Hemoglobin Levels Above Anemia Thresholds Are Maximally Predictive for Long-Term Survival in COPD With Chronic Respiratory Failure

Florian Kollert MD, Andrea Tippelt, Carolin Müller, Rudolf A Jörres PhD, Christine Porzelius, Michael Pfeifer MD, and Stephan Budweiser MD

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 subjects with COPD and chronic respiratory failure prior to initiation of noninvasive ventilation, accounting for confounders that might affect Hb. Subjects were categorized as anemic (Hb < 12 g/dL in females, Hb < 13 g/dL in males), polycythemic (Hb ≥ 15 g/dL in females, Hb ≥ 17 g/dL in males), or normocythemic. In addition, percentiles of Hb values were analyzed with regard to mortality from any cause. RESULTS: Two-hundred seven subjects (67.0%) showed normal Hb levels, 46 (14.9%) had anemia, and 56 (18.1%) had polycythemia. Polycythemic subjects showed a higher survival rate than anemic ($P = .01$) and normocythemic subjects ($P = .043$). In a univariate Cox hazards model, Hb was associated with long-term survival (hazard ratio 0.855; 95% CI 0.783–0.934, $P < .001$). The 58th percentiles of Hb (14.3 g/dL in females, 15.1 g/dL in males) yielded the highest discriminative value for predicting survival (hazard ratio 0.463, 95% CI 0.324–0.660, $P < .001$). In the multivariate analysis this cutoff was an independent predictor for survival (hazard ratio 0.627, 95% CI 0.414–0.949, $P = .03$), in addition to age and body mass index. CONCLUSIONS: In subjects with COPD and chronic respiratory failure undergoing treatment with noninvasive ventilation and LTOT, high Hb levels are associated with better long-term survival. The optimal cutoff 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. *Key words: COPD; chronic respiratory failure; long-term survival; hemoglobin; anemia; noninvasive ventilation; polycythemia.* [Respir Care 2013;58(7):1204–1212. © 2013 Daedalus Enterprises]

Introduction

COPD is characterized by chronic air-flow limitation, inflammation, and lung remodeling,[1] and associated with extra-pulmonary systemic manifestations (eg, cardiovascular diseases, malnutrition, osteoporosis, renal failure, depression, and anxiety).[2-4] Anemia, most likely of multifac-

The authors are affiliated with the Center for Pneumology, Donaustauf Hospital, Donaustauf, Germany, with the exception of Dr Jörres, who is affiliated with the Institute and Out-Patient Clinic for Occupational, Social, and Environmental Medicine, Ludwig Maximilians University, Munich, Germany, and Mrs Porzelius, who is affiliated with the Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany. Dr Kollert is also affiliated with the Department of Rheumatology and Clinical Immunology, University Medical Center, Freiburg, Germany. Drs Kollert and Pfeifer are also affiliated with the Department of Internal Medicine II, Division of Respirology, University of Regensburg, Regensburg, Germany. Dr Budweiser is also affiliated with the Department of Internal Medicine III, Division of Pulmonary and Respiratory Medicine, RoMed Clinical Center, Rosenheim, Germany.

The authors have disclosed no conflicts of interest.

Correspondence: Stephan Budweiser MD, Division of Pulmonary and Respiratory Medicine, Department of Internal Medicine III, RoMed Clinical Center Rosenheim, Pettenkoferstraße 10, 83022 Rosenheim, Germany. E-mail: stephan.budweiser@ro-med.de.

DOI: 10.4187/respcare.01961

torial origin, is also a common comorbidity.[5-8] In a large cohort of subjects with severe COPD receiving long-term oxygen therapy (LTOT), Chambellan and co-workers found that a low hematocrit (Hc) was not uncommon, and was 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 poor prognosis.[17] However, most of these studies were performed prior to the widespread use of LTOT and domiciliary noninvasive 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 mechanical 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 $\geq$ 17 g/dL) was low (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 was based on Hc levels and did not exclude patients with comorbidities 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 subjects with chronic respiratory failure, 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 cutoff levels for the prediction of long-term survival are similar to or different from the common clinically used cutoff values of anemia or polycythemia.

QUICK LOOK

Current knowledge

In patients with COPD, anemia is a common comorbidity and is associated with reduced functional capacity, poor outcome, and early mortality. Anemia may represent inability to compensate for hypoxemia in COPD patients with chronic respiratory failure.

What this paper contributes to our knowledge

In patients with COPD and chronic respiratory failure, higher hemoglobin level was associated with longer survival. Hemoglobin of $\geq$ 14.3 g/dL in females, and $\geq$ 15.1 g/dL in males was independently associated with better outcome.

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, β blockers, β_2 agonists, parasympatholytics, theophylline, systemic steroids); blood gas values; parameters of lung function and exercise testing; and laboratory parameters were documented. Starting in January 2002, data were entered 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 FEV_1 to inspiratory vital capacity of $< 70\%$, and FEV_1 being $< 30\%$ of predicted or $< 50\%$ of predicted plus chronic respiratory failure.[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: previous invasive ventilation; renal failure with estimated glomerular filtration rate < 30 mL/min/1.73 m^2; malignancies/hematological disorders within the last 5 years; surgeries, interventions, accidents or hemorrhage within the last 3 months; additional

chronic inflammatory, autoimmune or infectious disease; previous gastrointestinal resection; substitution of iron, folate, or vitamin B_{12}; and phlebotomy due to polycythemia or blood transfusion.

Measurements

Demographic, anthropometric, and laboratory data (Hb, leukocytes, C-reactive protein, creatinine) were assessed upon admission. Subjects were categorized as anemic (Hb $<$ 12 g/dL in females, Hb $<$ 13 g/dL in males),[20] polycythemic (Hb 15 $\geq$ g/dL in females, Hb $\geq$ 17 g/dL in males),[8] or normocythemic. The estimated glomerular filtration rate 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, Cardinal Health, Höchberg, Germany) were performed according to the guidelines of the American Thoracic Society/European Respiratory Society,[22] using European Respiratory Society reference values.[23] Six-min walk distance was determined according to the American Thoracic Society statement,[24] using 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, Leverkusen, Germany). Only values obtained without oxygen supply were included.

Follow-up

Vital status was determined through telephone contact to the subjects' relatives or family physicians, and by review of medical records. Informed written consent of the subjects or their relatives was obtained. All subjects underwent a follow-up period of at least 5 months, until July 1, 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 medians and IQRs. For the comparison of subgroups the non-parametric Kruskal-Wallis test was used, for categorical variables the chi-square test. Univariate Cox proportional hazards regression models were run to assess the impact of single predictors on survival. Predictors with $P < .05$ were included in a multivariate Cox proportional hazards regression model to adjust for prognostic factors other than Hb.

To identify the optimal cutoff values for Hb and to compare them with the standard cutoff 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 2 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 cutoff 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 cutoff values and the standard Hb categories, univariate Cox proportional hazards regression models were employed.

Results

Subjects' Characteristics

A total of 534 subjects with COPD GOLD stage III/IV were analyzed. After exclusion of subjects with comorbidities, or conditions potentially contributing to abnormalities in red blood cell count, and subjects with a lack of follow-up, 309 subjects remained. Their median (IQR) Hb was 14.5 g/dL (15.9–13.1 g/dL), and 207 subjects (67.0%) were categorized as normocythemic, 102 (33.0%) as abnormal. Among the latter, 46 subjects (14.9%) were anemic and 56 (18.1%) polycythemic. There were differences in the distributions of sex ($P = .002$), age ($P < .001$), survival time ($P = .008$), and comorbidities between anemic, normocythemic and polycythemic subjects (Table 1). Medical therapy (angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, β blockers, β_2 agonists, parasympatholytics, 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%, $P = .002$). Before inclusion, 170 subjects (55.0%) were treated with LTOT. At discharge, all subjects were treated with NIV ($n = 309$, 100%) and nearly all had LTOT ($n = 293$, 94.8%). Further subject characteristics are given in Table 1.

Hemoglobin Levels and Long-Term Survival

A total of 139 subjects (45.0%) died during the study period (mean $\pm$ SD follow-up 36.1 $\pm$ 31.1 months). The causes of death were cardiopulmonary 116 (83.5%), malignancy 7 (5.0%), other 5 (3.6%), and unknown 11 (7.9%).

Table 1. Subjects' Demographic and Clinical Characteristics According to Hemoglobin Categories

	Anemia*	Normocythemia	Polycythemia	*P*
Subjects, no. (%)	46 (14.9)	207 (67.0)	56 (18.1}	
Female/male, no.	6/40	56/151	25/31	.002†
Age, y	70.3 (73.8–62.8)	66.2 (71.4–59.1)	61.2 (68.4–55.4)	< .001
Body mass index, kg/m^2‡	24.3 (30.0–20.6)	27.7 (33.0–21.6)	29.5 (34.8–22.6)	.09
Long-term oxygen therapy, no. (%)	45 (97.8)	196 (94.7)	52 (92.9)	.52†
Percent-of-predicted FEV_1‡	28.5 (38.0–22.4)	29.8 (38.0–22.3)	31.5 (38.0–25.0)	.37
P_{aO_2}, mm Hg‡	54.5 (63.3–46.0)	49.5–(55.0–42.8)	46.0 (50.0–40.5)	.002
P_{aCO_2}, mm Hg‡	48.5 (56.5–40.8)	52.0 (58.0–48.0)	56.0 (61.5–50.5)	.62
pH‡	7.45 (7.49–7.4)	7.42 (7.45–7.39)	7.4 (7.43–7.37)	.003
6-min walk distance, m‡	267 (360–180)	264 (340–174)	336 (371–235)	.08
Leukocytes, $10^3/\mu L$	9.3 (11.7–7.6)	9.2 (11.7–7.5)	9.4 (12.3–7.4)	.89
C-reactive protein, mg/L‡	8.7 (34.8–4.0)	6.7 (21.7–4.5)	8.6 (20.0–4.8)	.90
Creatinine, mmol/L‡	70.7 (97.3–61.9)	79.6 (97.3–61.9)	70.7 (88.4–61.9)	.29
Estimated glomerular filtration rate, mL/min/1.73 m^2‡	89.3 (117.2–63.7)	86.8 (103.1–68.8)	89.4 (99.6–75.3)	.94
Coronary heart disease, no. (%)	14 (30.4)	29 (14.0)	4 (7.1)	.003
Left heart failure, no. (%)	6 (13.0)	40 (19.3)	9 (16.1)	.56
Arterial hypertension, no. (%)	21 (45.7)	84 (40.6)	23 (41.1)	.82
Diabetes mellitus, no. (%)	20 (43.5)	43 (20.8)	13 (23.2)	.005
Cardiac arrhythmia, no. (%)	13 (28.3)	29 (14.0)	2 (3.6)	.002
Median survival time, months	29	51	112	.008§

Values are median (IQR), except where otherwise stated.

* Anemia: female: hemoglobin < 12 g/dL; male: hemoglobin < 13 g/dL. Polycythemia: female: hemoglobin ≥ 15 g/dL; male: hemoglobin ≥ 17 g/dL. Only measurements parallel to determination of hemoglobin levels were used.

† Via Kruskal-Wallis rank sum or chi-square test.

‡ Not all subjects were included; there were missing values for body mass index (2), FEV_1 (9), 6-min walk distance (175), C-reactive protein (2), creatinine (5), estimated glomerular filtration rate (5), P_{aO_2}/P_{aCO_2}/pH (without oxygen supply) (140), anemic (28), normocythemic (97), polycythemic (15).

§ Via log rank sum test.

Twenty-two anemic (15.8%), 95 normocythemic (68.3%), and 22 polycythemic (15.8%) subjects died. The median survival of polycythemic subjects was 112 months, while normocythemic subjects survived 51 and anemic subjects 29 months. The survival probability of polycythemic subjects was higher than that of normocythemic ($P = .043$) and anemic subjects ($P = .01$), and that of normocythemic was higher than that of anemic subjects ($P = .041$, Fig. 1). The 1-year survival probability of all subjects 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 cutoff value of Hb was identified as 14.3 g/dL for females and 15.1 g/dL for males (58th percentiles each, Table 2). Regarding the association with the probability of death, these values were superior to the cutoffs used for the definition of anemia according to the World Health Organization (Hb < 12 g/dL in females, Hb < 13 g/dL in males, Fig. 3).

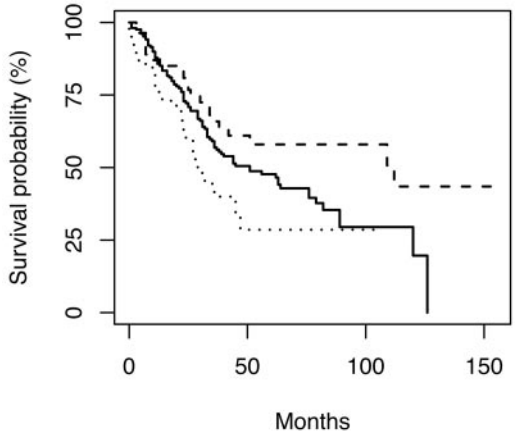

Fig. 1. Kaplan-Meier survival curves for anemic (dotted line), normocythemic (solid line), and polycythemic (dashed line) subjects. The log rank sum test showed differences between these conditions: $P = .043$ for polycythemic vs normocythemic, $P = .01$ for polycythemic vs anemic, $P = .041$ for normocythemic vs anemic.

Multivariate Analysis

In the univariate Cox proportional hazards models, age, sex, body mass index (BMI), FEV_1, 6-min walk distance, Hb, leukocyte levels, and arterial hypertension were associated with survival ($P < .05$ for each, Table 3). A multivariate Cox proportional hazards model containing age, sex, BMI, FEV_1, Hb, leukocyte level, and arterial hyper-

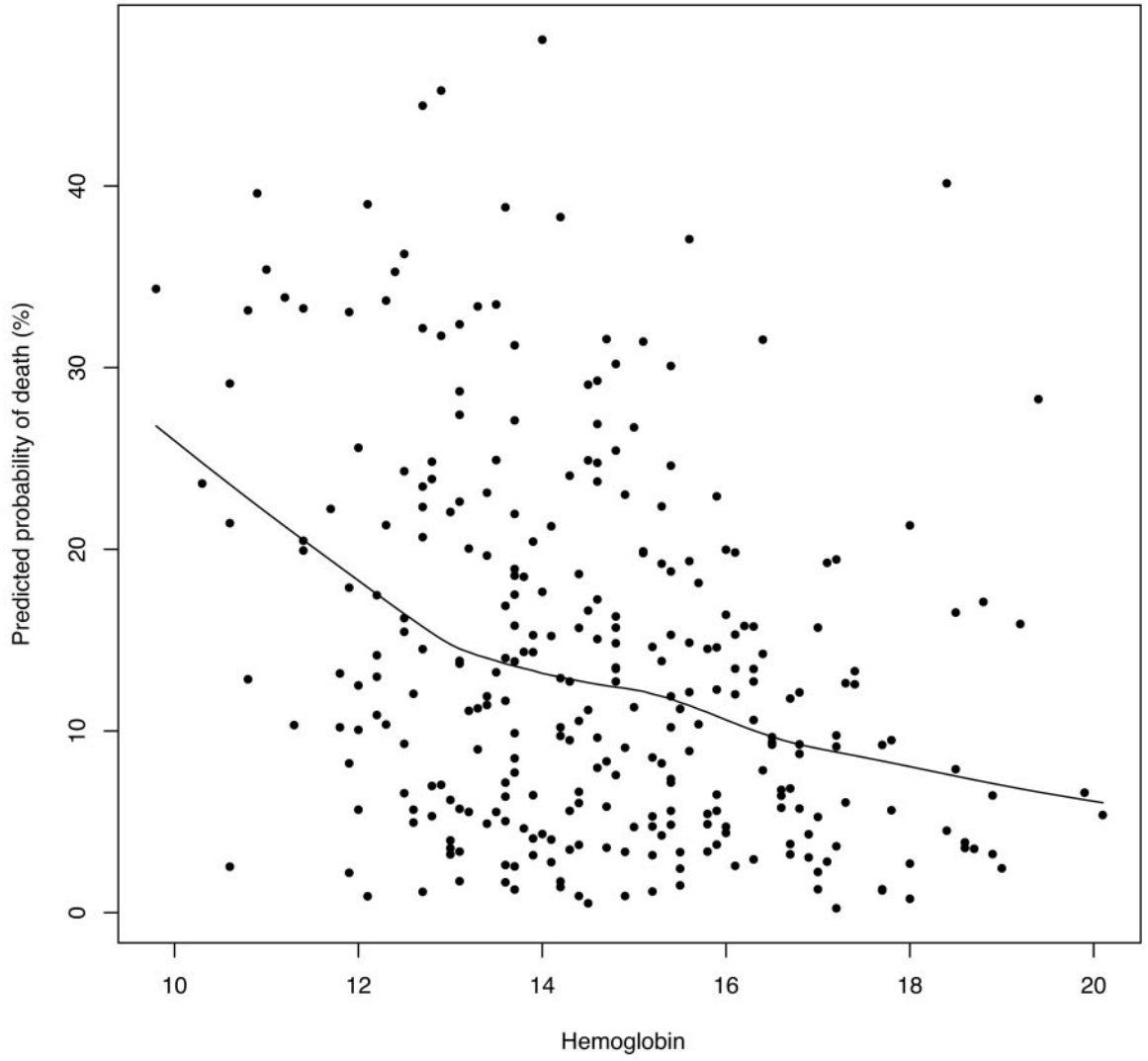

Fig. 2. LOESS (locally weighted polynomial regression) smoother curve for hemoglobin level versus predicted probability of death (1 year).

Table 2. Univariate Cox Proportional Hazards Models for the Prediction of Death Regarding Percentiles of Hemoglobin

Percentile	Hemoglobin Value		Hazard Ratio (95% CI)	*P*
	Female	Male		
10th	12.16	12.20	0.568 (0.325–0.992)	.047
20th	12.80	13.02	0.682 (0.440–1.057)	.09
30th	13.10	13.70	0.585 (0.404–0.846)	.004
40th	13.54	14.20	0.635 (0.450–0.895)	.009
50th	13.90	14.60	0.549 (0.391–0.770)	.001
58th	14.30	15.10	0.463 (0.324–0.660)	< .001
60th	14.40	15.26	0.490 (0.343–0.701)	< .001
70th	14.90	15.80	0.514 (0.350–0.755)	.001
80th	15.74	16.40	0.653 (0.430–0.990)	.045
90th	16.94	17.67	0.540 (0.303–0.961)	.04

tension revealed only age and BMI to be predictive, while Hb as a continuous linear variable failed statistical significance ($P = .09$). However, when the categorical Hb cutoff values (female 14.3 g/dL, male 15.1 g/dL) were included in the multivariate panel, these cutoffs were also revealed as independent predictors of survival (Table 4), which indicates a nonlinear relationship.

Discussion

The present study demonstrates that in subjects with severe COPD and chronic respiratory failure, Hb levels prior to the initiation of NIV were linked to long-term survival. We identified Hb values of 14.3 g/dL for females and 15.1 g/dL for males as conferring the highest predictive value. These Hb values were, in addition to age and

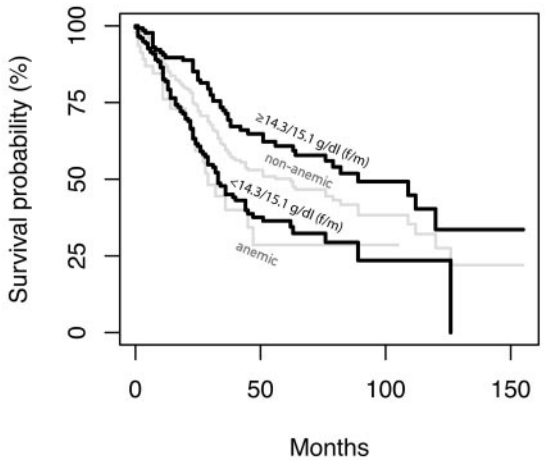

Fig. 3. Kaplan-Meier survival curves of subjects either above or below the optimal cutoff value. The upper black line illustrates either female subjects with hemoglobin ≥ 14.3 g/dL or male subjects with hemoglobin ≥ 15.1 g/dL. The lower black line illustrates either female subjects with hemoglobin < 14.3 g/dL or male subjects with hemoglobin < 15.1 g/dL. The grey lines show survival of subjects with or without anemia using the threshold of the World Health Organization (12 g/dL for female or 13 g/dL for male). The black lines represent the 58th percentile: females 14.3 g/dL, males 15.1 g/dL, hazard ratio 0.463, IQR 0.324–0.660, $P < .001$. The gray lines represents anemic versus non-anemic subjects: hazard ratio 0.572, IQR 0.361–0.907, $P = .02$.

Table 3. Univariate Cox Proportional Hazards Models for Predicted Probability of Death

Variable	Hazard Ratio (95% CI)	*P*
Age	1.064 (1.041–1.088)	< .001
Female/male	1.503 (1.003–2.252)	.049
BMI*	0.912 (0.889–0.936)	< .001
FEV_1*	0.970 (0.950–0.989)	.002
P_{aO_2} (without oxygen supply)*	0.969 (0.969–1.024)	.79
P_{aCO_2} (without oxygen supply)*	1.003 (0.974–1.034)	.84
6-min walk distance*	0.996 (0.993–0.999)	.02
Hemoglobin	0.855 (0.783–0.934)	< .001
Leukocytes	1.067 (1.025–1.111)	.002
C-reactive protein*	1.002 (0.999–1.005)	.28
Creatinine*	1.441 (0.781–2.662)	.24
Estimated glomerular filtration rate*	0.999 (0.993–1.004)	.65
Coronary heart disease	1.227 (0.746–2.016)	.42
Left heart failure	1.296 (0.873–1.924)	.20
Arterial hypertension	0.609 (0.426–0.870)	.007
Diabetes mellitus	0.988 (0.659–1.482)	.95
Cardiac arrhythmia	1.559 (0.968–2.641)	.07

* Not all subjects were included; there were missing values for BMI (2), FEV_1 (9), 6-min walk distance (175), C-reactive protein (2), creatinine (5), estimated glomerular filtration rate (5), P_{aO_2}/P_{aCO_2}/pH (140), anemia (28), normocythemia (97), and polycythemia (15).

BMI, independent predictors for survival, and markedly higher than the World Health Organization's definitions of anemia. Our findings demonstrate that in subjects with COPD and chronic respiratory failure the prognostic value of Hb is not fully exploited when only using the common cutoff values for anemia that have been introduced to define pathological conditions, but not as clinical predictors.

Table 4. Multivariate Cox Proportional Hazards Model for Predicted Probability of Death*

	Hazard Ratio (95% CI)	*P*
Age	1.056 (1.032–1.081)	< .001
Body mass index	0.915 (0.890–0.941)	< .001
Hemoglobin cut-off: female 14.3 g/L, male 15.1 g/L	0.627 (0.414–0.949)	.03

* 6-min walk distance was excluded due to a large number of missing values (175).

As part of the view that COPD is a disease with multiple alterations beyond the lung,[2] chronic anemia has been revealed as a 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 chronic respiratory failure. 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 World Health Organization's 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 the subjects 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 subjects with polycythemia. These subjects 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 subjects 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 subjects.[8] In a large investigation of subjects with COPD and hypoxemic respiratory failure requiring LTOT,[7] anemia occurred in 8.2% of fe-

males and 12.6% of males, while polycythemia again was present in only 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 Hc may underestimate anemia.[28] Moreover, in comparison to our investigation, the authors provided no data on comorbidities (eg, cancer, renal failure, or other chronic inflammatory diseases) or conditions (eg, gastrointestinal hemorrhage or blood loss) that might lead to changes in the red blood cell count. In our experience, this is a substantial proportion of patients, and a potential source of bias, as most of these comorbidities 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 subjects 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 the subjects in the present study received NIV and LTOT, which counteract polycythemia and hyperviscosity,[29-31,18] the "protective" effect of polycythemia might, however, be true only 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 chronic respiratory failure. Univariate Cox regression analyses showed Hb to be a predictor of long-term survival, similarly to age, sex, BMI, FEV_1, 6-min walk distance, and leukocyte number. In a multivariate model, however, Hb as a continuous variable failed statistical significance ($P = .09$). 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 comorbidities that 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 importance of Hb and/or Hc in COPD have focused on the common definitions of anemia and polycythemia,[32-34] despite the fact that the respective cutoff 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 cutoff values of 14.3 g/dL for females and 15.1 g/dL for males for predicting long-term survival. These cutoff 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 $\geq$ 12 g/dL, males $\geq$ 13 g/dL) suggests that, in COPD, Hb levels are related to prognosis at levels far away from common "anemia." Noteworthy enough, when the optimal cutoff 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 toward 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 World Health Organization cutoff values. Of course, this does not invalidate the usefulness of those values, which are for clinical purposes, and not for prediction of survival. Our data point out that cutoff values must be adapted to their purpose and 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 chronic respiratory failure 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 unbiased as possible. With regard to the prognostic impact of Hb, we also accounted for additional comorbidities 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 the subjects were seen regularly at follow-up visits in the hospital, adherence to 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 subjects, which could affect their value as potential predictors.

Conclusions

In conclusion, in subjects with severe COPD and chronic respiratory failure requiring NIV and LTOT, Hb levels were gradually linked to long-term survival, and a higher Hb was associated with better survival. This is in line with known data. However, as optimal independent predictors of survival, we identified 14.3 g/dL for females and 15.1 g/dL for males, which corresponded to the 58th percentiles of the distributions. These values are markedly higher than the World Health Organization's definition of anemia or similar clinical criteria that are suited to define a definite pathological condition but do not fully exploit the prognostic potential of Hb values in severe COPD.

REFERENCES

1. Rabe KF, Beghé B, Luppi F, Fabbri LM. Update in chronic obstructive pulmonary disease 2006. Am J Respir Crit Care Med 2007; 175(12):1222-1232.
2. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33(5):1165-1185.
3. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370(9589):797-799.
4. Incalzi RA, Corsonello A, Pedone C, Battaglia S, Paglino G, Bellia V; Extrapulmonary Consequences of COPD in the Elderly Study Investiators. Chronic renal failure: a neglected comorbidity of COPD. Chest 2010;137(4):831-837.
5. Kollert F, Müller C, Tippelt A, Jörres RA, Heidinger D, Probst C, et al. Anaemia in chronic respiratory failure. Int J Clin Pract 2011; 65(4):479-486.
6. Similowski T, Agustí A, MacNee W, Schönhofer B. The potential impact of anaemia of chronic disease in COPD. Eur Respir J 2006; 27(2):390-396.
7. Chambellan A, Chailleux E, Similowski T; ANTADIR Observatory Group. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. Chest 2005;128(3):1201-1208. Erratum in: Chest 2006;129(3):831.
8. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 2007;29(5):923-929.
9. Rasmussen L, Christensen S, Lenler-Petersen P, Johnsen SP. Anemia and 90-day mortality in COPD patients requiring invasive mechanical ventilation. Clin Epidemiol 2010;3:1-5.
10. Wade JP, Pearson TC, Russell RW, Wetherley-Mein G. Cerebral blood flow and blood viscosity in patients with polycythaemia secondary to hypoxic lung disease. BMJ (Clin Res Ed) 1981;283(6293): 689-692.
11. Wedzicha JA, Rudd RM, Apps MC, Cotter FE, Newland AC, Empey DW. Erythrapheresis in patients with polycythaemia secondary to hypoxic lung disease. BMJ (Clin Res Ed) 1983;286(6364):511-514.
12. Weisse AB, Moschos CB, Frank MJ, Levinson GE, Cannilla JE, Regan TJ. Hemodynamic effects of staged hematocrit reduction in patients with stable cor pulmonale and severely elevated hematocrit levels. Am J Med 1975;58(1):92-98.
13. Menon D, York EL, Bornstein RA, Jones RL, Sproule BJ. Optimal hematocrit and blood viscosity in secondary polycythemia as determined from cerebral blood flow. Clin Invest Med 1981;4(2):117-121.
14. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Evaluation and management. Chest 1991;99(3):715-723.
15. Harrison BD, Stokes TC. Secondary polycythaemia: its causes, effects and treatment. Br J Dis Chest 1982;76(4):313-340.
16. Segel N, Bishop JM. The circulation in patients with chronic bronchitis and emphysema at rest and during exercise, with special reference to the influence of changes in blood viscosity and blood volume on the pulmonary circulation. J Clin Invest 1966;45(10): 1555-1568.
17. Criner GJ. Effects of long-term oxygen therapy on mortality and morbidity. Respir Care 2000;45(1):105-118.
18. McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, Hunt B, et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 2005; 130(2):174-195.
19. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation: a consensus conference report. Chest 1999; 116(2):521-534.
20. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968;405:5-37.
21. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function: measured and estimated glomerular filtration rate. N Engl J Med 2006;354(23):2473-2483.
22. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.
23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993;(Suppl 16):5-40.
24. American Thoracic Society Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117.
25. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158(5 Pt 1): 1384-1387.
26. Macnee W. Right heart function in COPD. Semin Respir Crit Care Med 2010;31(3):295-312.
27. Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis 2011;6:199-208.
28. Quintó L, Aponte JJ, Menéndez C, Sacarlal J, Aide P, Espasa M, et al. Relationship between haemoglobin and haematocrit in the definition of anaemia. Trop Med Int Health 2006;11(8):1295-302.
29. Budweiser S, Jörres RA, Riedl T, Heinemann F, Hitzl AP, Windisch W, et al. Predictors of survival in COPD patients with chronic hypercapnic respiratory failure receiving noninvasive home ventilation. Chest 2007;131(6):1650-1658.
30. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity noninvasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci 2009;6(2):72-76.

31. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J 2007;30(2):293-306.
32. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and inflammation in COPD. Chest 2005;127:825-829.
33. John M, Lange A, Hoernig S, Witt C, Anker SD. Prevalence of anemia in chronic obstructive pulmonary disease: comparison to other chronic diseases. Int J Cardiol 2006;111(3):365-370.
34. Krishnan G, Grant BJ, Muti PC, Mishra A, Ochs-Balcom HM, Freudenheim JL, et al. Association between anemia and quality of life in a population sample of individuals with chronic obstructive pulmonary disease. BMC Pulm Med 2006;6:23.
35. Weil JV, Jamieson G, Brown DW, Grover RF. The red cell mass-arterial oxygen relationship in normal man. Application to patients with chronic obstructive airway disease. J Clin Invest 1968;47(7): 1627-1639.