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Original Article

Prevalence of Multi-drug Resistance in Iraqi Patients with Tuberculosis

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ABSTRACT

Objective: Tuberculosis (TB) is a bacterial, infectious disease caused by Mycobacterium Tuberculosis complex. TB causes a wide range of clinical infections affecting many parts of the body. Multi-drug resistant tuberculosis (MDR-TB) is caused by bacteria that are resistant to both isoniazid and rifampicin, the most effective anti- TB drugs, or more. MDR-TB presents a major concern in many countries and continues to threaten TB control.
Methods: A retrospective cohort study carried out from 5 Jan 2020 to 30 March 2020 at the Specialized Chest and Respiratory Disease Center in Baghdad. The records of the patients who received multidrug treatment were included in the study. On the other hand, all the records that not contain full information about the socio-demographic characteristics, history of travelling or other disease, type and duration of treatment, and drug culture sensitivity excluded from the study.
Results: From the 650 patients whom there records were reviewed, 130 patients had single or multi-drug resistance mainly to rifampicin and isoniazide. Comparing the presence of drug resistance according the gender showed that the number of males who had resistance to drugs was higher than that of females.
Conclusion: Tuberculosis affects mainly the productive age group. It affects males more than females. Resistance to anti TB drugs was found in one fifth of patients who received treatment.

Keywords: Respiratory disease, resistance, tuberculosis, treatment.

INTRODUCTION

Mycobacterium tuberculosis (T.B) is a bacterial, infectious disease. Because they form a lesion known as a tubercle, the organisms known together as the tuberculosis complex (Human, Bovis, and Africana) are sometimes referred to as acid fast bacilli (A.F.B.) or tubercle bacilli [1]. All races, all ages, and all organs are impacted by T.B. Consequently, it is still viewed as a significant global public health issue [2].

TB is the ninth leading cause of mortality and the second leading cause of death from all infectious diseases worldwide, despite the availability of numerous treatment options [3]. An estimated 1.3-2 million people worldwide die from tuberculosis each year, and 9 million new cases are reported each year [2].

Iraq has a health issue with tuberculosis, just as many other places throughout the globe. Iraq has seen significant changes as a result of 13 years of harsh economic sanctions, which have had an impact on the country's health system. From 46.1 per 100,000 persons in 1989 to an estimated 131.6 per 100,000 people in 2000, the number of new TB cases nearly tripled years of recovery following years of war, sanctions, health worker losses, and political intervention are then followed by years of struggle [1].

During the two epochs, the detection rates for tuberculosis alternated between rising and falling [4]. The Iraqi Ministry of Health claims ,Iraq is ranked 11th for TB mortality but 44th for TB incidence globally. 3% of all TB cases in the Eastern Mediterranean region are from Iraq [5].

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Despite the Directly Observed Treatment (DOT) Strategy for TB Control being widely used, TB incidence in Iraq has grown since 2003 and reached 117 per 100 000 people in 2010 [6].

Inhaling tubercle bacilli causes infection nearly solely through the respiratory system. TB brings on many different clinical infections. Usually, the infection targets the lungs. However, the bacterium is also spread to additional bodily parts, such as the kidney, brain, and spine [7].

Mycobacterium tuberculosis, the disease's causative bacteria, exhibits a unique capacity for long-lasting asymptomatic infection due to its central biology [8].

Typically, vague signs and symptoms accompany pulmonary TB. In addition to cough, which is the most typical symptom, systemic signs may also include anorexia, weariness, low-grade fever, night sweats, and weight loss [9].

The pulmonary TB type affects about 80% of TB patients. However, some people with pulmonary TB also have extra pulmonary TB, a more dangerous condition, present at the same time. This implies that Mycobacterium tuberculosis bacilli can spread outside of the lung parenchyma even in pulmonary TB patients who also develop extra pulmonary TB [10].

The initial phase in the therapy of tuberculosis (TB) guarantees that patients are registered and that the proper standard regimen administered. Following a clinical examination and laboratory investigations, a diagnosis based on the presence of Mycobacterium tuberculosis made. In addition, the outcome of therapy, such as relapse, default, or failure, may be used to define a case [10].

The objectives of a TB treatment regimen include achieving cure, preventing resistance, and enhancing patient quality of life. The WHO recommendation states that for new cases. It is advised to follow a 6 month conventional regimen that includes 2 months of intensive phase therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol.Isoniazid and rifampicin are then used in a 4 month continuous phase of treatment after that. As part of efforts to identify multidrug resistance early, drug susceptibility testing (DST) is advised for all patients who have already received treatment [10].

The DST results establish the personalized, each patient's course of treatment. Before or at the start of the treatment, sputum samples from these individuals are collected for culture and DST tests, which must be resistant to at least isoniazid and rifampicin [12]. A patient who does not finish their TB treatment for any reason is a significant obstacle for most TB programs, which contributes to the growth of multidrug resistant (MDR) TB [13].

The bacteria that cause multidrug resistant tuberculosis (MDR-TB) are resistant to at least one anti-TB treatment, preferably both isoniazid and rifampicin. MDR-TB continues to pose a serious threat to TB control and is a major problem in many countries [14].

An estimated 558 000 patients were diagnosed with rifampicin resistant tuberculosis in 2017, and 82% of these individuals had MDR-TB [15]. Because treatment is difficult, cure rates for MDR-TB are lower than for drug susceptible TB., and patients may still be contagious for months or years even after getting the best available therapy, MDR-TB is a serious public health concern. Soon after streptomycin was introduced for the treatment of tuberculosis, the phenomenon of resistance was discovered.

When the medication administered alone, the patient's symptoms initially improved dramatically, and there was a rapid drop in the number of bacilli in the sputum. However, typically, the bacilli quickly grew again, and the patient's condition deteriorated [16]. Additionally, because rifampicin is the primary sterilizing agent in short-term Tb treatment, resistance to it significantly raises the rate of failure and recurrence when typical three-drug regimens are utilized [17].

While acquired resistance occurs when a patient is posted cure-rates are lower than for drug-susceptible TB, and patients may remain infectious for months or years despite receiving the best available therapy, primary resistance is infection with a resistant strain coming from a patient who has never taken a drug in the past. Resistance to a single drug as a result of selective drug use, erratic drug supply, poor drug quality, or incorrect prescriptions, or as a result of the programmer's failure to ensure treatment adherence [18].

Moreover, 9.7% of those who have MDR-TB, on average, MDR-TB plus resistance to a second line injectable medication and at least one fluoroquinolone is known as extensively drug-

resistant TB (XDR-TB) [19].

Understanding the mechanisms of mycobacterial resistance to anti- tuberculosis medications not only provides implications for the creation of novel Anti-tuberculosis treatments, but it also aids in the implementation of strategies to avoid the development of such resistance [20].

The WHO recommended a treatment plan in 2016 that included extensive chemotherapy, at least four potent TB medications during the intensive phase, including fluoroquinolones and second line injections as core medications. The total course of treatment lasts 18 to 24 months, with the intensive phase enduring six months.

Additionally, second line medicines (SLDs) can result in a variety of harmful side effects and are exceedingly expensive when compared to the medications used for conventional new TB treatment [21]. Treatment for XDR-TB is more difficult. Treatment for MDR/XDR-TB has a dismal success rate, even in industrialized nations [22].

The WHO has called for stronger measures to prevent MDR/XDR-TB due to its concern over the emergence of dangerous drug-resistant strains of M. tuberculosis. According to estimates, new and retreated TB patients experience over 440,000 MDR-TB cases per year [23]. There were few investigations about the prevalence of MDR-TB in Iraq. This study's objective is to determine the frequency of TB multidrug resistance.

Materials And Methods

A retrospective cohort study carried out from the 1 Dec. 2019 to 30 March 2020 at the Specialized Chest and Respiratory Disease Center in Baghdad. All the records of the patients attending the center and received more than one category of treatment for T.B reviewed. The records of the patients who received multidrug treatment were included in the study. On the other hand, all the records that not contain full information about the socio-demographic characteristics, history of travelling or other disease, type and duration of treatment, and drug culture sensitivity were excluded from the study.

The researchers constructed a questionnaire form. It was consisted of demographic characteristics and information about the patients, focusing on the following points: Age, Gender (male or female), Residence , Occupation (type of occupation), Duration of the disease, Treatment that patient received for TB, Drugs culture sensitivity, History of travelling before getting infection with TB , History of other disease, History of taking other medications.

Data entered and analyzed using SPSS (Statistical Packages for Social Sciences) program, version 18. Descriptive data expressed as means and standard deviations for continuous measurements and as frequencies and percentages for categorical measurements. $P<0.05$ set as statistically significant.

Results

By this retrospective study, the records of 650 patients who diagnosed to have tuberculosis reviewed. The mean age of them was 40.61 years, 413 (63.5%) were males and 237(36.5%) were females, slightly more than one fifth (22.5%) were from rural areas and the rest (77.5%) were from urban areas, the patients had different types of occupations as shown in Table 1.

The table also showed that a very small number (only 4) of the studied patients had history of travelling, while nearly more than one quarter of them (25.7%) had a history of other diseases like hypertension and diabetes mellitus, on the other hand, (30.6%) of them were using drugs other than anti-tuberculosis drugs.

The mean duration of disease was 16.34 months, and the mean number of drugs used was 6.15. During this duration of disease, about half of the patients (49.7%) received two courses of treatment with anti-tuberculosis drugs, as shown in Table 2.

The sensitivity tests showed that (80%) of patients had no resistance to drugs while (20%) showed resistance to drugs (6% showed resistance to one drug, 9% showed resistance to two drugs, and 5% showed resistance to three drugs), as shown in Table 2 and Figure 1, respectively.

From 130 patients who had resistance against drugs,30 (23%) had resistance for Rifampicin only, while 8 patients had resistance for isoniazide. On the other hand, 45 patients had resistance to both of them, 18 patients showed resistance to both of them in addition to ehambutol, and 15 patients showed resistance to both of them in addition to streptomycin.

Only 6 patients showed resistance to Rifampicin and ethambutol, and 8 patients showed resistance to ethambutol and streptomycin, see Table 2 and Figure 2.

Comparing the presence of drug resistance according the gender showed that the number of males who had no resistance to drugs was higher than that of females who had no resistance. Also, the number of males with one drug or multidrug resistance was higher (for most of drugs) than that of females with drug resistance. However, the difference between males and females was statistically not significant (P value was 0.164), as shown in Figure 3.

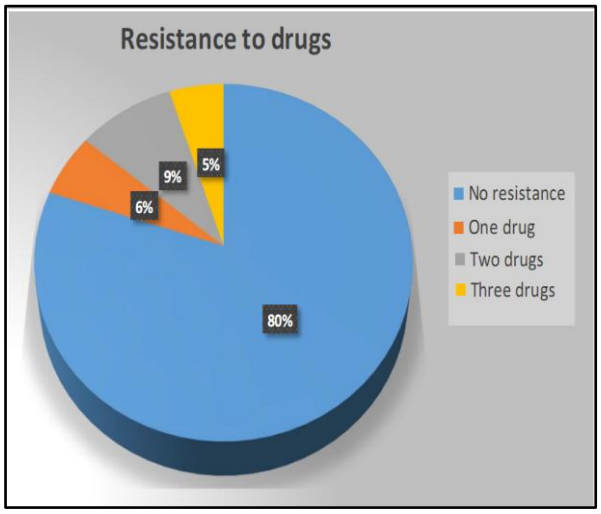

Figure 1. Distribution of the number of drugs that failed in sensitivity test.

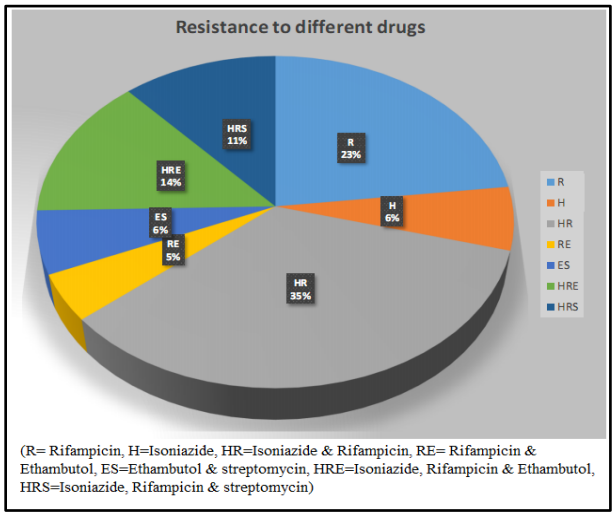

Figure 2. Distribution of the types of drugs that in failed sensitivity test.

Table 1. Socio demographic characteristics of patients.

Variables		Number (%)
Gender	Male	413 (63.5)
	Female	237 (36.5)
Residency	Rural	146 (22.5)
	Urban	504 (77.5)
Occupation	Employed	40 (6.2)
	Unemployed	122 (18.8)
	Student	16 (2.5)
	Housewife	201 (30.9)
	Free work	164 (25.2)
	Officer	105 (16.2)
	Prisoner	2 (0.3)
History of travelling	Yes	4 (0.6)
	No	646 (99.4)
History of other disease	Yes	167 (25.7)
	No	483 (74.3)
History of using other drug	Yes	199 (30.6)
	No	451 (69.4)

Age (years) Mean ± SD (Range) : 40.61 ± 14.78 (15 - 90)

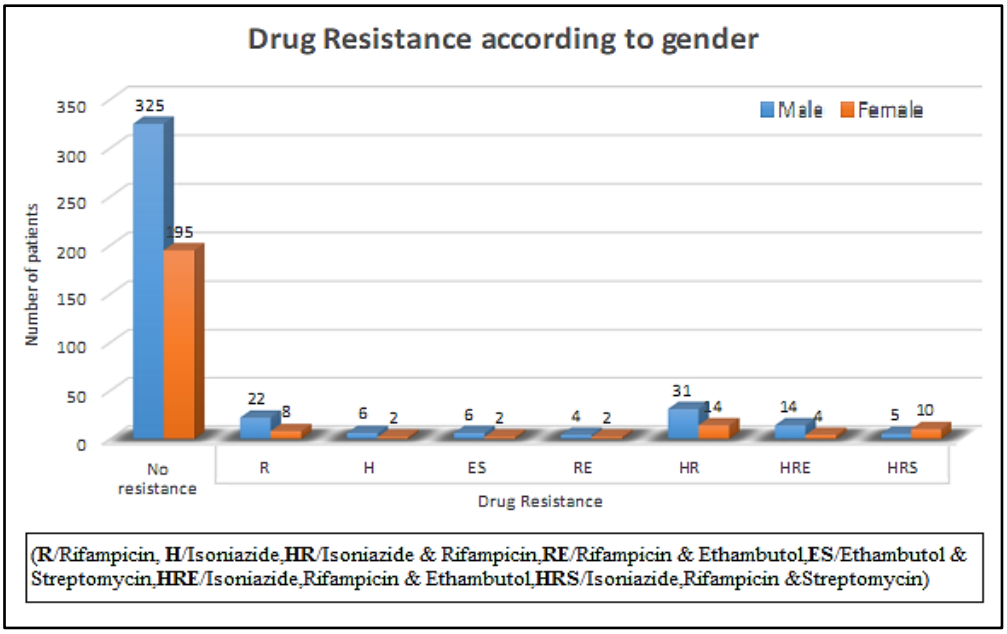

Figure 3. Distribution of the drugs that failed in sensitivity test in relation to gender.

Table 2. Duration of disease and treatment characteristics

Variables		Number (%)
Courses of treatment	One	327 (50.3)
	Two	323 (49.7)
Resistance to drugs	Yes	130 (80)
	No	520 (20)
Types of drugs that showed resistance	Rifampicin	30 (2)
	Isoniazide	8 (6.2)
	Isoniazide & Rifampicin	45 (34.6)
	Rifampicin & Ethambutol	6 (4.6)
	Ethambutol & Streptomycin	8 (6.2)
	Isoniazide, Rifampicin & Ethambutol	18 (13.8)
	Isoniazide, Rifampicin & Streptomycin	15 (11.6)

Disease Duration (months) Mean ± SD (Range): 16.34±14.29 (2-96),
Number of drugs used Mean ± SD (Range): 6.15±1.14 (4-8)

DISCUSSION

The diagnosis of TB and MDR-TB is dependent on time-consuming, culture-based assays that have been in use for many decades and represent a substantial barrier to worldwide TB control, especially in developing countries. The ability to quickly identify TB medication resistance is essential for patient treatment, but the clinical benefit of culture-based drug sensitivity tests is reduced by their short turnaround time.

Resistance developing, especially MDR-TB, has become a significant public health issue in Iraq [5]. In 35 countries, the WHO conducted surveys on MDR-TB prevalence between 1994 and 1997.The effectiveness of the TB control program found to be correlated with the prevalence of MDR-TB. Countries' TB control rated as better or worse.

Any country that had un adapted DOTS or that had coverage of less than 13% of national territory defined as having poorer TB control. Better control was defined as full coverage with direct observation therapy (DOTS), coverage of at least 1/3 of national territory, or TB notification rate below 10/100.000 population.

According to data analysis, the prevalence of MDR-TB was 7.7% in nations with better TB control and 17% in those with worse TB control. These findings imply that where MDR-TB does not yet exist, effective DOTS programs can minimize the spread of the disease by achieving proper TB control [23].

There were no records for patients under the age of 15 in this study, which had a mean age of 40.61 years and a range of 15 to 90 years. These results support those of other studies, which discovered that tuberculosis infection affects people of all ages, with 75% of cases occurring in those who are the most economically productive [24].

On the other hand, the BCG vaccine given at a young age may be responsible for the low percentage of TB cases among the age group less than 14 years; vaccination gives children good protection, but this immunity wane with age [25].

The study also revealed that 63.5% of TB patients were men; this finding was nearly identical to the one from Iraq, where the majority of TB patients (67.33%) were men. This finding is consistent with reports that indicate men are 1.7 times more likely than women to contract TB, and it also concurs with studies that found men were more affected than women in Iraq [26,27]. According to an Iranian study, males are more likely to have pulmonary tuberculosis than females in Iran's western regions [28].

The incidence of tuberculosis in men is typically two to one, but a study from Pakistan found that rates of TB cases were 20 - 30% higher in young women than in men, and that this was especially true in Africa, where women are more likely to contract HIV than men [29].

This phenomena might be caused on by the fact that men are more involved in their communities, more exposed to carriers, and work in crowded, unhygienic environments in many different fields, especially when they are poor. Additionally, this outcome could be linked to behavioral factors including smoking, which increases the risk of TB and is more common in men than in women, drinking alcohol, malnutrition, and men's delays in seeking medical attention [30].

More than three-quarters of the patients in the study resided in urban areas; this higher percentage may be attributed to the high population density that results in congested areas. As well as the availability of more diagnostic tools there than in rural areas, which allowed for the recording of more TB cases among patients who were suspected of having the disease.

Studies that examined the prevalence of multidrug resistance among TB patients in Iraq are rare. However, a prior global survey placed Iraq, which has an 8.3% prevalence of MDR-TB, between Ivanovo (Russia) and the Dominican Republic, both of which had worse TB control.

On the other hand, a systematic study conducted in India discovered a prevalence of MDR-TB of 23.3% among all TB cases [31]. This is much higher than the study that given. This may be the result of differences in the patient population investigated.The healthcare system, MDR-TB screening, and socioeconomic status differences between the two countries' populations could all be factors in the variance.

Rifampicin-resistant TB, which accounts for roughly 75% of all single drug resistance, is highly prevalent in Iraq, according to an analysis of the country's single drug resistance. Rifampicin is a crucial sterilizing antibiotic in the brief treatment program, but recent research suggests

that treatment success rates of rifampicin resistant cases are lower than those of drug rifampicin resistance, both as a single drug and as a multidrug resistance. This might be because of this medication being misused for other infectious disorders [32].

These numbers are significantly higher than the rates of rifampicin resistance observed in Turkey (10.6%(683)), Saudi Arabia (7/214 [3.3%] in new patients and 3/108 [2.8%]), and India (74.4%) .

Additionally, this investigation discovered 32 patients (24.6%) to be ethambutol resistant. These findings are almost identical to those of a major, 5 year Indian investigation, which revealed that ethambutol resistance was present in 21.7% of 673 samples [33].

However, they are different from a Saudi study that found ethambutol resistance in 22 out of 214 (10.1%) new patients and 5 out of 108 (4.6%) samples of patients who had previously had treatment [34].

Ethambutol resistance in this study was substantially higher than the 2.4% (n:863) finding of a similar study conducted in Turkey . 86 (66.1%) of the patients had isoniazid drug resistance, either single or multidrug resistant. These results are significantly better than those from Turkey (14.4%) and Saudi Arabia (20.6% in the new group and 22.2% of samples in the old group).

In comparison to India, where resistance is equally strong (53.2%), are also higher. Streptomycin resistance was found in 23 (17.7%) of the patients with multidrug resistance. This contrasts with Saudi Arabia (32.2% in new group samples and 19.4% in old group samples) and India (70%) but is almost identical to Turkey (21.1%) [33-35].

There was no statistically significant difference between both gender regarding the pattern of drug resistance (P>0.05). The findings of this study differ from those from Saudi Arabia, where samples with greater rates of MDR (22%) and mono- drug resistance (60%) and significantly lower rates of multi-drug resistance (16%) observed .

Additionally, it differs from the Turkish study's findings, which indicated a larger percentage of single drug resistance (32%) and alower percentage of MDR (6.6%) and multidrug resistance (4.4%) [35].

resistant TB. This investigation revealed that 104 (80%) of the patients had very significant

Conclusion

Tuberculosis affects mainly the productive age group. It affects males more than females. Resistance to anti TB drugs found in one fifth of patients who received treatment. The resistance was found either in form of single drug resistance which was for rifampicin and isoniazid; or in form of multidrug resistance which was also either to both rifampicin and isoniazid or to both of them in addition with another drug like ethambutol or streptomycin.

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Conflicts of Interest

There are no conflicts of interest

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