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Hemoglobin Level and Its Clinical Impact in a Cohort of Patients with COPD

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ABSTRACT [200 words; journal limit: 200 words]

Hemoglobin (Hb) abnormalities in chronic obstructive pulmonary disease (COPD) are not well characterized. We investigated the prevalence and association of abnormal Hb with clinical outcomes.

Analysis of a prospective cohort of stable COPD outpatients (N = 683) in a US Veterans Administration pulmonary clinic was undertaken. Patients were classified as anemic (Hb <13 g/dL), polycythemic (Hb ≥17 g/dL, men and ≥15 g/dL, women) or normal. We compared demographic characteristics and physiologic/functional outcomes between the groups. Regression models adjusting for confounders examined independent association of anemia with clinical outcomes.

Anemia was present in 116 (17%), and polycythemia in 40 (6%) patients. While the only values that differed between polycythemic and non-polycythemic patients were mean BMI and Hb, anemic patients had a significantly higher modified Medical Research Council (MRC) dyspnea scale(2.8 vs. 2.6 points; p =0.04), lower 6-minute walk distance (6MWD) (265 vs. 325 meters; p <0.0001), and shorter median survival (49 vs. 74 months; p <0.01) than non-anemic patients. In regression models anemia independently predicted dyspnea and reduced exercise capacity.

Anemia in COPD was an independent risk factor for reduced functional capacity. Polycythemia prevalence was low, and had no association with worsened outcomes. Further work is required to evaluate effect of anemia correction on outcomes in COPD.

Chronic obstructive pulmonary disease (COPD) is highly prevalent and associated with substantial morbidity and mortality. An estimated 11.4 million adults in the United States were reported to have COPD in 2004 [1]. The forced expiratory volume in 1 second (FEV_1) after bronchodilators has been traditionally viewed as the most accurate predictor of death in these patients [2]. However, COPD produces systemic manifestations not reflected by the FEV_1 and, indeed, a number of other factors predictive of COPD-related mortality have been identified. These include malnutrition, poor exercise capacity, increased dyspnea and presence of co-morbidity [3-7]. Recent work indicates that a composite index consisting of markers of COPD severity (body mass index (BMI), airflow obstruction, dyspnea, and exercise capacity [BODE] index) is a more accurate predictor than FEV_1 alone of all-cause and respiratory mortality [8].

Anemia, a well-recognized co-morbidity in many chronic illnesses, is associated with reduced health-related quality of life (HRQL), increased morbidity and mortality in chronic kidney disease [9-10], congestive heart failure [11-13], human immunodeficiency virus (HIV) infection [14-15], hepatitis C virus infection [16] and cancer [17]. Anemia is also associated with disability, impaired physical performance, and lower muscle strength in persons 65 years and older [18].

There is limited information in the current literature describing the distribution of hemoglobin (Hb) and its impact on outcomes in the COPD population. Polycythemia, traditionally thought to be highly prevalent in COPD, occurs less frequently now with more rigorous correction of hypoxemia [19]. Conversely, recent reports suggest that anemia in patients with COPD is highly prevalent and associated with increased mortality [20-21]. Although the association between anemia and dyspnea is generally well established [22], the contribution of

Hb to breathlessness and other clinical manifestations in patients with COPD is not known and may be of great interest as a potential target for directed therapy [23]. The purpose of this study was to determine the prevalence of abnormalities in Hb levels in patients with COPD attending a pulmonary clinic, as well as to explore the associations between Hb levels and clinical outcomes.

MATERIALS AND METHODS

Study subjects

This was a retrospective analysis of data prospectively collected at one of the sites (Bay Pines Veterans Affairs Medical Center [VAMC], Bay Pines, FL, USA) of the multicenter BODE study cohort [8]. COPD was defined by a history of smoking exceeding 20 pack-years and a ratio of FEV_1 to forced vital capacity (FVC) of <0.7 measured 20 minutes after administration of albuterol. Outpatients with a wide range of COPD severity were included; all patients were clinically stable and receiving appropriate therapy for COPD. Patients were excluded if they had an illness other than COPD that was likely to result in death within 3 years, asthma (defined as an increase in FEV_1 of more than 15% above the baseline value or of 200 mL after administration of a bronchodilator), an inability to complete the lung function test or six minute walking distance (6MWD) test, a myocardial infarction within the preceding 4 months, unstable angina, or congestive heart failure (New York Heart Association class III or IV). Full methodology and results from the prospective study have been previously reported [8].

Study Design

Hemoglobin data were collected retrospectively, while all other data had been included in the prospective data collection. For each patient, the Hb value closest in time prior to or

following BODE testing was collected and analyzed. The patients were categorized in three groups according to Hb thresholds: anemic (Hb <13 g/dL for men and women [24]), polycythemic (Hb ≥17 g/dL for men and ≥15 g/dL for women [25]) and normal. Although the Hb threshold for anemia in women is defined by the World Health Organization as <12 g/dL, a threshold of <13 g/dL was chosen for all patients in this study because the issue of what the appropriate Hb threshold for anemia definition in post-menopausal females remains controversial [26], and because the vast majority (96%) of patients in the dataset were men. Because the number of polycythemic patients was small and their baseline characteristics and outcomes were not significantly different from the non-polycythemic group, only the descriptive data on the polycythemia subset are presented. For the analytic portion of this study, polycythemic patients were included in the group with normal Hb levels.

Clinical variables evaluated for each group consisted of dyspnea, exercise capacity, mortality, and healthcare resource utilization. Functional dyspnea was measured using the Medical Research Council (MRC) dyspnea scale, a validated instrument that quantitatively assesses the severity of COPD-related disability [27]. Scores on the MRC dyspnea scale range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing. Exercise capacity was measured by the 6-minute walk distance (6MWD) test, a standardized, validated test that is a predictor of functional status and death [28]. Mortality and cause of death were determined through family contact followed by the review of medical records and death certificates.

Scores on the Charlson Comorbidity index and the BODE index were also evaluated for each group of patients. The Charlson Comorbidity index is a validated method for classifying comorbid conditions that can alter the risk of mortality [29], and has been shown to predict

mortality [30]. Scores on the Charlson Comorbidity index range from 0 to 33, with higher scores indicating more coexisting conditions.

Statistical Analyses

Between-group differences in baseline demographic, physiologic, and disease characteristics were expressed as mean (± standard deviation [SD]) values. The between-group differences were calculated using a 2-sided Student's *t*-test or Chi-square statistic where appropriate; a p value of <0.05 was considered statistically significant. Linear regression analyses controlling for age, FEV_1 expressed as a percentage of the predicted value ($FEV_1\%$), Charlson Comorbidity index, and BMI were performed to identify the independent association of anemia with the MRC dyspnea scale and the 6MWD. Median survival and the overall probability of survival between anemic and non-anemic patients were calculated using Kaplan-Meier estimates. A logistic regression and a Cox proportional hazards models were run to adjust the estimate of Hb association with mortality for age, Charlson Comorbidity index, and the BODE index.

RESULTS

Patient Characteristics

Of the 683 patients in the data set (656 male, 27 female; mean age 67 ± 9 years), 677 were eligible for analysis (650 males, 27 females; mean age 70 ± 9 years); the remaining 6 patients (all males; mean age 74 ± 5 years) were excluded because of missing Hb values. The mean Hb for all patients was 14.4 ± 1.7 g/dL. Anemia was present in 116 (17.1%) patients, while polycythemia was noted in 40 (5.9%) patients. Applying the Hb threshold of 13 g/dL, as opposed

to 12 g/dL, for anemia definition among females in our study resulted in potential misclassification of 3 subjects, whose Hb values were $\geq$ 12 g/dL and < 13 g/dL. Mean Hb levels for anemic and non-anemic patients were 11.8 ± 1.0 g/dL and 15.0 ± 1.2 g/dL, respectively (p <0.0001)**.** There was no difference in the mean Hb between patients receiving and those not receiving supplemental O_2 (14.4 $\pm$ 1.8 g/dL and 14.5 $\pm$ 1.6 g/dL, respectively, p =0.49), and there was no correlation between arterial O_2 tension and Hb (Pearson r =-0.06). Overall, anemic patients were significantly older and more chronically ill than their non-anemic counterparts, as manifested by significantly higher Charlson Co-morbidity and BODE index scores (Table 1). Conversely, except for higher mean Hb and BMI in the group with polycythemia, there were no significant differences in the baseline characteristics or outcome measures between polycythemic and non-polycythemic groups (Table 2).

Dyspnea and Functional Impairment

Dyspnea and functional status differed significantly between anemic and non-anemic patients. Mean MRC values were significantly higher (2.8 ± 0.9 vs. 2.6 ± 0.8; p =0.04) and mean 6MWD was significantly shorter (265 ± 122 meters vs. 325 ± 124 meters; p <0.0001) in anemic compared to non-anemic patients (Table 1). When MRC and 6MWD were evaluated as a function of Hb ranges, there was a linear relationship between declining Hb and increasing dyspnea and functional impairment (Figures 1 and 2). In regression models controlling for age, FEV_1%, Charlson Co-morbidity index, and BMI, anemia remained an independent predictor of increased MRC and reduced 6MWD (Table 3).

Mortality

Fifty-three (46.8%) anemic and 187 (31.2%) non-anemic patients died (p =0.01) during the study (mean follow-up 34 ± 22 months and 37 ± 22 months, respectively; p =0.15). Age (p <0.01), Hb (p <0.01), Charlson Co-morbidity index (p <0.0001), and BODE score (p <0.0001) differed significantly between survivors and non-survivors (Table 4). The median survival was 49 months in anemic patients and 74 months in non-anemic patients (p <0.01, Figure 3). While the BODE and the Charlson Co-morbidity indices were significantly associated with increased mortality in both the Cox model and the multivariate logistic regression analysis (Table 5**)**, anemia was not identified as a significant independent predictor of mortality.

DISCUSSION

In the current study anemia was prevalent (17%) among patients with COPD attending a VA pulmonary clinic, and was independently associated with increased dyspnea and reduced exercise capacity as measured by the 6MWD. In contrast, there was a very low prevalence of polycythemia and when present it carried no clinical relevance.

Although anemia has been associated with dyspnea and reduced exercise capacity in patients with predialysis chronic kidney disease [31], cancer [32], and heart failure [33], this is the first study to demonstrate that anemia is a strong independent predictor of dyspnea and reduced exercise capacity in patients with COPD. The exact mechanism by which anemia may decrease exercise capacity is complex and not fully understood. However, oxygen carrying capacity depends directly upon the level of hemoglobin, and oxygen delivery is crucial for maintenance of oxidative metabolism. Anemia may result in limited oxygen supply and early onset of anaerobic threshold with the consequent increase in ventilatory drive. Given the

decreased ventilatory reserve among patients with COPD, the accompanying increased ventilatory demand may result in dyspnea.

In the current study polycythemia was present in 6% of the COPD patients, and did not appear to be associated either with an increased COPD severity or with altered outcomes. The use of long-term oxygen therapy has been reported to control polycythemia in patients with COPD [19]. Thus, the fact that more than one-third of the patients received supplemental oxygen therapy may at least partially account for the low prevalence of polycythemia observed in our study.

The prevalence of anemia identified in our study (17%), while somewhat higher than the 10.6% prevalence observed among community-dwelling elderly [26], is similar to that reported in recent studies of COPD patients [20-21]. Anemic patients in general were somewhat older and carried a higher physiologic dysfunction burden, as evidenced by a higher mean Charlson Co-morbidity and BODE index scores. Even after adjusting for this unequal disease burden distribution, anemia was strongly and independently associated with worse MRC dyspnea scores and reduced 6MWD, indicating a possible link between Hb and functional status.

Anemia of inflammation or anemia of chronic disease (ACD) [34] is likely to play a major role in the setting of COPD, particularly since it has been identified as the cause of one third of all anemia seen in the community-dwelling elderly population [26]. At least one recent study has documented that anemia in COPD is at least in part due to inflammation and resistance to elevated levels of serum erythropoietin [20]. This is not surprising, given the systemic inflammatory state that has been documented in patients with COPD [35]. However, more research is needed to gain a better understanding of the potential causes of anemia in COPD.

Etiology notwithstanding, anemia in COPD has been shown to be associated with adverse outcomes in recent clinical studies. In a study by Chambellan et al of 2,524 patients with severe COPD receiving long-term oxygen therapy, anemia was associated with a lower long-term survival rate, a higher hospital admission rate, and a longer duration of hospital stay compared with non-anemic patients [21]. The relative risk of death decreased by 14% with every 5% increase in hematocrit (P <0.001), and hematocrit was the strongest predictor of mortality next to age. In addition, hematocrit was inversely correlated with both the rate (r = -0.091; P =0.001) and duration of hospitalization (r = -0.095; P <0.001). In contrast to the study by Chambellan et al, the current analyses did not confirm a significant independent association between anemia and survival. This is perhaps best explained by the fact that Chambellan's et al study represents patients with more severe COPD compared to those in our cohort. Additionally, their study did not include as covariates either co-morbidity or COPD severity scores such as the BODE index. It is likely that these tools already incorporate factors that may be associated with anemia and thereby dilute the predictive power of anemia per-se on mortality. Future studies, however, need to continue to examine the association of anemia with worsened outcomes, including mortality, in patients with COPD.

The relationship between anemia and adverse clinical outcomes in patients with COPD is consistent with findings in other chronic disease states. Increased morbidity, mortality and decreased HRQL are well established in chronic kidney disease [10, 36] cancer [17, 32, 37], congestive heart failure [11, 13] and HIV infection [12, 14] with concomitant anemia. Further, numerous studies have demonstrated that correction of anemia improves outcomes in these populations, resulting in improved functional and exercise capacity, reduced dyspnea, and improved quality of life [14, 37]. In COPD, several small studies have suggested how correction

of anemia may affect outcomes in COPD. Schönhofer et al demonstrated that correction of anemia with blood transfusions among 20 patients with severe COPD significantly reduced disease-related elevations in minute ventilation and work of breathing [38], suggesting that anemia correction may be beneficial in alleviating dyspnea and improving exercise capacity. In a separate study, the same investigators demonstrated that among five patients with severe anemia, successful treatment of anemia resulted in an increased ability to wean patients from mechanical ventilation [39]. While the current study did not attempt to answer the question of how anemia correction affects outcomes, the results support the hypothesis that anemia is associated with adverse consequences in patients with COPD. Although anemia, a possible systemic manifestation of COPD, may be an epiphenomenon identifying sicker patients, it is reasonable to hypothesize based on others' and our findings that correction of anemia may result in improved outcomes. This hypothesis requires rigorous testing in a well-designed clinical trial.

The current study is limited by its retrospective design, and is therefore subject to the general biases inherent in such designs. For example, the Hb data, which were incomplete or unavailable in the prospectively collected dataset, had to be retrospectively collected for this analysis. As a result, the temporal relationship between the Hb values and other variables is not consistent. We attempted to minimize the effect of a random Hb selection on the outcomes of interest by choosing the Hb value temporally closest to the BODE index evaluation. This, however, does not eliminate the cross-sectional nature of the relationship of Hb and MRC and 6MWD outcomes, though the temporal relationship of the Hb measurement and mortality end point is preserved. Another potential limitation of this study is that patients were disproportionately male; thus, the results may not be generalizable to females. However, other studies have demonstrated adverse effects of anemia among elderly females, though not

specifically in the setting of COPD [40]. Likewise, because elderly veteran patients have been shown to have a poorer health status and higher disease burden than non-veterans [41], these data may not be generalizable to patients with COPD seen outside of a VA pulmonary clinic. Nevertheless, the current study serves as a basis for evaluating the relationship between anemia and clinical and functional outcomes in patients with COPD.

Though no inference of causality is possible, our results suggest that anemia is prevalent and associated with poor clinical and functional outcomes in patients with COPD, and provide support for the evaluation and monitoring of anemia in these patients. Since inflammation and EPO suppression are likely to be at least in part responsible for anemia in this population, future study designs need to incorporate evaluation of inflammatory mediators and their relationship to anemia in COPD. Prospective studies and controlled trials are warranted to confirm our observations and to test the hypothesis that correction of anemia can improve these clinical outcomes of patients with COPD.

References

1. American Lung Association. Chronic obstructive pulmonary disease (COPD) fact sheet. Available at: http://www.kintera.org/site/pp.asp?c=dvLUK9O0E&b=35020. Accessed December 11, 2006.
2. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;133:14-20.
3. Almagro P, Calbo E, de Echagüen O, Barreiro B, Quintana S, Heredia JL, et al. Mortality after hospitalization for COPD. Chest. 2002;121:1441-1448.
4. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996;9:431-435.
5. Hersh CP, DeMeo DL, Al-Ansari E, Carey VJ, Reilly JJ, Ginns LC, et al. Predictors of survival in severe, early onset COPD. *Chest* 2004;126:1443-1451.
6. Incalzi RA, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, et al. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2794-2800.
7. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856-1861.
8. Celli BR, Cote CG, Marin JM, Casanova C, de Oca MM, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005-1012.

9. National Kidney Foundation. K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. *Am J Kidney Dis* 2001;37(Suppl 1):S182-S238.
10. Silberberg JS, Rahal DP, Patton R, Sniderman AD. Role of anemia in the pathogenesis of left ventricular hypertrophy in end-stage renal disease. *Am J Cardiol* 1989;64:222-224.
11. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol* 2002;39:1780-1786.
12. McMurray JJV. What are the clinical consequences of anemia in patients with chronic heart failure? *J Card Fail* 2004;10(Suppl):S10-S12.
13. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJS, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J* 2004;25:1021-1028.
14. Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. *Am J Med* 2004;116:27S-43S.
15. Volberding P. The impact of anemia on quality of life in human immunodeficiency virus-infected patients. *J Infect Dis* 2002;185(Suppl 2):S110-S114.
16. Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology* 2004;40:1450-1458.
17. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in cancer patients. *Cancer* 2001;91:2214-2221.

18. Penninx BW, Pahor M, Cesari M, Corsi AM, Woodman RC, Bandinelli S, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004;52:719-724.
19. Zielinski J. Effects of long-term oxygen therapy in patients with chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999;5:81-87.
20. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and inflammation in COPD. *Chest* 2005;127:825-829.
21. Chambellan A, Chailleux E, Similowski T, and the ANTADIR Observatory Group. Prognostic value of hematocrit in patients with severe chronic obstructive pulmonary disease receiving long term oxygen therapy. *Chest* 2005;128:1201-1208.
22. Mansen TJ, McCance KL, Parker-Cohen PD. Alterations of erythrocyte function. In: McCance KL, Huether SE, eds. Pathophysiology. The Biologic Basis for Disease in Adults and Children. 2nd ed. St. Louis, MO: Mosby-Year Book, Inc.; 1994:860-877.
23. Similowski T, Agusti A, MacNee W, Schonhofer B. The potential impact of anemia of chronic disease in COPD. *Eur Respir J* 2006;27:390-6.
24. World Health Organization. Nutritional anemias: report of a WHO scientific group. WHO Technical Report Series 405. Geneva, Switzerland: World Health Organization 1968:1-37.
25. Kasper DL, Braunwald E, Fauci AS, et al. Anemia and Polycythemia. Harrison's Online Dictionary. 2005. Available at http://www.accessmedicine.com/content.aspx?aID=58150 Accessed December 11, 2006.
26. Guralnik JM, Ersshler WB, Schrier SL, et al. Anemia in the elderly: A public health crisis in hematology. *Hematology* 2005;1:528-532

27. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581-586.

28. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;23:28-33.

29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.

30. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47:1245-1251.

31. Lim VS, DeGowin RL, Zavala D, Kirchner PT, Abels R, Perry P, et al. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. *Ann Intern Med* 1989;110:108-114.

32. Dudgeon DJ, Lertzman M, Askew GR. Physiological changes and clinical correlations of dyspnea in cancer outpatients. *J Pain Symptom Manage* 2001;21:373-379.

33. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne A-S. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;107:294-299.

34. Weiss G, Goodnough LT. Anemia of Chronic Disease. *N Engl J Med* 2005;352:1011-23.

35. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers, and nonsmokers. *Thorax* 2006 ; 61:23-28

36. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC study. *Kidney Int* 2003;64:610-615.

37. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HJ, Nortier JW. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003;21:366-373.

38. Schönhofer B, Wenzel M, Geibel M, Köhler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 1998;26:1824-1828.

39. Schönhofer B, Böhrer H, Köhler D. Blood transfusion facilitating difficult weaning from ventilator. *Anaesthesia* 1998;53:181-184.

40. Chaves PHM, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? *J Am Geriatr Soc* 2002;50:1257-1264.

41. Selim AJ, Berlowitz DR, Fincke G, Cong Z, Rogers W, Haffer SC, et al. The health status of elderly veteran enrollees in the Veterans Health Administration. *J Am Geriatr Soc* 2004;52:1271-1276.

Table 1. Patient Demographics and Clinical Characteristics

Variable (mean ± SD)	Anemic (n = 116)	Not Anemic (n = 561)	*P* Value*
Age, years	72.8 ± 9.3	69.5 ± 8.8	0.0003
Hemoglobin, g/dL	11.8 ± 1.0	15.0 ± 1.2	<0.0001
FEV_1%	43.2 ± 17.0	42.1 ± 17.3	0.53
PaO_2, torr	72.1 ± 13.3	71.9 ± 11.9	0.87
MRC dyspnea scale, points	2.8 ± 0.9	2.6 ± 0.8	0.04
BMI, kg/m^2	27.1 ± 6.7	26.3 ± 5.8	0.22
6MWD, m	265.4 ± 122.1	325.1 ± 124.4	<0.0001
Charlson Comorbidity index, points	6.5 ± 3.5	4.8 ± 2.4	<0.0001
BODE index, points	5.3 ± 2.6	4.7 ± 2.4	0.01

Abbreviations: SD, standard deviation; FEV_1%, forced expiratory volume in one second expressed as a percent of predicted; PaO_2, arterial oxygen pressure; MRC, Medical Research Council; BMI, body mass index; 6MWD, distance walked in 6 minutes; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity.

*P values derived using a 2-sided Student's t-test.

Table 2. Characteristics of Patients With and Without Polycythemia (all values except mortality are expressed as mean ± SD)

Variable	Polycythemic (n = 40)	Not Polycythemic (n = 637)	*P* Value*
Age, years	69.6 ± 9.4	70.1 ± 9.0	0.71
Hemoglobin, g/dL	17.6 ± 0.8	14.2 ± 1.5	<0.0001
FEV_1%	43.6 ± 18.4	42.2 ± 17.1	0.62
PaO_2 resting, torr	68.7 ± 12.6	72.1 ± 12.2	0.09
6MWD, m	332.4 ± 129.4	314.1 ± 125.6	0.37
MRC dyspnea scale, points	2.5 ± 0.8	2.6 ± 0.9	0.28
BODE index, points	4.4 ± 2.3	4.8 ± 2.5	0.29
Charlson Comorbidity index, points	5.0 ± 2.1	5.1 ± 2.7	0.84
BMI, kg/m^2	28.2 ± 4.6	26.4 ± 6.0	0.02
Follow-up, months	34.6 ± 20.1	36.7 ± 22.1	0.56
2-year respiratory mortality, %	32.5	26.4	0.40
2-year all-cause mortality, %	37.5	35.3	0.78

Abbreviations: SD, standard deviation; FEV_1%, forced expiratory volume in one second expressed as a percent of predicted; PaO_2, arterial oxygen pressure; 6MWD, distance walked in 6 minutes; MRC, Medical Research Council; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; BMI, body mass index.

*P value for mortality calculated using Chi square test; all other P values calculated using a 2-sided Student's t-test.

Table 3. Multivariate Regression Analysis for Risk of Dyspnea and Functional Impairment

	MRC Dyspnea Scale			6MWD Test		
	ß Coefficient	**SE**	***P* Value**	**ß Coefficient**	**SE**	***P* Value**
Age	0.008	0.004	0.0199	-1.36	0.52	0.0097
Hemoglobin	-0.036	0.018	0.0479	8.61	2.68	0.0014
FEV_1%	-0.023	0.002	<0.0001	2.42	0.26	<0.0001
Charlson Comorbidity index	0.041	0.012	0.0006	-11.14	1.79	<0.0001
BMI	0.007	0.005	0.1962	-0.02	0.76	0.98

Abbreviations: MRC, Medical Research Council; 6MWD, distance walked in 6 minutes; SE, standard error; FEV_1%, forced expiratory volume in one second expressed as a percent of predicted; BMI, body mass index.

Table 4. Significant Differences in Patient Characteristics Between Survivors and Non-Survivors

Variable (mean ± SD)	Survivors (n = 437)	Non-Survivors (n = 240)	*P* Value*
Age, years	69.4 ± 9.0	71.3 ± 8.8	0.0086
Hemoglobin, g/dL	14.6 ± 1.5	14.2 ± 1.9	0.0021
Charlson Comorbidity index, points	4.6 ± 2.4	6.1 ± 2.9	<0.0001
BODE index, points	4.0 ± 2.0	6.3 ± 2.5	<0.0001

Abbreviations: SD, standard deviation; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

*P values calculated using a 2-sided Student's t-test.

Table 5. Multivariate Logistic Regression Analysis for Risk of Death

Parameter	Odds Ratio	95% CI
Age (by 1 year)	0.994	0.972-1.017
Hemoglobin (by 1 g/dL)	0.983	0.880-1.099
Charlson Comorbidity index (by 1 point)	1.234	1.143-1.332
BODE index (by 1 point)	1.535	1.412-1.668

Abbreviations: CI, confidence interval; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity index.

Figure Legends

Figure 1. Relationship between hemoglobin (Hb) level and the Medical Research Council (MRC) dyspnea scale.

Figure 2. Change in the 6 minute walking distance (6MWD) test by hemoglobin (Hb) level.

Figure 3. Kaplan-Meier probability of overall survival in anemic and non-anemic patients.

Figure 1.

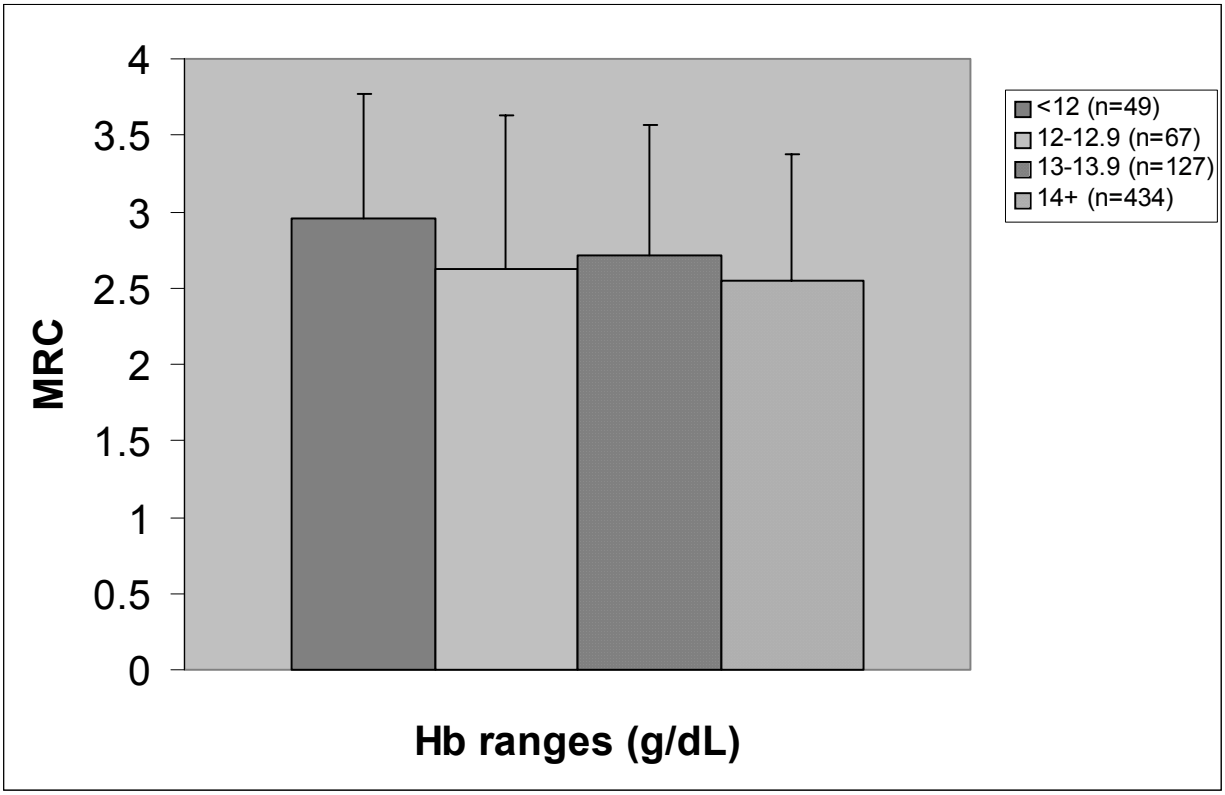

4
3.5
3
2.5
2
1.5
1
0.5
0
MRC
Hb ranges (g/dL)
<12 (n=49)
12-12.9 (n=67)
13-13.9 (n=127)
14+ (n=434)

Figure 2.

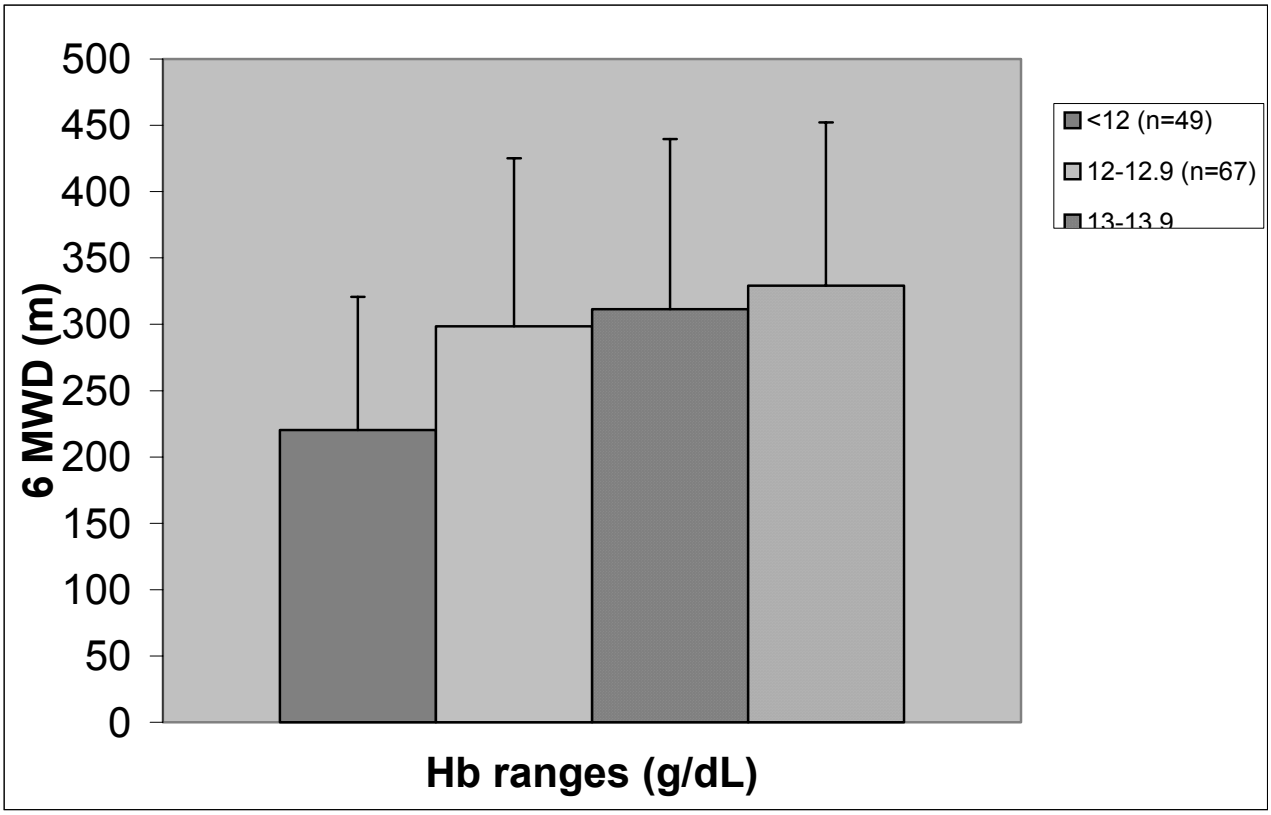
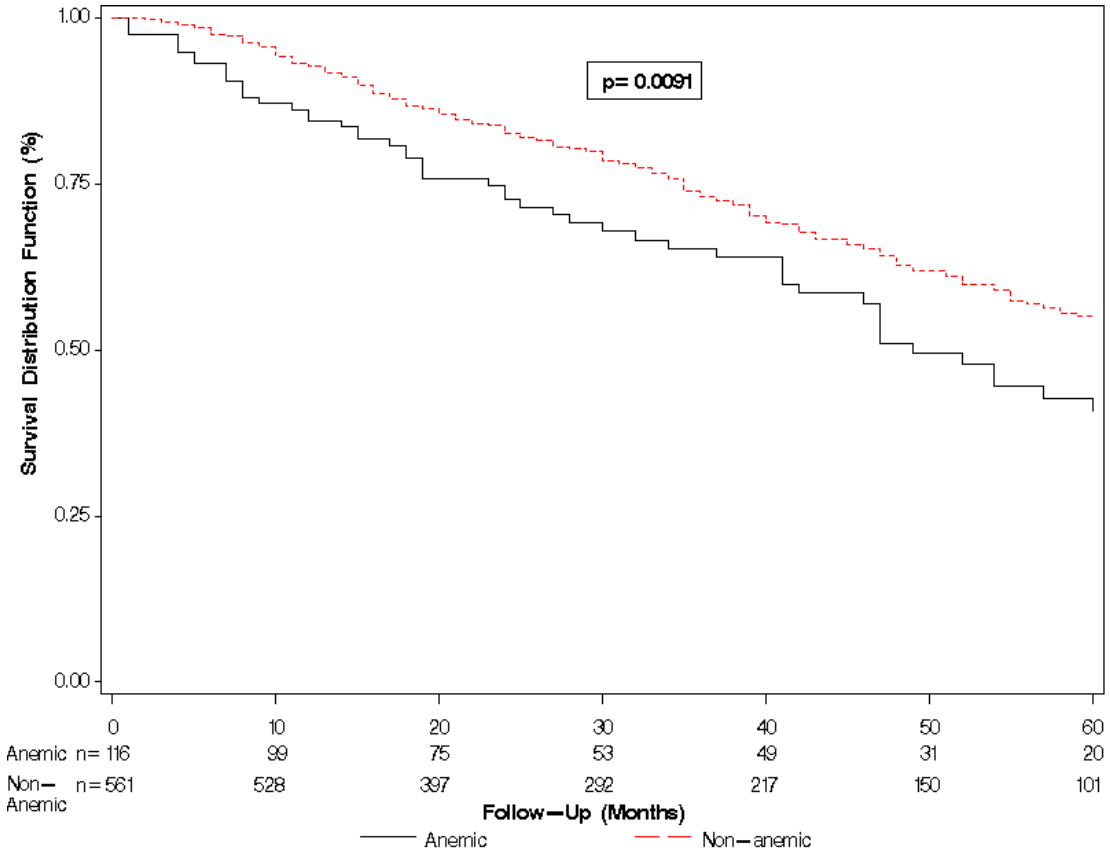

500
450
400
350
300
250
200
150
100
50
0
6 MWD (m)
Hb ranges (g/dL)
<12 (n=49)
12-12.9 (n=67)
13-13.9

Figure 3.


1.00
0.75
0.50
0.25
0.00
Survival Distribution Function (%)
p= 0.0091
0
10
20
30
40
50
60
Anemic n= 116
99
75
53
49
31
20
Non– Anemic n= 561
528
397
292
217
150
101
Follow–Up (Months)
Anemic
Non–anemic