Relation of grading of sputum smears with clinical features of tuberculosis patients in routine practice in Sudan

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_____ S U M M A R Y

SETTING: Health services in Khartoum, Red Sea, Gadarif, Kassala, Bahr el Jebel, Gezira and North Kordofan States of Sudan.

OBJECTIVE: To investigate the association of presenting symptoms and clinical history with grade of sputum smear positivity in tuberculosis patients.

METHODS: The 5338 tuberculosis suspects aged 15 to 49 years who consulted between March 1998 and March 1999 underwent sputum smear microscopy, with smears graded by a standardised method. Patients who gave consent had a structured interview concerning the nature and duration of their symptoms and whether they had a sick relative at home. Statistical analysis determined the association of symptoms and home characteristics with the results of smear examination.

RESULTS: A total of 514 suspects (9.6%) demonstrated acid-fast bacilli: 45 (8.8%) grade +1, 167 (32.5%) grade +2 and 302 (58.8%) grade +3. Most of the patients had a duration of symptoms of 6–9 weeks, while 100 had symptoms of more than one year's duration, many ($n =$ 47) with other chronic respiratory diseases. Multiple chest symptoms were positively, and duration of symptoms negatively associated with grade of positivity ($P =$ 0.018 and 0.028, respectively). A high grade of smear positivity (+3) and the longest duration of symptoms, among those reporting symptoms of less than one year's duration, were significant predictors of the presence of a sick household member (OR = 1.99, 95%CI 1.12–3.55; OR = 1.004, 95%CI 1.000–1.008).

CONCLUSION: This study demonstrates a relation between the grade of smear positivity and the clinical features of tuberculosis patients.

KEY WORDS: tuberculosis; diagnosis; direct microscopy; infection; Sudan

TUBERCULOSIS RANKS among the world's most serious health problems. Some countries where the disease was previously under control are now experiencing an increase in cases.[1–5] For most national tuberculosis programmes in developing countries, direct microscopy of sputum for acid-fast bacilli remains the standard diagnostic procedure,[6] and grading of sputum positivity is routinely carried out. The significance and utility of grading sputum positivity has not been previously evaluated at the community level.

Higher grades of positivity might be expected to be related to diagnostic delay. Diagnostic delay is affected by the understanding of symptoms, attitudes to disease, expectations and accessibility of health services (patient's delay),[7,8] and the health system's performance (doctor's delay).[9–12] Delays in diagnosis have a significant impact on the patient by increasing the risk of severe disease and mortality,[12] and very likely increasing the probability of transmission of infection in the community.

Infectiousness of tuberculosis correlates with the number of bacilli in the sputum (reflected by the sputum grading) and the length of infectiousness.[13] It is reasonable to suppose that patients with higher grading by smear microscopy have a longer duration of symptoms than patients with lower grading. Few papers have looked into the importance of sputum grading and its association with symptoms. In our study we investigated the association between symptoms and clinical history of tuberculosis and the grading of sputum smear for acid-fast bacilli.

PATIENTS AND METHODS

All persons aged 15–49 years with respiratory symptoms seen in the general health services from March 1998 to March 1999, in Gezira, Bahr el Jebel, Khartoum, Red Sea, Gadarif, North Kordofan and Kassala states, were considered eligible for the study. In accordance with the policy of the National Tuberculosis

Programme, all patients presenting with cough for as much as 3 weeks are designated suspects for tuberculosis and referred for sputum smear examination for acid-fast bacilli. Direct microscopy for acid-fast bacilli is performed on three sputum specimens stained using the Ziehl Neelsen method and graded according to a standard classification.[6,14] In this study, of the three sputum smears evaluated for each patient, the highest grading of sputum was taken as the grade to be evaluated. Those patients whose smear examination did not exhibit sufficient bacilli to be classified as +1 were grouped with smear-negative cases.

A routine programme of systematic re-reading of smear samples is carried out in the National Tuberculosis Programme, the results of which have been reported previously.[15]

All eligible patients were requested to give oral consent to participating in the study; six refused to participate. Severely ill patients and those with a history of previous treatment were excluded. A structured interview was then completed to collect information on age, sex, residence, past medical history, type and duration of symptoms, and whether or not there was a household member who was ill. The results of sputum smear microscopy routinely carried out in the local laboratory, including the grading of sputum, were recorded.

Data were entered into the computer using SPSS version 9.05 (SPSS Inc, Chicago, IL). Results were cross-tabulated to examine the relationships between the variables. Statistical analysis was performed using χ^2 for tests of association. Where multiple variables were examined, logistic regression analysis was used.

A P value of less than 0.05 was considered significant in all statistical analysis.

RESULTS

Of 5338 individuals presenting to the health service who were identified as suspects for tuberculosis, 514 (67.4% of treated patients and 9.6% of those identified as suspects) were sputum smear-positive. An ad-
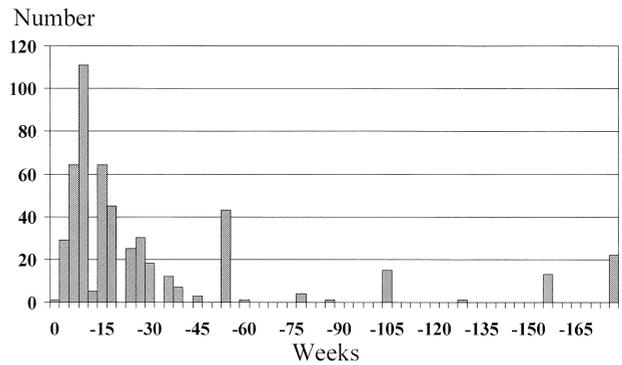

Figure 1 Distribution of patients according to the longest duration of their reported symptoms. (−) indicates the interval from the last figure to the next; for example −90 indicates a duration of 76–90 weeks.

ditional 10 patients had sputum smears that demonstrated too few acid-fast bacilli to be classified as grade +1, and were classified as sputum smear-negative cases. The average age of the sputum smear-positive patients was 29.3 years (standard deviation 9.2), with 188 (36.6%) aged 15–24 years, 174 (33.9%) aged 25–34 years and 152 (29.6%) aged 35–49 years. The majority of the patients (327, 63.3%) were men (Table 1).

The symptoms reported, in order of frequency, were as follows: cough (504, 98.1%), weight loss (471, 91.6%), tiredness (439, 85.4%), fever (402, 78.2%) chest pain (391, 76.1%), night sweats (323, 62.8%), breathlessness (299, 58.2%) and haemoptysis (97, 18.9%). Figure 1 presents the distribution of patients according to the longest duration of their reported symptoms. The duration of symptoms had a logarithmic distribution. One hundred patients (19.5%) reported symptoms of 52 weeks or more duration. In this group, the precision of the duration recorded is clearly inexact. Of these, 47 had chronic respiratory conditions that were the likely cause of the symp-

Table 1 Patient characteristics

Characteristic	Sputum smear grade			
	+1 n (%)	+2 n (%)	+3 n (%)	P value*
Sex				
Male	26 (57.8)	113 (67.7)	188 (62.3)	0.352
Female	19 (42.2)	54 (32.3)	114 (37.7)	
All	45 (100)	167 (100)	302 (100)	
Age (years)				
15–24	16 (35.6)	60 (35.9)	112 (37.1)	0.655
25–34	15 (33.3)	51 (30.5)	108 (35.8)	
35–49	14 (31.1)	56 (33.5)	82 (27.2)	
All	45 (100)	167 (100)	302 (100)	

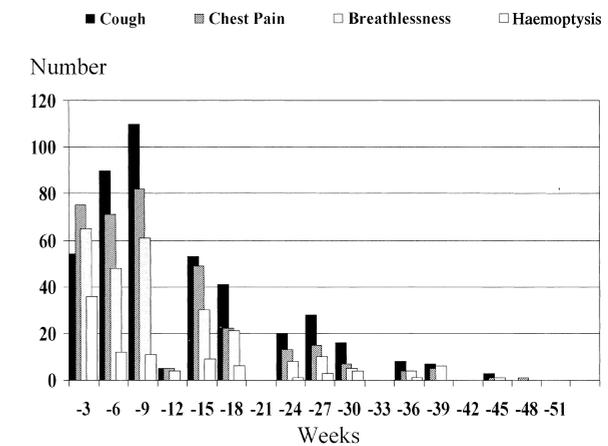* P values from Nyman Pearson χ^2 test.

Figure 2 Duration of chest symptoms. (−) indicates the interval from the last figure to the next; for example −9 indicates a duration of 7–9 weeks.

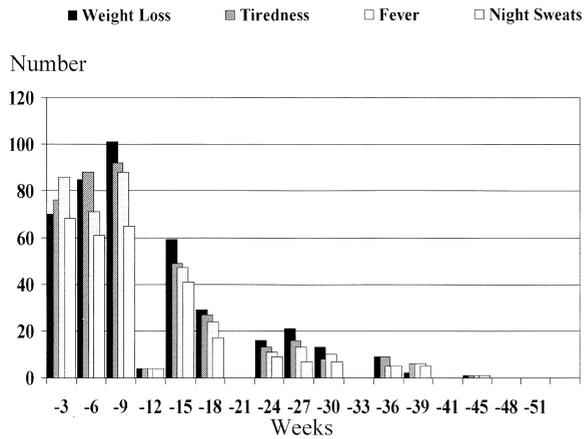■ Weight Loss   ▨ Tiredness   ☐ Fever   ☐ Night Sweats

Number

Figure 3   Duration of systemic symptoms. (−) indicates the interval from the last figure to the next; for example −9 indicates a duration of 7–9 weeks.

■ Chest Pain   ▨ Breathlessness   ☐ Haemoptysis
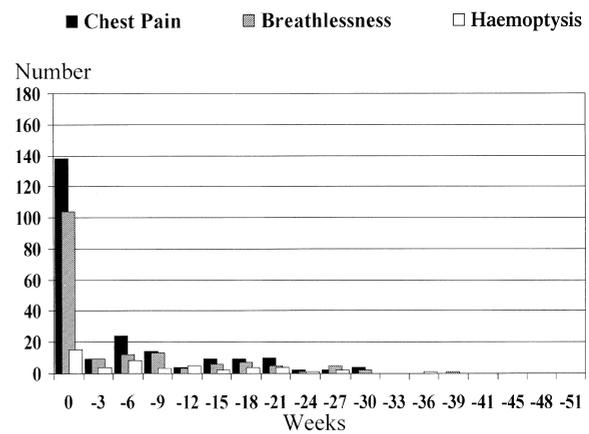
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Figure 4   Duration of chest symptoms in patients with cough. (−) indicates the interval from the last figure to the next; for example −9 indicates a duration of 7–9 weeks.

toms, and consequently the duration of the tuberculosis symptoms is unknown; 25 had asthma, seven had bronchiectasis, six had fibrosing alveolitis, five had rhinitis, and four had sarcoidosis, emphysema or aspergillosis. Seven patients had consulted the health services but the diagnosis had been missed, and another four had failed to consult the health services for a prolonged period.

The duration of the reported symptoms in those patients reporting chest symptoms is illustrated in Figure 2. A similar picture for those patients reporting systemic symptoms is illustrated in Figure 3.

Cough predominated among symptoms at every stage, except in those whose reported symptoms were less than 3 weeks' duration. Of those with a reported cough, 46 (9.1%) reported the cough to be less than 3 weeks' duration. Cough was reported as the first symptom to appear in 369 (71.8%) of the patients, followed by weight loss (68, 13.2%), chest pain (36, 7.0%), breathlessness (14, 2.7%), tiredness (12, 2.3%), fever (9, 1.8%), haemoptysis (4, 0.8%) and night sweats (1, 0.2%). Among those who reported cough as a symptom, 434 (86.1%) reported cough with other chest symptoms, 64 (12.7%) reported cough with systemic symptoms and six (1.2%) reported cough alone. Of the 10 reporting no cough, eight had other chest symptoms, one had systemic symptoms and one reported no symptoms. The longest duration of symptoms was greater ($P < 0.01$) in

Table 2   Duration of symptoms among those who have cough with any other symptoms and those who have cough alone

	Mean duration*	Standard deviation	P value†
Cough only	146.46	272.18	0.001
Cough with other symptoms	287.97	620.31	

* Duration in days.
† *P* value from *t*-test, equal variances not assumed.

those reporting cough with other chest symptoms than among those reporting cough alone (Table 2).

Figures 4 and 5 illustrate the sequence of symptoms in those who presented with cough. The majority reported a combination of symptoms at the outset, with a small proportion reporting the appearance of other symptoms subsequent to cough.

Of the sputum smear-positive patients, 45 (8.8%) had a sputum smear grade of +1, 167 (32.5%) a grade of +2 and 302 (58.8%) a grade of +3. The association of grade of smear positivity with neither age nor sex was statistically significant, and there was no significant association with any of the individual symptoms reported by the patients (χ^2, $P > 0.05$) (Tables 1 and 3).

There was no association of grade of smear positivity with any combination of systemic symptoms (Table 4).

Among those reporting chest symptoms, however, those with a combination of chest symptoms were significantly more likely to have higher grades of positivity (χ^2, $P = 0.018$) (Table 5). In those whose symptoms

■ Weight Loss   ▨ Tiredness   ☐ Fever   ☐ Night Sweats
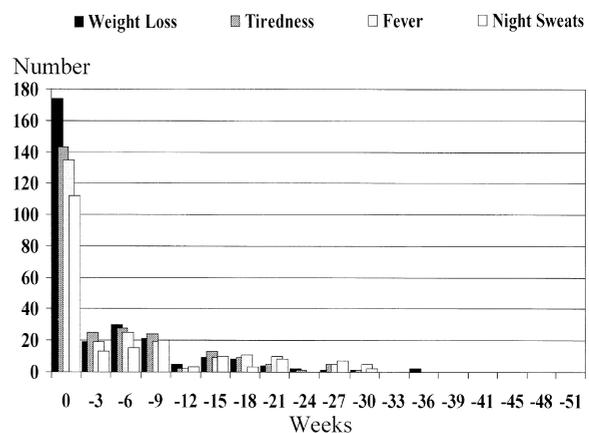
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Figure 5   Duration of systemic symptoms in patients with cough. (−) indicates the interval from the last figure to the next; for example −9 indicates a duration of 7–9 weeks.

Table 3 Association of sputum grade with symptoms by age and sex

Symptom	Sex	Age group (years)	Total n (%)	Sputum grade positivity +1 n (%)	+2 n (%)	+3 n (%)	P value*
Cough	Male	15–24	105 (100)	5 (4.8)	38 (36.2)	62 (59.0)	0.709
		25–34	109 (100)	11 (10.1)	33 (30.3)	65 (59.6)	0.714
		35–49	108 (100)	10 (9.3)	40 (37.0)	58 (53.7)	0.554
	Female	15–24	82 (100)	11 (13.4)	22 (26.8)	49 (59.0)	†
		25–34	62 (100)	4 (6.5)	17 (27.4)	41 (66.1)	0.757
		35–49	33 (100)	3 (7.9)	14 (36.8)	21 (55.3)	0.222
Chest pain	Male	15–24	34 (100)	2 (2.8)	26 (36.1)	44 (61.1)	0.387
		25–34	85 (100)	10 (11.8)	24 (28.2)	51 (60.0)	0.46
		35–49	83 (100)	6 (7.2)	36 (43.4)	41 (49.4)	0.096
	Female	15–24	65 (100)	7 (10.8)	15 (23.1)	43 (66.2)	0.066
		25–34	52 (100)	3 (5.8)	14 (26.9)	35 (67.3)	0.833
		35–49	34 (100)	4 (11.8)	12 (35.3)	18 (52.9)	0.534
Shortness of breath	Male	15–24	57 (100)	2 (3.5)	21 (36.8)	34 (59.6)	0.812
		25–34	65 (100)	10 (15.4)	21 (32.3)	34 (52.3)	0.058
		35–49	65 (100)	4 (6.2)	24 (36.9)	37 (59.9)	0.392
	Female	15–24	44 (100)	6 (13.6)	10 (22.7)	28 (63.6)	0.658
		25–34	40 (100)	2 (5.0)	13 (32.5)	25 (62.5)	0.562
		35–49	28 (100)	3 (10.7)	9 (32.1)	16 (57.1)	0.903
Haemoptysis	Male	15–24	21 (100)	2 (9.5)	6 (28.6)	13 (61.9)	0.428
		25–34	19 (100)	3 (15.8)	3 (15.8)	13 (68.4)	0.274
		35–49	26 (100)	3 (11.5)	10 (38.5)	13 (50.0)	0.857
	Female	15–24	17 (100)	2 (11.8)	2 (11.8)	13 (76.5)	0.239
		25–34	9 (100)	1 (11.1)	2 (22.2)	6 (66.7)	0.768
		35–49	5 (100)	0 (0)	2 (40.0)	3 (60.0)	0.73
Weight loss	Male	15–24	100 (100)	4 (4.0)	37 (37.0)	59 (59.0)	0.268
		25–34	105 (100)	11 (10.5)	32 (30.5)	62 (59.0)	0.592
		35–49	100 (100)	10 (10.0)	38 (38.0)	52 (52.0)	0.507
	Female	15–24	71 (100)	11 (15.5)	17 (23.9)	43 (60.6)	0.182
		25–34	57 (100)	4 (7.0)	17 (29.8)	36 (63.2)	0.47
		35–49	38 (100)	3 (7.9)	14 (36.8)	21 (55.3)	0.222
Tiredness	Male	15–24	86 (100)	3 (3.5)	34 (39.5)	49 (57.0)	0.161
		25–34	98 (100)	10 (10.2)	33 (33.7)	55 (56.1)	0.056
		35–49	88 (100)	7 (8.0)	34 (38.6)	47 (53.4)	0.74
	Female	15–24	69 (100)	10 (14.5)	17 (24.6)	42 (60.9)	0.655
		25–34	59 (100)	4 (6.8)	17 (28.8)	38 (64.4)	0.727
		35–49	39 (100)	4 (10.3)	14 (35.9)	21 (53.8)	0.439
Fever	Male	15–24	84 (100)	4 (4.8)	31 (36.9)	49 (58.3)	0.9
		25–34	88 (100)	8 (9.1)	28 (31.8)	52 (59.1)	0.635
		35–49	80 (100)	8 (10.0)	30 (37.5)	42 (52.5)	0.842
	Female	15–24	67 (100)	10 (14.9)	17 (25.4)	40 (59.7)	0.634
		25–34	50 (100)	3 (6.0)	14 (28.0)	33 (66.0)	0.986
		35–49	33 (100)	3 (9.1)	12 (36.4)	18 (54.5)	0.822
Night sweats	Male	15–24	62 (100)	4 (6.5)	27 (43.5)	31 (50.0)	0.059
		25–34	77 (100)	9 (11.7)	22 (28.6)	46 (59.7)	0.635
		35–49	64 (100)	5 (7.8)	27 (42.2)	32 (50.0)	0.528
	Female	15–24	54 (100)	6 (11.1)	16 (29.6)	32 (59.3)	0.579
		25–34	39 (100)	3 (7.7)	10 (25.6)	26 (66.7)	0.753
		35–49	27 (100)	2 (7.4)	9 (33.3)	16 (59.3)	0.74

* P value from Nyman Pearson χ^2 test.
† P value was not calculated because cough was constant.

were less than one year in duration, there was a negative association of longest duration of symptoms with the degree of smear positivity (χ^2, $P = 0.028$) (Table 6).

Of the 414 patients who reported the longest duration of symptoms as less than one year, 67 (16.2%) reported having a household member who was sick (Table 7). The highest grade of smear positivity (+3)

and the longest duration of symptoms, among those reporting symptoms of less than one year's duration, were significant predictors of the presence of a sick household member. The odds ratio (OR) for highest grade of smear positivity was 1.99 (95% confidence interval [CI] 1.12–3.55) and for longest duration of symptoms it was 1.004 (95%CI 1.000–1.008).

Table 4 Association of smear positivity with any combination of systemic symptoms

| | Sputum smear grade | | | |
| | +1 | +2 | +3 | |
Symptoms	n (%)	n (%)	n (%)	P value*
Tiredness and weight loss	4 (8.9)	23 (14.2)	42 (14.2)	0.403
Fever	12 (26.7)	28 (17.3)	70 (23.7)	
Night sweats	29 (64.4)	111 (68.5)	183 (62.0)	
All	45 (100)	162 (100)	295 (100)	

* P value from Nyman Pearson χ² test.

Table 5 Distribution of positive grade of sputum smear microscopy by chest and systemic symptoms in patients with smear-positive pulmonary tuberculosis in Sudan

| | | Smear positivity grade | | | |
| | Total* | +1 | +2 | +3 | |
Symptoms	n (%)	n (%)	n (%)	n (%)	P value†
All	504 (100)	44 (8.7)	164 (32.5)	296 (58.7)	
Cough only	70 (100)	9 (12.9)	29 (41.4)	32 (45.7)	0.018
Cough plus other	434 (100)	35 (8.1)	135 (31.1)	264 (60.8)	

* 10 patients reported no cough.
† From χ² test, linear-by-linear association.

Among those with symptoms of longer than one year, these associations did not hold.

DISCUSSION

The ability to identify patients with tuberculosis, when the predominant means of case-finding relies on the presentation of patients to the health services, depends crucially on the recognition of a pattern of symptoms specific for tuberculosis. Cough of a minimum of 3 weeks has traditionally been proposed as defining a tuberculosis suspect.[13] In the present study, very few of the cases reported no cough among the symptoms with which they presented. Of those reporting cough, an important minority reported a duration of less than 3 weeks. The great majority had a combination of symptoms at the time of the appearance of the first symptoms, and it is this combination of symptoms that was associated with higher grades of smear positivity. Moreover, those reporting cough alone (without other chest symptoms) had a duration of symptoms significantly shorter than those with a combination of symptoms, suggesting that this group was detected at an earlier stage in their disease. The pattern for all other individual symptoms resembled that for cough, with the exception of haemoptysis, where the majority of patients presented within 3 weeks of the appearance of these symptoms, an observation noted previously.[16]

The minority of patients in this series with long delays between the appearance of symptoms and diagnosis represents a complex group. They might have included on the one hand those who, for a variety of reasons (some areas of the country are undergoing severe civil disturbance), did not have easy access to health services, and on the other a group of patients with other diseases whose symptoms masked the recognition of tuberculosis.

The negative association of longest duration of symptoms with grade of smear positivity was a surprising finding in this study. In fact, one of the hypotheses that this study was designed to address was that the opposite would be the case. It is not at all clear why this should be the case. Patients with higher grades of positivity may have more worrying symptoms that motivate them to seek medical care at an earlier time.

The observation that the highest grade of smear positivity, as well as longer durations of symptoms, are predictors of having a sick person in the household suggests the possibility that there are undetected cases in the community leading to transmission of infection.[17–20] This, however, is speculative, as it was not determined in this study what condition these household members suffered from.

Table 6 Distribution of positive grade of sputum smear microscopy by longest duration of symptoms in smear-positive pulmonary tuberculosis patients in Sudan

| | | Smear positivity grade | | | |
| Longest duration of | Total | +1 | +2 | +3 | |
symptoms	n (%)	n (%)	n (%)	n (%)	P value*
All	514 (100)	45 (8.7)	167 (31.6)	302 (58.8)	
Subtotal up to 52 weeks	414 (100)	36 (8.7)	131 (31.6)	247 (59.7)	0.028
0–3 weeks	23 (100)	1 (4.3)	5 (21.7)	17 (73.9)	
4–6 weeks	71 (100)	3 (4.2)	30 (42.3)	38 (53.5)	
7–9 weeks	111 (100)	8 (7.2)	29 (26.1)	74 (66.7)	
10–15 weeks	69 (100)	5 (7.2)	22 (31.9)	42 (60.9)	
16–22 weeks	70 (100)	10 (14.3)	20 (28.6)	40 (57.1)	
23–51 weeks	70 (100)	9 (12.9)	25 (36.7)	36 (51.4)	
More than 51 weeks	100 (100)	9 (9.0)	36 (36.0)	55 (55.0)	0.495

* P value from χ² test, linear–by-linear association.

Table 7   Distribution of positive grade of sputum smear microscopy by presence of a sick relative in the household

Duration	Sick relative	n %	Smear positivity grade			P value*
			+1 n (%)	+2 n (%)	+3 n (%)	
Less than 1 year	All	414 (100)	36 (8.7)	131 (31.7)	247 (59.7)	0.028
	No	347 (100)	31 (8.9)	117 (33.7)	199 (57.3)	
	Yes	67 (100)	5 (7.5)	14 (20.9)	49 (71.6)	
More than 1 year	All	100 (100)	9 (9.0)	36 (36.0)	55 (55.0)	0.964
	No	80 (100)	7 (8.8)	29 (36.3)	44 (55.0)	
	Yes	20 (100)	2 (10.0)	7 (35.0)	11 (55.0)	

* χ^2 test.

This study indicates that grading of sputum smear positivity is useful in that it reflects a variation in patterns of symptoms reported by the patients.

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R É S U M É

CADRE : Services de santé dans les Etats de Khartoum, de la Mer Rouge, de Gadarif, de Kassala, de Bahr el Jebel, de Gezira et de Nord Kordofan, au Soudan.
OBJECTIF : Investiguer l'association entre les antécédents cliniques de symptômes lors de la première consultation et le degré de positivité des frottis d'expectoration chez les patients tuberculeux.
MÉTHODES : Les patients suspects de tuberculose, âgés de 15 à 49 ans, se présentant entre mars 1998 et mars 1999, ont subi un examen microscopique des frottis d'expectoration avec une gradation des frottis par une méthode standardisée. Les patients ayant donné leur consentement ont subi une interview structurée concernant la nature et la durée des symptômes et s'ils avaient un parent malade à leur domicile. L'analyse statistique a déterminé l'association entre les symptômes et les caractéristiques du domicile et d'autre part les résultats de l'examen des frottis.
RÉSULTATS : Des bacilles acido-résistants ont été mis en évidence dans un total de 514 cas (9,6% des suspects) ; 45 (8,8%) étaient au stade +1, 167 (32,5%) au stade +2 et 302 (58,8%) au stade +3. Chez le plus grand

nombre de patients, la durée des symptômes était de 6 à 9 semaines. Chez 100 patients, les symptômes duraient depuis plus d'une année, et beaucoup (47) avaient d'autres maladies respiratoires. L'association avec le degré de positivité s'est avérée positive pour la présence de symptômes thoraciques multiples et négative pour la durée des symptômes (respectivement $P = 0,018$ et 0,028). Un degré élevé de positivité des frottis (+3) et la plus longue durée des symptômes parmi les sujets faisant

état de symptômes durant depuis moins d'un an, sont des facteurs prédictifs significatifs de la présence d'un membre malade au sein de la famille (OR = 1,99 ; IC95% 1,12–3,55 et OR = 1,004 ; IC95% 1,000–1,008, respectivement).

CONCLUSION : Cette étude met en évidence une relation entre le degré de positivité du frottis et les caractéristiques cliniques des patients tuberculeux.

RESUMEN

MARCO DE REFERENCIA : Servicios de salud en los estados de Khartoum, Red Sea, Gadarif, Kassala, Bahr y Jebel, Gezira y North Kordofan, en Sudán.

OBJETIVO : Investigar la asociación entre los antecedentes clínicos de síntomas y el grado de positividad de las baciloscopias en pacientes con tuberculosis.

MÉTODO : Se realizó una baciloscopia, con graduación de los frotis de expectoración con un método estandarizado, en pacientes sospechosos de tuberculosis, de 15 a 49 años de edad, que se presentaron entre marzo de 1998 y marzo de 1999. Se realizó una entrevista estructurada, con respecto a la naturaleza y duración de los síntomas y a si había una persona enferma a su domicilio, en los sujetos que dieron su consentimiento. El análisis estadístico determinó la asociación entre los síntomas y las características del domicilio, con los resultados de las baciloscopias.

RESULTADOS : Se encontraron bacilos ácido-alcohol resistentes en 514 casos (9,6% de los sospechosos) : 45

(8,8%) grado +1 ; 167 (32,5%) grado +2 y 302 (58,8%) grado +3. En la mayoría de los pacientes los síntomas tenían una duración de 6 a 9 semanas. En 100 pacientes la duración era de más de un año y muchos de ellos (47) tenían otras enfermedades respiratorias. La asociación con el grado de positividad de las baciloscopias fue positiva para la presencia de síntomas respiratorios múltiples y fue negativa para la duración de los síntomas ($P = 0,018$ y 0,028, respectivamente). Un grado elevado de positividad de las baciloscopias (+3) y una duración más larga de los síntomas entre los pacientes con síntomas durante menos de un año, son factores predictivos significativos de la presencia de un miembro de la familia enfermo (OR = 1,99, IC95% 1,12–3,55 y OR = 1,004, IC95% 1,00–1,008, respectivamente).

CONCLUSIÓN : El estudio demostró una relación entre el grado de positividad de la baciloscopia y las características clínicas de los pacientes tuberculosos.