

the findings by John, a recent study by Chambellan and coworkers in a cohort of COPD patients with severe oxygen-dependent COPD demonstrated that anemia (defined by laboratory values according to the WHO criteria [14]), present in 8.2–12.6%, was in fact correlated with age and disease severity in this population, and, consistent with the current findings, hematocrit was an independent predictor of survival, hospital admission rate and duration of hospitalization [11]. Cote and co-workers, focusing on a population from a US Veterans Affairs pulmonary clinic, estimated the prevalence of anemia at 30% [9]. As in the John et al. study, these investigators had patient level hemoglobin data available. Similar to the present findings, Cote et al. reported that anemic COPD patients had more co-morbid illnesses [9,10]. They also concluded that the presence of anemia independently correlated with mortality [9,10].

While it is likely that CKD, advanced age or certain medication exposure may play a role in the development of anemia in this population, at least one study points to the possible role of inflammation and resistance to elevated levels of erythropoietin [12]. Etiology notwithstanding, our study suggests anemia is highly prevalent in the COPD population and associated with worse clinical and economic outcomes.

The present study builds on prior data and suggests that anemia is common in COPD. As it was necessary in the present study to use ICD-9 codes rather than hemoglobin values, these findings likely underestimate the frequency of anemia. Examining a very large sample, however, adds to the robustness of the conclusions. Furthermore, this study was able to control for many confounders that the earlier reports could not assess. Specifically, the current analysis accounted for prior health care utilization and factors associated with COPD severity, such as the frequency of episodes of AECB and pneumonia. This study is also unique in that it measures the economic impact of anemia in COPD and describes the increased utilization of various healthcare resources among patients with anemia. Finally, this study was also able to corroborate previous work indicating that COPD patients with anemia are at higher risk for death.

The association between anemia and increased risk of mortality seen here among COPD patients parallels previous reports of links between anemia and decreased survival in other disease states. For example, in subjects with left ventricular dysfunction, anemia independently adversely affects survival [15,16]. Similarly, in chronic kidney disease, anemia not only affects quality of life but also worsens survival [17]. This study's finding of relatively high costs of medical care for individuals with COPD (even those who do not have anemia) is not sur-

prising, given that both increased age and decreased health status are associated with increased costs in several different components of healthcare [18]. Specifically, in COPD, direct healthcare costs in the United States were estimated to exceed \$18 billion in 2002 and COPD led to nearly 750,000 hospital admissions [19]. These hospitalizations, along with treatment of AECB, are major drivers of costs. Results of this study, indicating that inpatient care was the single largest category of Medicare claims for this population, support findings from previous studies.

This study has several important limitations. First, as a retrospective study, it is exposed to various forms of bias. Second, since the data source was administrative claims data, findings may have been affected by coding bias; that is, only those COPD patients and the subset with anemia who had Medicare claims with appropriate ICD-9 diagnosis codes could be identified, though the presence of such codes could not guarantee the appropriateness of these diagnoses. The large sample size, however, balances these concerns, and for some endpoints, such as mortality and hospitalizations, the results are in accordance with other studies. Further, prior large chart audits indicate that ICD-9 codes for COPD are actually both specific and sensitive for this condition [20]. Third, as mentioned earlier, anemia was defined based on ICD-9 coding. As a majority of US pulmonologists participating in a recent survey did not classify anemia as being present among COPD patients using a threshold hemoglobin value of 12 g/dL, it is unlikely that this study overestimated the true prevalence of anemia in this population and may well have underestimated it [21]. If clinicians do not believe anemia is present, they are unlikely to use an anemia diagnosis code for the provided services. Additionally, there is no reason to believe, a priori, that bias in recording anemia would lead to the more "expensive" patients consistently being labeled as anemic. Finally, no specific measures of disease severity were available. Hence surrogate markers of severity of illness, which correlate with outcomes and have been validated in previous health services research in COPD, were utilized. Moreover, other than the recently proposed BODE index, no global, validated severity score in COPD exists [22]. Despite these best efforts at adjusting for identifiable confounders, residual confounding cannot be excluded as a potential source of the independent relationship between anemia and worsened outcomes shown in this study.

In conclusion, anemia is a comorbidity commonly associated with COPD. Although the nature of this retrospective observational study precludes any inference of causality, it is clear that anemia in this patient population is associated with increased healthcare costs and resource utilization, as well as worsened survival. Future research is warranted to define more accurately the epidemiology