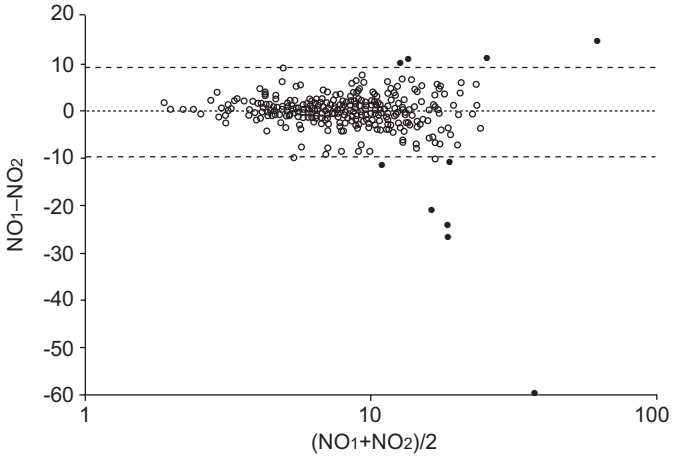


**FIGURE 1.** Bland Altman plot of the agreement between the duplicate fraction of exhaled nitric oxide ($F_{ENO}$) measurements, indicating the mean difference between the duplicate $F_{ENO}$ measurements (·····) and the mean difference ±2SD (-----). The open and solid circles indicate the children for whom the difference between duplicate $F_{ENO}$ measurements was <10 ppb or >10 ppb, respectively. The x-axis is logarithmic.

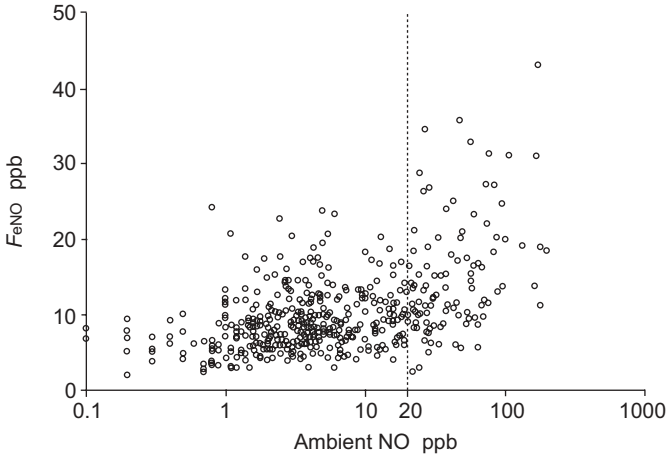


**FIGURE 2.** The influence of ambient nitric oxide (NO) levels on the fraction of exhaled nitric oxide ($F_{ENO}$) values in the study population. The x-axis is logarithmic.

criteria were applied, the $F_{ENO}$ values were not more discriminative between children with and without asthma or atopy.

With respect to the ambient nitric oxide values, we have examined their effect on exhaled nitric oxide. Since there was no significant influence of ambient nitric oxide levels <20 ppb on the fraction of exhaled nitric oxide values in our study population (figs 2 and 3), we decided to include all children with ambient nitric oxide levels <20 ppb in the analyses. When the analyses were repeated, including only those children for whom the ambient nitric oxide values were <10 ppb, similar results were observed.

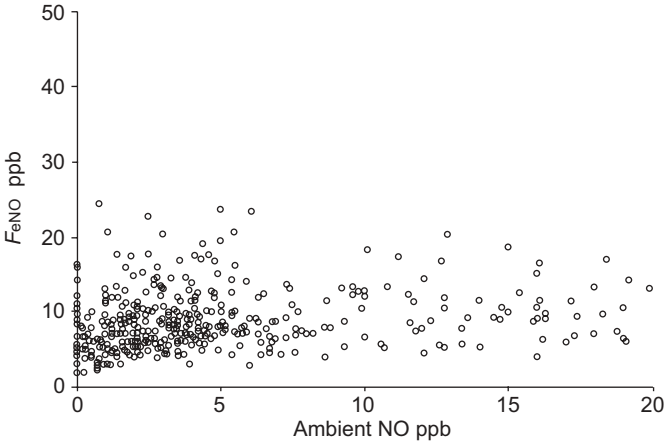


**FIGURE 3.** The influence of ambient nitric oxide (NO) levels <20 ppb on the fraction of exhaled nitric oxide ($F_{ENO}$) levels in the study population.

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# Predictive value of BAL cellular analysis in differentiating pulmonary tuberculosis and sarcoidosis

*To the Editors:*

In a recent issue of the *European Respiratory Journal*, WELKER *et al*. [1] assessed the utility of bronchoalveolar lavage (BAL) cell counts and CD4/CD8 ratios as a test panel for the differential diagnosis of interstitial lung diseases (ILDs), and reported that their usage significantly modified the pre- *versus* post-test probability of a correct diagnosis. The diagnostic gain appeared particularly high in sarcoidosis, a disease where distinctive findings such as low BAL neutrophil counts, higher

lymphocyte percentages and CD4/CD8 ratios, together with the high prevalence, increase the test panel predictive values [1].

In paucibacillary tuberculosis (TB), whose frequency is estimated between 29% and 80% of TB cases in Europe, BAL cytology is widely used, since confirmatory microbiology is lacking and different patterns of alveolar inflammation have been described in these two disorders [2–5]. Assessing the usefulness of BAL cellular profiles in differentiating sarcoidosis from TB may be of considerable clinical importance. In order to verify the reproducibility of the diagnostic tests described by WELKER *et al*. [1], we retrospectively analysed a series of consecutive patients undergoing pre-treatment BAL in a tertiary care centre (Carlo Forlanini Hospital, Rome, Italy) during a 4-yr period and in whom a final diagnosis of biopsy-proven sarcoidosis or culture-positive pulmonary TB was established. The 88 sarcoidosis and 76 TB patients displayed significant differences (Mann-Whitney U-test) in BAL lymphocyte percentage (median (interquartile range) 30% (16–49) in sarcoidosis *versus* 14% (4–29) in TB), neutrophil percentage (2% (1–5) *versus* 3% (2–12)) and CD4/CD8 ratio (3.9 (2.3–6.2) *versus* 2.2 (1.2–3.8)).

By applying the same cut-off used by WELKER *et al*. [1] to these three variables, it was found that the high-grade lymphocytosis (>50%) was the best predictor. Since it was rarely observed in TB patients, as a consequence, its presence increased the probability of sarcoidosis from 0.54 (pre-test) to 0.91 ($p=0.001$, Chi-squared test). The diagnostic gain was even higher if either a low (<4%) neutrophil percentage or a high (>3.5) CD4/CD8 ratio was associated with it (post-test probability 1, $p=0.001$, in both cases).

The value of a high CD4/CD8 ratio as an independent predictor of sarcoidosis was diminished by the scattered CD4/CD8 ratio distribution in TB patients: 29% of the TB patients evaluated had values of >3.5 (16% had values of >5). As a result, the pre-test probability of sarcoidosis only increased from 0.54 to 0.69 ($p=0.049$), a diagnostic gain lower than that observed by WELKER *et al*. [1] in their nonsarcoid ILD patient group. It is worth mentioning that very low (<0.5) CD4/CD8 ratios (post-test probability 0.14, $p=0.047$), particularly when combined with low lymphocyte percentages (0.35, $p=0.016$), retained their ability to exclude sarcoidosis.

As normal values (<4%) of neutrophil counts were found in half of TB patients, this criterion was unhelpful in differentiating sarcoidosis from TB. To the contrary, the presence of high-grade neutrophilic alveolitis (>20%) rendered the diagnosis of sarcoidosis very unlikely (post-test probability 0.20, $p=0.026$).

Consistent with the data described by WELKER *et al*. [1], in our hands too, BAL cellular analysis provided additional information that either increased or decreased the probability of sarcoidosis with TB as the competing diagnosis. It should be stressed, however, that the proportion of sarcoidosis patients to which the predictive values apply is rather low: as a result of the poor sensitivity and specificity of the BAL parameters (55% and 76%, respectively, for high CD4/CD8 ratio, and 25% and 97%, respectively, for high-grade lymphocytosis), only 48 had a ''diagnostic'' CD4/CD8 ratio and 22 a ''diagnostic'' lymphocytosis.

We also applied stepwise discriminant analysis for the diagnosis of sarcoidosis by using the leave-one-out cross-validation method. While WELKER *et al*. [1] obtained a correct classification rate of ~90% of sarcoidosis, 50% of hypersensitivity pneumonitis, 25% of usual interstitial pneumonia, 10% of bronchiolitis obliterans organising pneumonia and none of the nonspecific interstitial pneumonia patients, we found that the linear combination of the selected variables (CD4/CD8 ratio, lymphocyte and neutrophil percentages) correctly diagnosed ~70% of our 164 patients either as sarcoid or tuberculosis. By considering the discriminant score as a single diagnostic test for sarcoidosis, sensitivity, specificity, positive and negative predictive values were 73%, 67%, 72% and 68%, respectively. The use of cut-off values to classify variable and largely overlapping test results is expected to reduce the diagnostic power of the numeric data. Thus, although the use of cut-off values in the interpretation of bronchoalveolar lavage cellular results may appear more practical, the use of a discriminant score can provide clinicians with more accurate information guiding them through the diagnostic process, as previously suggested by DRENT *et al*. [6].

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