Comparison between Xpert MTB\RIF Threshold Cycle Value and Smear Microscopy of Bronchial Lavage for Diagnosis of Pulmonary Tuberculosis in Bronchoscoped Patients

A Thesis

Submitted for partial fulfillment of master degree
in Chest Diseases

By

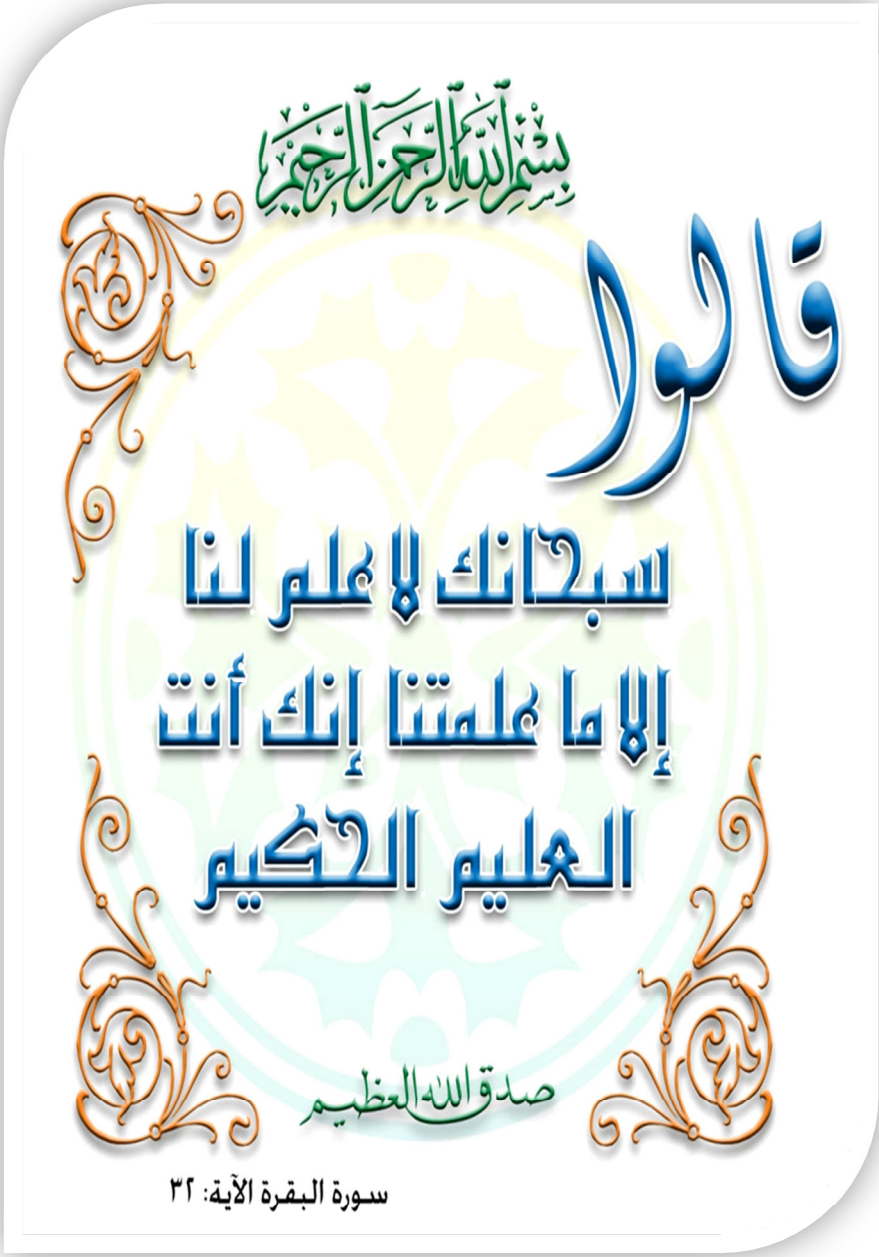
Gehad Youssef Ahmed Salem
M.B.B.Ch., Alexandria University.

Under Supervision of

Prof. / Magdy Mohammed Khalil
Professor of Chest Diseases
Faculty of Medicine, Ain Shams University

Prof./ Hesham Atef Abd-Elhalim
Professor of Chest Diseases
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2020


بسم الله الرحمن الرحيم
قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم
صدق الله العظيم
سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to **Allah**, *the* ***Most Beneficent*** *and* ***Merciful,*** *who gave me the strength to accomplish this work.*

My deepest gratitude to my supervisor, **Prof. Magdy Mohammed Khalil,** *Professor of Chest Diseases, Faculty of Medicine, Ain Shams University, for his valuable guidance and expert supervision, in addition to his great deal of support and encouragement. I really have the honor to complete this work under his supervision.*

I would like to express my great and deep appreciation and thanks to **Prof./ Hesham Atef Abd-Elhalim,** *Professor of Chest Diseases, Faculty of Medicine, Ain Shams University, for her meticulous supervision, and her patience in reviewing and correcting this work.*

Special thanks to my **Parents,** *my* **Husband** *and all my* **Family** *members for their continuous encouragement, enduring me and standing by me.*

✍ *Gehad Youssef Ahmed Salem*

List of Contents

List of Tables

List of Figures

List of Figures *(Cont...)*

List of Abbreviations

Abb.	Full term
AFB	*Acid-Fast Bacilli*
ART	*Antiretroviral Therapy*
BAL	*Bronchoalveolar Lavage*
CBC	*Complete Blood Count*
CDC	*Centers for Disease Control*
CT	*Computed Tomography*
Ct	*threshold cycle*
CBNAAT	*Cartridge Based Nucleic Acid Amplification Test*
DOT	*Directly Observed Therapy*
DST	*Drug Susceptibility Testing*
EMB	*Ethambutol*
FDA	*Food and Drug Administration*
GX	*GeneXpert*
IGRAs	*Interferon-Gamma Release Assays*
INH	*Isoniazid*
LJ	*Lowenstein-Jensen*
LPA	*Line Probe Assay*
MDR	*Multi-Drug Resistant*
MDR TB	*Multidrug-Resistant Tuberculosis*
MTUBC	*Mycobacterium Tuberculosis Complex*
NAA	*Nucleic Acid Amplification*
NAATs	*Nucleic Acid Amplification Tests*
NTM	*Non Tuberculous Mycobacterial*
PCR	*Polymerase Chain Reaction*

List of Abbreviations *(Cont...)*

Abb.	Full term
PPV	*Positive Predictive Value*
PTB	*Pulmonary Tuberculosis*
PZA	*Pyrazinamide*
RIF	*Rifampicin*
ROC	*Receiver Operating Characteristic*
rpoB	*RNA Polymerase B Subunit*
rt-PCR	*Real-Time Polymerase Chain Reaction*
TB	*Tuberculosis*
TTD	*Time-to-Detection*
WHO	*World Health Organization*

Introduction

Tuberculosis (TB) is a medical, social and economic disaster of immense magnitude that occurs all over the world**(Tag El-Din, et al., 2015)**. Early diagnosis and treatment is necessary for TB control. The End TB Strategy-specific targets for 2030 worldwide: 90% reduction in the mortality rate and 80% reduction in TB incidence **(ElBouhy, AbdelHalim, & Boshra, 2020).** Globally, the average rate of decline in the TB incidence rate was 1.4% per year in 2000−2016, and 1.9% between 2015 and 2016. This needs to accelerate to 4–5% per year by 2020 to achieve the milestones for reductions in cases and deaths set in the End TB Strategy **(World Health Organization, 2017).**

According to position of Egypt, The World Health Organization (WHO) classified Egypt as a country with middle/low level of TB prevalence. In 2016,the estimated TB burden was 14 cases per 100,000 population who had smear positive active pulmonary tuberculosis (PTB) **(World Health Organization, 2017).**

Early diagnosis and prompt treatment remain the hallmark of TB control. Smear microscopy and culture techniques have been the mainstay of pulmonary TB (PTB) diagnosis for several decades now **(Prakash et al., 2018).**

Smear microscopy for acid-fast bacilli (AFB) is widely implemented method for quantifying mycobacterial load at the time of diagnosis. In addition, since patients who are sputum smear-positive are more likely to transmit tuberculosis **(Boehme et al., 2010; Wagih, Halim, & El Basuni, 2020).** Smear status is used to evaluate the infectiousness of patients in the context of public health contact management and screening **(Fradejas et al., 2018).**

Several studies have demonstrated that tuberculosis transmission can occur from smear-negative patients, with a minimum relative transmission rate estimated to 0.22 **(Kulaga, Behr, & Schwartzman, 1999).** The isolation is maintained until 3 serially collected sputum smears are acid-fast bacilli negative.

Since 2013, the World Health Organization has recommended the Xpert MTB/RIF as the initial test for tuberculosis microbial diagnosis for patients with suspected pulmonary tuberculosis including new cases; for retreatment cases; for suspected multidrug-resistant (MDR) tuberculosis; and for HIV-infected patients with suspected tuberculosis because of its excellent sensitivity and specificity associated with an

extremely short turnaround time **(Ahmed et al., 2020; WHO, 2013a)**.

The GeneXpert MTB/RIF (GX) estimates mycobacterial load by measuring the threshold-cycle (Ct) of multiple probes targeting the rpoB gene. Several small studies have shown that Ct values correlate well with the bacillary load in respiratory specimens compared with conventional methods, such as colony counts on solid agar growth media or measures of Time-to-Detection (TTD) in liquid culture **(Marlowe et al., 2011)**. However, there are few data about its diagnostic value for predicting the smear status in patients with pulmonary tuberculosis **(Blakemore et al., 2011; Fradejas et al., 2018; Opota et al., 2016; Theron et al., 2012)**.

The source of test samples has a significant influence on the performance of all diagnostic assays. Sputum, either spontaneously expectorated or induced, has been often linked to a low diagnostic yield for detecting M. tuberculosis, due to insufficient sample quantity and/or quality **(A. J. Meyer et al., 2017).** Although bronchoscopy is considered to be an invasive and costly technique that requires specific training of the infectious disease physician, it has been recommended for

patients with suspected pulmonary TB in regions with a high frequency of TB **(Iyer et al., 2011),** or at least for those who failed to spontaneously produce sputum **(Lee et al., 2013).** Recent studies have found that when combined with Xpert MTB/RIF, BAL could provide accurate results in detecting early-stage pulmonary TB, in particular in smear-negative patients **(Theron et al., 2013).**

Since infection control programs and contact tracing guidelines rely upon the smear status, further studies are needed to clarify how patients who undergo only GX testing should be managed. Thus, we assess the utility of GX Ct values as a rule-in test for smear positivity status.

Aim of the Work

The current study aims to assess the utility of GeneXpert threshold cycle values compared to smear status in bronchial lavage fluid sample in a suspected patient unable to give sputum or give hemoptysis in patients with pulmonary tuberculosis in Kafr-Elsheikh chest hospital to determine the potential added value of GX-Ct for tuberculosis diagnosis.

.

Chapter (1)
Pulmonary Tuberculosis

I. Introduction:

Tuberculosis (TB) has afflicted people for millennia and, unfortunately, despite effective treatment was the leading cause of death from an infection in 2016, killing 1.7 million people globally. TB is also a common cause of disease and death among people living with HIV **(El Khéchine & Drancourt, 2011).** Egypt is a middle/low TB burden country. Egyptian Ministry of Health and Population adopted the latest National Tuberculosis Control Program since September 2007 and showed progressive decrease in the incidence of TB from 21/100 000 populations in 2006 to 13/100 000 populations in 2017; TB prevention, diagnosis, and treatment saved 37 million lives **(Ibrahem & Elhelbawy, 2020).**

Recent estimates suggest that one-quarter of the world's population is infected with TB and more than 10 million people develop active disease each year. Infection occurs primarily through airborne transmission and usually requires prolonged exposure to a person with pulmonary TB.