Original research

CHARACTERISTICS AND TREATMENT OUTCOMES OF NEW PULMONARY TUBERCULOSIS PATIENTS WITH COMORBIDITIES IN THE SAMARKAND REGION, UZBEKISTAN

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ABSTRACT

Despite good progress made in the fight against tuberculosis (TB), the disease remains a major public health threat worldwide. Comorbid diseases that increase the risk of developing active TB and have a negative impact on final treatment outcomes include HIV and diabetes mellitus. The effect of other conditions such as peptic ulcer and asthma/chronic obstructive pulmonary disease (together defined as COPD for this study) on TB is not clear. There is also little information in Uzbekistan about the interaction between these comorbidities and TB. This study was therefore carried out to assess the characteristics and treatment outcomes of TB patients with these specific comorbid conditions. This was a descriptive study of a cohort of patients with newly diagnosed pulmonary TB with specific comorbidities in the Samarkand region, Uzbekistan, from 2012 to 2013. There were 1260 patients with newly diagnosed TB, of whom 193 (15%) had comorbidities: diabetes (n = 116, 9%), HIV (n = 27, 2%), COPD (n = 29, 2%) or peptic ulcer (n = 22, 2%). Diabetes, COPD and peptic ulcer disease were mainly found in patients aged 55 years and above, while HIV coinfection was mainly found in patients aged 25–54 years. Clinical characteristics were fairly similar between those with and without comorbidities. Compared with those who had no comorbidities, patients with comorbidities had significantly reduced treatment success (78% versus 92%), a higher rate of death (9% versus 2%) and higher treatment failure (2% versus <1%). In conclusion, more attention needs to be paid to a systematic and timely approach to the screening and treatment of comorbidities in TB patients, to improve treatment outcomes and reduce mortality.

Keywords: ASTHMA AND CHRONIC OBSTRUCTIVE AIRWAYS DISEASE, CENTRAL ASIA, DIABETES MELLITUS, HIV, OPERATIONAL RESEARCH, PEPTIC ULCER, SORT IT, TUBERCULOSIS

INTRODUCTION

Despite good progress in the fight against tuberculosis (TB), the disease remains a major public health threat worldwide and an important killer of men, women and children. TB is highly linked to poverty and the socioeconomic environment, but there are also important codeterminants and comorbidities associated with the risk of active disease and outcomes during treatment *(1)*. Indeed, the association with comorbidities and their management is explicit in pillar 1 of the World Health Organization's (WHO's) new *End TB Strategy (2)*. Important comorbidities

that can increase the risk of active TB in persons with latent TB infection, and therefore can adversely affect final treatment outcomes, include HIV and diabetes mellitus, as well as other conditions such as peptic ulcer disease, asthma and chronic obstructive pulmonary disease (together defined as COPD for the purpose of this study).

HIV increases the risk of TB by about 30 times compared with the normal population, and TB patients who are coinfected with HIV and receiving only standardized chemotherapy for TB have poor outcomes compared with those who have TB only *(3)*. The case-fatality rate is higher, and in those who complete treatment there is a higher rate of recurrent TB. Treatment outcomes are worse for several reasons: stigma leading to delays in seeking care and thus more advanced disease at the time of presentation to health services; difficulties in making an accurate diagnosis of smear-negative TB; and HIV-related opportunistic infections *(4)*. In 2013, it was estimated that 1.1 million persons had HIV-associated TB, of whom 360 000 died *(5)*.

Diabetes increases the risk of TB by about two or three times *(6, 7)* and although the interaction between the two diseases is not as strong as with HIV, the absolute numbers of persons with diabetes (estimated at 382 million worldwide in 2013, compared with 35 million living with HIV) means the association is of important public health and programmatic significance *(8)*. In 2012, the population-attributable fraction of diabetes for adult TB cases globally was estimated at 15%, and the number of adult TB cases associated with diabetes was 1 042 000, almost the same the number observed for HIV-associated TB *(9)*. TB patients who also have diabetes tend to take a longer time for sputum conversion from positive to negative, and are also at increased risk of unfavourable outcomes such as death and treatment failure, or of relapse after successful completion of treatment *(10)*.

Although the effects of HIV and diabetes on the risk of TB and TB treatment outcomes are well documented and established, this is not the case for COPD and peptic ulcer, for which there is limited evidence on their effects on TB treatment outcomes. There is anecdotal evidence that, anti-TB medication may aggravate peptic ulcer, which may affect adherence to treatment and negatively affect treatment outcomes. Conditions such as COPD may be associated with fibrotic changes in the lung and reduced drug penetration into lung tissues, all of which may have an adverse effect on treatment success. Furthermore, the use of corticosteroids to manage COPD may increase the risk of active TB *(1)*.

Uzbekistan is a country with a high TB burden *(11)*. In addition, high levels of multidrug-resistant TB (MDR-TB – defined as resistance to both isoniazid and rifampicin) may further complicate the management of comorbidities and particularly TB treatment outcomes. In the Samarkand region of Uzbekistan, as per national guidelines *(12)*, individuals with HIV, diabetes, chronic lung diseases and peptic ulcer are routinely screened for TB in the TB facilities, using a questionnaire, tuberculin skin test, radiography and sputum investigation. To the authors' knowledge, there is no published literature from the region that has assessed the outcomes of TB patients with such comorbid conditions. This retrospective cohort study was therefore carried out in order to better understand the influence of these specific comorbidities on TB treatment outcomes. The aim of this study was to assess the characteristics and treatment outcomes of TB patients in the Samarkand region of Uzbekistan who had specific comorbid conditions. Specific objectives for the period 2012–2013 among newly registered TB patients were to report on: (i) the number (and proportion) with specific comorbidities such as diabetes, HIV, peptic ulcer and COPD; (ii) their sociodemographic and clinical characteristics; and (iii) treatment outcomes stratified by the presence and type of comorbidity.

METHODS

STUDY DESIGN

This was a retrospective descriptive cohort study of new pulmonary TB patients with comorbid diseases.

SETTING

General setting

Uzbekistan is a central Asian country with an estimated population of around 30 million. Uzbekistan comprises 12 provinces (oblasts), one autonomous republic (Republic of Karakalpakstan) and the capital city, Tashkent. Samarkand is one of the 12 provinces, with a population of approximately 3.4 million; more than 40% of the population lives in urban areas.

TB control

The DOTS strategy (Directly Observed Treatment, Short course) *(13)* was adopted in Samarkand in 2000 and expanded to the entire region by the end of 2004. Case finding, diagnosis, treatment regimens, treatment outcomes and monitoring and evaluation follow WHO guidelines for the treatment of TB *(14)*. TB control measures in the region are maintained by a network of TB facilities and the primary health-care system.

In the Samarkand region, there are three TB clinics, 14 TB departments and one specialized sanatorium for children. In line with local guidelines, all new TB patients start treatment through inpatient care and continue it in outpatient primary health-care facilities *(15)*. Only two TB clinics have inpatient units; a total of 765 hospital beds are designated for TB patients in the region. Patients are sent to one of the two inpatient units, according to their place of residence. Thus, information about all new patients is collected in the registers of the two TB inpatient departments. These two inpatient clinics are basic medical units for the region and each patient's registration details and notes about treatment outcomes are collected there. In 2012, one of the two TB clinics was closed for reconstructions works and some patients started treatment outside the Samarkand region in the neighbouring region. Therefore, the database for 2012 included new pulmonary TB patients from only one clinic, located in Samarkand region, while, for 2013, information from both TB clinics was included.

STUDY POPULATION

The study included all new pulmonary TB patients who started treatment in the inpatient TB clinics of the Samarkand oblast, during 2012–2013. Patients with MDR-TB were excluded from the study.

DATA VARIABLES, SOURCES OF DATA AND DATA COLLECTION

Data variables included baseline data of TB registration number, date of starting treatment, site of TB, sputum smear results, residence status, age, sex, education, employment status, marital status, HIV status, a past history of diabetes or a new diagnosis of diabetes based on results of fasting blood glucose at the time of TB registration, and a past or current history of COPD or peptic ulcer. Treatment outcomes were based on standardized definitions of cured, treatment completed, died, failed, lost to follow-up and transferred out. The sources of data for the study were the TB patient registers and individual TB patient cards from the two inpatient departments in Samarkand. Data were collected from July to December 2014 using a paper-based questionnaire.

DATA ANALYSIS

The data were single entered to EpiData 3.1 (EpiData Association, Odense, Denmark). Sociodemographic and clinical characteristics of patients with pulmonary TB and comorbidities were described using frequencies and proportions. In addition, treatment outcomes of patients according to the presence or absence of comorbidities were described and compared using the chi-square test (adjusted), with relative risks (RRs) and 95% confidence intervals (CIs). Levels of significance were set at 5%, using two-tailed *P* values.

ETHICS

Permission to conduct this study was obtained from the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan. Ethical approval was additionally sought from the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease in Paris, France.

RESULTS

During the 2-year period, there were 1260 patients registered with new TB, of whom 193 (15%) had a comorbid condition such as diabetes, HIV, COPD or peptic ulcer (see Table 1). One patient had two comorbidities. There was no significant difference in the frequency of comorbid conditions among new pulmonary TB patients between the two years. The most common comorbidity was diabetes, which

TABLE 1. THE NUMBER AND PROPORTION OF NEW TUBERCULOSIS PATIENTS WITH COMORBIDITIES, SAMARKAND REGION, UZBEKISTAN, 2012–2013

Characteristics	2012, n (%)	2013, n (%)	Total, n (%)
All new TB patients	461	799	1260
TB patients with comorbidities	64 (14)	129 (16)	193 (15)
Diabetes mellitus	41 (9)	75 (9)	116 (9)
HIV	12 (3)	15 (2)	27 (2)
COPD	5 (1)	24 (3)	29 (2)
Peptic ulcer	6 (1)	15 (2)	22 (2)

COPD: asthma and/or chronic obstructive pulmonary disease; TB: tuberculosis.

accounted for 60% of the specified comorbid conditions over the 2 years.

Sociodemographic and clinical characteristics of TB patients with and without comorbidities are shown in Table 2 . There were more men than women in all groups, and especially those with HIV infection. For those with no comorbidities, there was a fairly even spread of age; however, in patients with diabetes, COPD or peptic ulcer, substantially more patients were aged 55 years and above (72% for diabetes, 72% for COPD and 55% for peptic ulcer), while all patients with HIV infection were aged 25–54 years. Residence was rural in over 80% of all groups, except for HIV, where 33% of the patients had an urban residence. Most patients were married, although the percentage was lower for those with HIV infection. For those with no comorbidities, there was a fairly even spread of employment categories. However, the majority of those with HIV were unemployed (89%), while the majority of those with diabetes, COPD or peptic ulcer were pensioners or recorded as invalids (73% for diabetes, 72% for COPD and 68% for peptic ulcer). Clinical characteristics were fairly similar between the different groups, with more patients being sputum smear negative for acid-fast bacilli and more having no cavities on chest radiography. In patients with HIV infection, there was a higher frequency of negative sputum smears and no radiographic cavities, while in those with diabetes there was a higher frequency of positive sputum smears and radiographic cavities.

Treatment outcomes in all patients, and stratified by those with no comorbidities and those with comorbidities (combined and separate), are shown in Table 3. There was a significantly lower risk of treatment success in patients with comorbidities

TABLE 2. SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE NEW TUBERCULOSIS PATIENTS WITH AND WITHOUT COMORBIDITIES, SAMARKAND REGION, UZBEKISTAN, 2012–2013

Characteristics	Patients with no comorbidities, n (%)	Patients with comorbidities			
		Diabetes mellitus, n (%)	HIV, n (%)	COPD, n (%)	Peptic ulcer n (%)
All patients	1067	116	27	29	22
Male	602 (56)	63 (55)	22 (81)	17 (59)	12 (54)
Female	465 (44)	53 (45)	5 (19)	12 (41)	10 (46)
Age, years					
0–14	3 (<1)	0	0	0	0
15–24	80 (7)	1 (1)	0	0	2 (9)
25–34	176 (17)	3 (3)	6 (22)	3 (10)	2 (9)
35–44	176 (17)	2 (2)	11 (41)	1 (3)	1 (4)
45–54	156 (15)	26 (22)	10 (37)	4 (14)	5 (23)
55–64	189 (18)	47 (40)	0	10 (34)	7 (32)
≥65	287 (27)	37 (32)	0	11 (38)	5 (23)
Residence					
Urban	154 (14)	11 (10)	9 (33)	5 (17)	0
Rural	913 (86)	105 (90)	18 (67)	24 (83)	22 (100)
Marital status					
Married	874 (82)	109 (94)	20 (74)	26 (90)	19 (86)
Single	167 (16)	5 (4)	3 (11)	2 (7)	3 (14)
No data	26 (2)	2 (2)	4 (15)	1 (3)	0
Employment					
Employed	51 (5)	3 (3)	1 (4)	1 (3)	1 (4)
Not employed	504 (47)	28 (24)	24 (89)	7 (24)	6 (27)
Student/pupil	17 (2)	0	0	0	0
Pensioner	413 (39)	73 (63)	0	18 (62)	12 (54)
Invalid	78 (7)	12 (10)	2 (7)	3 (10)	3 (14)
No data	4 (<1)	0	0	0	0
Sputum smear results for acid-fast bacilli					
Sputum positive	354 (33)	48 (41)	9 (33)	10 (34)	8 (36)
Sputum negative	713 (67)	68 (59)	18 (67)	19 (66)	14 (64)
Cavities on chest X-ray					
Yes	439 (41)	52 (45)	7 (26)	12 (41)	9 (41)
No	627 (59)	64 (55)	20 (74)	17 (59)	13 (59)
Site of TB					
Pulmonary	1046 (98)	114 (98)	25 (93)	29 (100)	22 (100)
Pulmonary and extrapulmonary	21 (2)	2 (2)	2 (7)	0	0

COPD: asthma and/or chronic obstructive pulmonary disease;
TB: tuberculosis.

TABLE 3. TREATMENT OUTCOMES AMONG NEW TUBERCULOSIS PATIENTS WITH AND WITHOUT COMORBIDITIES, SAMARKAND REGION, UZBEKISTAN, 2012–2013

Characteristics	Enrolled for treatment, n	Treatment success, n(%)	Unfavourable treatment outcome			
			Died, n (%)	Failure, n (%)	Lost to follow-up, n (%)	Not evaluated, n(%)
All patients	1260	1136 (90)	45 (3)	8 (<1)	27 (2)	44 (3)
Patients with no comorbidities	1067	985 (92)	27 (2)	4 (<1)	20 (2)	31 (3)
Patients with comorbidities	193	151 (78)	18 (9)	4 (2)	7 (4)	13 (7)
Diabetes mellitus	116	97 (84)	9 (7)	3 (3)	1 (1)	6 (5)
HIV	27	14 (52)	4 (15)	3 (11)	1 (4)	5 (18)
COPD	29	23 (79)	3 (10)	1 (4)	1(4)	1 (4)
Peptic ulcer	22	18 (82)	2 (9)	0	1 (4)	1 (4)

COPD: asthma and/or chronic obstructive pulmonary disease;
TB: tuberculosis.

compared with those with no comorbidities (RR: 0.8, 95% CI: 0.8– 0.9, $P < 0.001$) and these differences were also significant when patients with diabetes (RR: 0.9, 95% CI: 0.8–0.98, $P < 0.01$) and patients with HIV infection (RR: 0.6, 95% CI: 0.4–0.8, $P < 0.001$) were also compared with those who had no comorbidities. In those with comorbidities, there was a significantly higher risk of death (RR: 3.7, 95% CI: 2.1–6.6, $P < 0.001$), treatment failure (RR: 5.5, 95% CI: 1.4–22.0, $P = 0.04$) and transfer out (RR: 2.4, 95% CI: 1.2–5.0, $P = 0.02$) compared with those who had no comorbidities. Again, these differences in the risk of death were also significant for patients with diabetes (RR: 3.1, 95% CI: 1.5–6.4, $P < 0.01$) and patients with HIV infection (RR: 5.9, 95% CI: 2.2–15.6, $P < 0.01$) compared with those who had no comorbidities.

Unfavourable treatment outcomes (defined as any outcome other than treatment success) are shown in Table 4. There was a significantly higher risk of unfavourable outcomes in patients with comorbidities compared with those who had no comorbidities and these significant risks were also found for patients with diabetes, HIV and COPD.

TABLE 4. UNFAVOURABLE TREATMENT OUTCOMES AMONG NEW TUBERCULOSIS PATIENTS WITH AND WITHOUT COMORBIDITIES, SAMARKAND REGION, UZBEKISTAN, 2012–2013

Characteristics	Enrolled for treatment, n	Unfavourable treatment outcome,[a] n (%)	RR (95% CI)	P value[b]
All patients	1260	124 (9.8)		
Patients with no comorbidities	1067	82 (7.7)	Reference	
Patients with comorbidities	193	42 (21.8)	2.8 (2.0–4.0)	<0.001
Diabetes	116	19 (16.4)	2.1 (1.3–3.4)	<0.01
HIV	27	13 (48.1)	6.3 (4.1–9.8)	<0.001
COPD	29	6 (20.7)	2.7 (1.3–5.7)	0.02
Peptic ulcer	22	4 (18.1)	2.4 (0.9–5.9)	NS

CI: confidence interval; COPD: asthma and/or chronic obstructive pulmonary disease; NS: not significant; RR: relative risk; TB: tuberculosis.
[a]Died, treatment failure, lost to follow-up, transferred out and not evaluated.
[b]Compared with patients who had no comorbidities.

DISCUSSION

This is the first report from the Samarkand region, Uzbekistan, on the characteristics and treatment outcomes of new TB patients with four specific comorbidities – diabetes, HIV, COPD and peptic ulcer. About 15% of patients had a coexisting comorbid condition, with diabetes accounting for more than half of these diseases. Of note, those with diabetes, COPD or peptic ulcer were mostly older than 55 years and tended to be pensioners and/or recorded as invalids. HIV infection was less common and tended to occur in younger and unemployed persons. Treatment success was reduced and adverse outcomes were increased in those with comorbid conditions, especially for patients with diabetes, HIV infection or COPD, and this was largely due to an increased risk of death, treatment failure and transfer out.

The strengths of this study were the large consecutive sample of new TB patients registered under routine conditions in the Samarkand region over 2 years, which makes the results representative of the situation in the country. STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines and sound ethical principles were also followed for conducting and reporting on this observational study *(16, 17)*. There were some limitations in that data were sometimes missing from the registers and treatment cards and some treatment outcomes were not evaluated.

The findings of this study are consistent with previous and current literature *(18, 19)*. HIV infection in the patients in this study tended to occur in younger and unemployed persons, and, although these data were not collected, they may include high-risk vulnerable groups, such as adolescents, men who have sex with men, injecting drug users, prisoners and migrants *(19)*. Smear-negative pulmonary disease with less evidence of cavities on chest radiography is more characteristic of HIV-associated TB, and treatment outcomes in patients with TB are also known to be adversely affected by HIV *(3)*. In 2012 and part of 2013, antiretroviral therapy in Uzbekistan was only started in HIV-infected TB patients at the end of anti-TB therapy, and such a delay is known to be associated with significantly increased mortality during therapy *(20)*.

The patients in this study with diabetes, and TB tended to be older than patients without diabetes and this is consistent with studies carried out in other parts of the world *(21, 22)*. Similarly, cavitation and smear-positive disease were more common in

TB patients with diabetes compared with the other groups; this is in line with other studies that found lower lung involvement, extensive parenchymal lesions, multiple cavities and large cavities more often in diabetes patients, and particularly in those diabetes patients with poor glycaemic control *(23)*. It is well established that treatment outcomes are worse in TB patients with diabetes, with the risk of death and failure being particularly increased *(10, 24)*. There was no measure of diabetes control in the study patients, but hyperglycaemia and poor control of diabetes are associated with an increased risk of unfavourable outcomes and higher 1-year mortality *(25)*.

The association between TB and other comorbidities such as COPD and peptic ulcer is less clear. Certainly, the use of acid-suppressive medication for peptic ulcer disease is associated with an increased risk of infection with *Mycobacterium tuberculosis* and active TB *(26)*. Furthermore, TB of the stomach or duodenum can mimic non-healing peptic ulcers *(27)*, so vigilance is needed if these two conditions are suspected or diagnosed. Corticosteroids, given either by inhalation or orally, and often used in the prevention and treatment of asthma and chronic obstructive airways disease, can increase the risk of incident active TB *(28)*. There was no information available in this study about the use of corticosteroids, but this will be important data to collect in future studies.

The study has some important policy implications. First, given the association of HIV and diabetes with TB treatment outcomes, it will be important for Uzbekistan to ensure that all TB patients are regularly and systematically screened for HIV and diabetes at the time of registration, in line with recommendations of the *WHO policy on collaborative TB/HIV activities (29)* and the WHO/International Union Against Tuberculosis and Lung Disease. *Collaborative framework for care and control of tuberculosis and diabetes (30)*. Second, in patients with HIV-associated TB, it will be important to start antiretroviral therapy as soon as possible after the start of TB treatment, along with co-trimoxazole preventive therapy, as both these interventions are recommended by WHO and are well established to reduce HIV-related morbidity and mortality *(3, 31)*. Similarly, patients with both diabetes and TB need referral for good quality diabetes care, to reduce the risk of diabetes-related complications and to improve the outcomes of TB treatment *(25)*. Third, more work needs to be done to both measure and understand the association of COPD and peptic ulcer with active TB. At the same time, further research should be carried out locally to determine whether other possible comorbidities are associated with TB *(1)*.

In conclusion, this study has shown that about 15% of new pulmonary TB patients-in the Samarkand region of Uzbekistan had one of four specific comorbidities, with diabetes being the most common disease. The comorbidities of diabetes, COPD and peptic ulcer were particularly associated with older age, while HIV infection tended to occur in younger age groups. Patients with comorbidities had worse treatment outcomes compared with those who had no documented comorbidities, especially for death or treatment failure. A more systematic approach to screening and treatment of comorbidities in TB patients will be needed to improve treatment outcomes and reduce mortality.

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