

## Pulmonary Tuberculosis and COVID-19 Co-infections in Lahore, Pakistan: A retrospective cohort study

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**Abstract:** Tuberculosis (TB) and Coronavirus disease-2019 (COVID-19) are two major re-emerging diseases that poses significant health issues. Increase in disease burden and subsequent misuse of anti-TB drugs has become a serious health challenge. Early diagnosis followed by antibiotic susceptibility testing can lower the increase in occurrence of multidrug resistant TB. The present study was designed to compare the performance of GeneXpert and microscopy to the gold standard (culture) in sputum and broncho-alveolar lavage samples ( $n = 2862$ ) and to check the prevalence of COVID-19 coinfections among the TB patients in Lahore, Pakistan. Results of the present study showed that, a total of 642 samples were found positive for TB via BD MGIT Liquid cultures method, 483 using Ziehl-Neelsen staining technique, 507 with fluorescent staining technique and 663 using GeneXpert respectively. In overall, 23% prevalence of TB was seen in the current study. The positive ratio of TB using GeneXpert in broncho alveolar lavage samples (24.56%) was more as compare to the Sputum (23.07%). Out of these 663 TB positive patients, a total of 197 were having COVID-19 like symptoms and were tested for COVID-19 using PCR. Among these 197 cases, 13 were found positive for COVID-19, from which 3 were resistant to Rifampicin (Rif). The diagnostic tests like GeneXpert have made improvements in the rapid diagnosis of TB and has high specificity and sensitivity.

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## Introduction

The corona virus diseases-2019 (COVID-19) caused by a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been spreading over the world since December 2019 (Ahmed et al., 2020; Anis et al., 2021). COVID-19 patients with preexisting comorbidities such diabetes, hypertension, and cardiovascular disease seem to be at higher risk of mortality, however few studies have reported that COVID-19 patients are also afflicted with other respiratory infectious diseases like

TB (Kalil et al., 2021). COVID-19 has symptoms that are similar to those of other respiratory infections including TB and influenza. Coinfections with common viral, bacterial, and fungal pathogens are widespread among COVID-19 patients, which might complicate COVID-19 diagnosis and therapy (Ahmed et al., 2022). TB has been the world's most deadly infectious disease for many years prior to the COVID-19 pandemic (Aggarwal et al., 2021; McQuaid et al., 2021).

The TB stands amongst top ten causes of deaths worldwide (Yaqoob et al., 2021). Pakistan ranks 5<sup>th</sup>, amongst high burden countries for TB, globally (Abubakar et al., 2021). The biggest issue in the treatment, prevention and control of TB is drug resistance (Malik et al., 2018). Occurrence of multidrug resistant (MDR) TB is a serious issue which needs to be addressed. New patients of TB have MDR and Rif resistance rate of up to 4.2% and 16% among those who previously received treatment (Maori et al., 2021). There is another issue of emergence of extensive drug resistance (XDR); which is a more complicated form of MDR-TB as it also shows resistance to fluoroquinolones and at least one additional group A drug (Gautam et al., 2021).

The most important first line drug used to treat TB is Rif and is considered as a key in determining the efficacy of different treatment regimens adopted for TB (Abubakar et al., 2021). The rapid spread and emergence of drug resistant TB represents a challenge for healthcare systems (Kim et al., 2021). Culture for TB diagnosis are the gold standard in diagnosing TB and as compared to the solid agar media cultures, the liquid agar cultures (e.g. MGIT) are relatively faster to get the diagnosis within 7-10 days but these methods are still time consuming as more time efficient tests can aid in early diagnosis (Jabbar et al., 2006). In 2011, WHO endorsed the use of a fully automated molecular test utilizing the real-time polymerase chain reaction (PCR) and is called Xpert MTB/RIF assay (WHO, 2011). It has the ability to simultaneously detect MTB and resistance mutations in the *rpoB* gene against Rif (Andama et al., 2021).

Keeping in mind the COVID-19 pandemic versus TB scenario, everyday increase in the prevalence of TB and higher antimicrobial resistance (AMR) rates in Pakistan, the present study was conducted to see the prevalence of pulmonary TB, COVID-19 coinfections among symptomatic TB patients, and to determine the frequency of Rif resistance in *Mycobacterium Tuberculosis*.

## Materials and Methods

A retrospective cohort study was conducted on pulmonary TB patients, who visited the TB clinic of a tertiary care hospital in Lahore, Pakistan during the duration of 3<sup>rd</sup> August 2021 to 20<sup>th</sup> April 2022. Broncho-alveolar lavage (BAL) and sputum samples were collected initially from the patients initially for the diagnosis of TB. To avoid contamination, sterile containers were provided for sample collection. After collection, samples were immediately transported to biosafety level III laboratory, by following standard protocols.

A total of 2862 samples from the suspected pulmonary TB patients. From the total samples 171 were BAL while other 2691 were sputum. The socio demographic characteristics of patients were also noted before the collection of samples. All of the samples were proceeded for BD MGIT liquid culture system, fluorescent microscopy, ZN staining and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) GeneXpert.

### **Processing of samples for staining and TB cultures**

The samples were proceeded for TB culture using BD MGIT liquid culture media. After inoculation of samples in the liquid culture system the tubes were incubated and the remaining samples were processed for ZN and fluorescent staining. ZN staining technique was used to differentiate the acid-fast bacteria from other bacteria. Acid fast bacilli (AFB), a member of genus *Mycobacterium* is a type

of bacteria which remains unstained by gram stains used in gram staining, and they can only be visualized by using acid fast or ZN staining (Kumar et al., 2021).

For fluorescent staining, an equally distributed 2×4 cm smear was made in the middle of a glass slide. Sample must be dry during smear preparation or leave it for air dry. Heat fix at 40-60 °C. Place the slides on staining rack with 1cm apart from each other. Pour auramine rhodamine for 20 minutes. Wash with tap water. Pour decolorizer (acid-alcohol) for 2-3 minutes. Use tap water to wash the smear. Pour the smear with methylene blue for 2-3 minutes. Lastly, air dry the slide (Maori et al., 2021).

### **Testing on CBNAAT GeneXpert**

The collected samples were treated with lysing buffer and shaking well on vortex mixer and was allowed to liquefy for 10-20 minutes. Buffered sample was shifted to MTB/RIF Assay cartridge by dropper. Cartridge was loaded on GeneXpert instrument by scanning the barcode present on cartridge. This procedure takes less than two hours for one test (Maori et al., 2021).

### **MTB culture sensitivity testing**

MTB culture was performed by Mycobacteria Growth Indicator Tube (MGIT) which was a tube system that decides whether or not TB bacteria thrives in the presence of anti-TB medications. If the bacteria multiply, they become resistant to the treatments since the drugs were unable to inhibit their growth. The TB medications function if the germs do not proliferate. In this scenario, experts and medical personnel believe the bacteria are 'susceptible' to the medications.

### **COVID-19 Test**

Corona virus detection was done using real time PCR. Nasopharyngeal (NP) swabs were collected from the the TB positive and COVID-19 suspected patients. PCR test was run in two steps, first one was DNA extraction and second was amplification. The DNA extraction was performed on Abbott RealTime SARS-CoV-2 assay. In order to qualitatively detect SARS-CoV-2 nucleic acid in NP swabs, the Abbott RealTime SARS-CoV-2 assay is a real-time reverse transcriptase polymerase chain reaction (PCR). TaqPath COVID-19 combo kit used which target 3 sites of COVID genome including ORF1a and ORF1b, Spike protein and N protein.

### **Data presentation and statistical analysis**

For statistical analysis, the Microsoft Excel (version 2017) and SPSS (version 21) software were used. At first, the data was entered in MS excel sheet and SPSS separately. Descriptive statistics was applied to get the summaries of tested parameter. Chi square test was applied to see that is there any association between the type of clinical samples and TB diagnosis using GeneXpert assay, and to see is there any significant association between TB/COVID-19 coinfections. A *P*-value of < 0.05 was considered as significant.

## **Results**

### **3.1. Collection of samples**

A total of 2862 samples were collected from suspected patients of TB. The patients were suspected for suffering from TB based on their sign and symptoms and their referral to TB clinics after radiological examination (chest X-Rays). Overall, out of 2862 collected samples 663 (23%) were found positive for TB. While sample wise distribution showed 23% (621/2691) and 24% (42/171) from sputum and BAL respectively. The demographic characteristics of studied population has been shown in **Table 1**, while the **Table 2** shows the prevalence of collected samples in relation to positive cases.

**Table 1.** Socio demographic characteristics of TB patients (GeneXpert).

Characteristics		Total (n = 2862)	Tuberculosis (n = 663)
Age (Years)	10-19	123	21 (3.16%)
	20-30	1536	294 (44.34%)
	31-49	942	321 (48.41%)
	>50	261	27 (4.07%)
Gender	Male	2526	621 (93.66%)
	Female	336	42 (6.33 %)
Residence area	Urban	1511	438 (66.06%) *
	Rural	1351	225 (33.93%)
Education status	Educated	1668	285 (42.98%)
	Uneducated	1194	378 (57.01%) **

\*The prevalence of TB was 1.9 times higher in the urban areas as compare to rural areas. \*\* The prevalence of TB was 1.32 times higher in uneducated population as compare to the educated ones.

**Table 2.** Prevalence of positive TB (GeneXpert) cases from different samples.

Type of sample	Total number of samples	Positive Samples for TB	P-value
Sputum	2691	21.69 % (n = 621)	> 0.05
Broncho-alveolar Lavage (BAL)	171	1.46 % (n = 42)	
Total	2862	23.16% (n = 663)	

### 3.2. Results of staining and liquid culture media

Out of 2862 samples, a total of 483 samples were found to be positive for ZN-staining. Fluorescent stain is little more specific as compared to conventional ZN-staining. Out of 2862 samples, 507 samples were found positive for fluorescent staining. While results of the MGIT liquid culture system showed that a total of 642 samples were positive for TB. The difference between the positive ratio of tuberculosis using different techniques has been shown in **Table 3**.

**Table 3.** Positive samples ratio of various techniques used to detect TB in different sample sources.

Testing techniques	Sputum (n/%)	Broncho-alveolar lavage (n/%)	Total (n/%)
BD MGIT Liquid cultures	624 (94.11)	18 (2.71)	642 (96.83)
ZN staining	468 (70.58)	15 (2.26)	483 (72.85)
Fluorescent staining	483 (72.85)	24 (3.61)	507 (76.47)
GeneXpert	621 (93.66)	42 (6.33)	663

Four drugs were tested for positive MTB liquid media culture, from which only streptomycin has shown the highest resistance (17.7%). A total of 22 (3.42%) isolates have shown the MDR pattern with all four drugs resistance while 4.2% of cases were resistant to both Rif and isoniazid. Among the tested isolates, no extensive drug resistance case was found. The sensitivity pattern of tested isolates has been shown in **Table 4**.

**Table 4.** The antibiotic susceptibility pattern of *Mycobacterium tuberculosis*.

Tested Drug	Sensitive (n/%)	Intermediate (n/%)	Resistance (n/%)
Rifampicin *	589 (91.7)	11 (1.5)	42 (6.5)
Streptomycin **	511 (79.6)	17 (2.6)	114 (17.7)
Isoniazid *	523 (81.46)	34 (5.2)	85 (13.2)
Ethambutol ***	594 (92.5)	9 (1.4)	39 (6.0)

\* Drug concentration: 1 mg/L. \*\* Drug concentration: 0.25 µg/ml. \*\*\* Drug concentration: 5 mg/L.

### 3.3. Results of GeneXpert detection

Results of GeneXpert assay showed that, a total of 663 patients were positive for tuberculosis via GeneXpert assays as shown in **Table 5**. From these 663 cases, 42 cases were found resistant against Rifampicin.

**Table 5.** Prevalence of Rifampicin resistant cases by GeneXpert.

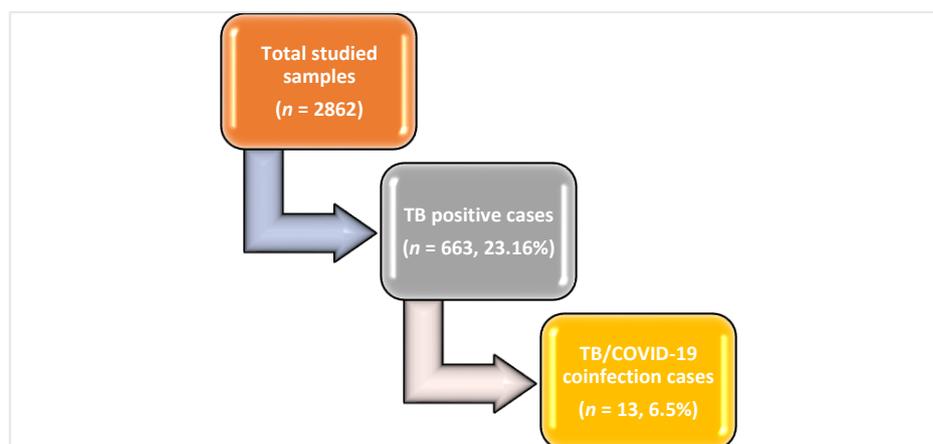
Type of sample	MTB detected in GeneXpert	Rif. resistant cases	P-value
Sputum	621 (93.66%)	39 (5.88%)	> 0.05
Broncho-alveolar Lavage (BAL)	42 (6.33%)	03 (0.45%)	
Total	663	42 (6.33%)	

### 3.3. Results of Corona virus PCR

Out of these 663 MTB positive patients 197 were having symptoms of COVID-19. All 197 cases were tested for COVID-19 via PCR, from which a total of 13 cases were found positive for COVID-19 as described in **Table 6**. Among these 13 COVID-19 cases, only 3 were found resistant to Rif. **Figure 1** shows the prevalence of TB and COVID-19 among tested population.

**Table 6.** Prevalence of COVID-19 among TB positive and Rif resistant tuberculosis.

COVID PCR	TB positive cases	Rif. resistant cases
Positive	13 (6.5%)	3 (1.5%)
Negative	184 (93.5%)	26 (13.1)
Total	197	29 (14.6%)

**Figure 1.** Prevalence of Tuberculosis among studied population and the prevalence of COVID-19 among TB positive cases.

## Discussion

In recent years, the COVID-19 pandemic has disrupted TB treatment and service delivery, setting back progress against TB in the battle of many years (Tamuzi et al., 2020). Patients with TB generally have underlying co-morbidities and lung impairment, making them on increase risk to acquire severe COVID-19 infection. COVID-19 and TB have symptoms that are similar, such as fever and cough. Because of the fear of COVID-19, this might not only cause diagnostic uncertainty, but it could also increase the stigmatisation of TB patients, particularly in low- and middle-income countries (Gupta et al., 2020; McQuaid et al., 2021). Tuberculosis has turned out to be the most common re-emerging disease worldwide. According to World Health Organization (WHO) the main reason of re-emergence of it is pandemic nature of HIV as poor living standards and increase in multi drug resistance in tubercle bacilli, aids in spreading the disease (Yaqoob et al., 2021). The TB remains the major cause of morbidity and mortality worldwide because of its solitarily irresistible nature. The present study was conducted in the TB clinic at a tertiary care hospital in Lahore, Pakistan to see the overall prevalence of TB and Rif resistant TB among the tested population, and to overview the prevalence of COVID-19 coinfections among symptomatic TB positive patients.

According to different studies, for smear positive samples, sensitivity and specificity for TB found to be > 97%, while it may be as high as 70–80% for smear negative samples (Maori et al., 2021; Saleem et al., 2018; Shrestha et al., 2018). Therefore, the WHO endorsed its use for the detection of pulmonary TB (Kim et al., 2021). The MTB/RIF test is based on real time PCR that detects specific DNA sequence of MTB in the tested samples. The assay is automated, software based and amplifies 81-bp fragment of *rpoB* gene of MTB to identify mutation in *rpoB* gene. The mutation in *rpoB* gene causes Rif resistance, while the mutation in *katG* and in the promotor region of *inhA* gene causes isoniazid resistance, which are very important drugs for TB treatment (Sweeney et al., 2016). TB has become a major medical issue in under developing countries with poor standard of living, with 60% of adult population getting infected by it (Abubakar et al., 2021). According to international survey, the Nepal is positioned 27<sup>th</sup> for TB cases and the prevalence rate of disease is 40%. Consistently 40,000 patients are suffering from active TB, while 20,000 have irresistible aspiratory infections (Yadav et al., 2020). According to a recently published study from Pakistan, there was a dramatically increased in the use of GeneXpert method for diagnosis of PTB in adults from less than 1% tested alone in 2016, to 81.6% by 2018 (Tahseen et al., 2020). Tahseen et al., (2020) has found a significant increase in cases of PTB (from 64% to 77.3% in tested population) (Tahseen et al., 2020). Results of another study from Lahore, Pakistan has shown 22% prevalence of PTB among the tested population (Arshad et al., 2021). The present study was conducted on the total 2862 samples and the results showed that 663 (23.1%) sample were positive for TB via GeneXpert. From these total samples confirmed by GeneXpert MTB/RIF method, only 483 samples were found positive for AFBs using ZN staining and a total of 507 samples were positive for AFBs using fluorescent staining. The difference in the results was might be because of the high sensitivity and accuracy of GeneXpert MTB/RIF.

Rif works by stopping the DNA-directed RNA synthesis of MTB by working in relation with RNA polymerase subunit (Maori et al., 2021). According previous researches, 95% strains mutation (*rpoB*) of Rif resistance are located in 81-bp region (codons from 507 to 533), which are called as RIF resistance determining region (RRDR). In RRDR, mutations within codon 516,531,526 are responsible for about 90% of Rif-resistant strains (Abubakar et al., 2021; Shrestha et al., 2018; Yadav et al., 2020; Yaqoob et al., 2021). A previous study was conducted to check the resistance patterns of anti-TB drugs in TB patients. From 11-2018 to 01-2019, more than 385 cases were studied. From 385 patients of TB, 225 were found sensitive and 130 were resistance to isoniazid. These results were in accordance with results from other countries who utilized comparative study method (Andama et al., 2021; Guo et al., 2021; Mukhtar and Butt, 2018; Nagu et al., 2021). In a previously published study, authors analyzed the Recurrence of broadly MDR TB in Pakistan and found that the resistance

rate was expanded from 1.5% in 2006 to 4.5% in 2009 ( $p < 0.01$ ) (Atif et al., 2018a; Niaz et al., 2020). In comparison the present study results showed that 42/663 (6.3%) cases were resistant against Rif. The reason behind increase in cases of MDR-TB might be the missed diagnosed or negative smear for TB and subsequently leading it to remain undiscovered which ultimately causes the increase in the cases of MDR-TB. In case of positive smear of TB, there might be a chance that anti-TB drugs show different response and it might be difficult to discover MDR-TB.

Results of the present study showed that the incidence of tuberculosis in males (621/2526 = 24.6%) was 1.97 times higher than in females (42/336 = 12.5%). Similarly, 66.06% (438/1511) of the patients belongs to urban areas and the rest 33.93% (225/1351) belongs to rural areas. The rate of TB was 1.9 times higher in urban than rural areas. A previous study with similar results from Korea (Sotgiu et al., 2009), showed that the percentage of TB cases among male and female was 66.49 to 34.31%. Also, according to WHO's global TB report 2021, TB patients were 56%, 33%, and 11% for adult men, adult women, and children, respectively. The incidence of tuberculosis in males was 1.7 times higher than in females (WHO, 2021).

Both Isoniazid and streptomycin drugs showed higher level of resistance against TB (Atif et al., 2018b). These strains showed resistance to both drugs and accounts for 13-14% resistance percentage, individually. While strains isolated from new and recently treated patients showed 6.6% and 6.4% resistant to streptomycin individually (Abubakar et al., 2021; Maori et al., 2021). According to a previous study from Nepal (Shrestha et al., 2018), which analyzed the difficulties in the conclusion of medication safe TB by the GeneXpert MTB/Rif examine in Nepal and investigate the potential arrangements and confirmed that significant difficulties were deficient preparing, regular force disappointment, trouble in keeping up suitable consistent temperature, module disappointment which is frequently not supplanted in time, issues with alignment and convenient accessibility of cartridges just as proper approaches to store the new cartridges and safe removal of the pre-owned cartridges.

The current study has reported an overall 6.59% of TB/COVID-19 coinfection cases. Among these TB/COVID-19 coinfection cases, the prevalence of Rif. Resistant TB was 23.07%. The reported cases of COVID-19 in Punjab, Pakistan were 1839 in August 2021, which have been decreased upto 130 reported cases on 31<sup>st</sup> December 2021. In April 2022, very low COVID-19 positive ratio was seen ( $n=33$  to  $n=55$ ) in Punjab, Pakistan (MNHRC, 2022). The effect of COVID-19 on TB services has been extensively documented previously (Group, 2022; McQuaid et al., 2021), with a decrease in the number of TB patients reported and handled in most countries as a consequence of a combination of factors including limited access, delayed diagnosis with more advanced forms, and overburdened health systems (Group, 2022). According to the WHO study, the number of TB case reports decreased by 18% between 2019 and 2020 (McQuaid et al., 2021).

## Conclusions

The occurrence of MDR-TB is a serious health issues in Pakistan as well as throughout the world. This may get worse if TB is not detected and treated on time. To prevent the misuse or over-use of anti-TB drugs, it is important to the check the efficacy of different drugs which are being used for the treatment of TB. Appropriate and precise use of drugs play a vital role in the treatment of these types of invasive infections while keeping the issue of resistance to drugs, minimal. During the COVID-19 pandemic, the current study recommends screening for both COVID-19 and TB in patients with COVID-19/TB symptoms in countries with a high TB burden. To improve TB results, COVID-19 co-infection needs a simple approaches and management. In conclusion, to enhance COVID-19/TB co-infection outcomes, structured diagnostic techniques and clinical care are recommended.

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