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Performance evaluation of the Cobas TaqMan MTB assay on respiratory specimens according to clinical application

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ABSTRACT

Objective: To evaluate the performance of the Cobas TaqMan MTB assay (Cobas assay) with respect to its clinical application.
Methods: This was a retrospective analysis of 1154 results from 1034 patients for whom mycobacterial cultures and the Cobas assay were performed simultaneously. Based on the patient medical records, two categories of clinical application were defined: (1) the diagnosis of patients with a high probability of pulmonary tuberculosis according to clinical and radiological features ($n = 128$), and (2) the exclusion of tuberculosis in clinically indeterminate patients ($n = 1026$). Standard culture was used as the reference method.
Results: The sensitivity of the Cobas assay for the detection of *Mycobacterium tuberculosis* was 70.4% (95% confidence interval (CI) 49.7–85.5%) for category 1, but only 25.0% (95% CI 4.5–64.4%) for category 2. The specificity was ≥95.0% for both categories. The positive predictive value was 79.2% (95% CI 57.3–92.1%) for category 1 and 33.3% (95% CI 6.0–75.9%) for category 2, while the negative predictive value was 92.3% (95% CI 85.0–96.4%) for category 1 and 99.4% (95% CI 98.7–99.8%) for category 2.
Conclusions: The results of this study indicate that Cobas assay results must be interpreted carefully according to the clinical purpose of the assay.

Introduction

Tuberculosis (TB) is a major global public health problem and has one of the highest mortality burdens of any infectious disease. According to the 2015 World Health Organization (WHO) Global Tuberculosis Report, South Korea is categorized as a country with an intermediate TB burden. The TB incidence rate was 86 per 100 000 people in 2015, while the TB mortality rate was 3.8 deaths per 100 000 people in 2015 (World Health Organization, 2015). To prevent person-to-person transmission and reduce morbidity and mortality, rapid diagnosis and early treatment are essential (Dye and Williams, 2010). The US Centers for Disease Control and Prevention (CDC) have recommended that nucleic acid amplification (NAA) tests be performed on at least one respiratory specimen from every patient with symptoms or signs of TB (MMWR, 2009).

The Cobas TaqMan MTB assay (Cobas assay) (Roche Diagnostics, Basel, Switzerland) is one of the most widely used real-time PCR assays (UNITAID, 2015). The Cobas assay uses primers and TaqMan hydrolysis probes that bind to specific regions with highly conserved 16S rRNA sequences (UNITAID, 2015). Many studies have characterized the performance of the Cobas assay, with results varying from study to study (Bloemberg et al., 2013; Horita et al., 2015; Huh et al., 2015; Jonsson et al., 2015; Kim et al., 2011; Yang et al., 2011). Some studies have suggested that this variance is due to the acid-fast bacilli (AFB) smear status, variable specimen types, and incidence of TB (Huh et al., 2015; Jonsson et al., 2015). However, no study has yet addressed the performance of this assay in the context of different clinical purposes, and more specifically for diagnosis when TB is strongly suspected versus when TB is considered to be less likely.

This retrospective study was conducted to evaluate the performance of the Cobas assay on respiratory specimens

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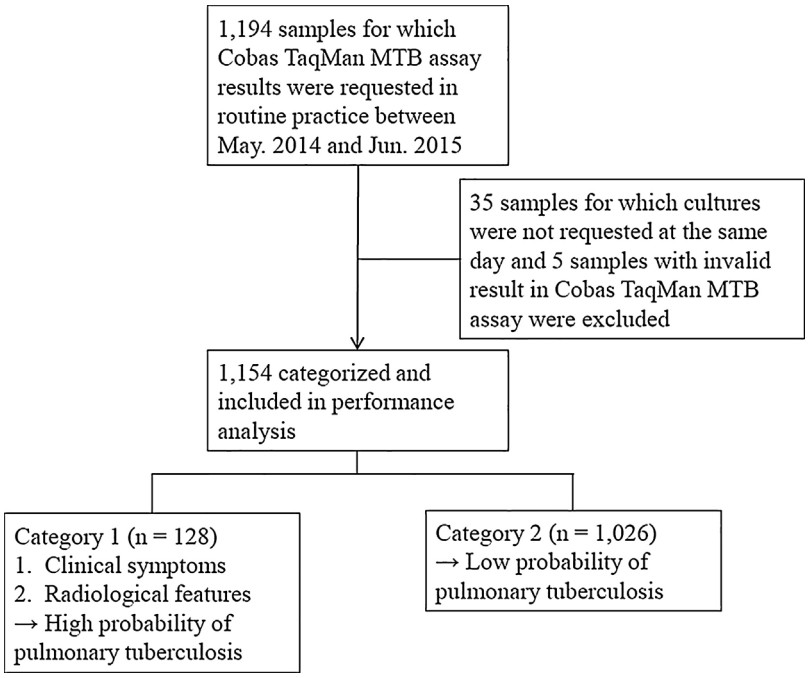

Figure 1. Flow diagram outlining patient enrollment and stratification for the analysis of the diagnostic performance of the Cobas TaqMan MTB assay.

according to the physician's assessment of the likelihood of TB on initial examination and according to clinical and laboratory diagnoses of TB in real clinical settings.

Methods

Study design

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, South Korea (#2016-08-170). A total of 1194 respiratory specimens were evaluated using the Cobas assay between May 2014 and June 2015, and the results were analyzed retrospectively. Thirty-five samples for which cultures were not requested on the same day and five samples with invalid Cobas assay results were excluded (Figure 1).

Patient medical records, AFB smear findings, and mycobacterial culture results were reviewed. The clinical application of the Cobas assay was identified in the patient medical records and the samples were divided into two categories, as outlined below. All cases were categorized independently by two doctors. All disagreements in data interpretation required final agreement between doctors.

Category 1 consisted of samples from patients with a high probability of pulmonary TB for whom a rapid diagnosis of TB was needed. High-probability pulmonary TB was defined as the presence of clinical symptoms (cough, sputum, fever, night sweats, or weight loss) and radiological features highly indicative of pulmonary TB on chest X-ray or a chest computed tomography, such as patchy or nodular shadows and cavitation (Jeong and Lee, 2008).

Category 2 consisted of samples from patients with a clinically low probability of pulmonary TB, i.e., patients for whom a diagnosis of pulmonary TB was not considered to be highly probable, but for whom a diagnosis of pulmonary TB could not be reliably excluded by clinicians. The patients in this clinical low-probability group were either asymptomatic or did not have any radiological features highly suggestive of TB. This group also included samples from patients with an AFB smear-positive specimen, for whom *Mycobacterium tuberculosis* (MTB) needed to be differentiated from non-tuberculous mycobacteria (NTM).

Specimen processing

All respiratory specimens were decontaminated with 2% *N*-acetyl-l-cysteine–sodium hydroxide (NALC–NaOH), followed by centrifugation at 3000 *g* for 20 min. After resuspension of the resulting sediments in phosphate buffer, acid-fast staining smears were prepared. Each mycobacterial culture was prepared by

Table 1
Performance of the Cobas TaqMan MTB assay according to smear status; results are presented as No./total No., % (95% CI).

	Total (n = 1154)	Smear result	
		Smear-positive (n = 38)	Smear-negative (n = 1116)
Sensitivity	21/35	13/13	8/22
	60.0 (42.2–75.6)	100.0 (71.7–100.0)	36.4 (18.0–59.2)
Specificity	1110/1119	24/25	1086/1094
	99.2 (98.4–99.6)	96.0 (77.7–99.8)	99.3 (98.5–99.7)
PPV	21/30	13/14	8/16
	70.0 (50.4–84.6)	92.9 (64.2–99.6)	50.0 (25.5–74.5)
NPV	1110/1124	24/24	1086/1100
	98.8 (97.9–99.3)	100.0 (82.8–100.0)	98.7 (97.8–99.3)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.