



## Guest Editorial

# Can we effectively use radiographic imaging and clinical parameters for making an earlier diagnosis of granulomatous interstitial lung disease in patients with common variable immunodeficiency?



Noninfectious complications in patients with common variable immunodeficiency (CVID) are increasingly being recognized as major sources of morbidity and mortality.<sup>1</sup> Chronic pulmonary disease directly due to infections, possibly as a consequence of delayed or under treatment with replacement immunoglobulin (Ig), has been well recognized as a cause of significant problems in patients with CVID but has decreased with appropriate replacement immunoglobulin therapy.<sup>2,3</sup> Although the underlying causes of noninfectious complications of the pulmonary system for most remain unknown, autoimmunity and post-infectious inflammatory reactions could be responsible, and these are surpassing infections as causes of morbidity and mortality.<sup>4</sup>

It is generally reported that approximately 15% of patients with CVID could develop granulomatous interstitial lung disease (GLILD), with an overall decrease in survival.<sup>5</sup> Further, a uniformly successful therapeutic intervention has not been established to adequately treat this complication in CVID. Thus, the concept arose that an earlier diagnosis with appropriate treatment would be beneficial for patients with GLILD. Diagnosis has generally been made by high-resolution computed tomography of the chest and lung biopsy examination demonstrating granulomatous disease.<sup>5,6</sup> The radiographic diagnosis of GLILD includes evidence of interstitial lung disease with nodularity and ground-glass appearance as the hallmarks.<sup>5–8</sup> The radiographic features can be present in other disorders, such as sarcoidosis, for which GLILD is sometimes misdiagnosed.<sup>5–8</sup> Confirmation of the diagnosis generally requires lung or lymphatic tissue biopsy examination demonstrating the presence of granulomatous disease.<sup>5–8</sup>

The article by Hartono et al.<sup>9</sup> approached the association by mapping via “network analysis” using specific clinical parameters for patients with computed tomographic and biopsy results consistent with GLILD to identify criteria for establishing an earlier diagnosis. Because some radiographic features might be nonspecific for GLILD and thus not allow for a specific early diagnosis, clinical parameters could be used in conjunction to establish the earlier diagnosis, with aims for decreasing potential morbidities of radiation exposure as a result of multiple computed tomographic scans and complications from obtaining tissue biopsy specimens. The overall goal of their study was to

establish an earlier diagnosis, with the implied concept to develop protocols for determining the best therapeutic options for treatment. Recently, Mannina et al.<sup>8</sup> also evaluated clinical parameters for establishing a diagnosis of GLILD in patients with CVID. They noted that 7.8 years after diagnosis of CVID is typically when the diagnosis of GLILD is made, although this was not noted by Hartono et al.<sup>9</sup> Hartono et al.<sup>9</sup> reported on 26 patients and 26 control subjects, whereas Mannina et al.<sup>8</sup> reported on 34 patients and 52 control subjects. Although there are overall demographic similarities, the patients in the study by Hartono et al.<sup>9</sup> study might have been diagnosed with CVID earlier, might have had a longer smoking history, but might have had better pulmonary function test results (forced vital capacity 95% vs 77%). Initial serum IgA levels were lower than those in control subjects in the 2 studies, but reached statistical significance only in the study by Mannina et al.<sup>8</sup> In addition, initial serum IgG and IgM levels were statistically significantly lower in patients in the study by Mannina et al.<sup>8</sup> Some differences could be explained by the larger number of subjects in the study by Mannina et al.<sup>8</sup> Lymphocyte immunophenotyping results were similar between the 2 studies, although Hartono et al.<sup>9</sup> also reported on high and low CD21 expression on B lymphocytes, with the relative percentage of B lymphocytes with low CD21 expression being used as an important mapping parameter for establishing a diagnosis of GLILD. Mannina et al.<sup>8</sup> used a multivariate statistical model with 9 clinical parameters potentially associated with GLILD and found 3 (hypersplenism, polyarthritis, and percentage of predicted forced vital capacity) with good prediction; positive and negative predictive values were approximately 85% and approximately 90%, respectively. Interestingly, they noted the percentage of predicted forced vital capacity (77%) did not change over a 7-year follow-up. Further, this would appear to be significantly lower than the 95% found in patients by Hartono et al.<sup>9</sup> Hartono et al. took the “network analysis” approach to develop a predictive model using Gephi 0.8.2 software (<http://www.gephi.org>) to produce a relation map of the parameters potentially indicating a diagnosis of GLILD. In this manner, specific associations can be more readily visualized, as can the relative magnitude of the associations from the positions on the map.<sup>9</sup> Of 11 parameters mapped, 6 (splenomegaly, low expression of CD21 on B lymphocytes, low absolute lymphocyte count, low initial serum IgA, hematologic disease [idiopathic thrombocytopenic purpura or autoimmune hemolytic anemia], and liver disease) “mapped”

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with patients with GLILD and not with control subjects; the positive and negative predictive values were 69% and 88%, respectively.<sup>9</sup> The 2 studies agree that splenomegaly is an important parameter and therefore likely an important clinical finding toward establishing a diagnosis of GLILD. Although the network analysis mapping model used by Hartono et al<sup>9</sup> is attractive in its utility, only 11 of the 26 patients (42%) mapped within the physical boundary of the map of the 6 parameters, in addition to 2 control subjects (10%). Even including the additional 8 patients near the map boundary, only 73% of patients were identified (and 1 additional control subject).<sup>9</sup> The investigators noted a relatively good negative predictive value (88%), but this means that 10% to 15% (using data from the map) of patients without GLILD could be misidentified and subjected to therapies with potential significant morbidities.<sup>9</sup>

The answer to the original question raised in the title of this report is “possibly.” Depending on the model, we have a positive predictive value of 69% to 85% and a negative predictive value of 88% to 90%. It would be interesting to use the 2 models with the 2 sets of study subjects to determine how well the models function. Combining the datasets to produce larger numbers also could yield data that might produce better results. A major limitation of the 2 studies is that neither performed “prospective” analyses for establishing a “new” diagnosis of GLILD. Therefore, the main question posed cannot be answered in the affirmative at this time, but we are taking steps in the direction of making an earlier diagnosis of GLILD. Perhaps genetic studies might indicate specific risk polymorphisms? Even with the diagnosis, we still need to determine which therapeutic interventions will be best to use.

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