Lung Function Data Interpretation

To the Editor:

The article by Mannino and Diaz-Gutzman in CHEST (January 2012) reiterates an argument previously published by Mannino et al. suggesting that the use of a fixed ratio of 0.7 for FEV<sub>1</sub>/FVC is justified in defining the presence of airflow obstruction because it identifies people who are at increased risk of dying. However, this misconstrues the true relationship between lung function and risk of death, which is a continuum. For FEV<sub>1</sub>, data, people with lung function just above their predicted value have an increased mortality when compared with those with the very best function. For FEV<sub>1</sub>/FVC, the risk is increased as soon as the level of function goes below predicted. If one was justified in using lung function to support the definition of a disease state on the basis of associated increased mortality, then at least one-half of the population would be diagnosed with the disease, which is clearly not meaningful. Furthermore, the approach by Mannino and Diaz-Gutzman of looking at those considered “abnormal” by the fixed ratio, but above the lower limit of normal (LLN), identifies an older age group (Table 3 of the article, mean age 67.9 years, SD 0.9), and this population will consequently have a higher mortality because age was not included in their model. The findings presented in this article could be demonstrated in endless other data sets, but this does not mean the argument by Mannino and Diaz-Gutzman is correct because it conveniently ignores the true relationship between lung function, age, and mortality.

The difference of opinion about how to define airflow obstruction from lung function data splits neatly into the groups of experts who have set down guidelines on how to record and use lung function data, who all favor lower limits of normal, and the groups of experts who have set down guidelines on the management of COPD who advocate the fixed ratio of 0.7. I have yet to see any recommendations about pulmonary disease management coming from the experts on lung function data, and yet the experts on COPD management are happy to adopt their own rules on the use of lung function data, which differ from the accepted methodology applied for all other routine laboratory tests. Mannino and Diaz-Gutzman have suggested that the use of LLN in my earlier article as the “gold standard” was unfounded, and the fixed ratio and percent-of-predicted method used by GOLD (Global Initiative for Chronic Obstructive Lung Disease) is, in fact, better. The LLN is based on statistical and scientific methodology that has been accepted worldwide by the medical and scientific community and published in journals as the best way for ensuring fairness and equity when analyzing data and drawing conclusions. The fixed ratio and % predicted method is not based on any scientific methodology and discriminates on the basis of both sex and age because of the biases they introduce. In the area of employment, it is illegal in many countries to discriminate on the basis of age and sex, and I see no reason why such discrimination should be seen as acceptable when it comes to making diagnoses on individual subjects.

It has been argued by some that the difference of opinion about the use of the fixed ratio is not important, but for individual patients it is extremely important. When a clinician tells a patient that unfortunately he or she has a particular disease, it is beholden on the clinician to be as certain as possible that this is correct. Using the fixed ratio means subjects whose lung function is within population norms for their age, sex, and height may be deemed to have airflow obstruction and be diagnosed with COPD. The psychologic impact on a patient from receiving this diagnosis can be profound in that it is a progressive disease with high mortality and, as yet, there is very little treatment that is effective. Research into this disease should concentrate on patients who definitely have the disease and not be clouded by adding subjects whose lung function is within the accepted normal limits for their age and sex. Adding these subjects to studies will add noise to any possible signal and so may prevent studies and drug trials from finding a clear result. If this noise was avoided, such studies would then not need to be so large and expensive (a point that may be of interest to the pharmaceutical industry) and patients would stand a greater chance of benefiting from therapeutic discoveries that are so desperately needed in this condition.

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REFERENCES
We read with great interest the case report by Cadavid et al 1 in a recent issue of CHEST (January 2011). Although Cadavid et al 1 reported an excellent case of extranodal marginal zone B-cell lymphoma (MZBL) of mucosa-associated lymphoid tissue (MALT), we would like to raise some concerns about the diagnosis of extranodal MZBL of MALT. To our knowledge, the optimal diagnosis of the disease requires careful integration of morphologic, immunohistochemical, and molecular information, given the non-specific nature of clinical manifestation, physical examination, and radiographic features. 2 It is worth noting that this case report presented only one endobronchial biopsy specimen demonstrating extensive infiltration of the mucosa and submucosa by a homogeneous population of lymphocytes. We question whether it is sufficient to diagnose the disease by histologic examination only. The histologic differentiation between extranodal MZBL of MALT and reactive lymphocytic proliferation may sometimes be difficult. 3 This is the reason why some of the patients with extranodal MZBL of MALT are given a misdiagnosis of pneumonia, pulmonary tuberculosis, or interstitial lung disease. Furthermore, extranodal MZBL of MALT typically expresses B-cell-associated antigens, such as CD20 and CD79a, but lacks CD5, CD10, CD23, and cyclinD1. Thus, immunophenotyping is used to exclude B-chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and follicular lymphomas to aid in the correct diagnosis. We would propose that the authors of this case report supplement immunohistochemistry and/or examine gene rearrangement to validate the diagnosis of extranodal MZBL of MALT.

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References

IV Delivery of Fluorescent Beads

To the Editor:

Cell-based therapies using induced pluripotent stem (iPS) cells have emerged as potential novel approaches for several devastating and otherwise incurable lung diseases like emphysema, pulmonary fibrosis, pulmonary hypertension, and ARDS. 1 The article by Yang et al 2 in a recent issue of CHEST (November 2011) evaluating the role of iPS cells in the treatment of endotoxic-induced acute lung injury revealed a possible protective effect mediated by iPS cells, which significantly diminishes the histopathologic changes of acute lung injury and the lung injury score. Moreover, it was shown that the protective effects were not replicated by control cell therapy carried with fibroblasts.

However, in our opinion, the strength of the article would be enhanced substantially by a more precise evaluation of the area of iPS cell integration into the lung and by an assessment of the iPS cell dynamic through different parenchymal organs. The latter would help to establish iPS cell lung-homing capacity.

To illustrate the importance of these points, we will describe the results of a recent experiment performed in our laboratory. A total of 1 × 10^6 fluorescent beads (FBs) (2.5 μm, λex: 630-660 nm, λem: 670-720 nm; Invitrogen) were suspended in 50 μL of phosphate-buffered saline and injected into the tail vein of Cby.CgFoxi^-/- 1-month-old nude mice (Charles River). Location of FBs was registered by in vivo fluorescent imaging (Pearl-Impulse; LI-COR Biotechnology), at different times after the injection: 5 min, 1, 2, 3, and 4 weeks. After 4 weeks, the mice were killed according to approved methods, and their internal organs inspected for fluorescent emission. In order to localize with more precision the location of the beads, 10-μm tissue sections were analyzed by standard fluorescent microscopy (DMI 6000B; Leica Microsystems).

In agreement with our previous findings in nude rats, 3 5 min after injection many of the FBs were localized in the breast area of animals (Fig 1A). However, a week after the injection almost all the FBs were present in the abdominal part of the body (Fig 1B). This image remained unaltered at 4 weeks after the injection. The analysis of autopsies material (Fig 1C, 1D) clearly shows that almost all the FBs were located in spleen and liver, being undetectable in kidney, heart, and lung.