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Risk factors associated to the death of tubercular patients in treatment in five tuberculosis care centers in northern Cote d'ivoire

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Abstract
The objective of this survey was to identify the risk factors for the death of tubercular patients. This was a longitudinal study which took place between January 1st, 2013 and June 30th, 2014. The tubercular patients in any guise of five treatment centers located in northern Côte d'Ivoire were included exhaustively in the survey and followed-up clinically and para- clinically.
On 615 tubercular patients, the pulmonary tuberculosis accounted for 85.6% of all tubercular patients, among of which 90.7% were bacillary form. In total, 15.6% of patients died. The risk factors for death in the multivariate analysis ($p < 0.05$) were bacillary form of the tuberculosis (ORa = 3.3 [1.6-6.7]), the biological anemia (ORa=5,7 [2-16,4]), the HIV1 seropositivity (ORa = 2.2 [1.3-3.7]), decrease in CD4 lymphocyte count (ORa = 6.4 [1, 4-29,3]) and the lack of antiretroviral prescribing in HIV-infected tubercular patients (ORa = 6.2 [1,1-36,3]).

Keywords: risk factors - tuberculosis - Treatment- HIV- Côte d'Ivoire

1. Introduction
The tuberculosis is one of the health priorities because of its severity, its world prevalence and its economic weight [1]. In spite of the implementation of the DOTS strategy recommended by the World Health Organization (WHO) to fight tuberculosis effectively, the morbidity and the mortality bond to this disease are still high in developing countries [1, 2, 3].The objectives of the mortality reduction seem to be difficult to achieve in sub-Saharan Africa. Indeed, the mortality but also the lethality remain high and are likely to constitute threats to the credibility of tuberculosis control programs [5, 6].
Côte d'Ivoire is strongly affected by this pathology, which constitutes a major public health problem. According to the WHO, the annual incidence of the disease is at least 105 cases for 100 000 inhabitants [7]. The mortality bound to the tuberculosis at the national level is steadily increasing from 2054 deaths in 2011 to 2325 in 2012 and to 2684 deaths en 2013 [8]. The sociopolitical crisis that the country experienced from 2002 has contributed to the increase of the mortality and the lethality of tuberculosis incidence in the country [9]. In the northern half of the country, this crisis has led to the closure of almost all health structures in general and of the Diagnostic and Treatment Centers (DTCs) of tuberculosis in particular [9].
The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) provides financial support to the Ivorian health system. Funds totaling an estimated 43 million US dollars between 2004 and 2013 have been used to finance various projects at national level in general and particularly in the north of the country [10] These projects essentially focused on the staff training, the anti-tuberculosis drugs purchasing, the equipment, the management tools purchasing and the treatment centers reahabilitation [10].
The role of these centers in the screening, the treatment and the follow-up of the patients is essential. Therefore, the understanding of the predisposing factors for poor performance of these tuberculosis centers, particularly those relating to death, could lead to the development of more appropriate strategies. The objective of this survey was to analyze the risk factors associated with the death of patients receiving anti-tuberculosis treatment in northern Côte d'Ivoire.

2. Méthodes
Type and period of survey
This was a longitudinal study with descriptive and analytical aim, which took place from January 1st, 2013 to June 30th, 2014. During this period, the patients meeting the inclusion criteria were followed for at least 6 month, time required for first-line treatment.

Framework for the Survey
Our survey took place in five Tuberculosis Diagnosis and Treatment Centers in the Savannah District (northern part of the country). These include the Anti-Tuberculosis Center (ATC) in Korhogo (a specialized urban health center, a reference center for tuberculosis control in the region), the Baptist Health Center (BHC) of Torgokaha in Korhogo, the integrated center of the health District of Ferkessédougou, the Baptist Hospital (BH) of Ferkessédougou and finally the Community Health Center (CHC) Pianzola of Ouangolodougou. Among these five structures are two public

structures and three denominational private structures. The population of the Savannah District was estimated at 1,607,497 inhabitants.

Study Population

Target population: Tubercular patients.

Source population: patients visiting the five treatment centers of the Savannah District selected between January 1st, 2013 and June 30th, 2014 and in whom a form of tuberculosis has been diagnosed by clinical and biological examination.

Sample

Inclusion criteria

We included in our survey all patients diagnosed with tuberculosis by the clinic and para-clinical examinations, registered in the five Tuberculosis Diagnosis and Treatment Centers of the Savannah District, and having freely agreed to participate in the survey, during the above-mentioned period.

Non-Inclusion Criteria

- Patients transferred to another Diagnosis and Treatment Center before the end of anti-tuberculosis treatment and for whom no information could be obtained regarding the outcome of their treatment.
- Lost sight patients, or those for whom the information collected in this study was found to be incomplete (ie patients in whom at least two parameters could not be measured).

  The above-mentioned criteria were used to select 615 patients in the 5 Diagnostic and Treatment Centers.

Collection of data

To complete the data collection, eight interviewers who were already working in the selected Diagnostic and Treatment Centers interviewed the patients using a questionnaire to collect socio-demographic data, personal histories, clinical signs presented and their duration of development before the consultation.

The patients were also all undergoing a complete physical examination by a physician with assessment of the nutritional status (Body Mass Index). For each of them, a biological check-up (Blood Count, ELISA for HIV, CD4 T-cell count) and a face chest X-ray were requested. All these steps constitute the procedures implemented in all the Diagnostic and Treatment Centers when a patient is suspected of having tuberculosis.

These interviews were supplemented by an analysis of the management tools present in the centers (Tuberculosis reporting registers, treatment cards, patients records). This analysis allowed us to determine the type of anti-tuberculosis treatment conducted in the patient, whether the patient was eligible for Cotrimoxazole primary prophylaxis or antiretroviral therapy and, in the event of death, the period of onset. For the standard treatment, these tools were analyzed at the 2nd, 5th and 6th month and for reprocessing at the 3rd, 5th and 8th month.

Data Analysis

The univariate and multivariate statistical analyzes were carried out successively with the software Epi info version 3.5.4. And STATA 13. The chi² test was used for statistical comparisons with a significance level $p < 0.05$. The variable of interest was the death and the explanatory variables were:

- The socio-demographic characteristics (age, sex, occupation, level of education, distance from home-based diagnostic center);
- The clinical characteristics of the disease (vaccination status, duration of development, clinical forms, signs and nutritional status);
- The results of the para-clinical examinations (examination of sputum, hemoglobin level, HIV / AIDS, CD4 count, radiographic examination);
- The ongoing treatments (cotrimoxazole, antiretroviral drugs).

Ethical Aspects

The verbal consent of the respondents was obtained after complet information. The anonymous survey forms, bearing an identification number, were stored in closed cupboards and were accessible only to the investigators' team.

3. Results

In the Savannah Health District, 615 cases of tuberculosis were reported during the survey period with 96 deaths. The lethality was 15.6%. Of the 96 deaths registered, 53 (55.2%) occurred before 30 days of anti-tuberculosis treatment. About three-quarters of the survey deaths (72.9%) occurred during the initial phase of Tuberculosis treatment, which was 60 days.

The pulmonary form of tuberculosis (85.6%) was predominant and the interrogation revealed in 63% of the cases that the disease evolved for more than 2 months. The majority of patients (73.5%) had no specific medical history. The epidemiological profile was that of a man (57.5%), aged under 55 (36%), working in a profession (68%) and not literate (55.5%) (Table 1).

The mean age for all cases collected was 35 years. The population aged from 25 to 34 years was the most significant, accounting for 36% of all patients, followed by that from 35-44 year olds (21.3%). The bacilliform patients accounted for 90.7% of our sample (Pulmonary Tuberculosis with a positive Microscopy or PTM +). The prevalence of HIV was 23% (139 cases) among the tuberculosis patients in the survey. About 26% of co-infected patients had CD4 cell count <200 mm3. (Table 2).

The absence of cotrimoxazole prophylaxis and antiretroviral treatment respectively accounted for 72.6% and 72.6% of patients (Table 3).

The risk factors for death in multivariate analysis ($p < 0.05$) were the bacillary form of tuberculosis, the biological anemia, the positive serology for HIV 1, the decrease in CD4 lymphocyte count and the lack of antiretroviral prescribing in HIV-infected tubercular patients (Table 4).

4. Table

Table 1: Association between death of tubercular patients and socio-demographic characteristics

Sex	Death	Alive	Total	p
Male	51 (53,1%)	303 (58,4%)	354	
Female	45 (46,9%)	216 (41,6%)	261	0,39
Total	96 (100%)	519 (100%)	615	
Age (year)	Death	Alive	Total	p
55 and +	25 (26,0%)	47 (9,0%)	72	
- 55	71 (74,0%)	472 (91,0%)	543	0,000
Total	96 (100%)	519 (100%)	615	
Profession	Death	Alive	Total	p
Without profession	40 (41,7%)	157 (30,3%)	197	
With profession	56 (58,3%)	362 (69,7%)	418	0,03
Total	96 (100%)	519 (100%)	615	
Education	Death	Alive	Total	p
Unliterated	61 (63,5%)	281 (54,1%)	342	
Literated	35 (36,5%)	238 (45,9%)	273	0,11
Total	96 (100%)	519 (100%)	615	
Distance from home	Death	Alive	Total	p
15 km and more	39 (40,6%)	167 (32,2%)	206	
Less than 15 km	57 (59,4%)	352 (67,8%)	409	0,135
Total	96 (100%)	519 (100%)	615	

Table 2: Association between death of tubercular patients and para- clinical exams

Pulmonary form	Death	Alive	Total	p
PTM+	55 (75,3%)	423 (93,2%)	478	0,000
PTM -	18 (24,7%)	31 (6,8%)	49	
Total	73 (100%)	454 (100%)	527	
Anemia	Death	Alive	Total	p
Presence of anemia	71 (75,5%)	328 (63,9%)	399	
Absence of anemia	23 (24,5%)	185 (36,1%)	208	0,03
Total	94 (100%)	513 (100%)	607	
HIV serology	Death	Alive	Total	p
HIV positive	39 (41,1%)	100 (19,6%)	139	
HIV negative	56 (58,9%)	411 (80,4%)	467	0,0000
Total	95 (100%)	511 (100%)	606	
CD4 rate	Death	Alive	Total	p
CD4 < 200 mm^3	17 (43,5%)	19 (19%)	36	
Other value of CD4	16 (41,2%)	66 (66%)	82	0,002
CD4 unspecified	06 (15,3%)	15 (15%)	21	
Total	39 (100%)	100 (100%)	139	
Pulmonary radiography	Death	Alive	Total	p
Major lesions	30 (60%)	186 (47,3%)	216	0,09
Minor lesions	20 (40%)	207 (52,7%)	227	
Total	50 (100%)	393 (100%)	443	

Table 3: Association between death of tubercular patients and therapy

Supervision of treatment	Death	Alive	Total	p
No supervision	6 (6,2%)	26 (5,0%)	32	
Supervision	90 (93,8%)	493 (95,0%)	583	0,8
Total	96 (100%)	519 (100%)	615	
Cotrimoxazole	Death	Alive	Total	p
Yes	17 (43,6%)	21 (21,0%)	38	
No	22 (56,4%)	79 (79,0%)	101	0,01
Total	39 (100%)	100 (100%)	139	
Antiretroviral therapy	Death	Alive	Total	p
Yes	21 (53,8%)	17 (17,0%)	38	
No	18 (46,2%)	83 (83,0%)	101	0,000
Total	39 (100%)	100 (100%)	139	

Table 4: Multivariate analyze of risk factors for death

Variables	P-Value	OR ajusted	Confidence Interval [CI]
PTM -	-	**1**	
PTM+	0, 054	2, 176	[0,98 - 4,79]
PTM++	0, 005	3, 165	[1,41 - 7,05]
PTM+++	0, 001	3, 338	[1,65 - 6,73]
Hemoglobin > 12 g/dl]	-	1	
Hemoglobin < 6 g/dl	0, 000	5,75	[2,01 – 16,44]
CD4 rate > 400	-	1	
CD4 rate < 200	0,016	6.446	[1.42 – 29,30]
ARV therapy	-	1	
No ARV therapy	0,042	6.238	[1,07 – 36,36]
Tuberculosis without HIV	-	1	
Tuberculosis + HIV 1	0,002	2,229	[1,33- 3,71]
Tuberculosis + HIV 2	0,127	3,751	[0,68- 20,51]

p-value of final model = 0,0089< 0,05
p-value of final model = 0,0000<<0,05
Area under ROC curve = 0,8539 >> 0,5

5. Discussion

A total of 615 cases of tuberculosis were included in our survey and followed-up clinically and biologically. More than half of the patients with tuberculosis (57%) were men. This male predominance is generally found in sub-Saharan Africa [1] and similar to that of Balkissou (57.3%) in Cameroon and Mtiraoui (66%) in Tunisia [2, 3]. It could be explained by the fact that men are the most economically active, working in various fields of activity and in contact with the outside environment. This would increase the risk of contagion and spread of the disease. This position is supported by the Raviglore survey, which showed that domestic activities are a protective factor in tuberculosis [4]. The follow-up patients were generally young with ages between 25 and 34 years. This age group was also found in Senegal [5], but does not include the median age of Bemba in the Congo which was 42.9 years [6] or even that of Dovonou in Benin (37.4 years) [7]. However, despite these disparities, it is important to note that the patients remain young and active populations. Concerning the profession, 68% of the patients had one. Our age and occupation results are in line with our initial analysis and could provide an explanation. Indeed, young men and those who practice a profession would have a greater risk of contagion and spread of the disease. As for educational attainment, more than half (55.5%) were unliterate. This could be explained by the high rate of illiteracy in the north Côte d'Ivoire, where live the rural and poor population who have limited literacy. Indeed, the proportion of illiteracy was 61.6% in men and 71.6% in women [11].The lack of education, a source of ignorance, is also a factor in the spread of communicable infectious diseases.

Our survey showed a lethality of 15.6%. This is 1.5 times superior to the national average in 2013 and to the average found in Lubumbashi in the Democratic Republic of Congo which was 10.6% [8]. It is similar to the world rate of 2015 (16%) [10] but much lower than that found in 2014 in Senegal (31%) [12]. This difference could be explained by the fact that our survey was carried out in health facilities at the primary level of the health pyramid. These facilities would have referred the complications to a higher level of the pyramid. The survey of Senegal, on the other hand, was carried out in a Teaching Hospital (TH) constituting the top of the health pyramid and having more complicated forms liable to be lethal. As a reminder, more than 95% of cases and more than 98% of tuberculosis deaths are reported in African, Asian and Latin American countries [13]. This situation is aggravated by the impoverishment of the populations [14].

The clinical form of tuberculosis was dominated by the pulmonary tuberculosis with a percentage of 85.5% of which 90.7% were bacillary form. These results get closer to those found in Cameroon [2] but differ from those in the Congo [8] or the island of Reunion [9] were the dominant formes in both cases were pleuric tuberculosis. In Gabon, the pulmonary tuberculosis in an anti-tuberculosis center was 97%, of which 58% were bacillary form. The detection of cases of contagious tuberculosis is still insufficient in the world and in Africa. It was less than 70% in sub-Saharan Africa between 2005 and 2015 [13]. As a result, more than half of the contagious cases are not detected, treated, and continue to transmit the disease around them.

Among the bacillary form patients, the risk of death was 3 times higher in patients with positive bacilloscopy with two and three crosses. While this risk of death was not significant in patients with only one cross. The contagiousness of tuberculosis is an important lethality factor. This report was also made by Ngama [8] but differs from that of Waitt, who rather concluded that negative bacilloscopy was a risk factor for death [15]. However, it should be noted that negative bacilloscopy was a risk factor in populations with high HIV prevalence. Indeed, this negativity would be due to the important immunodeficiency which would constitute a confounding factor not taken into account in these survey.

The co-infection Tuberculosis / HIV was 23% in our survey, slightly lower than that of Nkoghe in Gabon (26%) [14]. This rate is superimposable to the figures observed in several Sub-Saharan African countries [1,2]. Between 2010 and 2020, WHO estimates that 10% of tuberculosis cases worldwide and 20% of tuberculosis deaths will affect people living with HIV [13]. This is corroborated by our findings, which show in the multivariate analysis that 4 death factors were related to HIV / AIDS.

The patients infected with the HIV 1 had significantly twice more the risk of death. On the other hand, those who were infected with the HIV 2 did not have a significant risk. This difference in risk between the patients infected by the HIV-1

and the HIV-2 could be explained by a low prevalence of HIV-2 infection as shown in the Gnaore survey [16]. Several surveys, including those of Kuaban and Nunn, confirmed that HIV positive status was a risk factor for death [17,18]. The study of blood-immune changes during the HIV infection and during the tuberculosis is of diagnostic and prognostic value. An important immune depression (CD4 <200) would be a factor of death in our survey, increasing by 6 times the risk. In the Dagnra survey in Togo in 2011, 55.8% of the co-infected had a CD4 cell count lower than 200 / µl [19]. The cure rate in this group was 47.8% versus 84.4% in the group of the HIV-positive patients with a CD4 cell count superior to 200 / µl. The anemia was also a risk factor for death. Patients with hemoglobin level less than 6 g / dl were 5.7 times more likely to die than the patients without anemia. A similar result was found by Mugusi and Kourbatova who found a risk of death identical to ours [20,21]. Hane highlighted a decrease of the mean of red blood cell count and hemoglobin level in co-infected (Tuberculosis / HIV) and non-co-infected patients, but this anemia was significantly more marked in co-infected patients (P = 0.001) [22].

The tuberculosis and the HIV infection are diseases that have an adverse effect on hematopoiesis and the body's defense mechanisms [22]. Their association aggravates the hematological and immunological abnormalities encountered in each of the pathologies [22]. Our results show the negative impact of HIV on the tuberculosis and the need for global care, especially through the prescription of antiretroviral. Moreover, the patients who were not prescribed antiretrovial were 6 times more likely to die than patients receiving treatment.

Some biological check-up may have been biased in our results

- The large variability of the interpretation of the radiographic image could have constituted, in the case of pulmonary tuberculosis, a bias in the assessment of the risk of death related to the chest lesions presented.
- The variability in the quantitation, from one technician to another, of Acid-and-Alcoolo-Fast Bacilli observed on smears carried out in the laboratory could have constituted interpretation bias.
- Since biological check-up have been carried out in different laboratories, it is likely that there were variations in the interpretation of the results from one laboratory to another.

6. Conclusion

The tuberculosis continues to prevail, in particular with a lethality of 15.6% in Côte d'Ivoire. This affection affects young people in 36% cases and the unliterate population (55.5%). The pulmonary form of the tuberculosis (85.6%) is the most common. Among the co-infected subjects (HIV/tuberculosis), 90% were positive for the HIV 1. This co-infection with HIV increases the risk of death due to this disease. However, the bacillary form of the tuberculosis, the biological anemia, the HIV-1 positivity, the decrease of CD4 cell count and the lack of antiretroviral prescribing in the HIV co-infected tuberculosis patients are the risk factors for death. Measures must be taken in terms of health in order not to disregard this co-infection, hence the interest of systematic screening of any tubercular patient.

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Conflict of interest: None

7. References

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