In many parts of the world, tuberculosis effusion remains the most common cause of pleural effusion, and it can be secondary either to a primary infection or reactivation tuberculosis (TB).\textsuperscript{1,2} When infection occurs early in life, tuberculous pleurisy with effusion follows the primary infection within weeks or months. The pathogenesis is rupture of a subpleural component of the primary infection and delivery of tubercle bacilli into the pleural space, with inflammation and seeding of foci over the visceral and parietal pleura. In the past, this affected mostly adolescents and young adults. More than 50% of patients not treated with appropriate anti-TB medication will develop active TB within 5 years.\textsuperscript{3,4} An increasing proportion of pleurisy with effusions occurs in older individuals with chronic pulmonary TB, often with complicating comorbid illnesses such as cirrhosis or congestive heart failure to which the effusion is mistakenly attributed.\textsuperscript{4,5}

The diagnosis of tuberculous pleural effusion is made by identifying the existence of tubercle bacilli in the sputum, the pleural fluid, or the pleural biopsy specimen, or by demonstrating the existence of granulomas in the pleura.\textsuperscript{6,7} However, there are several difficulties in the diagnosis of TB, such as specimen collection, low sensitivity of detection method and the time delay in waiting for culture results. Studies on the pathogenesis indicate that only a few organisms may gain access to the pleura in the early stage of tuberculous infection, and cause a hypersensitivity response in the presence of cell-mediated immunity.\textsuperscript{8,9} Therefore, the number of organisms in pleural fluid for tuberculous pleural effusion is very small. In the absence of concurrent pulmonary TB, the diagnosis of pleural TB requires thoracentesis and even pleural biopsy.\textsuperscript{10}

In early postprimary pleurisy with effusion, the acid-fast stain of the fluid sediment is seldom positive, the culture is positive in 25–30% of cases, pleural needle biopsy yields granulomas in 75%, and culture of a needle biopsy specimen may be positive even in the 25% of cases with nonspecific pleuritis on histologic examination.\textsuperscript{4,5} Cases complicating chronic pulmonary TB more often have positive pleural acid-fast smears (50%) and positive cultures (60%) but are less likely (25%) to demonstrate granulomas on pleural biopsy.\textsuperscript{4,5} Repeat pleural biopsy may be necessary to establish the diagnosis, and a small open pleural biopsy or pleuroscopy is diagnostic in virtually all cases.

The combination of microscopic examination and culture of pleural biopsy specimens was reported to increase the diagnosis rate; however, it was time consuming. Thus, for obtaining a rapid and accurate diagnosis of pleural TB, including polymerase chain reaction (PCR) testing of pleural effusion specimens, many commercial and in-house nucleic acid amplification tests (NATs) have been developed and reported with variable results. Why have the previous studies shown highly variable results regarding the usefulness of NATs? First, different in-house NAT methods with different primers to detect \textit{Mycobacterium tuberculosis} in pleural fluid samples were used. Second, small study populations were enrolled. Third, diverse criteria were used for diagnosis of pleural TB. In many studies, only the culture-positive cases were included in the pleural TB group.\textsuperscript{11–14} Because cases with positive cultures for \textit{M. tuberculosis} represent a relatively small portion of all the cases of pleural TB, and because the sensitivity of \textit{M. tuberculosis} PCR testing largely depends on the bacillary load, the sensitivity for the
study group of patients with culture results positive for *M. tuberculosis* does not reflect the sensitivity for all patients with pleural tuberculosis. For these reasons, there has been no consensus regarding the usefulness of *M. tuberculosis* PCR in the diagnosis of tuberculous pleural effusion. Basically, the low bacterial load in pleural effusion seems to limit the clinical utility of PCR testing.  

In this issue, Liu et al.\(^{16}\) evaluate the clinical utility of *M. tuberculosis* nucleic acid amplification testing for pleural effusion specimens with negative acid-fast smears. The diagnosis of TB pleurisy was based on culture, clinical, and biopsy findings. Of the 163 patients enrolled, the sensitivity and specificity of PCR for TB pleurisy were 43.4% (23/53) and 95.5% (105/110), respectively. Among 53 TB pleurisy patients, 27 received pleural biopsy and 55.6% (15/27) disclosed chronic granulomatous inflammation with or without caseous necrosis. Of these 27 patients, PCR and culture of pleural fluid were positive in 12 (44.4%) and 3 (11.1%) patients, respectively. Among 12 of the 27 TB pleurisy patients without granulomatous inflammation, PCR was positive in 4 patients. Moreover, the sensitivity of diagnosis increased to 70.3% if PCR was combined with pleural biopsy. The authors concluded that PCR alone has limited value in the diagnosis of TB pleurisy with negative smear. By using a combination of PCR with pleural biopsy, the value for early diagnosis of TB pleurisy in patients with negative smears can be increased. The range of sensitivities for previous studies using in-house PCR with the same DNA target (a target sequence of IS6110 in the genome *M. tuberculosis*) have been 60–81%, and of specificities 90–100%.\(^{17–19}\)

In addition to the detection of organisms, combined analysis with other tests such as adenosine deaminase, absolute lymphocyte count, interferon-gamma, and specific antibodies against mycobacterial glycolipid in pleural fluid could be more helpful in the diagnosis of tuberculous effusion, although these assays are not routinely available in many countries.\(^{20,21}\)

In conclusion, PCR for pleural effusion should not be relied on as a single test. When used in combination with pleural biopsy or other tests, the value of PCR in the early diagnosis of TB pleurisy in patients with negative smears can be heightened.

### References


