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DIAGNOSIS OF RIFAMPICIN-RESISTANT TUBERCULOSIS AND BIOMARKER-BASED ASSESSMENT OF DISEASE SEVERITY WITH DENTAL AND PHYSICAL THERAPY FINDINGS IN DISTRICT PESHAWAR

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Abstract

Tuberculosis remains a leading global cause of infectious mortality, with multidrug-resistant tuberculosis (MDR-TB), particularly rifampicin resistance, posing a major therapeutic challenge. Despite the widespread use of molecular diagnostics, the relationship between rifampicin resistance and inflammatory biomarkers remains underexplored. This study assessed rifampicin resistance using the GeneXpert assay and evaluated its association with selected inflammatory markers in pulmonary *tuberculosis*.A total of 150 sputum and 150 blood samples were collected from patients with confirmed pulmonary *Mycobacterium tuberculosis* infection. Sputum samples were examined by Ziehl–Neelsen staining and analyzed using GeneXpert for rifampicin resistance. Blood samples were evaluated for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimer levels.GeneXpert analysis identified 87% non-MDR and 13% MDR cases, with rifampicin resistance detected in 26 samples. Elevated CRP levels were observed in 143 (95.3%) patients, while ESR was increased in 119 (79.3%) cases. In contrast, D-dimer positivity was detected in only 7 (4.7%) patients.In conclusion, CRP and ESR were markedly elevated in GeneXpert-confirmed tuberculosis cases, whereas D-dimer showed limited diagnostic or prognostic relevance. These findings suggest that CRP and ESR may serve as valuable adjunct biomarkers for assessing disease severity in pulmonary *tuberculosis*, complementing molecular diagnostic approaches in clinical practice.

Keywords: *Biomarkers Rifampicin Resistant; Mycobacterium tuberculosis; GeneXpert.*

INTRODUCTION

Tuberculosis (TB) is a contagious disease that is spread by a group of closely related mycobacterial species called *Mycobacterium tuberculosis* (MTB) complex [1]. It is estimated that 9 million new cases of TB occur worldwide in which 1.7 million death occurs among infected people every year because of MTBC and about 1 million people are infected with Multi-Drug Resistant (MDR) strains [2].Tuberculosis is one of the most significant contagious disease worldwide, and the incidence of TB has been increasing globally [3]. TB causes serious health problems throughout the world,

but this disease is mostly present in the poor countries. Mortality of TB is over 95% in low and middle-income countries [4].Among all age groups TB is the most common causes of death and disease. It is assessed that one 3rdpopulation of the globe is infected with latent TBCausative agent for TB disease is *Mycobacterium-Tuberculosis-Complex* (MTBC). *Mycobacterium* species mostly infect lungs causing pulmonary TB [5].

Topographically, more cases of TB in the year 2018 reported in Southeast Asia were 44%, in Africa were 24% and in the Western-Pacific were 18%, with little rates in the Eastern-Mediterranean were 8%, in USA and Europe were also 3%. Eight nations represented 66% of the worldwide aggregate of tuberculosis. The prevalence in India is 27%, in China 9%, in Indonesia 8%, in the Philippines 6%, in Pakistan it is 6%, in Nigeria 4%, in Bangladesh 4% and in South-Africa 3% as per WHO, Global TB report [6]. All around the world, a normal 1.7 billion individuals were infected with TB adherence at risk of developing the infection. The quantity of instances happening every year can likewise be pushed down initially by diminishing the commonness of health-related danger factors for TB [7].

The process of TB infection can be divided into 3 distinct stages. The 1st stage is the transmission of air borne droplets having bacilli from an infected person to a healthy one. Once inside the lungs, bacilli enter and dwell inside alveolar macrophages (AMs) and dendritic cells [8]. At this level, MTB develops under confined tissue. After 6 to 8 weeks of post-infection, DCs have migrated to the site of lymph-nodes where T-lymphocytes are initiated and selected. Excited T-lymphocytes that relocated in the region of disease multiply framing a beginning phase granuloma, where macrophages become initiated to finish intra-cellular bacilli. However, persisting T cell excitation prompts development of granulomas that mark the continuous phase of the disease, where the development and transmission of bacilli into more tissue sites are restricted [9, 10].

The sign and symptoms of TB including an individual constantly coughing for at least three weeks, or under three weeks, or of unsure span, however some individuals are presumptive cases if they are having hemoptysis fever most probably at night, weight reduction, anorexia, dyspnea, chest pain and close contact of TB patient, especially a smear positive patients can co-exist with other conditions such as Patients with Asthma and HIV may develop TB in addition to their chronic illness [11].

M. tuberculosis most commonly target immunocompromised people such as HIV, diabetic, transplanted malnutrition, and cancer etc [12]. The therapy nowadays use for mycobacterial infection are pyrazinamide, isoniazid, ethambutol and rifampicin for a long duration of six to nine month [13]. In 2019 according to the world health organization about 85% of TBcases were successfully treated. However, due to misuse of TB drugs administration emergence of drug resistance in MTB were reported. To control the evolution of antibiotics resistance in MTBthere is a need of following strategy like diagnosis on initial infection, effective drug combination awareness and patient compliance on therapy duration [14].

Conventional light microscopy is a highly specific, simple, and quick method for determining the acid-fast bacilli (AFB) which are used for the routine diagnosis of TB in both PTB (Pulmonary-TB) and EPTB (Extrapulmonary-TB) [15]. The patient's sputum contains 5000 AFB/ml after ZN-staining which is also known as negative on conventional light ZN microscopy while in culture MTBC can grow up. For this purpose, FM or ZN staining is used [16].

For MTBdetection, a solid media is used known as Lowenstein Jensen (LJ) which is an egg-based medium and for their growth, it usually takes 45-46 days. This medium was made by a person named Lowenstein and modified by Jensen. Another modern technique in MTBC diagnosis is GeneXpert MTB/RIF assay that is used for the detection and diagnosis of TB [16]. Inside clinical samples, MTBC is usually detected which is a semi-quantitative real-time polymerase chain reaction.In *M. tuberculosis* Infectionseveral pro inflammatory responses occur in which CRP, ESR and D-dimer are mainly increased, and we should consider a type of biomarkers in the case TB infection. Since MTB is a chronic inflammatory disease, therefore the biomarker c relative proteins (CRP), Erythrocyte Sedimentation Rate (ESR) are valuable, in determining the severity of the disease [17].

Therefore, for the present research work has been design to investigate co relation CRP, ESR and D-Dimer among MDR, TB patients to assess the severity of diseases based on biomarker. This study aims to evaluate the rifampicin resistance in *Mycobacterium tuberculosis* and further analysis of biomarkers for detection of severity of pulmonary tuberculosis based on elevation CRP, ESR and D-Dimer, while the objectives are to,

MATERIAL AND METHOD

The research was planned to be a cross-sectional study in a hospital, which has to be carried out on patients with pulmonary tuberculosis. 300 samples were gathered, comprising of sputum and blood samples, of patients visiting a tertiary care teaching hospital in Peshawar. The research was conducted using ethical approval of the concerned institutional review board and informed consent of all the participants was taken before collecting samples. The study did not violate patient confidentiality [18].

The study included patients with verified infections of *Mycobacterium tuberculosis* of the lungs and who were already under combination therapy of anti-tuberculosis. All people of different ages and both sexes could participate. Extrapulmonary tuberculosis patients and those who did not take combination therapy were eliminated. The structured questionnaire was used to record the basic demographic data (age and gender). Inflammatory and coagulation biomarkers were also taken into consideration in the study, since tuberculosis is linked to the strong pro-inflammatory reactions.

Sputum specimens were put into sterile-containers and subjected to Ziehl-Neelsen staining to identify acid-fast bacilli microscopically and then graded as per the standard principles. Molecular identification of M. tuberculosis and rifampicin resistant was done using GeneXpert MTB/RIF assay. The inflammatory biomarkers such as CRP, ESR, and D-dimer were assessed in blood samples utilizing the standard laboratory protocols. CRP was evaluated by qualitative and quantitative procedures, ESR was evaluated by the standard sedimentation procedure and D-dimer level was assessed by means of an automated immunoassay system. The statistical analysis was done through the use of suitable parametric and non-parametric tests to determine the relationships between the microbiological results and the level of biomarkers.

RESULTS

All individuals who presented with symptoms were suspected of having pulmonary TB. Sputum samples were collected for PTB illness testing. A total of 150 first-morning sputum specimens were collected from patients attending Prime hospital Peshawar. Specimens were gathered in sterile, leak-proof, disposable, laboratory-approved containers that were suitably labeled. The study was conducted from January 2023 to July 2023. All obtained samples were immediately taken to the laboratory and processed.

The collected sample were further processed for Zn Staining for M. tuberculosis. All 150 samples received were Zn positive. After Zn Staining the samples were further send for GeneXpert assay. Among 150 positive sputum smear AFB 1+ are 47, AFB 2+ 23 and AFB 3+ 47 as presented in Figure 1.

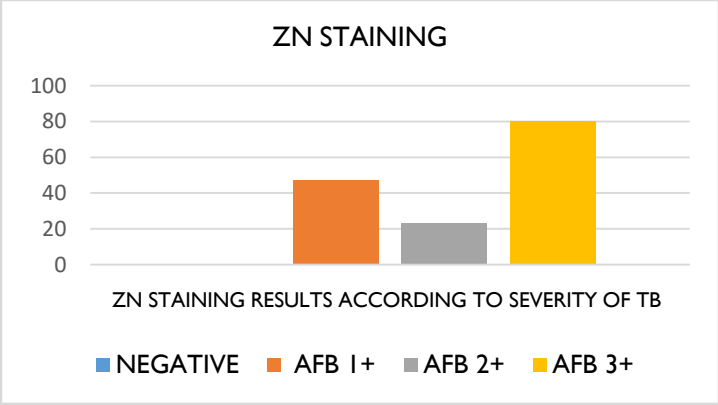

Figure 01: Zn Staining of Sputum sample.

Gender wise Distribution of MTB patients via GeneXpert Assay

In the table below, the severity of 79 male MTB patients was examined using GeneXpert, and the findings of high, medium, low, very low and trace were 10, 17, 35, 07, and 10 accordingly. The results from a total of 71 female MTB patients were 10, 13, 28, 08, and 12 with high, medium, low, very low, and trace respectively. With a P-value of 0.004, the total number of MTB patients with high, medium, low, very low, and trace was 20, 30, 63, 15, and 02 correspondingly as presented in Table 1.

Table 01: Gender wise Table of MTB patients with severity via GeneXpert Assay

Gender	*High*	*Medium*	*Low*	*Very Low*	*Trace*	*P-value*
Male	10	17	35	8	10	0.004
Female	10	13	25	9	13	
Total	20	30	60	17	23	

Sputum sample via Genexpert assay

In the graph, 150 sputum samples were tested, with 20 samples being high, 30 samples as medium, 60 samples comprising low, 17 samples indicating extremely low, and 23 samples showing trace as presented in Figure 2.

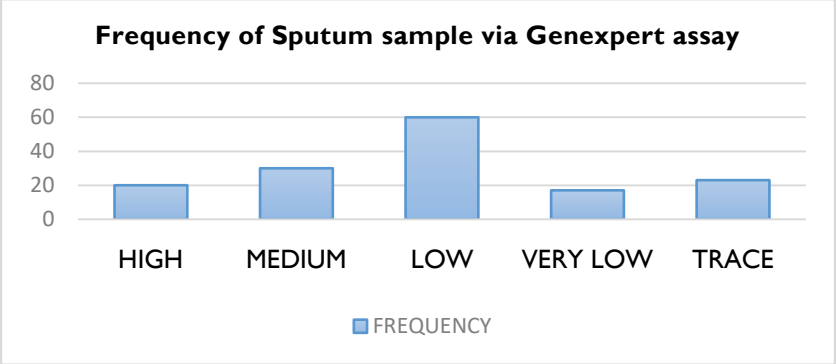

Figure 2 Sputum sample via Genexpert assay.

Rifampicin Resistance (sputum samples further for sensitivity)

In given table total of 79 MTB male patients were assessed for Rifampicin Resistance in which ratio of Detected, not detected, and intermediate resistance were 01, 73, 05 respectively. While in 71 female MTB patients Rifampicin Resistance was detected in 4 patients not detected in 51 and intermediate resistance was in 16 patients. In total 150 MTB patient's resistance was detected in 5 while intermediate resistance was 21 and resistance was not detected 124 MTB Patients with P-value 0.004.Morever Rifampicin Resistance data for further sensitive is presented in Table 2

Table 02: Rifampicin Resistance (Sputum samples further for sensitivity)

Gender	Detected	Not detected	Intermediate	Total	P-value
Male	1	73	5	79	0.004
Female	4	51	16	71	
Total	5	124	21	150	

Gender wise MTB patients via GeneXpert Assay

This given table represent total 150 MTB patients arranged gender wise with 79 male and 71 female patients % of male to female was 52.7 and 57.3 respectively as mentioned in Figure 4, while Figure 5, depict gender wise Frequency of MTB patients via GeneXpert Assay. Table 3 depict gender wise Table of MTB patients

Table 03: Gender wise Table of MTB patients

Gender	Number of patients	Percentage%
Male	79	52.7
Female	71	47.3
Total	150	10

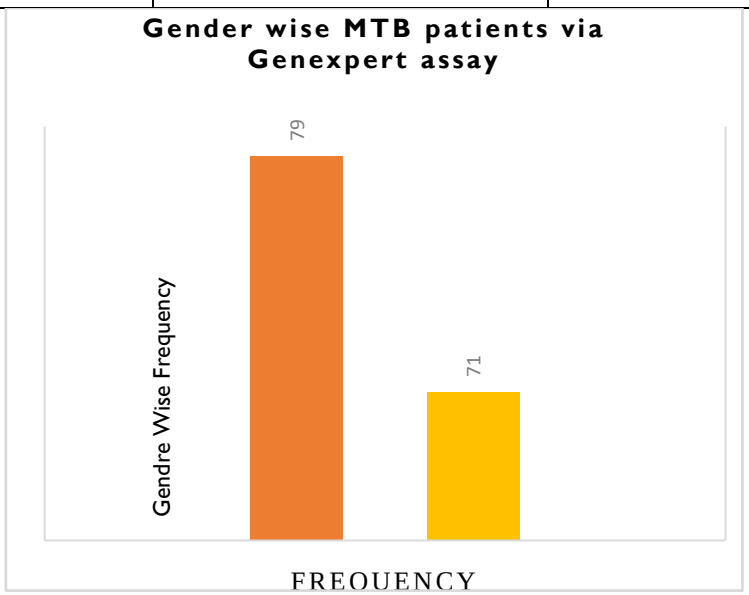

Figure 04: Gender wise distributions of MTB patients via GeneXpert Assay

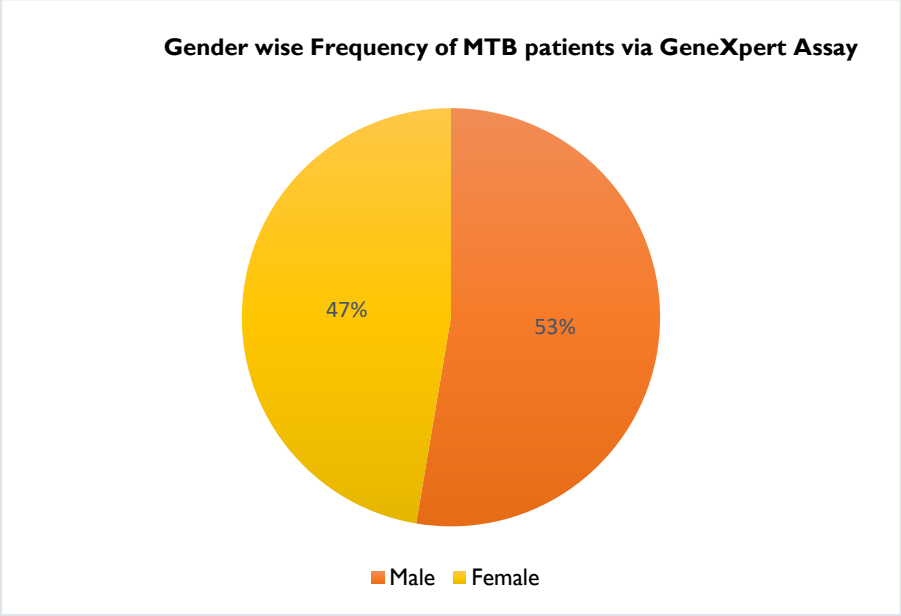

Figure 05 Gender wise Frequency of MTB patients via GeneXpert Assay

MTB detection via genexpert assay

Pie chart representation of MTB detection via Genexpert assay as presented in Figure 6.

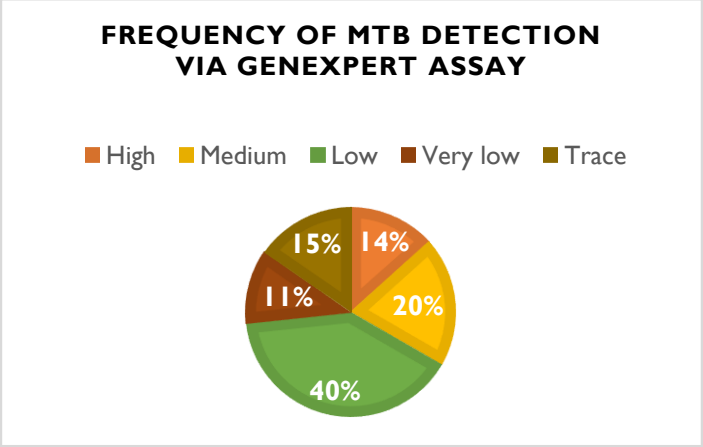

Figure 06: MTB detection via genexpert assay

Age wise Table of MTB patients via GeneXpert Assay

There were 150 patients, divided into six age groups, namely Groups 1, 2, 3, 4, 5, and 6. Group 1 patients (10-20 years old) accounted up 11.0% of the total.42.0% of Group 2 patients (aged 21-30). 21.3% (21) were in Group 3 (31-40 years old). Group 4 (41-50 years old) accounted for 10.7% (11). And 6.0% (6.0) in Group 5 (those aged 51-60). And 8.7% (09) were in Group 6 (those aged 61 and older), The Age wise Table of MTB patients via GeneXpert Assay results are tabulated in Table 4

Table 04: Age wise Table of MTB patients via GeneXpert Assay

Age Group	Number of patients	Percentage
10-20	17	11.3
21-30	63	42.0
31-40	32	21.3
41-50	16	10.7
51-60	9	6.0
>61	13	8.7
Total	150	100
Average Age	35.12	

Evaluation of Blood biomarkers in MTB Patients

According to the blood biomarkers analysis the mean CRP level in MTB patients is noted as 40.41 mg/L while ESR and D-dimer 40.39 mm/hr and 0.511 mg/L FEU respectively. Total 150 samples were analyzed for CRP level the number of CRP positive male were 78 (98.73%) and CRP negative were 1 (1.26%) while CRP positive female were 65 (91.54%) and negative were 6 (08.46%). Our results indicated that the level of CRP could be used for the assessment of TB presumes with negative results of their smears. CRP can possibly be added to future calculations for the essential consideration finding of tuberculosis in combination with clinical evaluation. Out of 150 samples the number of ESR positive male were 63 (79.74%) and ESR negative were 16 (20.26%) while ESR positive female were 56 (78.8%) and negative were 15 (21.12%). Total 150 samples were analyzed for D-dimer levels in MTB patients the number of D-dimer positive male were 05 (6.32%) and D-dimer negative were 74 (93.68%) while D-dimer positive female were 02 (2.81and negative were 69 (97.18%).

Table 05: The Biomarkers of MTB patients are tabulated

Name of Biomarkers	Unit	n	Mean	P-Value
D-dimer levels in MTB patients	mg/L FEU	150	.511	0.001
C- reactive Protein (crp) level in MTB patients	mg/L	150	40.41	0.001
ESR level in MTB patients	mm/hr	150	40.39	0.001

Correlation of different blood biomarkers with Rifampicin Resistance

According to bivariate analysis there is weak positive correlation (r= 0.006) between D-dimer and Rifampicin Resistance. Similarly, significantly (0.001) intermediate negative correlation (r= -.271)was found with CRP. Our study also noted weak negative correlation (r= -240) between Rifampicin Resistance and ESR level in MTB patients as mentioned in Table 6.

Table 06: Correlation between blood biomarkers

Correlations of Rifampicin Resistance with biomarkers		**Rifampicin Resistance (Sputum samples Further for Sensitivity)**	**D-dimer (mg/L FEU) levels in MTB patients**	**C- reactive Protein level (mg/L) in MTB patients**	**ESR level in (mm/hr) in MTB patients**
Rifampicin Resistance (Sputum samples Further for Sensitivity)	Correlation	1	0.006	-.271**	-.240**
	P-Value		0.945	.001	.289**
	Samples size	150			150
D-dimer (mg/L FEU) levels in MTB patients	Correlation	1	0.006	.311**	.289**
	Correlation	0.945		.000	.000
	Samples size	150		150	150
C-reactive Protein level (mg/L) in MTB patients	Correlation	-.271**	.311**	1	.868**
	Significant	.001	.000		.000
	Samples size	150	150	150	150

ESR level in (mm/hr) in MTB patients	Correlation	-.240**	.289**	.868**	1
	Significant	.003	.000	.000	
	Samples Size	150	150	150	150

DISCUSSION

In this study the prevalence of TB was determined to provide the baseline epidemiological information for population living in District Peshawar, KPK, Pakistan who come for clinical examination to Prime Hospital Warsak road Peshawar. The consequences of the present study will be useful to manage and root out the TB infection. The epidemiological study is significant for the planning to stop tuberculosis [19].

In the current research overall 150 samples were positive for Ziehl–Neelsen and GeneXpert, Furthermore in MDR and XDR in which out of 150, 26 were detected as rifampicin resistant and 124 were none detected for rifampicin resistant gene. Additionally, blood samples of positive cases were analyzed for CRP, ESR and D-dimer. In CRP test out of 150, 143 were detected as CRP positive and 7 were detected as a CRP negative [20]. In ESR test out of 150,119 samples were positive for ESR while in 31 ESR were not raised, moreover in D –Dimer test 7 samples out of 150, were positive while in 143 samples in D – Dimer were not detected [21].

This study shows that the Gene-Xpert MTB/RIF testing system can quickly recognizes the existence of MTB and diagnoses the alterations related with the resistance of rifampicin immediately from smear positive and negative clinical specimens of sputum [22]. Our results recommended a direct relationship with the former investigations. This elevated distinction in female/male proportion of tuberculosis is due to the absence of female education, hard work, inattention, and substandard-health facilities offered to them [23]. The individuals of the region like other regions are terrified to expose the results because of the fear of separation by the society and believe that once this disease happens then it causes death. The fundamental reason of high predominance is lack of education. Despite these all our study includes total of 150 samples for the prevalence of TB in male & female in which 35% were MDR Isolates and 64.5% Non-MDR Isolates. Among these all-Rifampicin resistances were found in the age of 35-55 (19%) which is followed by age 55-65 (13%). Past researches indicated that the specificity of Gene-Xpert was 79.0%, while sensitivity of Gene-Xpert was 97.3%. Overall, the combined sensitivity and specificity were calculated to be 77.3% and 98.2% [24]. Another study demonstrated that the specificity of Gene-Xpert was 95% and sensitivity of Gene-Xpert was 100%,for the Xpert MTB/RIF assay kit in 340 positive samples [25]. In a study of Agrawal the overall sensitivity, specificity of Gene-Xpert was 86.8% and 96% respectively. Past researches indicated that the specificity of Gene-Xpert was 79.0%, while sensitivity of Gene-Xpert was 97.3% [26].

A study showed that it was striking that high CRP correlated with much more frequent and rapid detection of MTB in clinical samples. A total of 15 patients had direct evidence of disseminated TB in both sputum and urine samples using culture and Xpert MTB/RIF. Of these 80% had a CRP concentration ⩾50 mg /l [27]. Another study showed that the C-reactive protein levels were found to be significantly higher in smear positive group as compared with the smear negative group. Among the smear positive patients, CRP levels were highest in smear 3+ group as compared with the smear 2+ patients. Correlation of CRP levels with extent of disease also revealed that these values were significantly higher in stage III disease as compared with stage II and stage I disease [28]. In a study the serum concentration of CRP was determined in 60 PTB patients, 30 individuals previously treated with TB treatment and healthy volunteers. Statistically the difference was significant. There was a positive correlation between the serum CRP level and smear positive patients [29]. In our study the elevated levels of CRP were found in 97.06% smear positive patients while the elevated levels of CRP were also found in 39.13% smear negative patients. According to the blood biomarkers analysis the mean CRP level in MTB patients is noted as 40.41 mg/L while ESR and D-dimer 40.39 mm/hr and 0.511 mg/L FEU respectively.The analysis revealed that the MDR positive sample is highly co related with ESR and CRP rather than D-Dimer as there is no increase in D-dimer [30].

CONCLUSION

The GeneXpert MTB/RIF assay has good diagnostic capabilities to identify rifampicin resistance,the test is appropriate to be implemented as a starting test in a normal laboratory. Its adoption can contribute to the timely diagnosis of multidrug-resistant tuberculosis, make the right treatment choices, and contribute to the decrease of the spread of the disease. These findings demonstrated a better percentage of drug-sensitive results and were in agreement with the inflammatory markers, including CRP, ESR, and D-dimer. They also had a tendency of age-specific difference in rifampicin resistance, which means that the probability of resistance is higher as age increases, and this may be because of weakened immunity.

RECOMMENDATIONS

There is a high demand to raise awareness among the communities about tuberculosis infection. The patients are to be advised to take the entire course of proper antibacterial therapy to avoid drug resistance. Both the public health and the private organizations should have appropriate and well-transplanted strategies that will take care of the spread of TB. CRP, ESR, and D-dimer analysis have been useful in ruling out pulmonary tuberculosis, and can be a useful tool in nurses and physicians operating in TB-infested areas. Moreover, CRP levels in serum can be very vital in determining the level of disease and complications in patients with tuberculosis.

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