Letter to the Editor

Calpain and spectrin breakdown products in tuberculous pleural effusion

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We read with interest the paper of Hong *et al.* recently published in *Journal of Thoracic Disease* (1). In that study, the researchers prospectively enrolled 163 adult subjects who received thoracentesis. After excluding subjects with hemothorax, parapneumonic effusion and unknown etiology, 86 subjects were enrolled. Among these subjects, 47 were tuberculous, 28 were malignant and 10 were transudative. With this cohort, the researchers investigated the diagnostic accuracy of adenosine deaminase (ADA), calpain-1, angiotensin-converting enzyme (ACE), spectrin breakdown products (SBDP) and matrix metalloproteinase-1 (MMP-1) levels in pleural effusion (PE) for tuberculous pleural effusion (TPE). Using receiver operating characteristic (ROC) curve analysis and multivariable logistic regression model, the researchers found that all of these PE biomarkers are useful for TPE diagnosis. Because calpain-1, ADA and SBDP are independently associated with TPE, the researchers created a three-factor diagnostic model based on them. Compared with ADA, the model exhibits a moderate increment in the sensitivity (from 89.3% to 97.9%) and a mild reduction in the specificity (from 89.4% to 86.8%). Based on these findings, the researchers concluded that simultaneous measurement of calpain-1 and SBDP l in PE may improve the diagnostic efficacy. This is an interesting and valuable work. It is the first study investigating the diagnostic accuracy of pleural fibrosis related markers for TPE.

During past decades, several TPE biomarkers have been identified, such as ADA, interferon-gamma, interleukin 27, nucleic acid amplification tests, interferon-gamma release assays and interferon-gamma-induced protein of 10 kDa (2-4). Among the available biomarkers, ADA has been recommended by British Thoracic Society guideline (5). This is due to the fact that ADA is an inexpensive, standardized and easy to perform test (5). In the Hong's study, the researchers investigated whether calpain-1, ACE, SBDP and MMP-1 provides added value beyond ADA. This research aim is reasonable because the sensitivity and specificity of ADA for TPE were 92% and 90%, respectively, as indicated by a meta-analysis (6). However, the study design and statistical methods of this study are questionable.

First, the researchers found that the three-factor model has high sensitivity than ADA (89.3% *vs.* 97.9%), but whether the difference was statistically significant was not tested. Furthermore, sensitivity and specificity are not good indicators of a diagnostic test, because it is well recognized that they are threshold-dependent and there is a trade-off between them (7). By contrast, the area under ROC curve (AUC), an index independent of threshold, is usually used to measure the overall diagnostic accuracy of a diagnostic test (7). Therefore, to address whether calpain-1 and SBDP provides added value beyond ADA, we strongly suggest the researchers to compare the AUC of ADA and three-factor model. Besides, other statistical methods such as net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (8,9) can also be used to address this issue.

Second, the researchers transformed continuous variables

to dichotomous variables when performing ROC curve analysis. This is not a reasonable approach. ROC curve is used to outline the interdependency of specificity and sensitivity for a given quantitative diagnostic test, rather than a dichotomous one (7).

Third, according to the criteria proposed by Light, PE is categorized into transudate and exudate (10). The common causes of exudate are malignancy, parapneumonic effusions and tuberculosis, while the common causes of transudate are heart failure and liver cirrhosis (5). An important early step in narrowing the differential diagnosis is categorization of PE into exudates and transudates (5). While in the Hong's study, the parapneumonic effusion was excluded, while transudates were included. This is a participation selection bias and thus may affect the reliability and generalization of this study's results.

Taken together, Hong *et al*. reported four novel biomarkers for TPE and gives us new insight into the diagnosis of TPE. However, due to its study design and statistical weakness, further well-designed studies are needed to rigorously evaluate the diagnostic value of these biomarkers.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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