FVC, Total Lung Capacity, and the Differential Association to Mortality

To the Editor:

I would like to thank Pedone et al1 for their recent article in CHEST (April 2012). The article presented data on the association between pulmonary restriction, properly defined as having a total lung capacity (TLC) below the fifth percentile of the reference population (lower limit of normal [LLN]), and all-cause mortality. As the authors correctly pointed out, defining restriction as FVC < 80% predicted (or even lower than the LLN) is neither specific nor sensitive as an indicator of true restriction.2 They presented a hazard ratio for death of 2.73 when FVC < LLN and of 6.87 when TLC < LLN. Assumably, much of the increased risk due to FVC < LLN is due to true restriction (the subset of FVC < LLN that also has TLC < LLN), although this was not specifically presented in the article. I believe that it would be a very helpful (and probably fairly easy) addition to their analysis to present the hazard ratio for death separately for those with FVC < LLN and TLC < LLN compared with FVC < LLN but TLC > LLN. The hypothesis behind this requested analysis would be that FVC < LLN but without true restriction (TLC > LLN) does not show increased risk of death (or shows a lower risk of death). I realize that with only 17 deaths total, this may not give results that achieve statistical significance, but lacking other similar data, the results may help us to interpret studies of FVC where TLC is not available.

An additional comment: In Figure 2, the survival lines for the reference categories, respectively for FVC > LLN and TLC > LLN, are identical. This seems a bit strange because even though the deaths represented in these two lines could be identical, the numerator of the percentage must be different.

Jon Andrew Hardie, MD, PhD
Bergen, Norway

Affiliations: From the Institute of Medicine, University of Bergen.
Financial/nonfinancial disclosures: The author has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Correspondence to: Jon Andrew Hardie, MD, PhD, Institute of Medicine, University of Bergen, Laboratory Bldg, N-5021 Bergen, Norway; e-mail: Jon.hardie@med.uib.no

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Response

To the Editor:

We thank Dr Hardie for his suggestion to expand the analyses we presented in our article in CHEST2 to test the hypothesis that people with FVC < the lower limit of normal (LLN) but without true restriction (total lung capacity [TLC] > LLN) do not have an increased risk of death. Indeed, compared with people with normal TLC and normal FVC, those with a reduced FVC (but normal TLC) do not have an increased risk of death (mortality rate ratio, 0.86; 95% CI, 0.12-3.66). People with decreased TLC and normal FVC, on the contrary, have a sixfold increased mortality risk (mortality rate ratio, 6.68; 95% CI, 2.36-19.4). Compared with patients with FVC < LLN and TLC ≥ LLN, those with FVC < LLN and TLC < LLN had a mortality rate ratio of 7.78 (95% CI, 1.9-56.67). Although the estimates may not be completely reliable because of the small number of events (only two deaths in the group with TLC > LLN and FVC < LLN), these results seem to support the hypothesis that the association between reduced FVC and mortality repeatedly reported in the literature is supported by the association between TLC and mortality.

As for the figure, because of the small number of events, the reference lines are actually very similar but not identical. For example, at close scrutiny it can be seen that the reference curve in the first panel (FVC ≥ LLN) has one “step” fewer in the first 6 months of follow-up.

Claudio Pedone, MD, PhD
Simone Scarlata, MD
Domenica Chiurco, MD
Maria Elisabetta Conte, MD
Francesco Forastiere, MD
Rome, Italy
Raffaele Antonelli-Incalzi, MD
Taranto, Italy

Affiliations: From the Unit of Respiratory Pathophysiology (Drs Pedone, Scarlata, Chiurco, and Conte and Antonelli-Incalzi), Università Campus Bio Medico; the “Alberto Sordi” Foundation (Drs Pedone and Scarlata), the Department of Epidemiology (Dr Forastiere), Roma E. Health Authority; and Fondazione San Raffaele (Dr Antonelli-Incalzi), Cittadella della Carità.
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Correspondence to: Claudio Pedone, MD, PhD, Università Campus Bio Medico, Via Alvaro del Portillo, 200, 00128 Rome, Italy; e-mail: c.pedone@unicampus.it
A Word on False Positives

To the Editor:

The article by Wang Memoli et al1 in an issue of CHEST (December 2011) on the use of endobronchial ultrasound (EBUS) to predict lymph node metastasis due to lung cancer was well presented and helpful for the interpretation and diagnosis of metastatic carcinoma. The authors discussed the widely accepted criteria suggestive of metastatic malignancy, including a positive PET scan and a short-axis lymph node diameter > 1 cm on CT scan. Although these criteria are strongly suggestive, they do not prove that the patient in fact has metastatic nodal disease.

Further diagnostic or interventional studies may be necessary to confirm or disprove the presence of metastatic lung cancer.2 Such studies may include mediastinoscopy or needle biopsy either percutaneously or through EBUS. Each technique has limitations regarding its diagnostic accuracy and risk for complications. False-negative as well as false-positive results may be obtained. Each situation must be interpreted with this in mind for the benefit of the patient and the best therapeutic program to recommend.

We recently evaluated a patient with adenocarcinoma of the right-side lung. The PET scan was interpreted as positive for bilateral hilar and mediastinal node metastasis. EBUS biopsy specimens from both the right-side and the left-side paratracheal and hilar areas demonstrated malignant cells in the right-side biopsy specimen and none in the left. The patient was informed of this finding and told that nonoperative therapy was recommended. She came to us for a consultation. We believed, on review, that the nodes were negative and recommended surgery. During right-side thoracotomy, 18 hilar and mediastinal lymph node lymph nodes were removed along with the involved lobe. All lymph nodes were negative for tumor presence. On review of the original EBUS biopsy specimen, lymphoid cells were present along with malignant cells, thus leading to the diagnosis of nodal metastasis. In retrospect, it appears that the false-positive study suggestive of metastatic disease resulted from the EBUS needle passing through the node and into the lung or paracardial tumor, thus the misinterpretation of positive nodal metastasis and the different therapeutic program being recommended.

Raymond A. Dieter Jr, MD, FCCP
Naperville, IL

Affiliations: From the Center for Surgery and DuPage Medical Group.

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Correspondence to: Raymond A. Dieter Jr, MD, FCCP, Center for Surgery, 475 E Diehl Rd, Naperville, IL 60563; e-mail: lnickerson@centerforsurgery.com

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Response

To the Editor:

The correspondence from Dr Dieter regarding our article in CHEST1 on endobronchial ultrasound (EBUS) predictors of metastatic malignancy has pointed out an important issue related to all diagnostic procedures: the false-positive result. False-positive results by EBUS have been reported and are related to the proximity of the primary tumor to a hilar, thus more distal, lymph node. This occurrence is rare, as several prospective studies comparing EBUS to surgical staging (mediastinoscopy or lymph node dissection at lung resection) have not reported any cases of false-positive results.1,4

Some practitioners argue that a false-positive result is a problem presumably because it would lead to unnecessary procedures where a lesion is diagnosed as lung cancer but at resection, is not.1 Dr Dieter argues the opposite. His patient would not have undergone a potentially curative surgical resection because of a nodal metastasis diagnosis based on EBUS. Although his case may raise concern and make practitioners wary of their EBUS results, we have questions regarding Dr Dieter’s example. Which right-sided lymph node was positive on EBUS, mediastinal or hilar? If it was a hilar lymph node, the stage would likely be one in which curative resection was still possible despite lymph node metastasis. What made him doubt the results of the EBUS? The PET scan findings were considered positive, which supported the assumption that there was lymph node metastasis. Prior to surgical resection, should the patient have been referred for surgical confirmation with a mediastinoscopy if the EBUS-based diagnosis was in doubt? Before sending the patient for a thoracotomy, another method more invasive than EBUS but less invasive than thoracotomy to evaluate the mediastinum could have been performed. Was the lymph node that was positive at EBUS among the 18 hilar and mediastinal lymph nodes that were removed? This would verify the false-positive finding of the node sampled at EBUS. Is there any long-term follow-up on the patient to determine whether she has had subsequent recurrence?

Another aspect to consider in this case is the accuracy of the positive EBUS biopsy specimen. Part of the learning curve of performing EBUS lies in the ability to distinguish a lymph node and its borders from the surrounding structures. If the bronchoscopist guided the biopsy needle through the lymph node into the adjacent malignant mass, the needle could have become contaminated, resulting in the false-positive biopsy finding. Understanding the borders of the lymph node and avoiding contamination of the needle is crucial in all staging procedures.

Ultimately, false-positive results are rare. In most studies, when a positive result is obtained, that result is presumed to be a true