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Factors Related with Sputum Smear Conversion Time among Tuberculosis Patients

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Abstract

The article aims to determine the factors associated with smear sputum conversion in 64 patients with tuberculosis (TB) admitted at The Cuban Hospital (TCH) (Qatar). The patient characteristics at diagnosis (age, sex, smoking, alcohol, history of Diabetes mellitus or previous tuberculosis, and diagnostic's delay), nutritional indicators (Body mass index, Hemoglobin, lymphocytes count, iron, serum protein/albumin), platelet count, serial sputum, resistance to first line TB drugs, and radiological findings were collected. Kaplan Meier survival and log rank test or a Wilcoxon test were used. Significance level was set ≤ 0.05. The 75 % patients were below 39 years old (mean 32.61 years), male (78.1 %), non-smokers (90.6 %), no previous history of TB (96.9 %), 17.2 % had Diabetes mellitus. Diagnosis delay was over 30 days (65.6 %). Minimum smear conversion was 5 days and maximum 115 days (median: 30 days). The survival curves based on patient's demographics, nutritional and radiological characteristics were not statistically significantly different. Regarding bacterial load, 50 days after starting treatment, the 2 patient´s group with ≤ 1000 bacilli had negative sputum. Patients who had > 1500 bacilli, yet after 100 days of treatment, had positive sputum ($p = 0.02$). Differences between groups with lower and higher bacilli count was significant ($p = 0.04$). Our data has shown that the main factor related to sputum conversion is the bacterial load, which will be useful to fix the case management of tuberculosis in Qatar.

Keywords: Tuberculosis, sputum conversion, bacterial load, factors associated, Qatar

Introduction

The prevention and control of tuberculosis is a priority program for the Eastern Mediterranean countries according to the regional office of the World Health Organization. Its vision is to sustain the decline in tuberculosis incidence, to halve the number of deaths from tuberculosis, and to reduce its prevalence in the region by 2015 compared to the baselines in 1990. In the long term it will strive to eliminate tuberculosis in the lifetime of the first child born in this millennium [1]. In Qatar there are about 500 patients diagnosed with tuberculosis annually, 97.3 % being non Qatari citizens [2]. Correspondingly, the National Program for Tuberculosis Control in Qatar has multiple strategies, amongst which is the provision of free healthcare services to all tuberculosis patients, inclusive of diagnosis, treatment and follow-up. In addition, patients with tuberculosis are admitted and remain in hospital until 2 consecutive negative results of smear are obtained [3].

The sputum smear and culture conversion constitute important indicators for the effectiveness of treatment and the infectivity of patients. The sputum smear conversion time has been related with

multiple factors including smoking [4-7], alcohol consumption [5,8], history of diabetes mellitus [4,9-11], 8 - 10 and previous TB [11,12], nutritional deficiency [13-16], thrombocytosis [4], bacillary load at diagnosis [12,17-19], drug resistance [6,8,11,18], the diagnosis delay time and radiological lesions suggestive of extensive damage or cavitations [4,5,9,10,17,20,21].

The high frequency of TB nationally (more than 95 % imported tuberculosis in the expatriate population) and the limited availability of isolation rooms is a challenge for the National Program, making the efficient use of resources (especially the beds) an essential component for case management. Usually patients stay admitted in Qatar hospital more than 30 days until negative smear results are collected, with a great variability between patients. As per national policies after 2 weeks of treatment, the sputum is collected on a weekly basis until one smear becomes negative. A second negative smear is required for discharge. The factors associated with the sputum conversion time have not been identified in tuberculosis patients in Qatar, which in general comes from Southeast Asian countries (Indian and Nepal) where there is low incidence of HIV and multidrug resistant mycobacterium tuberculosis.

We conducted a retrospective cohort study to determine the factors associated with sputum conversion time in patients with tuberculosis admitted to The Cuban Hospital in Qatar.

Materials and methods

An analytical observational retrospective cohort study was carried out. The study group consisted of all newly diagnosed patients with pulmonary tuberculosis admitted at Cuban Hospital of Qatar (member of Hamad Medical Corporation (HMC), Qatar) during the period January 2013 to March 2014.

All data was collected from patient medical records. Age, sex, diagnostic delay (time between first symptom and diagnosis) and history of smoking, alcohol intake, previous tuberculosis and diabetes mellitus was registered. The following laboratory results were registered at diagnosis: absolute number of lymphocytes (reference value (rv): 1000 - 3000 / µl), hemoglobin (rv: men 13 - 17 g/L, women 12 to 15 g/L), platelet count (rv: 150 - 400 × 10^3), serum albumin (rv: men 32 - 47 g/L, women 29 - 42 g/L), total protein (rv: 60 - 80 g/L), serum creatinine (rv: men 71 - 123 µmol /L, women 53 - 97 µmol/L) and serum iron (rv: 8.1 to 28.6 men µmol/L, women 5.4 to 28.6 µmol/L). In the chest X-Ray at diagnosis were identified the presence of bilateral lesions, effusion, consolidation and cavities. Resistance to first line antituberculosis drugs (izoniacid, rifampicin, streptomycin, and ethambutol) was also collected.

The body mass index was calculated by the Quetelet formula ($BMI = \frac{\text{Weight (Kg)}}{\text{size (m)2}}$) using the first data collected on admission. The initial maximum number of bacilli to the highest number of bacilli in sputum made at diagnosis were considered. We also recorded the date/time that the patient began treatment and the date/time when the smear became negative. The treatment commencement date/time until smear conversion negative was the main response variable (Sputum Conversion Time).

All patients were treated with a standard regimen of izoniacid, rifampicin, streptomycin, and ethambutol, unless Rifampicin resistance was identified at diagnosis (using Gene Xpert PCR).

Statistics

SPSS version 15.0 was used for analysis. The statistical technique of analysis of frequency distribution was used in the initial description of the general characteristics of the studied patients and for each of the categories of variables, absolute and relative frequencies (percentages) were calculated. The Kaplan Meier method was used to calculate the survival time to sputum conversion. The start date of the specific treatment for the disease was considered the start of monitoring in each subject, and the date to negative sputum culture was taken as the terminal event or condition. There were no incomplete times. To identify variables associated with time to negative sputum, the survival curves obtained were compared among the different categories of variables by log rank test or Wilcoxon, depending on the existence of proportionality between them. For all tests of hypotheses performed a significance level of $\alpha = 0.05$ was set.

Results and discussion

During the study period 64 patients were admitted with smear positive tuberculosis (**Table 1**), of which 75 % were below 39 years old (mean 32.61 years, 11.91 years of age). Patients were predominantly male (78.1 %) and non-smokers (90.6 %), without previous history of pulmonary tuberculosis (96.9 %). Also, 11 patients (17.2 %) had diabetes mellitus and only one (1.56 %) had a history of HIV. Only 2 patients had mycobacterium tuberculosis resistant to isoniazid and to isoniazid-rifampicin respectively. The 65.6 % patients had more than 30 days of diagnostic delay.

Table 1 Baseline demographic and clinical characteristics of tuberculosis patients studied.

Characteristics		No	%
Age (years)			
	18 - 24	13	20.3
	25 - 28	17	26.6
	29 - 38	18	28.1
	39 - 86	16	25.0
Sex			
	Male	50	78.1
	Female	14	21.9
Smoking			
	Current smoker	3	4.7
	No smoker	58	90.6
	Ex smokers	3	4.7
Previous tuberculosis			
	Yes	2	3.1
	No	62	96.9
Diabetes Mellitus			
	Yes	11	17.2
	No	53	82.8
Diagnostic delay (days)			
	3 - 19	12	20.7
	20 - 29	8	13.8
	30 - 59	15	25.9
	60 - 365	23	39.7

Survival time to negative sputum culture can be seen in **Figure 1**. The minimum conversion time was 5 days and the maximum of 115 days, with a median of 30 days. The conversion time and demographic and clinical characteristics of the patients (**Table 2**) were not statistically significantly different for any of the variables, when the survival curves were compared between their respective categories. It is remarkable that the probability of having positive sputum at 12 weeks of treatment was 18.8 %, in patients aged between 39 and 86 years, compared with the other 3 groups of patients, which at this time had a 0.0 % probability of positive sputum.

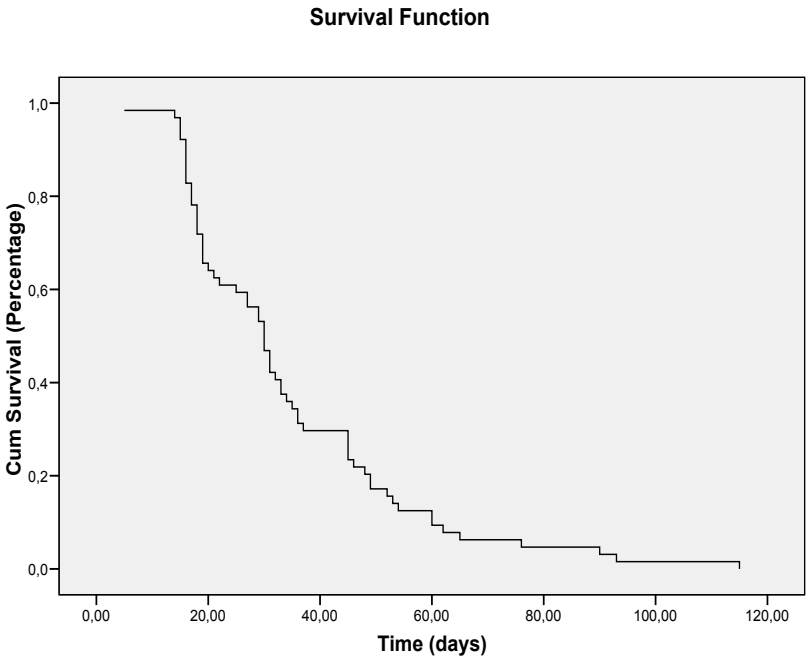

Figure 1 Kaplan-Meier survival curve of time to smear conversion.

Table 2 Survival time to smear conversion according demographic and clinical characteristics.

Characteristics	n	Time						
		2 Weeks	4 Weeks	6 Weeks	8 Weeks	12 Weeks	16 Weeks	Med*
Age (years)								
18 - 24	13	92,3 (7,4)	53,8 (13,8)	23,1 (11,7)	7,7 (7,4)	0,0 (0,0)	0,0 (0,0)	30
25 - 28	17	100 (0,0)	47,1 (12,1)	23,5 (10,3)	11,8 (7,8)	0,0 (0,0)	0,0 (0,0)	27
29 - 38	18	100 (0,0)	66,7 (11,1)	33,3 (11,1)	11,1 (7,4)	0,0 (0,0)	0,0 (0,0)	30
39 - 86	16	93,8 (6,1)	56,3 (12,4)	37,5 (12,1)	18,8 (9,8)	18,8 (9,8)	6,3 (6,1)	34
Sex								
Male	50	96,0 (2,8)	56,0 (7,0)	28,0 (6,3)	10,0 (4,2)	4,0 (2,8)	0,0 (0,0)	30
Female	14	100 (0,0)	57,1 (13,2)	35,7 (12,8)	21,4 (11,0)	7,1 (6,9)	7,1 (6,9)	30
Smoking								
Current smoker	3	100 (0,0)	66,7 (27,2)	66,7 (27,2)	33,3(27,2)	33,3 (27,2	0,0 (0,0)	54
No smoker	58	96,6 (2,4)	51,7 (6,6)	27,6 (5,9)	12,1 (4,3)	3,4 (2,4)	1,7 (1,7)	30
Ex smoker	3	100 (0,0)	100 (0,0)	33,3 (27,2)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)	31
Diabetes Mellitus								
Yes	11	90,9 (8,7)	54,5 (15,0)	36,4 (14,5)	9,1 (8,7)	9,1 (8,7)	0,0 (0,0)	34
No	53	98,1 (1,9)	56,6 (6,8)	28,3 (6,2)	13,2 (4,7)	3,8 (2,6)	1,9 (1,9)	30
Diagnostic delay (days)								
3 - 19	12	91,7 (8,0)	50,0 (14,4)	25,0 (12,5)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)	25
20 - 29	8	100 (0,0)	50,0 (17,7)	25,0 (15,3)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)	20
30 - 59	15	93,3 (6,4)	60,0 (12,6)	33,3 (12,2)	13,3 (8,8)	6,7 (6,4)	0,0 (0,0)	30
60 - 365	23	100 (0,0)	56,5 (10,3)	30,4 (9,6)	21,7 (8,6)	8,7 (5,9)	4,3 (4,3)	29

Data are survival percentage (standard deviation), unless otherwise indicated.
*Median (days).

With regard to smoking, it was important that smokers had a 33.3 % survival at 12 weeks (although there were only 3 patients), and the time in which the probability of continuing with positive sputum was the 3.4 % for non-smokers and ex-smokers 0.0 %. The median survival time to conversion was 54 days for smokers, compared with 30 and 31 days of non-smokers and former smokers, respectively. Also, the 2 groups of patients that had delayed diagnosis for 30 days or more, had a chance to continue with positive sputum at week 8 (13.3 %), by which time the other 2 groups of patients had become negative. All these differences, as previously mentioned, were not statistically significant (**Table 2**).

Table 3 Survival time to smear conversion according nutritional factors and platelet.

Factors and platelet	n	Time						
		2 Weeks	4 Weeks	6 Weeks	8 Weeks	12 Weeks	16 Weeks	Med*
BMI (Kg./m^2)								
< 18,5	21	100 (0,0)	71,4 (9,9)	33,3 (10,3)	14,3 (7,6)	4,8 (4,6)	0,0 (0,0)	32
≥ 18,5	43	95,3 (3,2)	48,8 (7,6)	27,9 (6,8)	11,6 (4,9)	4,7 (3,2)	2,3 (2,3)	27
Haemoglobin (g/L)								
Low	16	100 (0,0)	56,3 (12,4)	31,3 (11,6)	25,0 (10,8)	12,5 (8,3)	6,3 (6,1)	30
Normal	46	95,7 (3,0)	58,7 (7,3)	30,4 (6,8)	8,7 (4,2)	2,2 (2,2)	0,0 (0,0)	30
Serum creatinine (μmol/L)								
Low	12	100 (0,0)	41,7 (14,2)	41,7 (14,2)	25,0 (12,5)	8,3 (8,0)	8,3 (8,0)	19
Normal	47	95,7 (2,9)	61,7 (7,1)	27,7 (6,5)	10,6 (4,5)	4,3 (2,9)	0,0 (0,0)	31
Serum protein (g/L)								
Low	4	100 (0,0)	75,0 (21,7)	75,0 (21,7)	25,0 (21,7)	25,0 (21,7)	0,0 (0,0)	45
Normal	56	96,4 (2,5)	57,1 (6,6)	28,6 (6,0)	12,5 (4,4)	3,6 (2,5)	1,8 (1,8)	30
Serum albumin (g/L)								
Low	9	100 (0,0)	77,8 (13,9)	55,6 (16,6)	11,1 (10,5)	11,1 (10,5)	0,0 (0,0)	45
Normal	52	96,2 (2,7)	55,8 (6,9)	26,9 (6,2)	13,5 (4,7)	3,8 (2,7)	1,9 (1,9)	30
Absolute count of lymphocites (10^3/μl)								
Low	14	100 (0,0)	71,4 (12,1)	35,7 (12,8)	28,6 (12,1)	7,1 (6,9)	0,0 (0,0)	33
Normal	48	95,8 (2,9)	50,0 (7,2)	27,1 (6,4)	6,3 (3,5)	4,2 (2,9)	2,1 (2,1)	27
Hierro sérico (μmol/L)								
Bajo	16	100 (0,0)	50,0 (12,5)	37,5 (12,1)	12,5 (8,3)	12,5 (8,3)	6,3 (6,1)	27
Normal	17	94,1 (5,7)	47,1 (12,1)	17,6 (9,2)	5,9 (5,7)	0,0 (0,0)	0,0 (0,0)	27
Platelet (10^3/μl)								
127-285	15	100 (0,0)	60,0 (12,6)	40,0 (12,6)	26,7 (11,4)	13,3 (8,8)	0,0 (0,0)	32
286-342	17	100 (0,0)	64,7 (11,6)	41,2 (11,9)	5,9 (5,7)	0,0 (0,0)	0,0 (0,0)	33
343-410	16	93,8 (4,1)	50,0 (12,5)	12,5 (8,3)	6,3 (6,1)	0,0 (0,0)	0,0 (0,0)	19
411-615	16	93,8 (6,1)	50,0 (12,5)	25,0 (10,8)	12,5 (8,3)	6,3 (6,1)	6,3 (6,1)	27

Data are survival percentage (standard deviation), unless otherwise indicated.
*Median (days).

Median survival times to conversion were higher for patients with low levels of total protein, albumin and total lymphocyte count, when compared with median times of patients who had, in each case, normal values; respectively the medians were 45 days vs. 30 days for the first 2 variables aforementioned and 33 days vs. 27 days, for the lymphocyte count. In the 3 groups of patients who had low figures of nutritional indicators, it could be observed in almost all cases, that the probability that they had positive sputum was much higher than for patients with normal figures, although from week 16 these probabilities are almost nil, and similar to those with normal values. Hence time to negative sputum was higher for patients who did not have their nutritional figures within the normal range. In a similar way, the 2 groups of patients with lower platelet counts had the greatest median survival time (32 days and 33 days) and were more likely to continue with positive sputum each time, when compared with those with a platelet count over 343×10^3; the median survival time in the last 2 groups of patients were 19 days and 27 days respectively, and the chance to continue with positive sputum always decreased (**Table 3**). The pattern of survival according to serum creatinine was different; the median for patients with low creatinine was found to be 19 days, i.e. at day 19, 50 % of patients had become negative. However, after this time it can be noticed that the sputum conversion was faster in patients who had normal creatinine, and survival probabilities were higher for patients who had a lower figure (**Table 3**). For both nutritional variables and platelets there were no statistically significant differences when comparing survival curves between their respective categories ($p > 0.05$ for all comparisons).

With regard to the maximum number of bacilli at diagnosis it can be observed (**Figure 2**), that approximately 50 days after starting treatment, the 2 groups of patients with ≤ 1000 bacilli had become negative, compared with the other 2 groups with more than this figure. Patients who had between 1501 and 3000 bacilli, even after 100 days of starting treatment had positive sputum. Median survival times were found to be 19 days for patients with fewer bacilli, 33 days and 25 days respectively for the 2 intermediate groups and 48 days for the last group. Comparison of survival curves between the categories of this variable did show the existence of statistically significant differences ($p = 0.02$), the difference was found between the groups with lower and higher bacilli count at diagnosis ($p = 0, 04$).

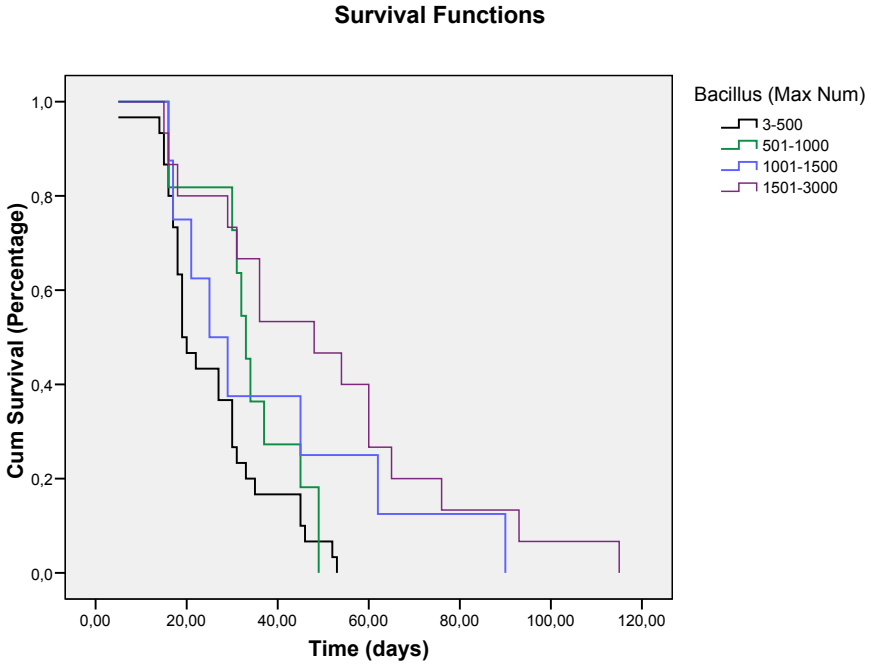

Figure 2 Kaplan-Meier survival curve of time to smear conversion according to the maximum number of bacillus.

In **Table 4** survival time is displayed according to the radiological findings. The odds of survival were quite similar at all times when comparing patients with and without cavitation, and was similar to the median survival time. Patients with consolidation had longer times to negative sputum and were found to have positive sputum even at weeks 16th, but the number with consolidation was low (1.9 %). The median time of survival for patients with and without these finding were similar. Paradoxically, patients with effusion or bilateral injuries had faster negativization of sputum; it should be noted that at week 8 after initiating treatment the likelihood to continue with positive sputum was 0 % for patients with effusion, with a median survival time of only 16 days, and was similar at week 12 for patients with bilateral lesions, although only 3 patients were found with effusion. For radiological findings, no statistically significant differences were found when comparing survival curves ($p > 0.05$).

Sputum conversion can be considered a valuable indicator of effective treatment for patients with tuberculosis, which is also associated with the possible transmission of the disease. Important elements in the published texts on this subject are the characteristics amongst TB patients studied, with particular emphasis on the incidence of infection of the Human Immunodeficiency Virus (AIDS), multidrug-resistant tuberculosis (MDR-TB), the nutritional status and incidence of tuberculosis at the national level. Patients studied came from different countries (mainly Nepal and India) those have low rate of AIDS and MDR-TB. Similarly, treatment failure due to lack of adherence is often referred [11]. This factor is not considered in our population due to the national regulation requiring the admission of patients with tuberculosis until no infectivity was confirmed, as well as the adherence to treatment being strictly controlled by health professionals.

Time of sputum conversion in patients of India as Parikh *et al*. [12] was 35 days, which is similar to our results, while in Turkey [11] it was 3±2.2 months, 2 studies were conducted in populations with low incidence of AIDS and MDR-TB, but yet with a high incidence of tuberculosis in India.

Similar results have been reported in studies conducted in different settings and patient population [3-6]. Smoking is strongly related to sputum conversion in many studies. In MDR-TB patients with high prevalence of smokers, smoking was a risk factor for lower rates of sputum culture conversion [22]. It is important to note that our patients are admitted during the conversion period and smoking is not allowed during admissions according to corporate policies. Furthermore, current smokers among patients are low (only 3 out of 64 patients). This may influence the results and comparison with other studies where the treatment is community based and the prevalence of active smokers is high.

Table 4 Survival time to smear conversion according radiological findings.

Radiological findings		n	Time						
			2 Weeks	4 Weeks	6 Weeks	8 Weeks	12 Weeks	16 Weeks	Med*
Cavitation									
	Yes	35	94,3 (3,9)	60,0 (8,3)	28,6 (7,6)	14,3 (5,9)	2,9 (2,8)	2,9 (2,8)	30
	No	29	100 (0,0)	51,7 (9,3)	31,0 (8,6)	10,3 (5,7)	6,9 (4,7)	0,0 (0,0)	31
Consolidation									
	Yes	52	98,1 (1,9)	51,9 (6,9)	32,7 (6,5)	15,4 (5,0)	5,8 (3,2)	1,9 (1,9)	29
	No	12	91,7 (8,0)	75,0 (12,5)	16,7 (10,8)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)	30
Pleural effusion									
	Yes	3	100 (0,0)	33,3 (27,2)	33,3 (27,2)	0,0 (0,0)	0,0 (0,0)	0,0 (0,0)	16
	No	61	96,7 (2,3)	57,4 (6,3)	29,5 (5,8)	13,1 (4,3)	4,9 (2,8)	1,6 (1,6)	30
Bilateral lesions									
	Yes	9	100 (0,0)	55,6 (16,6)	11,1 (10,5)	11,1 (10,5)	0,0 (0,0)	0,0 (0,0)	30
	No	55	96,4 (2,5)	56,4 (6,7)	32,7 (6,3)	12,7 (4,5)	5,5 (3,1)	1,8 (1,8)	30

Data are survival percentage (standard deviation), unless otherwise indicated.
*Median (days).

Diabetes mellitus (DM) strongly influences treatment outcomes, however, the effect on sputum conversion is contradictory in different studies [4,9,16,22]. Guler [4] and Stoffel [17] identified Diabetes mellitus as an independent risk factor for conversion of sputum in new TB patients, while Nakamura *et al.* [10] and Magee *et al.* [22] found no association. This could be explained by the influence of other specific elements in patients with diabetes as nutritional and immune status, metabolic control and severity of tuberculosis, requiring further studies.

Nutritional status is a risk factor for tuberculosis and for the treatment outcome. A study based on the US population identified that the estimated risk of developing TB for people with low BMI was 12.4 times (95 %; 5.7,26.9) more than for those with normal BMI. The most frequent hypoalbuminemia was also identified in patients with tuberculosis compared to a person who did not develop the disease [23]. Studies show that malnutrition is associated with delayed sputum conversion, with a focus primarily on BMI [13,14]. Others nutritional parameters may be considered (for example, protein, albumin, creatinine), but few studies provide data to support proper analysis. Nagu *et al.* [16] reported that anemic patients were three times more likely to have smear-positive compared with non-anemic patients in 2 months (RR = 3.05; 95 % CI 1.11 to 8.40). The high bacillary load was the main factor related to sputum conversion which is in line with others studies conducted in many settings and patient populations [4,11,14,16]. This information provides a support to review our current practice in case management of tuberculosis, especially in the frequency of sputum during the initial phase of treatment. Actually sputum are indicated after 2 weeks of treatment on a weekly basis and according to our results patients with high initial bacillary load would require different frequency of sputum collection, and therefore more efficient use of resources.

Although there are numerous references that have emphasized the presence of cavities as a factor related with the conversion it was not demonstrated in this study. The study has several limitations. First, a small sample size could interfere with the accurate identification of factors related to sputum conversions, like smoking habits or nutritional factors. Second, the majority of study patients are transferred from other facilities (related to bed crisis and limited availability of isolation rooms), which could introduce a selection bias because of particular characteristics of patients with eligible criteria to transfer between healthcare facilities.

Conclusions

The knowledge of factors associated with sputum conversion time, besides its clinical implication must be used to fix the case management policies and procedures. Our data has shown that the primary factor related to sputum conversion time is the bacterial load. If we take this finding into consideration, the frequency of sputum could be adjusted accordingly, mainly in patients with high bacterial load (over 1000 AFB).

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