)**. Medical therapy (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, beta-blockers, beta-2-agonists, parasympatholytica, theophylline, systemic steroids) was not linked to the presence of anemia.

In males (n=222) Hb abnormalities were predominately due to anemia (n=40; 18.0%) and not polycythemia (n=31; 14.0%). Females (n=87) mostly showed polycythemia (n=56; 28.7%), while anemia occurred less frequently (n=6; 6.9%; $p=0.002$). 170 patients (55.0%) were treated with LTOT before inclusion. At discharge all patients were treated with NIV (n=309; 100%) and nearly all had LTOT (n=293; 94.8%). Further patients' characteristics are given in **Table 1**.

Hemoglobin levels and long-term survival

A total of 139 patients (45.0%) died during the study period (mean±SD follow-up: 36.1±31.1

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months); the causes of death were: cardio-pulmonary causes 116 (83.5%), malignancy 7 (5.0%), others 5 (3.6%), unknown causes 11 (7.9%).

Twenty-two anemic (15.8%), 95 normocythemic (68.3%) and 22 polycythemic (15.8%) patients died. The median survival of polycythemic patients was 112 months, while normocythemic patients survived 51 and anemic patients 29 months. The survival probability of polycythemic patients was higher than that of normocythemic (p=0.043) and anemic patients (p=0.01), and that of normocythemic was higher than that of anemic patients (p=0.041; **Figure 1**). The 1-year survival probability of all patients as a function of Hb values is depicted in **Figure 2**.

When analyzing every percentile of Hb values with regard to long-term survival, the optimal cut-off value of Hb was identified as 14.3g/dl for females and 15.1g/dl for males (58^{th} percentiles each, **Table 2**). Regarding the association with the probability of death these values were superior to the cut-offs used for the definition of anemia according to the WHO (Hb <12g/dl in females; Hb<13g/dl in males; **Figure 3**).

Multivariate analysis

In univariate Cox proportional hazards models, age, sex, body-mass index (BMI), FEV_1, 6MWD, Hb, leukocyte levels, and arterial hypertension were associated with survival ($p<0.05$ each, **Table 3**). A multivariate Cox proportional hazards model containing age, sex, BMI, FEV_1, Hb, leucocyte levels, and arterial hypertension revealed only age and BMI to be predictive, while Hb as a continuous linear variable failed statistical significance (p=0.085). However, when the categorical Hb cut-off values (f: 14.3; m: 15.1 g/l) were included in the multivariate panel, these cut-offs were also revealed as independent predictors of survival **(Table 4**), which indicates a nonlinear relationship.

DISCUSSION

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The present study demonstrates that in patients with severe COPD and CRF, Hb levels prior to the initiation of NIV were linked to long-term survival. We identified values of Hb of 14.3g/dl for females and 15.1g/dl for males as conferring the highest predictive value. These Hb values were, in addition to age and BMI, independent predictors for survival and markedly higher than the WHO definitions of anemia. Our findings demonstrate that in patients with COPD and CRF the prognostic value of Hb is not fully exploited when only using the common cut-off values for anemia that have been introduced to define pathological conditions, but not clinical predictors.

As part of the view that COPD is a disease with multiple alterations beyond the lung (2), chronic anemia has been revealed as common systemic manifestation (6-9). Low red cell mass impairs pulmonary hemodynamics, oxygen delivery, and gas exchange (6), which seems particularly relevant for COPD patients presenting with CRF. Conversely, polycythemia can contribute to pulmonary hypertension, reduced cerebral blood flow, and increased risk of venous thromboembolic disease (26, 27), and thus may also negatively influence the prognosis. On the other hand, a higher red cell mass may indicate that an adequate physiologic response to hypoxemia is still present which may be particularly relevant in a systemic inflammatory disease such as COPD. Irrespective of these considerations it is an open question whether the WHO definition of anemia or other definitions adequately utilize the information conferred by Hb in COPD. Therefore, we analyzed the impact of a wide range of Hb levels on long-term survival in COPD patients undergoing NIV and LTOT in detail.

According to established definitions, 14.9% of patients of our sample presented with anemia, while 18.1% were polycythemic. In comparison to earlier studies (7-9) the present cohort comprised a considerably higher proportion of patients with polycythemia. These patients also showed a higher survival than those with anemia and even normocythemia. Using similar definitions, a study on stable, only moderately ill, predominately male (96%) COPD patients also found anemia to be common (17.1%) and associated with higher

mortality, while polycythemia was less frequent (5.9%). The prognostic value of polycythemia versus normoglobulia and anemia was not explicitly reported, but survival was at least not different between polycythemic and non-polycythemic patients (8). In a large investigation of patients with COPD and hypoxemic respiratory failure requiring LTOT (7), anemia occurred in 8.2% of females and 12.6% of males, while polycythemia again was present only in 5.9% of females and 8.9% of males, and associated with better survival. However, these findings were based on the assessment of Hc and not Hb (7). In contrast to Hc, Hb is a direct measure for oxygen carrying capacity, more stable against changes in plasma volume and thus more reliable for the assessment of anemia, while hematocrit may underestimate anemia (28). Moreover, in comparison to our investigation, the authors provided no data on co-morbidities (e.g. cancer, renal failure, or other chronic inflammatory diseases) or conditions (e.g. gastrointestinal hemorrhage or blood loss) that might lead to changes in the red blood cell count. In our experience this is a significant proportion of patients, and a potential source of bias, as most of these co-morbidities per se influence survival. We had to exclude 42% of primarily considered patients to circumvent this. Nonetheless, the previously studied population (7) appeared to be comparable to our cohort, insofar as all patients received LTOT. The fact that the prevalence of polycythemia was lower than in our cohort was possibly due to a more severely impaired gas exchange in our study cohort, as indicated by chronic hypercapnia and the need for NIV. The beneficial effect of polycythemia on survival stands in contrast to the traditional view on COPD (14). As all patients of the present study received NIV and LTOT which counteract polycythemia and hyperviscosity (29-31, 18), the "protective" effect of polycythemia might, however, only be true for patients with optimized treatment.

Our results confirm the high prevalence of anemia (14.9%) and its association with reduced survival in COPD (7-9) specifically in patients with CRF. Univariate Cox regression analyses showed Hb to be a predictor of long-term survival, similarly to age, sex, BMI, FEV_1,

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6MWD, and leukocyte number. In a multivariate model, however, Hb as a continuous variable failed statistical significance (p=0.085). In view of the inevitable correlations between predictors this does not appear as an unexpected finding. In the study by Chambellan et al. (7), red blood cell mass in terms of Hc was found as an independent prognostic factor. However, the authors did not exclude patients with severe co-morbidities which are often associated with both low Hb and worse long-term survival (7). This may have led to an overestimation of the prognostic impact of red cell mass in their cohort.

In a clinical setting, deviations of red blood cell count are often only recognized when values are not within the normal range. Most studies addressing the significance of Hb and/or Hc in COPD focussed on the common definitions of anemia and polycythemia (32-34), despite the fact that the respective cut-off values have never been validated with regard to their prognostic value in COPD. To evaluate the clinical impact of Hb levels in detail and to answer the question whether there is an optimal threshold and where it is, we checked all percentiles of Hb and found optimal cut-off values of 14.3g/dl for females and 15.1g/dl for males for predicting long-term survival. These cut-off values ultimately chosen optimized the prediction although the nature of the statistical analysis in combination with the still finite number of subjects resulted in broad and overlapping formal confidence intervals. The fact that these values are markedly higher than the common definitions of non-anemia (females >12g/dl; males >13g/dl) suggests that in COPD, Hb levels are related to prognosis at levels far away from common “anemia”. Noteworthy enough, when the optimal cut-off values were introduced as categorical variables in the multivariate model, Hb remained a significant independent predictor despite the fact that categories might be associated with a loss of statistical power compared to continuous variables. The discrepancy points towards a nonlinear relationship of Hb to survival. In view of this it is even more remarkable that this nonlinear transition occurred far above the established WHO cut-off values. Of course, this does not invalidate the usefulness of the WHO definitions, which are thought for clinical

purposes, and not for prediction of survival. Our data point out that cut-off values must be adapted to their purpose and underlines, that patients with Hb values above anemia levels can also be at risk. Possibly, a higher Hb level in the presence of chronic hypoxemia prior to treatment reflects adequate bone marrow function (35) and response to inflammation and/or hypoxia (26, 31) and therefore indicates patients with a better prognosis.

Of course, our findings are purely observational. Thus, the thresholds proposed should be validated prospectively in separate cohorts. In particular, the study design does not allow establishing a novel threshold for red blood cell transfusion. The association between higher threshold values and better prognosis most likely reflects an adequate physiological response to CRF in these patients. Which mechanisms are underlying these associations, possibly defining a specific phenotype of COPD, has to be addressed in future studies.

One of the limitations of the present study is that it was not designed to identify the patterns of pathophysiological factors underlying the abnormalities of Hb. We tried to deal with this as far as possible by the exclusion of known, trivial causes of anemia in order to keep the analysis as far unbiased as possible. With regard to the prognostic impact of Hb, we also accounted for additional co-morbidities and typical concomitant medication, which, however, cannot be fully distracted from COPD. In addition, data were collected over a long period of time and a change in therapeutic attitude including prescribed medication cannot be ruled out. Although patients were seen regularly at follow-up visits in the hospital, compliance with LTOT and NIV could not be assessed over the total study period. Finally, blood gas values were obtained from the earlobe and were not available without oxygen supply in all patients, which could affect their value as potential predictors.

In conclusion, in patients with severe COPD and CRF requiring NIV and LTOT, Hb levels were gradually linked to long-term survival whereas a higher Hb was associated with better survival. This is in line with known data. However, as optimal, independent predictors of survival we identified 14.3g/dl for females and 15.1g/dl for males which corresponded to

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the 58th percentiles of the distributions. These values are markedly higher than the WHO definition of anemia or similar clinical criteria which are suited to define a definite pathological condition, but not fully exploit the prognostic potential of Hb values in severe COPD.

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LEGENDS TO FIGURES

Figure 1. Kaplan-Meier survival curves for anemic (dotted), normocythemic (solid) and polycythemic (dashed) patients. The log rank sum test showed differences between these conditions (polycythemic versus normocythemic: p=0.043; polycythemic versus anemic: p=0.01; normocythemic versus anemic: p=0.041).

Figure 2. Loess smoother curve for hemoglobin levels versus predicted probability of death (1 year).

Figure 3. Kaplan-Meier survival curves of patients with either above or below the optimal cut-off value (**black line**; 58th percentile: females=14.3g/dl; males=15.1 g/dl; HR 0.463 (0.324; 0.660); p<0.001) and of anemic versus non-anemic patients (**grey line**; HR 0.572 (0.361; 0.907); p=0.016).

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Table 1. Patients' demographic and clinical characteristics according to hemoglobin categories

Variable	**Anemic** Hb<12g/dl (f) Hb<13g/dl (m)	**Normocythemic**	**Polycythemic** Hb≥15g/dl (f) Hb≥17g/dl (m)	**p-value**
Subjects (N/%)	46/14.9	207/67.0	56/18.1	
Sex (f/m)	6/40	56/151	25/31	†0.002
Age (years)	70.3 (73.8; 62.8)	66.2 (71.4; 59.1)	61.2 (68.4; 55.4)	<0.001
BMI (kg/m²)*	24.3 (30.0; 20.6)	27.7 (33.0; 21.6)	29.5 (34.8; 22.6)	0.085
LTOT (N/%)	45/97.8	196/94.7	52/92.9	†0.524
FEV_1 (%predicted)*	28.5 (38.0; 22.4)	29.8 (38.0; 22.3)	31.5 (38.0; 25.0)	0.369
PaO_2 (mmHg)*	54.5 (63.3; 46.0)	49.5; (55.0; 42.8)	46.0 (50.0; 40.5)	0.002
$PaCO_2$ (mmHg)*	48.5 (56.5; 40.8)	52.0 (58.0; 48.0)	56.0 (61.5; 50.5)	0.616
pH*	7.45 (7.49; 7.4)	7.42 (7.45; 7.39)	7.4 (7.43; 7.37)	0.003
6MWD (m)*	267 (360; 180)	264 (340; 174)	336 (371; 235)	0.078
Leukocyte number (10^3/µl)	9.3 (11.7; 7.6)	9.2 (11.7; 7.5)	9.4 (12.3; 7.4)	0.891
CRP (mg/l)*	8.7 (34.8; 4.0)	6.7 (21.7; 4.5)	8.6 (20.0; 4.8)	0.902
Creatinine (mmol/l)*	70.7 (97.3; 61.9)	79.6 (97.3; 61.9)	70.7 (88.4; 61.9)	0.291
eGFR (ml/min/1.73m²)*	89.3 (117.2; 63.7)	86.8 (103.1; 68.8)	89.4 (99.6; 75.3)	0.943
Coronary heart disease (N/%)	14/30.4	29/14.0	4/7.1	0.003
Left heart failure (N/%)	6/13.0	40/19.3	9/16.1	0.562
Arterial hypertension (N/%)	21/45.7	84/40.6	23/41.1	0.818
Diabetes mellitus (N/%)	20/43.5	43/20.8	13/23.2	0.005
Cardiac arrhythmia (N/%)	13/28.3	29/14.0	2/3.6	0.002
Median survival time (months)	29	51	112	‡0.008

Table legend: The table shows median values and quartiles. Kruskal-Wallis rank sum or Chi-square testing (†) or log rank sum test (‡) were used to compare the three haemoglobin categories. Only measurements parallel to determination of haemoglobin levels were used. *Not all subjects included (missing values: BMI: n=2; FEV_1: n=9; 6MWD: n=175; CRP: n=2; Creatinine: n=5; eGFR: n=5; PaO_2/$PaCO_2$/pH (without oxygen supply): n=140 (anemic: n=28; normocythaemic: n=97; polycythaemic n=15)).

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Definitions of abbreviations: f=female; m=male; BMI=body mass-index; LTOT=long-term oxygen therapy; FEV_1=forced expiratory volume in one second; PaO_2=arterial oxygen tension (without oxygen supply); $PaCO_2$=arterial carbon dioxide tension; 6MWD=6-minute walking distance test; CRP=C-reactive protein; eGFR=estimated glomerular filtration rate

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Table 2. Univariate Cox proportional hazards models for the prediction of death regarding percentiles of Hb

Variable	Hb values (f/m)	Hazard ratio (95% CI)	p-value
10th percentile	12.16/12.20	0.568 (0.325-0.992)	0.047
20th percentile	12.80/13.02	0.682 (0.440-1.057)	0.087
30th percentile	13.10/13.70	0.585 (0.404-0.846)	0.004
40th percentile	13.54/14.20	0.635 (0.450-0.895)	0.009
50th percentile	13.90/14.60	0.549 (0.391-0.770)	0.001
58th percentile	**14.30/15.10**	**0.463 (0.324-0.660)**	**<0.001**
60th percentile	14.40/15.26	0.490 (0.343-0.701)	<0.001
70th percentile	14.90/15.80	0.514 (0.350-0.755)	0.001
80th percentile	15.74/16.40	0.653 (0.430-0.990)	0.045
90th percentile	16.94/17.67	0.540 (0.303-0.961)	0.036

Definitions of abbreviations: Hb=hemoglobin; f=female; m=male; CI=confidence interval

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Table 3. Univariate Cox proportional hazards models for predicted probability of death

Variable	Hazard ratio (95% CI)	p-value
Age	1.064 (1.041-1.088)	<0.001
Sex (f/m)	1.503 (1.003-2.252)	0.049
BMI*	0.912 (0.889-0.936)	<0.001
FEV_1*	0.970 (0.950-0.989)	0.002
PaO_2*	0.969 (0.969-1.024)	0.788
$PaCO_2$*	1.003 (0.974-1.034)	0.839
6MWD*	0.996 (0.993-0.999)	0.018
Hb	0.855 (0.783-0.934)	<0.001
Leukocyte number	1.067 (1.025-1.111)	0.002
CRP*	1.002 (0.999-1.005)	0.276
Creatinine*	1.441 (0.781-2.662)	0.243
eGFR*	0.999 (0.993-1.004)	0.645
Coronary heart disease	1.227 (0.746-2.016)	0.420
Left heart failure	1.296 (0.873-1.924)	0.198
Arterial hypertension	0.609 (0.426-0.870)	0.007
Diabetes mellitus	0.988 (0.659-1.482)	0.954
Cardiac arrhythmia	1.559 (0.968-2.641)	0.067

Definitions of abbreviations: CI=confidence interval; f=female; m=male; BMI=body mass-index; FEV_1=forced expiratory volume in one second; PaO_2=arterial oxygen tension (without oxygen supply); $PaCO_2$=arterial carbon dioxide tension (without oxygen supply); 6MWD=6-minute walking distance test; Hb=hemoglobin; CRP=C-reactive protein; eGFR=estimated glomerular filtration rate. *Not all subjects included (missing values: BMI: n=2; FEV_1: n=9; 6MWD: n=175; CRP: n=2; Creatinine: n=5; eGFR: n=5; PaO_2/$PaCO_2$/pH: n=140 (anemic: n=28; normocythaemic: n=97; polycythaemic n=15)).

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Table 4. Multivariate Cox proportional hazards model for predicted probability of death

Variable	Hazard ratio (95% CI)	p-value
Age	1.056 (1.032-1.081)	<0.001
BMI	0.915 (0.890-0.941)	<0.001
Hb cut-off (f: 14.3; m: 15.1 g/l)	0.627 (0.414-0.949)	0.027

Definitions of abbreviations: CI=confidence interval; BMI=body mass-index; Hb=hemoglobin; f=female; m=male; 6-minute walking distance was excluded due to a great number of missing values (n=175).

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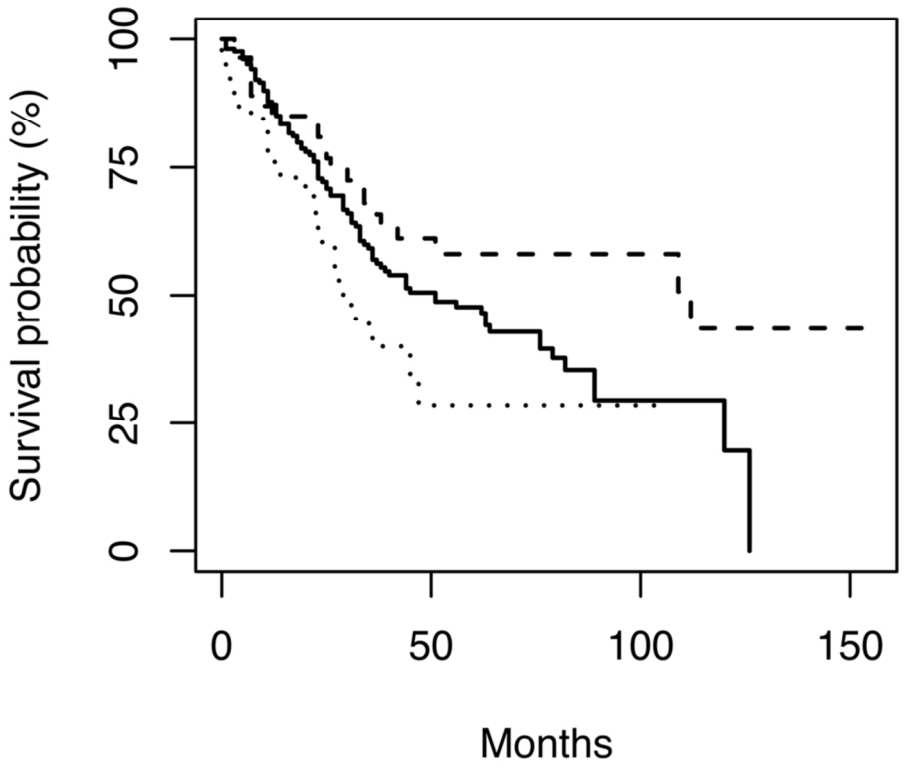

Figure 1: Kaplan-Meier survival curves for anemic (dotted), normocythemic (solid) and polycythemic (dashed) patients
86x86mm (300 x 300 DPI)

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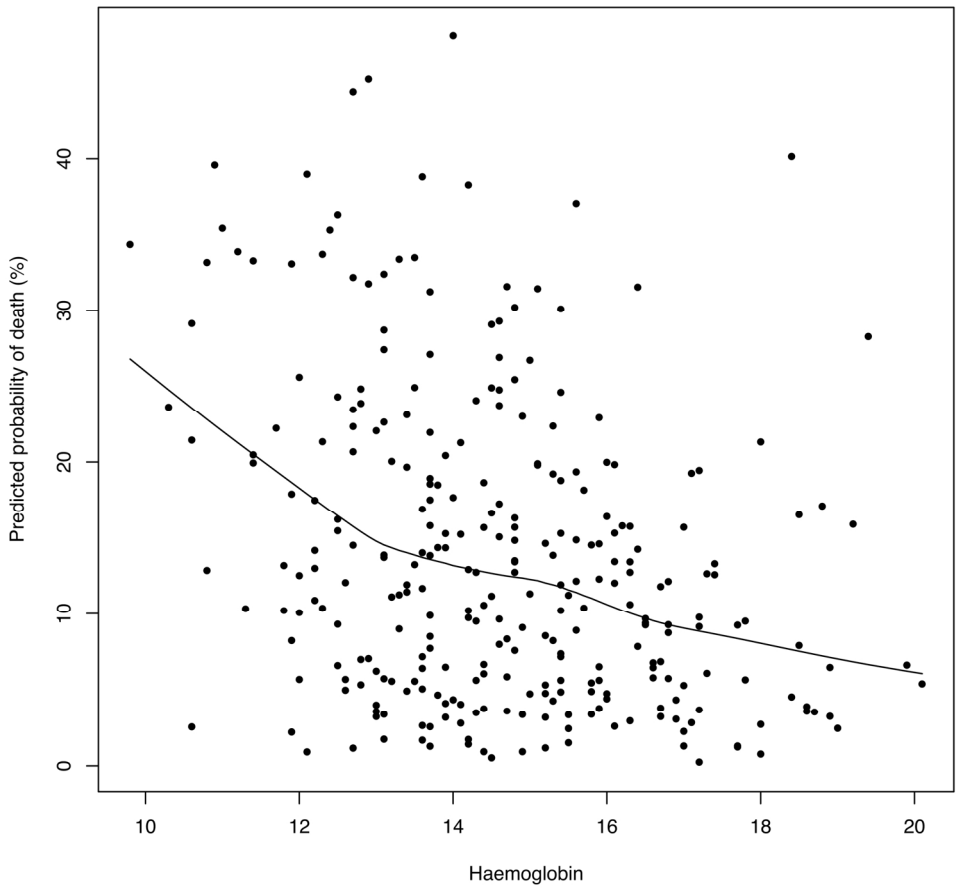

Figure 2: Loess smoother curve for hemoglobin levels versus predicted probability of death (1 year).
181x181mm (300 x 300 DPI)

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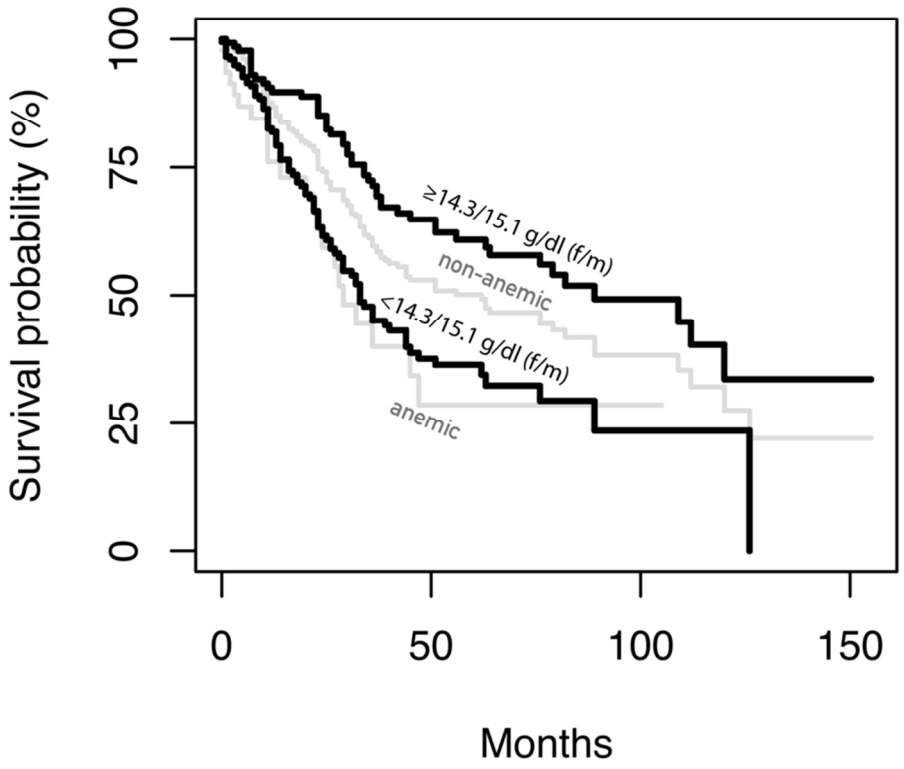

Kaplan-Meier survival curves of patients with either above or below the optimal cut-off value and of anemic versus non-anemic patients
86x86mm (300 x 300 DPI)