TREND OF MDR-TB IN KIRKUK- IRAQ-A 10 YEARS' EXPERIENCE AND CHALLENGES

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Article history:		Abstract:
		Tuberculosis is still regarded as one of major public health burden worldwide, and the emergence of multi-drug resistant TB which is defined by resistance to both Isoniazid (INH) and Rifampicin (R) with or without resistance together drug; is adding problems to public health across the continents.[1],[2] The probable causes of increasing the prevalence of multi-drugs resistance (MDR) may be attributed to the emergence of human immunodeficiency virus (HIV), poverty, migration narcotic abuse and displacement following wars, finally the poor performance of National Tuberculosis Program Strategy (NTPS) may be one of the contributing factors, as irregular treatment is worse than no treatment of initial Tuberculosis (TB) cases.[3],[4] Iraq is one of Eastern Mediterranean Region Organization (EMRO) countries and it has intermediate to relatively high burden of TB rate (651100000).[3] Although drug resistance to antibiotics is a natural phenomenon, but in case of TB it is regarded as manmade, which is attributed to interrupted treatment and poor health serves, here, it is crucial to explore types of drug resistance to anti TB, actually two important patterns of drug resistance had rayed attention, they are the multi-drug resistant (MDR) and extensively drug resistant (XDR). MDR being resistant to at least INH and Rifampicin, while (XDR) is defined as MDR TB with resistance to at least aflouroquinolone and one-second line injectable agent (amikacin, kanamycin and / or caprcomycin).[5],[6]

AIM OF THE STUDY

The aim of the current study is to explore the epidemiology and trend of multi-drug resistant (MDR) in Kirkuk with discussion of outcome of managed cases.

PATIENT AND METHODS

A total of (44) confirmed multi-drug resistant (MDR) patients were enrolled in the current study retrospectively; they were selected according to World Health Organization (WHO) strategy and global and national guidelines.

Their age were ranging from (15-60) with of both sexes for the successful diagnosis of drug resistance to anti-TB, all Acid Fast Bacilli (AFB) positive samples were included in the study, both per rapid test Poly Chain Reaction (PCR) is currently applied to all suspected samples as well as the conventional phenotyping Drug Sensitivity Test (DST) was use being a solid culture-based method that uses egg-based media; Although this method takes a relatively long time as 2-3 months to confirm the DST results due to long turnaround time of *Mycobacterium tuberculosis* MTB culture, but it is sensitive and had excellent clinical correction.[7]
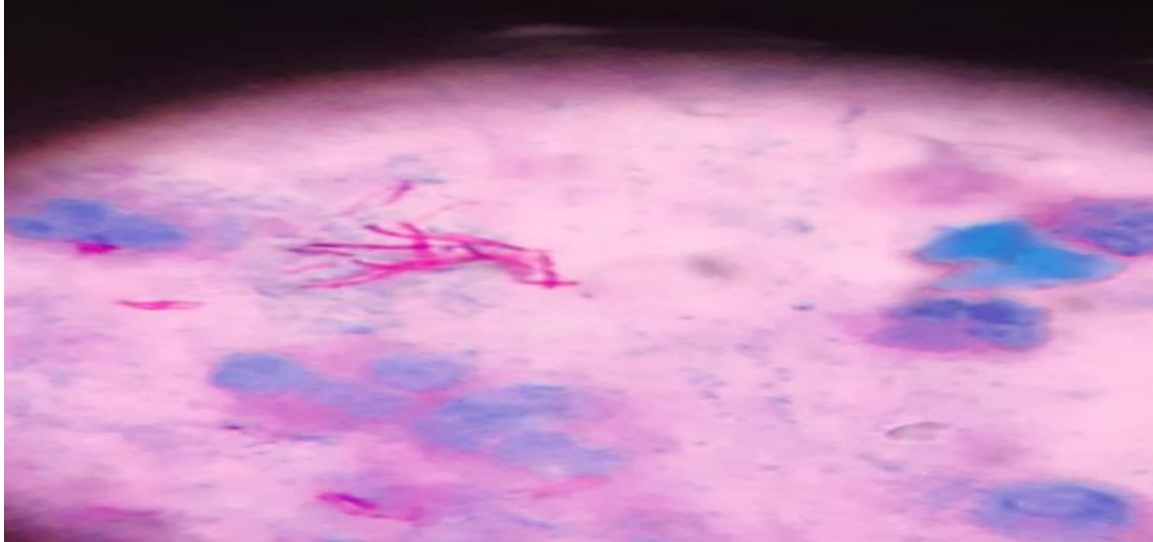
Fig1: Shows the positive *Mycobacterium tuberculosis* in Zeihl Nelseen stain.
By X100 oil immersion lens.

It is wise to mention few points on the role of PCR in rapid diagnosis of MDR; the currently used real time PCR, semi-nested under the name (Xpert MTB/ RIF) and Xpert MTB/ RIF Ultra), are both fast molecular-based tests, endorsed by WHO to detect resistant MTB and used for screening in suspected cases.**(8)**
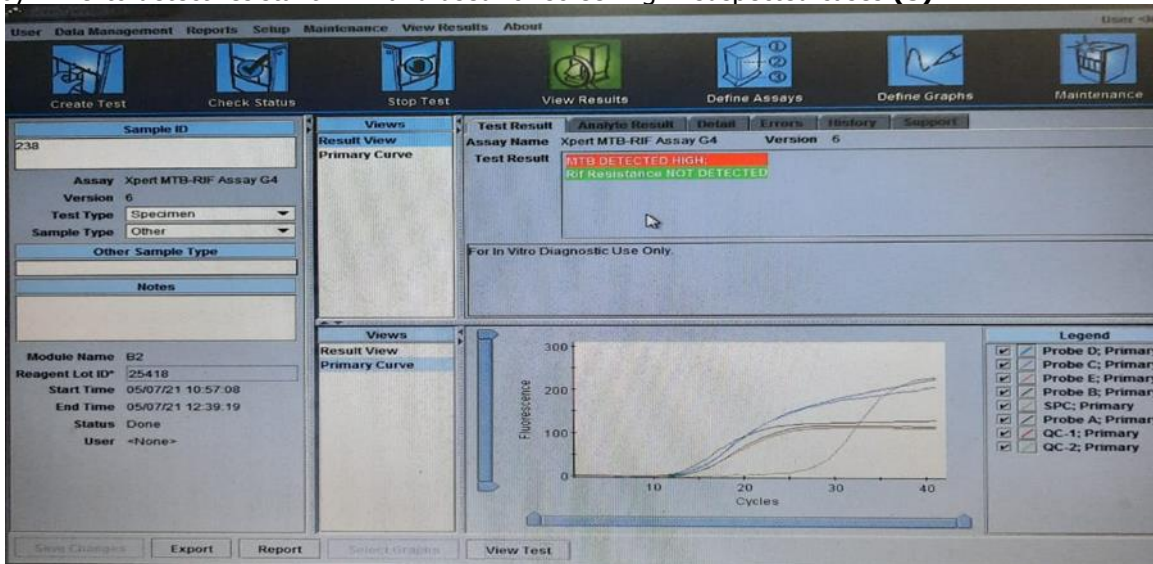

Fig. 2: Smear positive sample for TB, and diagnosis by real time PCR (Poly Chain Reaction), semi-nested which is Rifampicin sensitive.
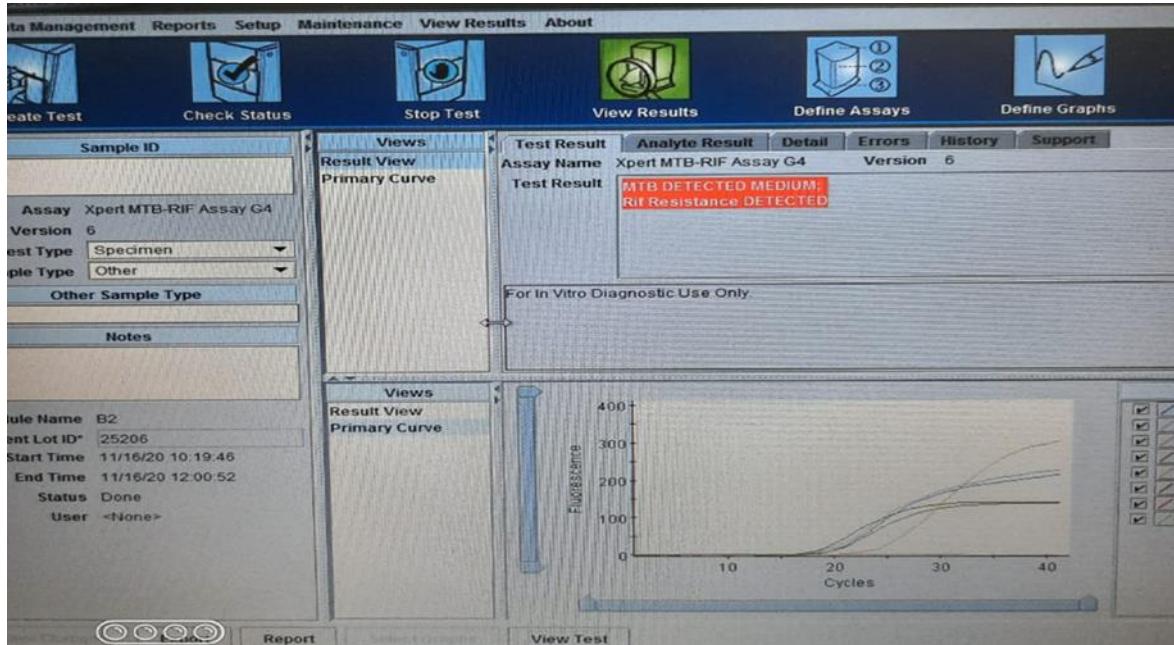
Fig. 3: Smear positive TB sample, and diagnosis by real time PCR (Poly Chain Reaction), semi-nested which is Rifampicin resistance.

Fig.4: Colony morphology of *Mycobacterium tuberculosis* (MTB) on   Lowenstein Jensen media (L J media). The colony looks rough, with   irregular surface; tough and to emulsify and creamy to light yellow which is can do Drug Sensitive Test (DST).

In the current study; both methods were used as (PCR) and solid media, egg-based conventional media. The criteria of patients selection for the culture and sensitivity in the present study was carried on according to (WHO) criteria; which included the following group of patients:-

-      Patients who had prior history.
-      Patients who have contacts with drug resistant.
-      Patients who had resistance to rifampicin or to other first line drugs.

-        Patients who have positive cultures after three or more months of treatment.

The decision of initiation of drug resistant treatment showed be reviewed be the Provincial Clinical advisory Committee (PCAC) or National Clinical Advisory Committee (NCAC) for selection of the drug regimen.

In Eastern Mediterranean region, a regional Green Light Committee (GLC) was established in 2012 to scale up the management of DR-TB; the committee's objective is to ensure adherence with (WHO) policies through technical advice.**(9)**
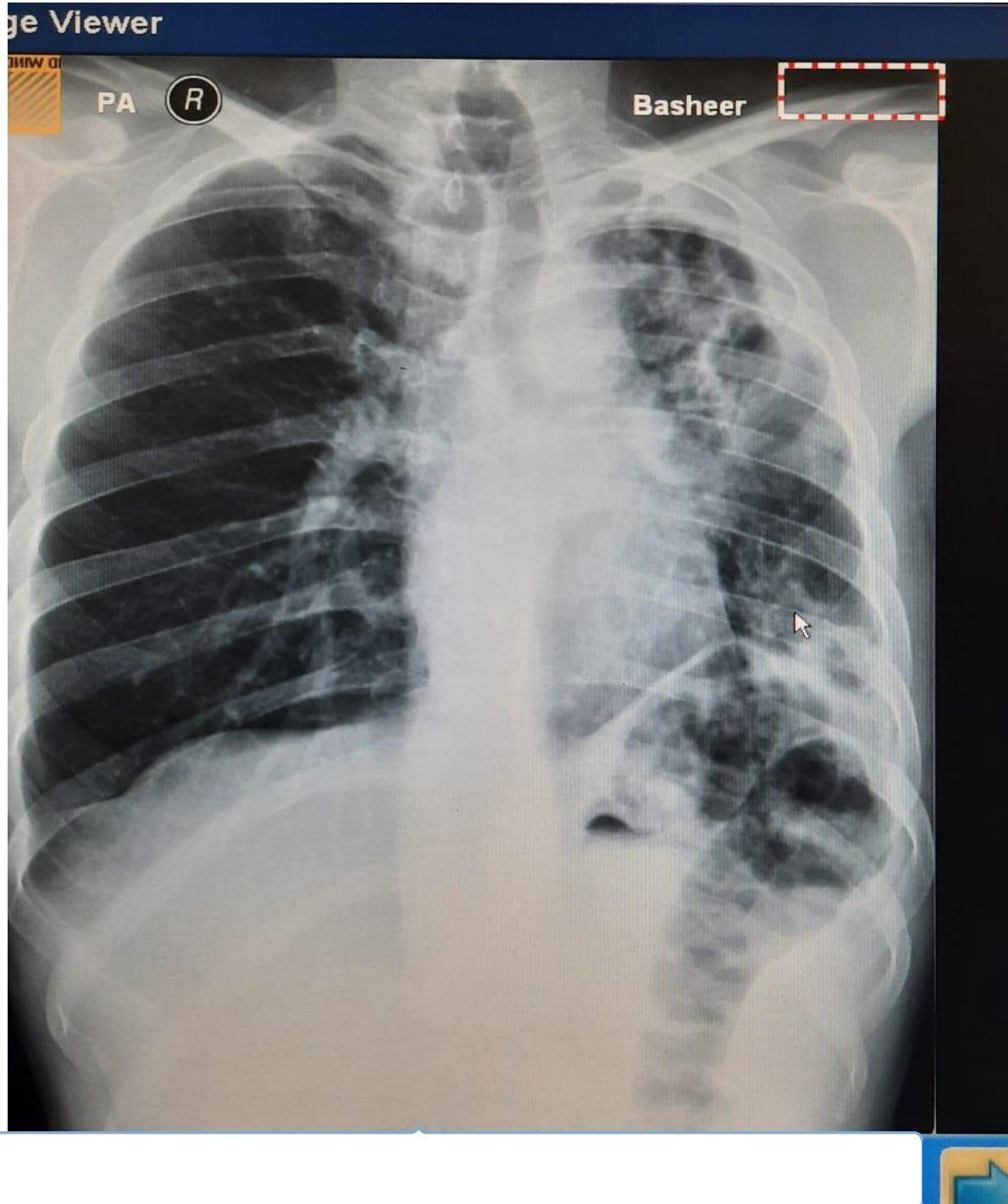
Fig. 6: Show X-Rays for lung to patient who is infected by *Mycobacterium tuberculosis* disease which it resistance to TB drugs.

RESULTS:

  A total of (2727) cases of various type of (TB) has been diagnosis in consolatory clinic of chest and respiratory diseases in Kirkuk along the last 10 years.

Table-1- shows number of confirmed (TB) cases; the highest percentage was reported in (2017), which was 358 in a percentage of (14.1%).

Table-1 show number of confirmed TB cases for last 10 years.

Years	Number of confirmed TB cases				Number cases
	Male	**Percentage**	**Female**	**Percentage**	
2014	129	49.6%	131	50.4%	260
2015	66	39%	103	61%	169
2016	101	38.4%	162	61.6%	263
2017	156	40.5%	229	59.5%	385
2018	169	47%	189	53%	358
2019	125	43%	166	57%	291
2020	97	44.5%	121	55.5%	218
2021	105	48.2%	113	51.8%	218
2022	116	42.5%	157	57.5%	273
2023	118	40.4%	174	59.6%	292
Total	1182	43.3%	1545	56.7%	2727

While table-2- shows the distribution of confirmed cases according to type of (TB) classification per WHO.
Table-2 show number cases confirmed according to type of TB-of WHO classification for last 10 years.

Year	Extra pulmonary TB		Smear negative confirmed TB		Smear positive confirmed TB		Total cases confirmed TB 10 years ago
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	
2014	48 18.5%	66 25.3%	41 15.8%	45 17.3%	40 15.4%	20 7.7%	260
2015	23 13.6%	45 26.6%	23 13.6%	28 16.6%	20 11.8%	30 17.8%	169
2016	30 11.4%	76 29%	40 15%	47 17.9%	31 11.8%	39 14.9%	263
2017	63 16.4%	79 20.7%	56 14.5%	97 25%	37 9.6%	53 13.8%	385

2018	61 17%	72 20%	74 20.7%	98 27.4%	34 9.5%	19 5.4%	358
2019	41 14.1%	78 26.8%	40 13.7%	55 19%	44 15%	33 11.3%	291
2020	38 17.4%	5525%	24 11%	4119%	35 16%	25 11.6%	218
2021	31 14%	5123.4%	39 18%	37 17%	35 16.1%	25 11.5%	218

Completed table-2- shows the distribution of confirmed cases according to type of (TB) classification per WHO.
Completed Table-2 show number cases confirmed according to type of TB-of WHO classification for last 10 years.

Year	Extra pulmonary TB		Smear negative confirmed TB		Smear positive confirmed TB		Total cases confirmed TB 10 years ago
	Male	Female	Male	Female	Male	Female	
2022	41 15%	79 29%	34 12.5%	35 12.8%	41 15%	43 15.7%	273
2023	49 16.8%	91 31.2%	24 8.2%	47 16%	45 15.5%	36 12.3%	292
Total	425 15.6%	692 25.4%	395 14.5%	530 19.4%	362 13.3%	323 11.8%	2727

To illustrate the percentage of (DR- TB) cases among all registered cases 44 in a percentage of (1.6%) form the total cases.

The table- 3 show percentage between total TB cases and DR TB of last 10 years and percentage of DR TB to TB cases.

Years	Total TB cases		Total DR to TB cases		Percentage% of DR TB to TB cases
	Number cases	Percentage cases to total cases	Number cases	Percentage cases to total cases	
2014	260	9.5%	8	18.2%	0.03
2015	169	6.2%	2	4.6%	0.01
2016	263	9.6%	4	9.1%	0.02
2017	385	14.1%	7	15.9%	0.02
2018	358	13.1%	4	9.1%	0.01
2019	291	10.7%	5	11.4%	0.02
2020	218	8%	6	13.6%	0.03
2021	218	8%	4	9.1%	0.02
2022	273	10.1%	3	6.8%	0.01
2023	292	10.7%	1	2.2%	0.003

Total	2727	100	44	100	**Percentage% of DR TB to TB cases of last 10 years 0.02**

Regarding sex distribution of DR cases, male showed higher percentage of infection (61.3%) than female (38.6%).

Table-4 The relationship of MDR TB cases in last 10 years with gender.

Age group/ year	Sex	Total

Years	Sex				Total
	Male	**Percentage**	**Female**	**Percentage**	**Total**
2014	5	62.5%	3	37.5%	8
2015	1	50%	1	50%	2
2016	3	75%	1	25%	4
2017	4	57.1%	3	42.9%	7
2018	2	50%	2	50%	4
2019	3	60%	2	40%	5
2020	4	66.7%	2	33.3	6
2021	3	75%	1	25%	4
2022	1	33.3%	2	66.7%	3
2023	1	100%	0	0%	1
Total	27	61.4%	17	38.6%	44

While table-5- shows the age distribution of drug resistance DR cases, the highest percentage was among the age group (10-24) years.

Table-5 Relationship of age group with gender of MDR TB for last 10 years among total 44 cases.

	Male	Percentage	Female	Percentage	
1-4	1	100%	0	0%	1
5-14	1	50%	1	50%	2
15-24	5	45.5%	6	54.5%	11
25-34	5	55.6%	4	44.4%	9
35-44	3	42.9%	4	57.1%	7
45-54	8	100%	0	0%	8
55-64	3	100%	0	0%	3
>65	1	33.3%	2	66.7%	3
Total	27	61.4%	17	38.6%	44

Table-6- demonstrates the distribution of drug resistance (DR) cases according to residence; the highest was among patients living in rural areas (61.3%).

Table-6 Relationship between residence and gender of MDR TB cases with their percentages.

Residence	Male	Percentage	Female	Percentage	Total number of cases
Rural	9	52.9%	8	47.1%	17
Urban	18	66.7%	9	33.3%	27
Total	27	61.4%	17	38.6%	44

Table-7- shows the relation of occupations with drug resistance (DR) cases, housewife showed highest percentage (29%) followed by students (9.1%) and only one child aged 4 years was proved to be a case of drug resistance (DR).

Table-7 Show relationship between occupation and gender with percentage , and MDR TB cases to second line drugs resistant for last 10 years among total 44 cases.

Occupation	Male	Percentage	Female	Percentage	Total	Resistant to Second line drugs

Housewife	0	0%	13	29.5%	13	**No**
Employee	2	4.5%	1	2.3%	3	**No**
Earner	20	45.5%	0	0%	20	**1 case Yes**
Retired	2	4.5%	0	0%	2	**No**
Student	1	2.3%	4	9.1%	5	**No**
Child four year	1	2.3%	0	0%	1 2	**No**
Total	26	59.1%	18	40.9%	44	**one case resistant to Second line drugs for last 10 years**

Table-8- demonstrates the baseline DST of DR among cases; the highest number were resistant to (HR) meaning MDR, (47%) followed by (HRE) (27.3%) and only 2 cases were resistant to Streptomycin and Rifampicin as mono resistant cases.

Table-8 Result of Baseline DST (resistance to 1st line drugs) of MDR TB cases with drugs resistance percentage for last 10 years among total 44 cases

DST	Number of MDR TB case	Drugs resistance (DR) percentage to total cases resistance
HRE	12	27.3%
HRES	9	20.4%
HR	21	47.7%
S	1	2.3%

R	1	2.3%
Total	**44**	**100%**

*Note DST= Drug Sensitivity Test, HRE= Isoniazid+ Rifampicin+ Ethambutol,
HRES= Isoniazid+ Rifampicin+ Ethambutol+ Streptomycin, HR= Isoniazid+
Rifampicin, S= Streptomycin, R= Rifampicin, MDR= Multi-Drugs Resistance.

Table-9- shows the outcome of treatment cases, (29.5%) were cured 45.5% had completed treatment and (11.4%) were died and one case was still under treatment .

Table-9 Show treatment outcome of MDR (Multi-Drugs Resistance) TB cases for last 10 years with percentage of MDR outcome.

Outcome of MDR TB	Number of case MDR	Percentage
Cured	**13**	**29.5%**
Loss to follow up	**5**	**11.4%**
Treatment completed	**20**	**45.5%**
Death	**5**	**11.4%**
Under treatment	**1**	**2.2%**
Total	**44**	**100%**

DISCUSSION:

WHO has ranked TB as the tenth leading cause of death and emerging as major global health problem**.(10)**   Drug resistance to anti-TB may be either primary or secondary or called acquired resistance due to poor adherence to dung or in proper regimen; in high-burden settings it many result from transmission rather than acquisition**.(11)** In Iraq, it has been documented that acquired TB resistance is expected to develop under special conditions as; in patients with large bacillary population, inappropriate or inadequate drugs, and drug complications, adding new drug to a failing regimen, interrupted treatment duration regimen which may have life threatening sequences**.(12)**   In 2008, WHO has reported that 3.6% of TB cases were confirmed to be MDR worldwide and almost 50% of them were from china and India**.(13)**   The risk factors that predispose for the development are, migration, poverty, housing, in addition to diseases as HIV, DM, all these factors has fueled the burden of MDR/ XDR- TB, so the best strategy is to apply evidence- based diagnosis and management of cases**. (14, 15)** Regarding the age group, MDR can affect all groups including children (0-14); in spite of little information and knowledge about the burden of the problem in children**.(16)** According to Jenkins et al, they reported that around 3% of children with TB have MDR- TB and unfortunately 3-5% are diagnosed, as a result 21% of children with MDR may die**.(17)** In a study carried on in Baghdad Iraq, it was shown that the ratio of male to female

with single drug resistance in previously treated TB patients was 4.211, meaning that male had far higher percentage of infection than female**.(18)**   An epidemiological study on pattern on.

DR- TB was carried on in Basra, south of Iraq for the period from 2016- 2020, for detection of DR among different types of TB (new and retreatment types), the rate of total drug resistance was increased from 2.2% to 6,7% when temporal trend was estimated, and about, on the sometime higher frequency of MDR in retreated cases has occurred in rural region**.(19)**

Regarding MDR in pediatric age group below 14 years of age; the results of the current study was in an agreement with a study carried out Zambia, that showed only one case of MDR- TB was confirmed; the reason beyond that may be difficult diagnosis of TB in children because of paucity of number of bacilli and inability of child to expectorate sputum**.(20)**   In comparing both successful and unsuccessful treatment outcome , Fayed *el tal*. In South- Africa during 2012-2019, had repeated that among HIV negative MDR- TB patient, the successful outcome was (75%) while the unsuccessful was25%)**.(21)**   WHO report summary on eleventh meeting of the regional Green Light Committee for the Eastern Mediterranean in Pakistan 2019; has documented that in Iraq, although there were strong challenges in fighting MDR- TB, the treatment success was reached to 81% among cases started treatment in 2016; on the other hand RR- TB was still under estimated as only 75 MDR- TB cases

were enrolled for treatment out of estimated 1100 cases.**(22)**

The definition of drug- resistant TB refers to active tuberculosis caused by *Mycobacterium tuberculosis* bacilli that are resistant to one or more anti- TB drugs ; the resistance is classified to different categories, mono- resistant, poly- resistant, indicating resistance to more than one drug other than both isoniazid and rifampicin; while multi- drug resistance refers to isoniazid and rifampicin with or without resistance to other anti- TB drugs; while rifampicin resistance means at least resistant to rifampicin with or without resistance to other drugs; this group includes MDR- TB, rifampicin, mono- resistant, pre- XDR and XDR- TB. The term extensively drug- resistant (XDR- TB), means MDR with resistance to any fluroquinolon and one or more of the three injectable drugs (amikacin, kanamycin, capreomycins; and the final category is the Pre- XDR- TB, referring to MDR- TB in addition to either a second- line injectable agent or a fluoroquinolone**. (23)**

Iraq, although being a country with weak health system; had started to manage Tuberculosis patients with collaboration of WHO and UNDP and the drugs are supplied free to patients, in contrast to a meta–analysis and a global review that described the catastrophic cost which is defined when a patient spends 20% or more of their annual household income on their MDR- TB diagnosis and care**. (24)**

In China a study was reported on the outcome of drug resistant cases of both genders and different age groups., out of (261) MDR cases, 186 (71.3%)had treatment success 157 (60.2%) were cured, 29 (11.1%) had treatment completed, 1 (0.4%) died, 25 (11.5%) had failure or relapse and 21 (8.1%) were lost to follow up and finally 23 (8.8%) were transferred out**.(25)** In Nigeria, male were affected as twice as female 66.93% versus 33.07%, while the highest age group affected by drug resistance (DR) was between 30- 39 years, whereas no infection was reported in pediatric age group**.(26)**

CONCLUSION

In the current study the overall total cases of DR- TB along 10 years was 1.6% among all registered TB cases. The favorable outcome (cure and successful treatment) was 75%, death was (11.4%) and loss to follow up was (11.4%).

RECOMMENDATION:

It is recommended to manage and follow up the new cases and to decrease the default and loss follow up in addition to decrease the burden of interruption by patient counseling and education specially in Iraq were the TB services are free and augmented by many international organization as World Health Organization (WHO), United National Development Programmed, (UNDP) International Organization Migration (IOM), and others, to prevent the development of DR- TB in Iraq.

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