Prevalence of rifampicin mono-resistance in tuberculosis patients in Baghdad 2020

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Abstract

Background: Tuberculosis (TB) is one of the top ten causes of mortality in the world. Globally, in 2017, there were an estimated 558 000 new cases of Rifampicin Resistant Tuberculosis (RR-TB). WHO endorsed the Gene Xpert MTB/RIF assay, which is a fast and automatic molecular system that detects both *Mycobacterium tuberculosis* DNA and Rifampicin-Resistance (RR). Researches established that RR can be a substitute marker for MDR-TB.

Aim: Assessment of rifampicin mono-resistance situation in tuberculous Iraqi patients.

Methodology: Descriptive cross sectional study was applied to include all tuberculosis patients attended The National Center for Chest and Respiratory Diseases in Baghdad from 1st October 2020 to 31st March 2021. The data were collected by a structured questionnaire and analyzed by SPSS-28 statistical software. Data included Gene/xpert results for rifampicin resistance, socio-demographic characteristics of the sample, and history of previous anti-TB treatment.

Results: Among 300 tuberculous participants in the study, 85 (28.3%) were previously treated and 215 (71.7%) were a new diagnosed cases. From the 85 previously treated patients, 22 (25.9%) were rifampicin resistant and among 215 newly diagnosed tuberculous patients, 13(6%) of them were rifampicin resistant. The peak resistance (27.1%) was in age group 30-39year. 26.7% of the patients referred to the center from other governorates, were rifampicin resistant. 12.7% of the patients with crowding index ≥4, were rifampicin resistance. 46.7% of those patients referred from the prisons were rifampicin resistant. All of the MDR-contact, 35% of the failure in treatment, 24.5% of the relapsed cases and 20% of the lost to follow up cases, were rifampicin resistant.

Conclusion: There was an increase in the prevalence of rifampicin resistance among the previously treated tuberculous patients. MDR contact, prisoners and failure in treatment considered highly associated factors with rifampicin resistance necessitating a continuous screening for those categories and enhancement the use of Gene/xpert in the primary diagnoses of tuberculosis to be taken into consideration.

Key words: Tuberculosis, rifampicin resistance, Gene/xpert.

Introduction

Tuberculosis (TB) is one of the top ten causes of mortality in the world, globally and in 2017, there were an estimated 558 000 new cases of Rifampicin Resistant Tuberculosis (RR-TB)[1]. WHO endorsed the Gene Xpert MTB/RIF assay, which is a fast and automatic molecular system that detects both Mycobacterium tuberculosis DNA and Rifampicin-Resistance (RR) related mutations simultaneously[2]. Initially, this framework was indicated for patients with TB/HIV co-infection, presumptive MDR-TB[3], but 3years afterward of its execution, it was advisable for all patients suspected of having TB[4]. Drug resistant (unsusceptible) tuberculosis is caused by hereditary mutation of bacilli, limited or poorly managed regimen and weak healthcare program[5]. Iraqi population is now about 40 million and population in Baghdad is about 7.5 million which is the highest population density among governorates of Iraq[6].

The estimated proportion of TB cases with MDR/RR-TB in Iraq 2018, by WHO was 6.1% for the new cases and 18% for the previously treated cases[7]. In 2017 TB incidence estimated in Iraq to be 42 new cases per 100 000 population. Annual deaths in Iraq because of TB disease are estimated at 1100[8]. Tuberculosis is still representing a major public health problem in Iraq[9]. Iraq is one of the developing countries in which antibiotics are frequently and easily available over-the-counter, rather than usage on prescription by a doctor[10]. Rifampicin resistance considered a proxy for multi-drug resistance (MDR)[11]. High costs of second line drugs are a major impediment to successful tuberculosis control and prevention in Iraq[12]. The aim of the study is to estimate the prevalence of rifampicin mono-resistance among tuberculosis patients in Baghdad and to explore any associated determinants, and related factors.

Method:

A descriptive cross sectional study was applied from the 1st of October 2020 to 31st of March 2021 in the National Center for Chest and Respiratory Diseases/ Baghdad/ Iraq which is the main center in Iraq responsible for providing preventive, diagnostic, treatment and follow up services for tuberculosis patients and their contacts. In addition to that the center also responsible for establishing the preventive and control strategy in Iraq according to the researches and surveys done by the center. The Study involved all pulmonary and extra pulmonary tuberculosis patients attended or referred to the Center during the period of the study. All cases with sputum smear negative cases were excluded for (the pulmonary type).

By using confidence interval of 95% and p value of 0.05 and by considering the average prevalence of rifampicin mono-resistance in all

tuberculosis patients (25%) according to previous studies in Iraq, neighborhood countries and estimated prevalence by WHO / EMRO[7,13-16]**.** The sample size was 288, and around 10% (n=30) was added for the potential non responders, with 95% response rate giving a tended sample size to reach 300.

Operational Definitions:

Gene xpert: it is a rapid molecular diagnostic test produced by (Cephid.united states) endorsed by the WHO for the rapid diagnosis of tuberculosis and rifampicin resistant tuberculosis since 2010[17]**.**

New case: Patients who have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site[18]**.**

Previously treated: Patients have received one month or more of anti-TB drugs in the past, may have positive or negative bacteriological test and may have disease at any anatomical site. There are also further classifications by the outcome of their most recent course of treatment: Patients whose sputum is smear-positive at the end of / or returning from a second or subsequent course of treatment should be classified by the outcome of their most recent retreatment course into: relapsed, defaulted or failed[19]**.**

Category II pulmonary tuberculosis patient: Tuberculosis in those patients who had failed previous TB treatment, relapsed after treatment, or defaulted during previous treatment[20]**.**

Relapsed: Sputum smear-positive patient who previously declared cured or treatment completed by a physician, but reports back to the health care facility[21].

Treatment after default: Tuberculosis patient who received anti-tuberculosis treatment for one month or more from any source and returns to treatment after having defaulted, i.e. not taken ANTI -TB drugs consecutively for two months or more, and is found to be sputum smear-positive[21]**.**

Failure: Any TB patient who is smear-positive at five months or more after starting treatment[21]**.**

Data collection and analysis

The average daily outpatient and referred visitor to the respiratory center was about 15 (ranging from 10 to 20) diagnosed cases per day. During the period of the study and as a result from COVID-19 pandemic crisis, the average number of tuberculous outpatient and referred cases were declined to 7 patients per day with a range of (5-10) patients per day.

A systematic random sampling was done with a sampling interval of (3), so every 3rd patient from the gene Xpert/RR-MBT laboratory records (with positive result) with sputum smear positive (for pulmonary type) and presumptive extra pulmonary tuberculosis attending to the specialized center was selected to give enough time for questionnaire form to be filled adequately by the patient with the help of researcher if needed. The 1st three patients selected by simple random sampling.

Gene xpert and sample processing

After chest x- ray, sputum smear result (positive) by microscopic investigation for pulmonary type and ultra sound, CT scan, MRI, and histopathological investigations for extra-pulmonary type, a confirmatory test done by Gene/Xpert in which One milliliter of the clinical sample was transferred to a tube containing 2 mL of sample reagent at a ratio of 1:2; the mixture was then incubated for 15 minutes at room temperature and mixed every five minutes until liquefied. The mixture was transferred into the Xpert MTB/RIF cartridge. The inoculated cartridge was placed into the Gene/Xpert instrument Results were available in less than two hours automatically[22].

Results:

Out of 300 tuberculosis patients with gene/Xpert positive results, 154(51.3%) were female and 146(48.7%) were male. 43(14.3%) of the patients were less than 20 years old while the peak age group was 20-29 year and they form 24.3% of sample included in the study. 270 out of 300 (90%) were from the capital (Baghdad), 175(58.3%) from Rusafa side of Baghdad and 95(31.7%) from Al-Karkh side of Baghdad. From the total sample, 272(90.7%) were from urban area and 28(9.3%) were from rural area. Most of the affected patients with tuberculosis were married 171(57.8%). 145(48.3%) of patients had just a primary education, 40(13.3%) were illiterate and 168 (56%) were not employed. 196 (68.8%) of the total population had a monthly family income <1000 thousand Iraqi dinar (TID), the peak group with monthly income ≥ 500 TID and <1000 TID, they were 178 patients (62.4%) (Table 1).

Table 1: The characteristics of the studied sample of TB patients

		No.	%
Age (years)	<20years	43	14.3
	20---29	73	24.3
	30---39	48	16.0
	40---49	48	16.0
	50---59	36	12.0
	=>60years	52	17.4
Gender	Male	146	48.7
	Female	154	51.3
Marital Status	Single	92	30.7
	Married	171	57.8
	Divorced	10	3.3
	Widowed	27	9.0
Present Address	Rural	28	9.3
	Urban	272	90.7
Governorate	Baghdad Rusafa	175	58.3
	Baghdad Karkh	95	31.7
	Other governorates	30	10.0
Level of education	Illiterate	40	13.3
	Read & Write	44	14.7
	Primary	145	48.3
	Secondary	52	17.3
	College	19	6.3
Occupation	Governmental Employee	28	9.3
	Self-Employee	35	11.7
	Private Sector Employee	13	4.3
	Worker	17	5.7
	Not employed	168	56.0
	Retired	12	4.0
	Studying	27	9.0
Average monthly income in thousand Iraqi dinar	<500TID	18	6.3
	500---	178	62.4
	1000---	65	23.8
	≥1500	24	8.4

Out of 285 tuberculous patients (except 15 prisoners), 205(71.9%) did not have anyone infected with TB in their family (-ve) family history. While 71(24.9%) of them had (one person) infected with TB in the family (+ve) family history and 9(3.2%) had (two person) infected with TB in the family. The main family member affected other than the studied case, was the (parents) in 29(36.2.5%). Only 5 (1.7%) had a positive occupational contact with TB with a period ranging from two weeks - two years. Regarding referral source, 150(50%) of the visitor to the specialized center were referred from governmental hospitals, 104(34.7%) referred from private clinic, 21(7%) were visited the center as a follow up process, 15(5%) were referred from prisons and 10(3.3%) were visited the center directly as shown in table 2.

Table 2: The family, occupational contact history and patients' awareness

		No.	%
Family members with TB disease	No	205	71.9
	One	71	24.9
	Two	9	3.2
Type of family member with TB disease (n=80)	Spouse	8	10.0
	Father and mother (parents)	29	36.2
	Brother and sister (siblings)	28	35
	Son and daughter (sons)	14	17.5
	Grand Father and Grand mother	9	11.3
Positive occupational contact with TB	Yes	5	1.7
	No	295	98.3
Duration of occupational contact (months)(n=5)	0----	1	20.0
	3----	1	20.0
	6----	1	20.0
	=>12	2	40.0
Patient Visit The Respiratory Center As	Referred by govern. hospital	150	50.0
	Referred by a private clinic	104	34.7
	First time outpatient visitor	10	3.3
	For follow up	21	7.0
	Others (prisoner)	15	5.0

The results of gene xpert examination revealed that 35 (11.7%) were rifampicin resistant tuberculosis while the other 265 (88.3%) were rifampicin susceptible tuberculosis. 248 (82.7%) were AFB positive, 51 (17%) AFB not available and 1 (0.3%) was AFB negative. The most prevalent symptoms detected in the study sample were cough, undiagnosed fever, weight loss, night sweat and hemoptysis as 254 (84.7%), 217 (72.3%), 153 (51%), 106 (35.3%) and 33 (11%)respectively .The most prevalent (other) symptoms were shortness of breath, vomiting, and swollen lymph nodes detected in 12,11,9 patients respectively. The average duration of the symptoms detected at the period of the study were different among the patients .most prevalent duration of symptoms was (≥ 1 month- <2 months) in which, 100 (33.3%) of the patients were diagnosed. Regarding previous TB treatment, 85 (28.3%) were treated previously with anti-TB drug, while 215 (71.7%) not treated previously with anti-TB drugs. With peak previous anti-TB treatment (≥6months - <9months) in 51 (60%) out of 85 previously treated patients (Table 3).

Table 3: The distribution of patients' by gene xpert results, current symptoms and average duration of current symptoms

		No.	%
Diagnosis by gene xpert	TB	265	88.3
	RR TB	35	11.7
Symptoms	Cough	254	84.7
	Hemoptysis	33	11.0
	Undiagnosed Fever	217	72.3
	Night Sweat	106	35.3
	Weight Loss	153	51.0
	Other	27	9.0
Average duration of current symptoms (months)	<1month	76	25.3
	1---	100	33.3
	2---	54	18.0
	3---	28	9.3
	=>4months	42	14.0
Previous treatment with Anti TB drugs	Yes	85	28.3
	No	215	71.7
Average period of previous anti-TB treatment (months) (n=85)	<3months	5	5.9
	3---	17	20.0
	6---	51	60.0
	9---	3	3.5
	12months	9	10.6

Figure 1 showed that the prevalence of rifampicin resistance in previously treated cases was 22(25.9%) while prevalence of rifampicin resistance in previously untreated (new) cases was 13(6%) (P value<0.05).

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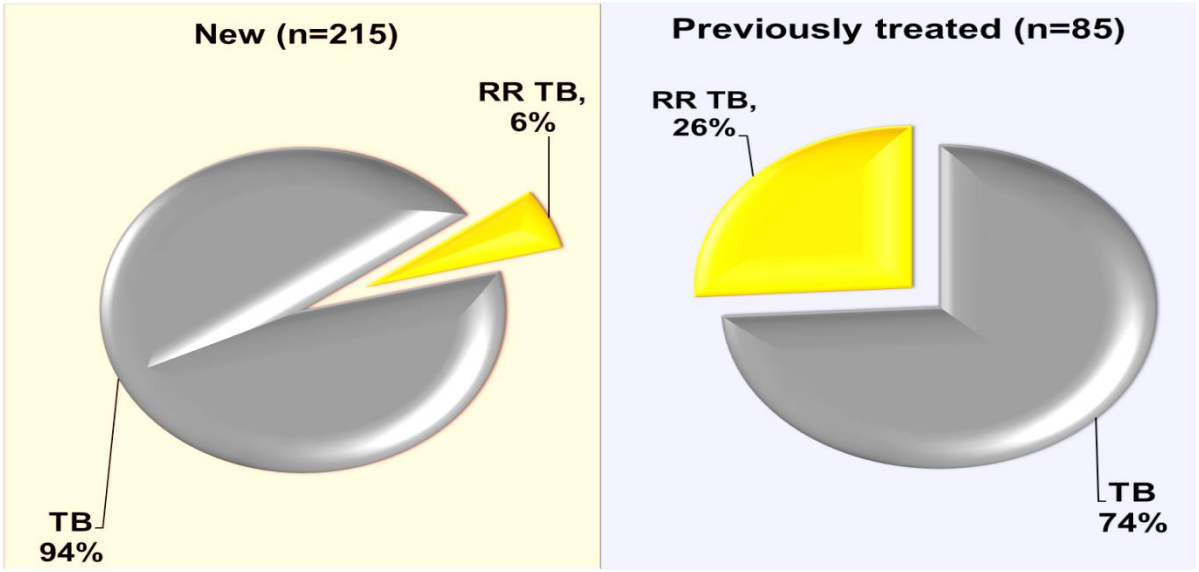

Figure 1: The prevalence of rifampicin resistance in the new & old cases.

From the total sample of the study (300); 208 (69.3%) were new cases, 7 (2.3%) MDR contact, 53 (17.6%) relapse cases, 17 (5.6%) failed in treatment cases and 15 (5%) lost to follow up cases. The pulmonary TB were 269 of 300 (89.7%) while the extra-pulmonary TB were 31 of 300 (10.3%). specimen of the study was sputum in 247 (82.3%), Broncho-alveolar lavage (BAL) in 22 (7.3%), pleural fluid in 16 (5.3%), lymph nodes in 10 (3.3%), and cerebrospinal fluid (CSF) in 5 (1.7%) (Table 4).

Table 4: The types of TB patients

		No.	%
Resistant	Yes	35	11.7
	No	265	88.3
Patient type	New TB case	208	69.3
	MDR contact	7	2.3
	Relapse TB	53	17.6
	Failure	17	5.6
	Lost to follow up	15	5.0
Presumptive drug resistant TB	New	6	2.0
	Relapse	13	4.3
	Failure	6	2.0
	Lost To Follow-up	3	1.0
	MDR Contact	7	2.3
	None of the above (drug Sensitive)	265	88.3
Site of Presumptive TB	Pulmonary	269	89.7
	Extra pulmonary	31	10.3
Type Of Specimen	Respiratory (Sputum)	247	82.3
	Bone	-	-
	Lymph Node	10	3.3
	CNS	5	1.7
	Pleural fluid	16	5.3
	Others (BAL)	22	7.3

Discussion

The prevalence of rifampicin mono-resistance in the total sample of the current study was (11.7%) and this included the resistance in old and new cases .this was more than the percentage reported in Saudi Arabia (2018) (5.9%) and Yemen (2019) (3.2%)[14,23]. The reported rate in the current study of RR is more than that estimated in Yemen because rifampicin resistance in Yemen could be under estimated due to the military conflict.in addition to that in Iraq the stable socio-political condition in the last years and the extended use of Gene/Xpert may play major role in the enhancement of the tuberculosis MDR monitoring program and increasing the number of RR TB.

The prevalence of rifampicin resistance was 6% in new cases and 25.9% in previously treated cases (P<0.05). When we compare these results to the prevalence of rifampicin resistance estimated by WHO for Iraq which was 6% for new cases and 18% for old cases[7] we noticed the same prevalence for the new cases but more in the current study for the old cases.

When comparing this study to a similar study done in Basrah /Iraq (2017)[13] in which the prevalence of rifampicin resistance was 4.22% for new cases and 16.95% for the old cases. The increase in the prevalence may be attributed to the increase in screening process by gene/xpert and improved data collection, or may be overestimation due to the effect of covid 19 pandemic.so we need to do more researches to investigate about the trend of rifampicin resistance in the previously treated cases. A probable reason of increasing rifampicin resistance in the previously treated cases could be attributed to the extensive use of antibiotics in Iraq without prescriptions and poor adherence to the treatment with anti-TB treatment[10].

Another study conducted in Iran (2019)[16] in which the prevalence of rifampicin mono-resistance in old cases showing an increase in the trend from 43% in 1996 to 60% in 2004(P<0.05).although this study different in methodology from this study but had the same trend (increase in resistance in old cases).

The current study is consistent to another study conducted in India (2018)[24] in which the prevalence of rifampicin resistance was 7.6% in the new cases and 37.8% in the old cases (p<0.05). Also it is consistent to another study consistent to another study done in Ethiopia (2019)[25] in which the prevalence of rifampicin resistance was 7.6% in new cases and 27.4% in old cases (P<0.05).

This study reported a less prevalence of RR from another study conducted in Iraq (2014)[15] in which the prevalence of RR was (58.6%) in the new cases and (72.4%) in the previously treated cases. The wide gap in findings could be related to the difference in the method and technique of this study and the small sample size.

In conclusion, the increased prevalence of rifampicin resistance among previously treated tuberculosis patients sounds the alarm in order to review the tuberculosis control program in Iraq and Gene/Xpert should be used as the primary diagnostic test in the patients suspected to have MDR-RR, especially previously treated patients. The strengthening of Directly Observed Short-Course Strategy is needed and ensure complete adherence of patients to the treatment regimen with encouraging researchers for more studies in order to monitor the trend of rifampicin mono-resistance in new and old cases. MDR contact and prisoner need to have continuous RR screening.

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