Reviewer's report

Title: Diagnostic significance of Tumor Necrosis Factor-alpha, Interferon-gamma, Interlukine-10 and Adenosine Deaminase 2 in tuberculosis pleural effusion

Version: 1 Date: 22 December 2013

Reviewer: Rafal Krenke

Reviewer's report:

Dear Editor,

Dear Authors,

I reviewed the manuscript by Li et al. entitled “Diagnostic significance of Tumor Necrosis Factor-alpha, Interferon-gamma, Interlukine-10 and Adenosine Deaminase 2 in tuberculosis pleural effusion”. The study aimed to evaluate the diagnostic performance of four different pleural fluid biomarkers in the differentiation between tuberculous and non-tuberculous (probably malignant) pleural effusion. The question posed by the authors is not new and data on the diagnostic yield of all markers used in this study have already been published. My review includes at least several significant doubts and objections which refer to different aspects of the manuscript. These are presented below.

Major Compulsory Revisions

Title; Material and methods.

The non-tuberculous effusion group is poorly defined. In some parts of the manuscript the authors label this group as malignant pleural effusion group (e.g. Table 1 and Table 2), while in the Material and methods section this group was defined as follows: 26 patients with lung cancer, 6 patients with breast cancer, 7 patients with unknown primary tumor site and 4 patients with other diseases. I wonder what the cause of pleural effusion in four patients with other diseases was. Did they have malignant or non-malignant pleural effusion? If they had benign pleural effusion they should not have been included in the malignant pleural effusion group but should have formed a new group of patients with benign pleural effusion. If they had malignant pleural effusion, the title of the manuscript should have reflected this, stating that the diagnostic yield of the applied biomarkers refers only to the differentiation between tuberculous and malignant pleural effusion.

Abstract

The study groups have not been adequately presented (no data on the number of patients, age, etc.). Moreover, there is not a single number in the results presented in abstract. Thus, there is no basis for drawing the conclusion presented by the authors.

Language
The language of the article is absolutely not acceptable. There are not only grammar errors but also the syntax of the sentences is incorrect making the content of numerous sentences confusing; e.g. „It’s the best choice for the doctors to make the diagnosis based on the frequencies of TNF-# and ADA2“.

Material and Methods
The authors did not present the methods they had used to assess the diagnostic yield of two (or more) biomarkers combined together. This is a crucial point. If an elevated level (above the diagnostic threshold) of only one biomarker was required to diagnose tuberculous pleural effusion (TPE), I would expect the increased sensitivity but decreased specificity of the test. Conversely, if elevated level (above the diagnostic threshold) of both biomarkers was required to diagnose TPE. I would expect increased specificity but at the cost of lower sensitivity.

Results and conclusions
Comparing the results presented in Table 3 and Table 4, I could not agree with the authors statement that “combined TNF-# with ADA2 shows the best sensitivity, specificity and accuracy…”. The sensitivity and accuracy of TNF-# is higher than the sensitivity and accuracy of TNF-# + ADA2 and the specificity of TNF-# is only marginally lower than the specificity of combined TNF-# + ADA2. Thus, in my opinion, the major conclusion drawn from the study is also incorrect.

Minor Essential Revisions
Introduction
A very high percentage of TPE has been cited in the Introduction (49.6%). This is true only for some populations with high prevalence of tuberculosis. In majority of developed countries the respective percentage is significantly lower.

Data on the diagnostic yield of pleural fluid ADA were based on an old, single center experience [reference #9]. Several metaanalyses and review papers summarizing data from many studies have been published in the last decade.

Material and Methods
Please, provide more detailed data on ADA2 measurement. Was ADA2 measured directly or calculated?

Discussion
The problem of the microbiological diagnosis of tuberculous pleural effusion is associated with the low sensitivity of M. tuberculosis detection in pleural fluid. However, the specificity of the microbiological diagnosis is very high. Thus, the main goal of the research on the field of biomarkers in TPE is to search for more sensitive (not specific biomarkers). I would not expect that any of the biomarkers will be more specific than culture.

The authors state that "Interestingly, our study revealed a significant increase of
IFN-# (114.97±27.85ng/L) in pleural fluid of TB than that of malignant cases (87.15±18.77ng/L). To my knowledge, there are plenty of original papers and some metaanalyses which show that pleural fluid IFN-# is significantly higher in TPE than in non-TPE. Therefore, these results were easily predictable and I do not understand in what way they are interesting.

Discretionary Revisions

The references seem to me somewhat out of date. Only approximately 25% of all cited papers were published in the last decade.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.