Original Research

Pharmacotherapy and associated risk factors for pulmonary tuberculosis

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Abstract

Tuberculosis is communicable disease which is common and often deadly infectious disease caused by *mycobacterium tuberculosis*. Tuberculosis continues to be a major public health problem in the world. The aim of this study is to assess prevalence and associated risk factors of pulmonary tuberculosis. Treatment and development of multidrug-resistant tuberculosis were also considered. Drugs for Pulmonary tuberculosis confirmed cases used in calculating tuberculosis prevalence in Libya which is obtained from archive department of Abu Seta Hospital. Data obtained from 427 files during 2019 determine the incidence and epidemiology of tuberculosis in Libya. For a total of 427 confirmed cases of pulmonary tuberculosis, about 75.0% of the cases were male and most of the patients (55.0%) were within the age group of 20 - 40 years old. Of the study patients, 114 patients (26.7%) were viral infected and most of the viral infected cases were in the age group of 20 - 40 years and the majority of this age group patients (n = 41, 53.2%) were infected with HIV/HCV, while the least percentage in this group age were infected with HIV/HBsAg (01.3%). Among 427 cases, 73 cases (17.1%) were comorbid with other chronic diseases. Of the 73 cases, 54 cases (74.0%) were diabetes mellitus whereas only 1.4% of them had bronchial asthma, Parkinsonism and renal failure. The drug therapy of active tuberculosis disease needs combination chemotherapy to escape the selection of naturally occurring drug-resistant mutants. Amongst current anti tuberculosis drugs, the rifamycins hold the highest potential for shortening treatment and improving effects. Prevalence of smear positive tuberculosis and bacteriologically confirmed that a high rate of tuberculosis among unemployed population. This study reported that the highest incidence rate is found in people who are smokers.

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Introduction

Tuberculosis (TB) is a potentially severe infectious disease caused by *Mycobacterium tuberculosis* which mainly affects lungs by spreading from a person to another through the air. TB usually attacks lungs (pulmonary TB) but it can affect other sites as kidney, spine and brain (extra-pulmonary TB) [1]. TB is curable and preventable, with most people (85%) who develop TB disease can successfully be treated [1, 2]. However, TB remains a common public health problem in Libya and other countries that affects all age group globally. According to the world health organization (WHO) latest data, 10.0 million people fell ill with TB in 2019, a number that has slowly been declining in recent years. There were estimated 1.2 million TB deaths among HIV-negative people in 2019 and an additional 208 000 deaths among HIV positive people. TB effects of both sexes and all age groups, however, the highest burden is adult men (aged ≥ 15 years) accounted for 56% of the people who

developed TB in 2019; women accounted for 32% and children (aged < 15 years) for 12%. Among all those affected 8.2% were people living with human immunodeficiency virus (HIV) [1, 2].

Pharmacotherapy of TB is well established discipline, with over the last seven decades of clinical knowledge and trials. The vital multidrug therapy of drug-susceptible TB lasts six months and sometimes more and has never been improved as to recent standards. Multi-drug resistant tuberculosis and tuberculosis in persons with other infection as HIV need additional therapy challenges [3]. Among existing anti-TB drugs, the rifamycins hold the greatest potential for shortening treatment and improving outcomes, in HIV-infected and HIV-uninfected populations, without dramatic increases in toxicity. The challenge in TB pharmacotherapy is to develop well-tolerated, efficacious, short-duration regimens that can successfully be used against drug-resistant and drug-resistant TB in a heterogeneous population of patients [4]. Anti-TB medications: rifampin, isoniazid, pyrazinamide and ethambutol are FDA-approved for treatment of TB [5]. Combination and duration of medication use in treatment count on several factors related to the patient and to the disease [6]. A serious complication is multi-drug-resistant tuberculosis (MDR-TB) which distinguished from its resistance to first-line drugs isoniazid and rifampin [7]. Treatment for MDR-TB is gradually advancing and plans are frequently changing. On the other hand, second-line drugs are kanamycin, capreomycin and amikacin. fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin) are used when drug resistance develops to the first-line medications. In addition, drugs that have lately received FDA approval for MDR-TB are pretomanid, bedaquiline and linezolid [8].

The important risk factors that increases the incidence of the disease are age, gender, malnutrition, HIV infection, diabetes mellitus, alcohol, use of immunosuppressive drugs, tobacco smoke and socioeconomic factors. All of them play a role at the individual and population levels [9, 10]. However, there is insufficient data in Libya. Thus, this study aimed at filling this gap by investigating the prevalence and risk factors contributing recent transmission of pulmonary TB in Libyan patients.

Materials and methods

Study design, area and period: A cross-sectional study was carried out from January to December 2019 among adults of confirmed diagnosis of pulmonary TB and on standard anti-TB treatment at a governmental hospital in Abu Seta Hospital, Tripoli, Libya. This is the only Referral Hospital for TB in Libya. This a retrospective study contains 427 patients with known cases of TB.

Study population and eligibility criteria: All TB-positive patients aged 15^{+} who began on anti-TB drugs during the period of study and were treated for at least one month were eligible for study enrolment.

Data collection procedure socio-demographic characteristics: Date was collected from medical records and recorded on predesigned-data sheet. Different variables which extracted from medical records of each case were included: Socio-demographic details (age, gender, educational level, occupation status, and smoking habit). Details about patient's disease and concomitant illness were recorded. Details of viral infectious disease such as HIV, HBV and HCV were also recorded.

Ethical considerations: This study was carried out in compliance with the International Declaration (Helsinki) on the ethical principles of medical research involving human subjects following approval by the Official Ethics Committee of University of Tripoli and a permission from National Center of Disease Control (CDC) as well as the Hospital (2019). Informed consent was granted by the Official Ethics Committee of the University, CDC, and the hospital due to the retrospective nature of the study, as all the data were collected from routine medical records. Confidentiality was guaranteed by neglecting names or any individual identifiers. Further, data were kept protected via out the research process to limit accessibility to others (not involved in projects).

Data collection procedure and socio-demographic characteristics: Data were entered using EpiData Version 3.1 and exported to SPSS Version 20.0 for analysis. Descriptive statistics were used for the analysis of socio-demographic and clinical characteristics. Statistical measures such as frequency distribution, percentage, mean and standard deviation were used.

Results

Four hundred and twenty-seven confirmed cases of pulmonary TB were enrolled in this study. The socio-demographic characteristics of the patients are shown in **Table 1**. 320 patients were males representing 75% of the cases and 107 (25%) were female patients.

The peak age group was in a group of 20 - 40 years, representing 278 (56.11%) of the patients followed by an age group of > 40 years, representing 29.04% of the cases. The smallest group consists of those patients with an age

group of < 20 years, representing 5.85% of the whole study population. However, the most of the patients with pulmonary TB were unemployed 163 (38.17%) while 124 of the patients (29.04%) were self-employed. Out of 320 male patients, 201 of the male patients representing 62.81% were smokers and none-smokers were females. Out of 427 patients with pulmonary TB, 73 patients (17.09%) were had other comorbid conditions as shown in **Table 2**. 54 cases were diabetes mellitus whereas only 1.4% of them had following diseases: bronchial asthma, Parkinsonism and renal failure. Of the study patients, 114 cases (26.7%) were viral infected and most viral infected cases were in age group of 20 - 40 years and the majority of this age group were infected with HIV and HCV by 41 cases (53.2%) while the least percentage was 1.3% were infected with HIV and HBsAg (**Table 3**).

Table 1: Socio-demographic and clinical characteristics of patients with pulmonary TB

Variables	Gender			Age group (years)			
	Male	**Female**	**Total**	**< 20**	**20-40**	**>40**	**Total**
n (%)	320 (74.94)	107 (25.06)	**427 (100)**	025 (5.85)	278 (56.11)	124 (29.04)	**427 (100)**

Variables	Occupation					
	Student	**Employed**	**Retired**	**Self-employed**	**Un-employed**	**Total**
n (%)	37 (8.67)	82 (19.20)	21 (4.92)	124 (29.04)	163 (38.17)	**427 (100)**

Variables	Smoking habit				Chronic diseases (comorbidity)			Infectious viral disease		
	Smokers	**Exposure smokers**	**Non smokers**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
n (%)	201 (47.07)	030 (7.03)	196 (45.90)	**427 (100)**	073 (17.09)	354 (82.90)	**427 (100)**	114 (26.7)	313 (73.3)	**427 (100)**

Table 2: Chronic diseases (comorbidity) associated with pulmonary TB

Comorbidity	Age group (years)			
	< 20 n (%)	**20 - 40 n (%)**	**> 40 n (%)**	**Total** n (%)
Bronchial Asthma	00	01(4.2)	00	01 (1.4)
Diabetic mellitus	03 (75)	18 (75)	33 (73.3)	54 (74)
Hypertension	01 (25)	02 (8.3)	04 (8.9)	07 (9.6)
Epilepsy	00	02 (8.3)	01(2.2)	03 (4.1)
Chronic obstructive pulmonary disease	00	00	04 (8.9)	04 (5.5)
Psychoses	00	01 (4.2)	01 (2.2)	02 (2.7)
Parkinsonism	00	00	01 (2.2)	01 (1.4)
Renal failure	00	00	01 (2.2)	01 (1.4)
Total	**04 (05.5)**	**24 (32.9)**	**45 (61.6)**	**73 (100)**

Table 3: Patients with viral infections, HBV, HCV and HIV co-infection with pulmonary TB

Viral infection	Age group (years)			
	< 20 n (%)	**20 - 40 n (%)**	**> 40 n (%)**	**Total** n (%)
HIV	01 (100)	17 (22.1)	04 (11.1)	22 (19.3)
HCV	00	6 (07.8)0	3 (08.3)0	9 (07.9)0
HBsAg	00	5 (06.5)0	2 (05.6)0	7 (06.1)0
HIV/HCV	00	41 (53.2)	25 (69.4)	66 (57.9)
HIV/HBsAg	00	1 (01.3)0	00	1 (00.9)0
HIV/HCV/HBsAg	00	7 (09.1)0	2 (05.6)0	09 (7.9)
Total	**01 (0.9)**	**77 (67.5)**	**36 (31.6)**	**114 (100)**

Discussion

The socio-demographic data and risk factors contributing pulmonary tuberculosis infection in Libyan patients revealed that the majority of patients are males (75%). This finding was in line with the previous study [11] who reported the same ratio. This can be explained that male patients are normally working in some conditions considered to be easy for transmission of TB and its pathogenicity. In Libya, the difference related to gender may also attributed to immune response which is known to be different in gender. Further evidence suggests that physiological levels, estrogen is beneficial to the immune system whereas the male gender hormone, testosterone, is immunosuppressive [12]. More than half of the patients in this study is 20 - 40 years old. In a similar previous study showed that about half of the cases were in the age group ranges of 26 - 45 years [13]. Whereas in another study showed that third of the patients were in age group of 20 - 29 years [14]. This can be explained that the reason lies in this group of people are the most exposed category to the crowds and are economically active age group and representing the majority of the population. The present findings indicate that a higher incidence is in non-employee people. This outcome can be explained either poor conditions of the work itself which increase the risk of incidence of TB. The poor quality of life has an effect of decreasing health care and increasing incidence of infections to the disease.

Smoking has been identified as significant risk factor for developing TB by four times [15], this is well established fact in several previous studies [16, 17]. However, in present study, out of 427 patients, about half of the male are smokers which represent a high percentage (65%) of the total male patients. Thus, smoking habit might have contributed to TB in male patients as this habit was not exist among female patients. Passive and active exposures to cigarette smoke are associated with an increased risk of infection of *M. tuberculosis* and development of active TB. However, present study showed that 5% were exposure smoker. A study published in 2007, reported a strong correlation between smoking and active TB as well as passive smoking correlated moderately with TB and the need for treatment [18, 19]. Smoking also increases mortality from TB by increasing the incidence of the disease [20]. TB can also lead to complications of other diseases, such diabetes mellitus, therefore, important to identify the comorbidities in TB patients in order to ensure receive appropriate therapy of both condition. Patients with diabetes mellitus are at higher risk of progressing from the initial infection to active TB [1]. Thus, the present study shows that a higher incidence of pulmonary TB found in patients of diabetes mellitus and most affected aged group of patients (> 40 years). This finding agrees with the study reported by Workneh et al. [19] who found that TB and diabetes mellitus comorbidity is universal globally and older age is a risk factor for this comorbidity. In another study, diabetes was reported to be a predominant risk factor [21]. This can be explained that this uncontrolled chronic disease can deteriorate the immune system which increased the incidence of TB. Viral infection also is another risk factor for pulmonary TB, HIV co-infection is the most immunosuppression risk factor for development of TB disease [22]. It increases the risk of latent TB reactivation by 20-fold [23]. Hepatitis B or C co-infection with TB increase the risk of treatment failure [24] and activates latent TB [25] and increase the risk of mortality [26]. Our results show that some patients are viral infected and most viral infected cases were in age group of 20 - 40 years old and the majority of this age group were co-infected with HIV and HCV, while the small percentage was infected with HIV and HBsAg. A recent study by Berhanu et al. [26] showed that in a total of 3537 TB patients, the prevalence of hepatitis B and C viral infection among TB patients were found to be 15 and 17%, respectively. While, the prevalence of hepatitis B virus infection among HIV positive TB patient was 35%, but this prevalence inflated to 50% of HIV infected TB patients [27]. This can be explained easily that HIV with HCV virus completely destroy the immune system of its patient which not increase the risk of TB infection but it opens the wide door for any other infection [20]. With regard to pharmacotherapy of TB, the treatment of active TB disease involves a combination chemotherapy to reduce the selection of naturally occurring drug-resistant mutants. Unlike other bacterial infections, combination initially chosen was not based on complementary or potentially synergistic, mechanisms of action. Rather, early regimen was defined by what was available in the middle of the last century, namely, streptomycin, *para*-aminosalicylic acid and isoniazid. As new medicines were developed, they were verified with older medicines until the present regimen of isoniazid, rifampin and pyrazinamide (often with ethambutol as fourth drug) was defined. Since not all possible combinations of drugs, doses and frequencies have been clinically tested, it is quite likely that other approaches based on the currently available drugs may yield superior regimens [3]. Thus, TB pharmacotherapy could have aimed to successfully plan for a well-tolerated, efficacious and short-duration

regimen especially against drug-resistant and drug-resistant TB in some patients.

Conclusion

TB continues to be a public health problem in Libya. However, this study demonstrated some of the factors contributing to occurrence of pulmonary TB as gender, uncontrolled diabetic mellitus, HIV and HCV. The most common drug used for Libyan TB patient is INH. This, however, is a causing drug for hepatitis after a long administration especially with high doses.

Ethical issues

Including plagiarism, Informed Consent, data fabrication or falsification and double publication or submission have completely been observed by authors.

Conflict of interest

The authors declare that there is no competing interest.

Author's contribution

Sherif RF collected and analyzed data. Saeed NM supervised the data collection. Sherif RF and Saeed NM interpreted the findings and wrote the manuscript. Sherif FM critically reviewed the final form of the manuscript. All authors proofread and approved the final version of this manuscript.

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