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Research Article

Predictive Factors of Mortality of Tuberculosis Patients Dead of Tuberculosis in Côte d'Ivoire

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Abstract

Introduction: study of the predictive factors of the deaths of tuberculosis patients to propose a decision tree for their best care in ambulatory TB centers. Methods: Prospective and observational survey, on a sample of 939 tuberculosis patients recruited in 30 CAT/CDT, carried out during supervision using collection tools such as survey forms and tuberculosis patient files. Results: 55 patients were notified dead. The mortality rate during tuberculosis was 5.9%. The Independent Factors Inducing Death (IFID) of TB were illiteracy, asthma associated with tuberculosis, assimilation of tuberculosis to witchcraft, radiological involvement of the pulmonary territories, serum creatinine ≥ 28 mg/L, HIV infection associated with TB. Associated with severe anemia for clinical concern, these factors allowed the development of the predictive score of death from TB. The ROC curve of the predictive score at death estimated the relevance of the predictive value of death with an area under the curve of 0.834 (0.755 – 0.912) ($p < 0.001$). The negative predictive value (NPV) of the predictive score for death during TB varied between 94.08% and 98.95%. This score is calculated on two groups of IFID. The 1st group is made up of socio-demographic factors. The 2nd group is made up of morbid situations requiring care in a specialized environment. Conclusion: The IFID imposes a management based on the use of the interrogation and the minimal radiological and biological assessment (the chest X-ray, the blood count, the dosage of creatinine and HIV serology). The decision tree-based death reduction strategy will contribute to better referral and management of patients.

Keywords

Risk Factor, Deaths of Tuberculosis, Tuberculosis Patients, Predictive Score, Decision Tree

1. Introduction

Tuberculosis is a contagious, non-immunizing, airborne endemic-epidemic disease caused by mycobacteria of the Tuberculosis complex, mainly Mycobacterium tuberculosis or Koch's bacillus (BK) [1]. The pulmonary form with posi-

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tive microscopy is the main source of dissemination. Despite the adoption of the WHO DOTS [1] and End TB [2] strategies, tuberculosis remains the 5th leading cause of death from contagious diseases [3] and the leading cause of death from a single infectious agent in Africa [4].

According to WHO [5], more than 95% of deaths occur in low- and middle-income countries such as Côte d'Ivoire [6; 7] where the death rate of people with tuberculosis has increased since 1996; this death rate remains high despite the management of TB carried out mainly on an outpatient basis as well as by reference services for diagnostic difficulties, either for complications of TB or for imbalance of an underlying defect by TB. Analysis of the results of the 2014 cohort shows a death rate of 8% of bacteriologically confirmed cases (new cases and relapses) at the national level, i.e. 1097 out of 14226. Analysis of observational data from CDTs showed a mortality rate of TB patients varying between 5 and 10%. The study on deaths in adults treated for TB during and after tuberculosis treatment shows that deaths occur during the first two (2) months of anti-tuberculosis treatment.

The rare epidemiological studies indicate that the different risk factors [8] for death from tuberculosis [9] are, in the non-infectious comorbidity component, respiratory diseases [10, 11], renal diseases [12, 13], such as cancer, measles and immunosuppression due to diabetes mellitus, to the administration of corticosteroids. Comorbidity promotes mortality [14]. TB represents 13% of deaths of PLHIV [2] and has increased the probability of death for tuberculosis of PLHIV by the difficulty of diagnosis at the advanced stage of HIV disease facilitating frequent extra-pulmonary and multifocal localizations. 24% of people with TB tested HIV positive [15]. Death during the first month of treatment occurred in 9% of HIV-negative patients. The increased mortality rate in older TB patients [16] is largely explained by the coexistence of other age-related diseases. In addition, the risk of death in TB smokers [17] compared to non-smokers is doubled so that in India [18], half of the deaths in TB patients were attributed to patients' smoking [19]. Other research [20] has concluded that the important risk factors for increased mortality from pulmonary TB are nutritional status [21] due to poor performance. Nutritional status [22], measured by serum albumin and haemoglobin levels, is an important predictor of survival from medical treatment. A prospective study [23], showed that malnutrition increases the risk of death from TB in a war setting.

Knowledge of the factors predisposing to death contributes to the development of complementary treatment strategies, or to closer clinical monitoring in high-risk individuals. Thus, this present study is based on the hypothesis that the tuberculosis patient who died of tuberculosis followed as an outpatient presented a particular profile, especially since there were criteria or predictive factors for the mortality of TB cases, the identification of which would contribute to better orientation of TB patients at the initiation of treatment. The verification of this hypothesis would then lead to achieving the objective of this study, which was the proposal of a decision tree for a better strategy for directing the management of tuberculosis patients at high risk of death in outpatient TB management centers.

2. Materials and Methods

2.1. Type and Framework of the Study

This is a prospective, observational study on national anti-tuberculosis activity carried out from 2016 to 2020.

The activities of the tuberculosis control program (PNLT) are organized according to the three-level health pyramid model:

The central level is ensured by the PNLT, responsible for ensuring the organization and coordination of activities to fight tuberculosis in Côte d'Ivoire. The management of the PNLT is composed of eight (8) services: the coordination service; the administrative and financial service; the service of community mobilization and communication; the TB/HIV service; TB-MR; the monitoring and evaluation service; the laboratory service; the pharmacy and supply service. The regional level is made up of the 17 anti-tuberculosis centers (CAT) which have more equipment and have a coordination function at the peripheral level although located at the district level and are part of the district management team. They are each headed by a chief physician. The peripheral level is made up by the diagnostic and treatment centers (CDT) which are the essential and primary basic units of the fight TB. It is headed either by a doctor or a nurse. In 2016, Côte d'Ivoire had 211 functional CDT which were the recruitment centers for patients included in this study.

The program's (PNLT) screening policy is passive. Individuals self-refer to the hospital or a CAT/CDT when they present a sign of tuberculosis impregnation with or without a chronic cough.

2.2. Study Parameters

The variable explained in this study was: the death of the tuberculosis patient during anti-tuberculosis treatment. The explanatory variables were:

1) Socio-demographic variables: Age, Sex, Profession, Religion, Level of education, Descent, Residence, Monthly income;
2) Co-morbidities and history: HBP, Diabetes, UGD, Sickle cell disease, Tuberculosis, HIV, Asthma, Previous psychiatric disorders, Alcoholism, Smoking;
3) Initial respiratory signs: Cough, Expectoration, Hemoptysis, Chest pain, Dyspnea;
4) Initial general signs: Fever, Asthenia, Anorexia, Weight loss, Night sweats, Pregnancy amenorrhea; Evolutionary modalities of signs: duration, mode of onset; Paraclinical aspects: Diagnostic elements of TB, Chest X-ray, CBC, Urea, Creatinine, TGP, TGO, HIV/CD4 serology,

Blood sugar; Therapeutic aspects: Anti-TB protocol, ARV protocol (type, start times), Cotrimoxazole prophylaxis, adjuvant treatment;

5) Conditions of compliance: TDO, community TDO, regularity of supply, financial autonomy, transport autonomy, regularity of bacteriological control;
6) Knowledge about TB, attitudes towards the disease and treatment. Subjects were categorized based on their score into good knowledge (score ≥15/20), partial knowledge (score between 10-14/20), Insufficient knowledge (score ≤ 09/20).

2.3. Sampling

The number of patients who died during treatment was calculated using the following formula:

$$n = (z)\ 2\ p\ (1 - p) / d2$$

n = sample size

z = confidence level according to the reduced centered normal distribution (for a confidence level of 95%, z = 1.96, for a confidence level of 99%, z = 2.575)

p = estimated proportion of the population that exhibits the characteristic (when unknown, use p = 0.5)

d = tolerated margin of error (for example, we want to know the real proportion to within 5%).

Mortality among tuberculosis patients ranged from 8 to 10% nationally in 2016. Considering a mortality (p) of 10% and Z = 1.96, the number of deaths was as follows: n = (1.96)2x 0.1 (1 - 0.1)/(0.05)2. Therefore, n = 138, 296.

To have 139 cases, a minimum of 1390 cases of TPB (+) will be required at inclusion (*Table 1*). In the cohorts of tuberculosis patients in Abidjan, the proportion of patients lost to follow-up varied between 5 -10%. Considering a proportion of 10% excluded (lost to follow-up), to have 1390 patients at the end of the study, it will then be necessary to include 174 additional patients. That is, a total of a minimum of 1564 cases of TPB (+) at inclusion. The number of patients with tuberculosis recruited per center will be calculated as follows: The weight of each CDT in the national screening of TPBC cases will be defined, calculated and the previously determined sample will be assigned this weight in order to define the number of TB cases who died in each center to be recruited systematically and successively.

Centers were selected if the death rate was ≥ 5% in 2014 and the total number of TB cases detected per center was ≥ 100 cases. Applying these criteria based on 2014 activity, 30 centers (CAT and CDT) were selected to conduct this study. On this basis, the number of patients to be recruited per center varied between 11 and 161 patients.

Table 1. *Selection criteria for patients in the sample.*

Inclusion criteria	Non-inclusion criteria	Exclusion criteria
Cases of TPB (+) starting first-line treatment	Subject < 15 years old	Patients who died from accidents, for causes other than TB and documented (stroke with brain CT, MI with ECG)
Chest X-ray available	Proven and progressive psychiatric disorders	Patients lost to follow-up
HIV serology available, CD4 if HIV positive	Non-consenting patients	Patients who discontinued treatment (due to major side effects or on their own)
Standard biological assessment available (NFS, Urea creatinine, Glycemia TGP, proteinemia, ionogram)		

2.4. Organization and Conduct of the Study

Before the start of the survey, the training of the investigators was carried out over one day. It covered the protocol, the study tools and the actual conduct of the study. The recruitment of patients was successive in the CAT/CDT involved in the study and was carried out in 3 stages: *pre-inclusion*: Inform the patient for whom a prescription for the search for tuberculosis bacilli is prescribed of the proposal to participate in a study on tuberculosis; *inclusion*: The patient recovers the result of the sputum bacilloscopy, if the bacilloscopy result is positive; monitoring and evaluation of the outcome at month (M2, M5): Retrieve the results of the BK, Clinical evaluation; Evaluation of the part of the questionnaire on knowledge of tuberculosis, attitudes towards the disease and treatment; Final evaluation at M6 of the treatment: Sputum bacilloscopy, Chest X-ray and clinical evaluation; *Patient monitoring*: informed by the doctor or nurse in charge of the patient's care, or who calls the trusted person in the absence of a patient to identify the status (lost to follow-up, deceased, causes of death).

2.5. Data Collection and Analysis Tools

The study was conducted during supervision using data collection tools such as survey forms and tuberculosis patient files registered in the CAT/CDT. The data were recorded in two Excel databases and processed with SPSS 20.0 software. The study population was described with the results of the univariate analysis. The proportions were used to describe the categorical variables; the quantitative variables were described with the means plus or minus standard deviation (SD).

The bivariate analysis made it possible to establish the statistical link between the variable studied (mortality) and the other variables (socio-demographic, co-morbidity, etc.). The comparison of proportions was made with the KHI2 test or the exact FISHER test. The OR made it possible to assess the power or importance of the statistical link between mortality and the other variables. The comparison of means was made by a non-parametric test. Eventually, the quantitative variables were transformed into categorical variables for a stratified analysis.

Categorical variables that showed a significant association with death with a p-value $P < 0.05$ or an interval of the odds ratio (OR), CI95%, were included in a logistic regression model for multivariate analysis. Thus, the independent factors inducing death (IFID) of patients with tuberculosis were identified and the importance of their impact on the occurrence of death was assessed by the odds ratio. These IFID made it possible to construct a score for predicting the death of patients undergoing anti-tuberculosis treatment followed as outpatients. The sensitivity, specificity of the negative and positive predictive value of this score were calculated in order to propose a decision tree. The P-value $P < 0.05$ will be considered as a significant threshold.

3. Results

3.1. Diagram of Analyzed TB Patients

Based on the inclusion and exclusion criteria, data from 939 patients were analyzed using a flow diagram (Figure 1). Thus, out of a sample of 1,046 patients included at the start of the study, a total of 939 patient records were included in the data analysis, after excluding the 6 transferred patients, the 29 cases of MDR-TB failure, and the 72 patients lost to follow-up. Mortality was 5.9% (55/939).

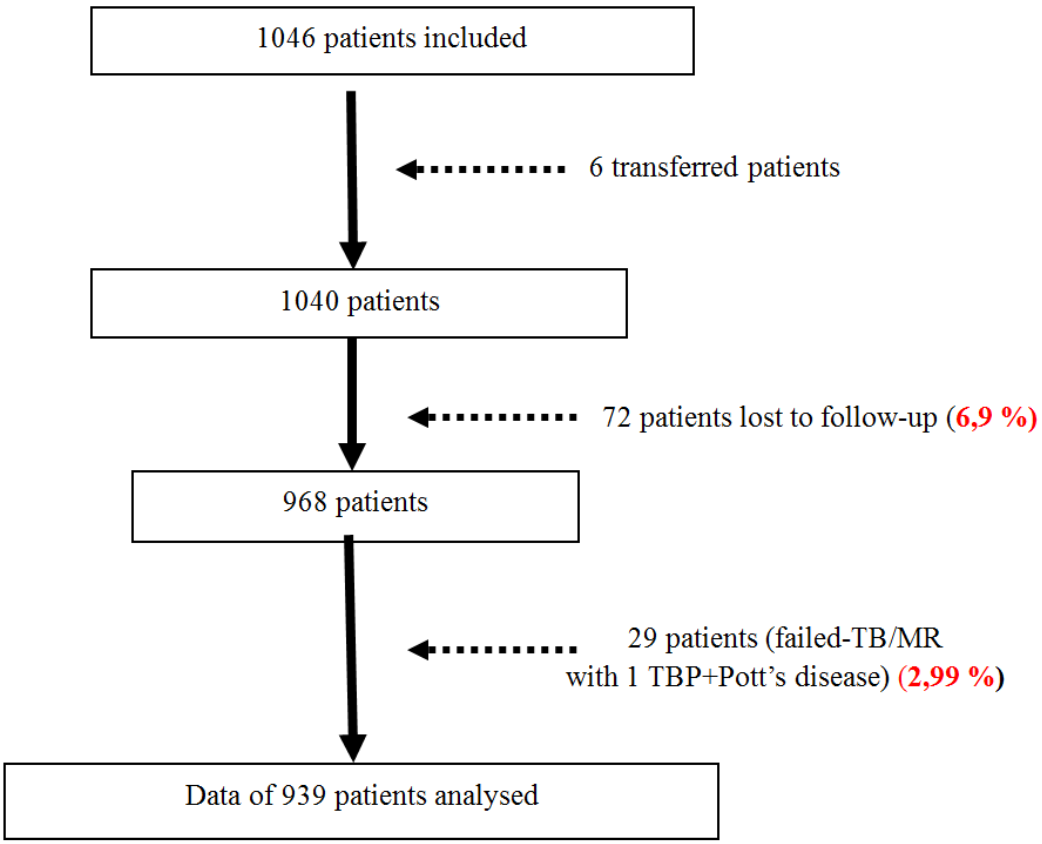

Figure 1. *Flow chart of patient exclusion for final analysis.*

3.2. Descriptive and Analytical Results

Sociodemographic aspects

The mean age was 34.52 years with a standard deviation (SD) of 12.817 years and extremes of 15 and 80 years. The proportion of patients aged 15 - 44 years was 80.1%. The proportion of male subjects represented 67.2% (618/920) of the population with a sex ratio of 2. In our study, 79% (701/887) of patients had their municipality of residence which housed the CAT or CDT in which they were followed. Of our patients, 44.6% (419/920) were Muslims, 30.4% (278/914) had not been educated. The death rate among patients aged ≥45 years was 10.3% (19/184) versus 4.6% (34/742) among subjects aged <45 years [p = 0.004 (OR, 95% CI = 2.254 (1.316–3.858)]. Mortality was highest among subjects of Muslim faith (8.6%) (p = 0.001) and subjects not in school (9%) (p = 0.012) (Table A1 in Appendix).

History and co-morbidities

High blood pressure (HBP), asthma, alcoholism and active smoking were found in the respective proportions of 3.1% (28/898), 2.7% (23/852), 26.9% (239/887) and 17.2 % (147/854). Patients were known to be infected with HIV in 19.2% (136/709). Tuberculosis infection was reported by 37.8% (286/757) of patients (Table A2 in Appendix). Mortality during tuberculosis was statistically higher in hypertensive patients (21.4% versus 5.1%), HIV-infected patients (15.4% versus 4.9%), asthmatic patients (17.4% versus 4.9%) and patients without alcohol intoxication (3.3% versus 6.8%) (Table A2 in Appendix).

Respiratory and general functional signs

The mean duration of respiratory functional signs (*Table 2*) varied between one week and 1825 days, with a mean of 58.41 days and SD of 88.410 days. Chronic cough and hemoptysis were signs of TB expression in 94.6% (866/915) and 14.8% (124/839) of cases. General signs were present during the symptomatology with proportions of 15.9% to 73.5%.

Table 2. *Mortality and respiratory functional signs during tuberculosis.*

Variables		Become		P	OR, 95% CI
		Death	Success		
Brutal start	Yes	4.5% (11/246)	95.5% (235/246)	0.261	0.763
	No	5.9% (38/648)	94.1% (610/648)		0.396 – 1.468
Duration of signs ≥ 90 days	Yes	7.8% (15/193)	92.2% (178/193)	0.098	1,552
	No	5% (36/719)	95% (683/719)		0.868 – 2.775
Cough	Yes	5.7% (49/866)	94.3% (817/866)	0.063	0.943
	No	0% (0/49)	100% (49/49)		0.928 – 0.959
Hemoptysis	Yes	2.4% (3/124)	97.6% (121/124)	0.057	0.384
	No	6.3% (45/715)	93.7% (670/715)		0.121 – 1.218
Chest pain	Yes	5.9% (37/631)	94.1% (594/931)	0.307	1,246
	No	4.7% (12/255)	95.3% (243/255)		0.661 – 2.351
Dyspnea	Yes	6.7% (21/312)	93.3% (291/312)	0.218	1,302
	No	5.2% (26/503)	94.8% (477/503)		0.746 – 2.274

Data analysis did not highlight a statistically significant relationship between mortality during tuberculosis and respiratory functional signs (Table 2) and general signs (Table 3).

Table 3. *Mortality and general signs of tuberculosis.*

Variables		Become		P	OR, 95% CI
		Death	Success		
Fever	Yes	5.4% (36/667)	94.6% (631/667)	0.364	0.864

Variables		Become Death	Success	P	OR, 95% CI
Asthenia	No	6.2% (15/240)	93.8% (225/240)	0.248	0.482 – 1.549
	Yes	6.1% (39/636)	93.9% (597/636)		1,327
Anorexia	No	4.6% (11/238)	95.4% (227/238)	0.112	0.691 – 2.547
	Yes	6.5% (36/550)	93.5% (514/550)		1,497
Weight loss	No	4.4% (15/343)	95.6% (328/343)	0.367	0.832 – 2.692
	Yes	5.5% (43/787)	94.5% (744/787)		0.826
Night sweats	No	6.6% (8/121)	93.4% (113/121	0.249	0.398 – 1.715
	Yes	6.2% (36/576)	93.8% (540/576)		1,283
	No	4.9% (15/308)	95.1% (293/308)		0.714 – 2.306

Extra-respiratory functional signs

Extra-respiratory signs were reported by patients, including headache [57.8% (531/919)] and insomnia [52.5% (476/906)] (Table 4). The existence of insomnia was associated with a high rate of death in patients: 7.8% versus 3.5% (p = 0.004; OR = 2.228; 1.241–4.002) (Table 4).

Table 4. *Mortality and extra-respiratory functional signs during tuberculosis.*

Variables		Become Death	Success	p	OR, 95% CI
Diarrhea	Yes	7.9% (8/101)	92.1% (93/101)	0.202	1,473
	No	5.4% (44/818)	94.6% (774/818)		0.714 – 3.039
Nausea	Yes	6.1% (13/213)	93.9% (200/213)	0.431	1,103
	No	5.5% (39/705)	94.5% (666/705)		0.600 – 2.028
Abdominal pain	Yes	7.3% (17/232)	92.7% (215/232)	0.121	1,470
	No	5% (34/682)	95% (648/682)		0.837 – 2.580
Vomiting	Yes	8.6% (15/174)	91.4% (159/174)	0.054	1,715
	No	5% (37/736)	95% (699/736)		0.963 – 3.053
Headaches	Yes	5.1% (27/531)	94.9% (504/531)	0.230	0.789
	No	6.4% (25/388)	93.6% (363/388)		0.465 – 1.338
Insomnia	Yes	7.8% (37/476)	92.2% (439/476)	0.004	2,228
	No	3.5% (15/430)	96.5% (415/430)		1,241 – 4,002

Physical signs

In 46.8% (377/805) of cases, patients had a BMI ≤ 18.5 kg/m2. The conjunctivas of patients were pale in 10.5% (93/883) of cases and icteric in 1.9% (16/863) of cases. Crackles were reported in 17.3% (128/738) of cases (*Table 5*).

Table 5. *Mortality and physical signs during tuberculosis.*

Variables		Become		P	OR, 95% CI
		Death	Success		
BMI < 18.5	Yes	7.4% (28/377)	92.6% (349/377)	0.067	1,589
	No	4.7% (20/428)	95.3% (408/428)		0.911 – 2.774
Pulse ≥ 125 beats/min	Yes	7.1% (1/14)	92.9% (13/14	0.543	1,333
	No	5.4% (41/765)	94.6% (724/765)		0.197 – 9.018
Conjunctival pallor	Yes	15.1% (14/93)	84.9% (79/93)	<0.001	3,214
	No	4.7% (37/790)	95.3% (753/790)		1,806 – 5,719
Jaundice	Yes	18.8% (3/16)	81.2% (13/16)	0.054	3,529
	No	5.3% (45/847)	94.7% (802/847)		1,224 – 10,175
IMO	Yes	11.9% (5/42)	88.1% (37/42)	0.077	2,276
	No	5.2% (41/784)	94.8% (743/784)		0.949 – 5.461
Crackling rales	Yes	10.2% (13/128)	89.8% (115/128)	0.015	2,213
	No	4.6% (28/610)	95.4% (582/610)		1,179 – 4,153

Mortality in tuberculosis was 15.1% in cases of conjunctival pallor versus 4.7% in the absence of conjunctival pallor [p<0.001, OR = 3.214 (1.806–5.719)]. The proportion of patients who died in cases of jaundice was 18.8% versus 5.3% in the absence of jaundice [p=0.054; OR = 3.529; OR = 3.529 (1.224–10.175)]. Among patients with crackles, the death rate was 10.2% and 4.6% in the opposite case [p=0.015; OR = 2.213 (1.179–4.153)] (Table 5).

Characteristics of radiological lesions

Radiological lesions were bilateral in 47.6% (322/676) of cases, found in all territories of the pulmonary fields in 43.1% (265/615) of cases. The lung was destroyed in 14.7% (116/681) of cases (Table 6). The location of radiological lesions in all pulmonary territories was positively associated with patient death [9.8% versus 3.4%: p = 0.001; OR = 2.862 (1.471 – 5.565)] (Table 6).

Table 6. *Mortality and characteristics of radiological lesions during tuberculosis.*

Variables		Become		P	OR, 95% CI
		Death	Success		
Site of injury	Unilateral	5.3% (17/322)	94.7% (305/322)	0.362	0.850
	Bilateral	6.2% (22/354)	93.8% (332/354)		0.459 – 1.571
Topography	Apical	1.9% (5/264)	98.1% (259/264)	0.01	----------
	Basal	8.1% (7/86)	91.9% (79/86)		
	All territories	9.8% (26/265)	90.2% (239/265)		
Lung destruction	No destruction	4.7% (22/465)	95.3% (443/465)	0.071	----------
	Destroyed lung	10.3% (12/116)	89.7% (104/116)		
	Destroyed lobe	6% (6/100)	94% (94/100)		
All territories reached	Yes	9.8% (26/265)	90.2% (239/265)	0.001	2,862
	No	3.4% (12/350)	96.6% (338/350)		1,471 – 5,565

Biological abnormalities

Plasma creatinine level was ≥ 28 mg/L in 1% (8/782) of cases. In 2.9% (21/734) of cases, hemoglobin level was ≤ 7 g/dL. HIV serology was positive in 12.6% (96/760) of cases (*Table 7*). Biological abnormalities during the initial assessment were positively associated with death during tuberculosis: Creatinemia ≥ 28 mg/L (37.5% versus 5.2%), Hemoglobin ≥ 7 g/dL (19% versus 5.5%) and HIV serology positive (15.6% versus 3.9%) (*Table 7*).

Table 7. *Mortality and biological abnormalities during tuberculosis.*

Variable		Become		p	OR, 95% CI
		Death	Success		
TGP ≥ 80 IU/L	Yes	5.7% (42/740)	94.3% (698/740)	0.467	0.766
	No	7.4% (2/27)	92.6% (25/27)		0.196 – 3.002
Creatinemia ≥ 28 mg/L	Yes	37.5% (3/8)	62.5% (5/8)	0.007	7,256
	No	5.2% (40/774)	94.8% (734/774)		2,823 – 18,653
Hemoglobin ≥ 7 g/dl	Yes	19% (4/21)	81% (17/21)	0.029	3,482
	No	5.5% (39/713)	94.5% (674/713)		1,370 – 8,853
Positive HIV serology	Yes	15.6% (15/96)	84.4% (81/96)	<0.001	3,990
	No	3.9% (26/664)	96.1% (638/664)		2,194 – 7,259

3.3. Prediction of Death in Tuberculosis Patients

Multivariate analysis

Ascending likelihood ratio was used for binary logistic regression. The final step of the results of this regression was presented in Table 8. The independent factors inducing death (IFID) of patients during tuberculosis were illiteracy, tuberculosis occurring in an asthmatic, serum creatinine ≥ 28 mg/L, associating tuberculosis with witchcraft, HIV infection, involvement of all lung territories on chest X-ray (*Table 8*).

Table 8. *Mortality and independent factors.*

	p	GOLD	IC OR, 95%
Illiteracy	0.003	4,059	1,599 - 10,304
"Tuberculosis is witchcraft"	0.011	3,816	1,360 - 10,705
Asthma	0.029	5,933	1,200 - 29,333
Radiological damage to all pulmonary territories	0.008	3,857	1,413 - 10,529
Creatinine > 28 mg/l	0.004	23,651	2,788 - 200,650
HIV infection	0.007	4,096	1,480 - 11,332

These six independent factors inducing death (IFID) are the constituent elements of the predictive score of death of patients during tuberculosis. The presence of each factor in a patient is assigned the coefficient 1. We included severe anemia in the calculation of the prediction score. The predictive score for each patient was obtained by the sum of the coefficients of each independent factor predicting death. Thus in theory, the predictive score could vary from 0 to 7.

Predictive score for patient death

In the study database, the calculation of this score was possible for 474 patients. This score varied between 0 and 4. In this population, 30.2% (143/474) of patients had an estimated score of 0: therefore? no predictive factor for death. On the other hand, 0.6% (3/474) of patients had an estimated score of 4 (Table 9). Among the deceased patients (26/474), the mean score was 2.3462, with SD = 0.9744 against 0.9821 with SD = 0.85903 among the non-deceased patients (p < 0.001).

Predicting death of tuberculosis patients based on predictive score

In multinomial logistic regression, and taking as reference value predictive score at 4 (no IFID), mortality during tuberculosis increased significantly with the number of IFID. From 3 IFID present in the same patient, mortality became ≥ 36.8% (Table 10 and Table 11).

Table 9. *Predictive score for death during tuberculosis.*

Total score	Staff	Proportions (%)
0	143	30.2
1	202	42.6
2	91	19.2
3	35	7.4
4	3	0.6
Total	474	100.0

Table 10. *Mortality and predictive score of death during tuberculosis.*

Total score	Become		P	OR, 95% CI
	Death	Not deceased		
= 0	0 % (0/143)	100% (143/143)	<0.001	3,480 ^{E} -011 3,480 ^{E} -011- 3,480 ^{E} -011
≥ 1	7.9 % (26/305)	92.1% (305/331)	<0.001	0.018 0.001 - 222
≥ 2	14.7% (19/129)	85.3% (110/129)	<0.001	0.29 0.002 – 0.378
≥ 3	36.8% (14/38)	63.2% (24/38)	0.002	0.261 0.021 – 3.178
= 4	66.7% (2/3)	33.3% (1/3)	-	-

Relevance of the predictive score for death during tuberculosis

The ROC curve linking the predictive score to death allowed an estimation of the relevance of the predictive value of death with an area under the curve of 0.834 (0.755 – 0.912) (p < 0.001) (Figure 2).

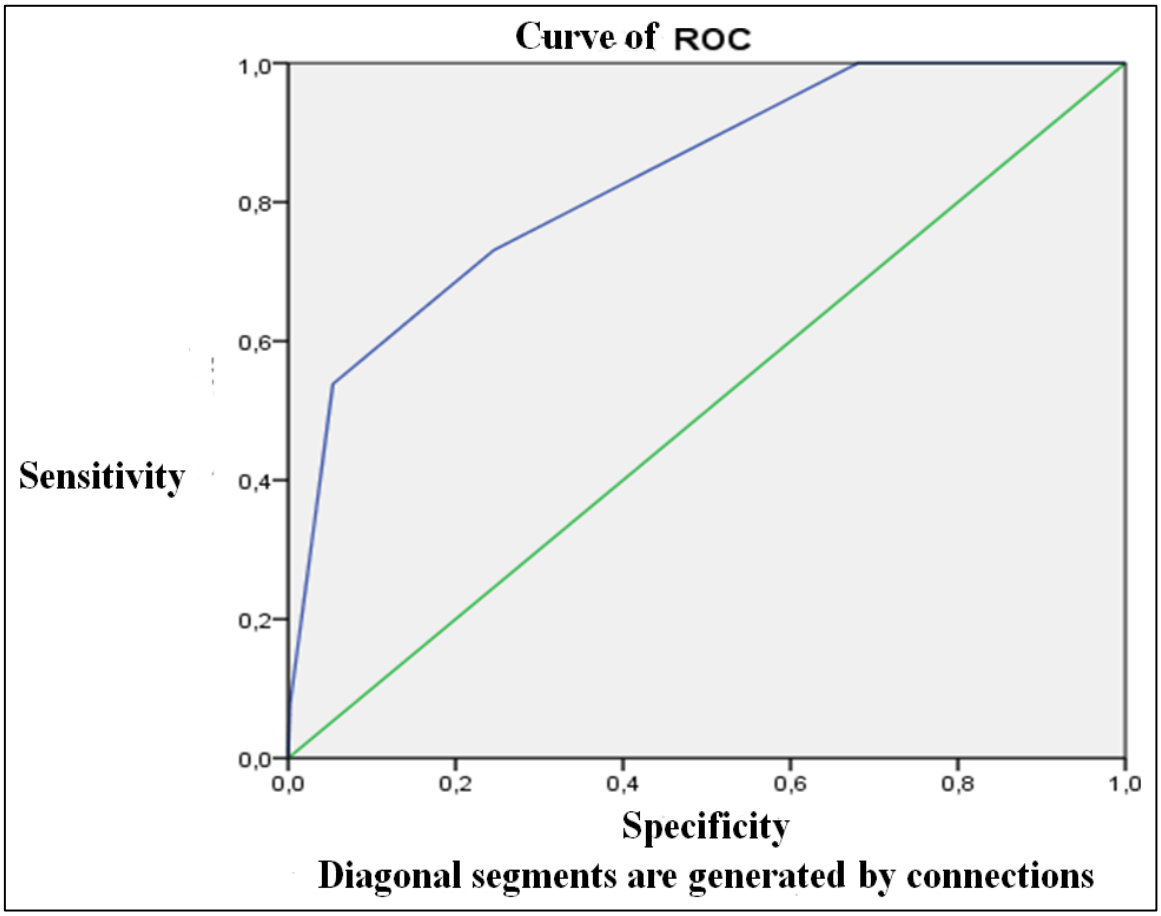

Figure 2. *Specificity and sensitivity of the predictive score for death in tuberculosis.*

The negative predictive value (NPV) of the score predicting death from TB ranged from 94.9% to 100%. The specificity of the score in predicting death from TB ranged from 31.92% to 99.78% (*Table 11*).

Table 11. *Mortality and predictive score of death (sensitivity and specificity test) during tuberculosis.*

Predictive score	Sensitivity	Specificity	VPP	VPN
≥ 1	100%	31.92%	7.85%	100%
≥ 2	53.85%	94.64%	36.84%	97.25%
≥ 3	7.69%	99.78%	66.67%	94.9%

Legend: NPV = Negative predictive value; PPV = Positive predictive value.

3.4. Proposal of Strategies for Reducing Deaths of Tuberculosis Patients

The identification of IFID during tuberculosis has made it possible to identify 2 groups of factors including a group of sociodemographic IFID and another group of IFID which are co-morbidities. The first group is composed of factors whose modification is necessary for the overall management of the patient. The means in this management are communication, information, therapeutic education. The second group includes factors for which medical management is sometimes possible in a specialized environment. They require a minimum radiological and biological assessment made up of blood count and creatinine dosage. In view of these elements, we propose the following decision tree (Figure 3).

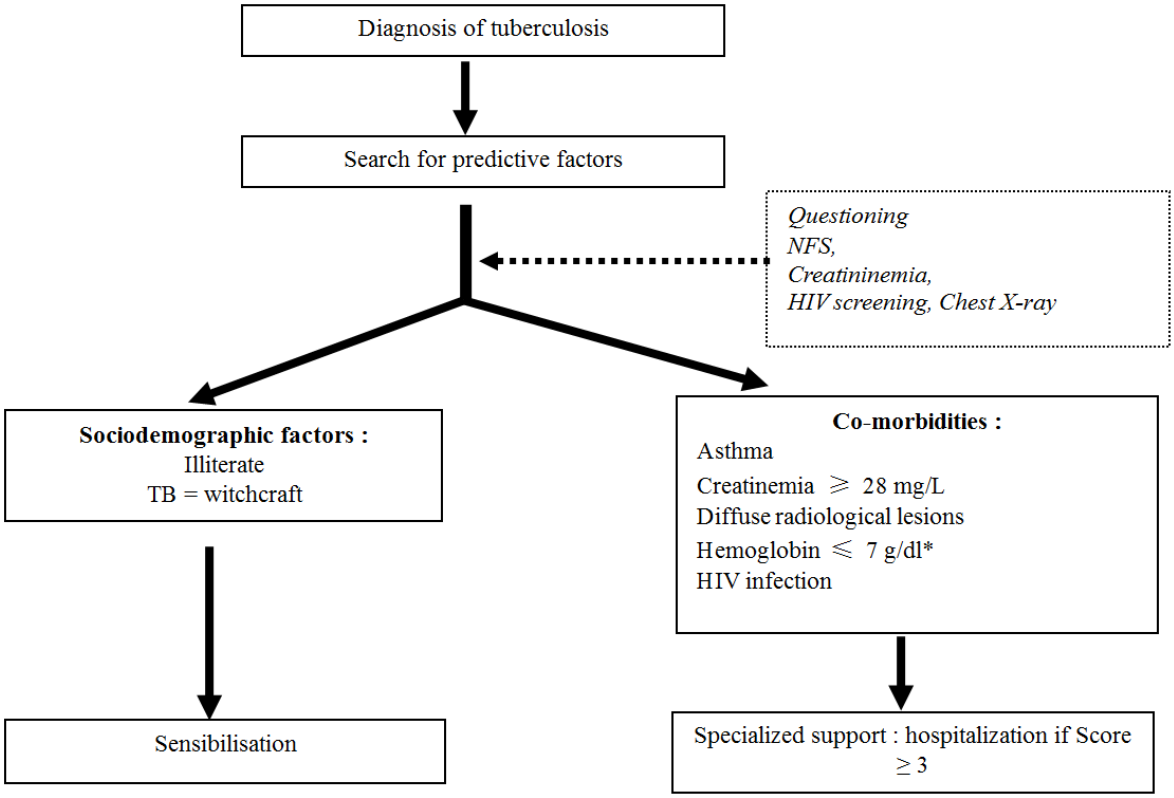

Figure 3. *Decision tree for the orientation of the tuberculosis patient at the time of diagnosis.*

4. Discussion

This study on TB mortality monitored in outpatient settings, rare throughout the world, is the first in Côte d'Ivoire.

4.1. Profile of Tuberculosis Patients

The singularity of our population profile [24] lies in the sociodemographic characteristics. The illiteracy rate is quite high. The patients with tuberculosis in our study have epidemiological characteristics [25] that are superimposable to those reported by the WHO [26], and at the Niamey national anti-tuberculosis center in Niger [37]. TB in Côte d'Ivoire remains a pathology of young adults. It occurs mainly in males. The association of TB with HIV is lower than that announced by the PNLT in 2016, even if the trend remains towards a decline in HIV infection overall.

The only supervision carried out during the study had made it possible to note an unsatisfactory level of completeness at the level of physiological constants and elements of the physical examination. In addition, the measurement of the constants was either not mastered or was not possible due to the unavailability of the measurement tools. The analysis of the characteristics of the patients from the transferred files sometimes showed an absence of a radiograph. Some centers after having completed the survey form did not transfer the chest X-ray. This study, by the mode of inclusion, is representative of the national epidemiology of TB followed in outpatient care compared to the numerous hospital studies [27]. It takes into account all the regions of Côte d'Ivoire. It made it possible to assess the management of TB in a real situation without intervention.

4.2. Independent Factors Inducing Death (IFID)

The identification of IFID [28] on the national territory is essential if we want to implement effective actions adapted to the typology of TB mortality. TB remains a curable disease with accessible and effective treatment. So deaths are said to be preventable deaths. In this context of mainly outpatient care [29], it is important to understand TB mortality in outpatient settings. Our study incriminated illiteracy and the belief that TB is caused by witchcraft as factors inducing death from TB. This is the expression of patients' ignorance associated with a low level of education. The fight against infectious diseases integrates the education of populations with accessibility to education, the fight against poverty and the improvement of living conditions [30]. Lack of awareness of TB is certainly the cause of late consultation of health centers. The importance of extensive lung lesions in our workforce is the expression of late consultations giving way to radiological lesions causing death. Awareness must continue especially by using languages or tools making information accessible.

We find IFID already described [31] as a cause of TB

mortality in hospitalization [27]. These factors have not been previously described in Côte d'Ivoire in the outpatient management of TB for the simple reason that no routine biological assessment [32] is systematic. It is the performance of a blood count and the dosage of creatinine, which are free for patients infected with HIV. This assessment enjoys relative availability and accessibility on the national territory. Even if severe anemia found in bivariate analysis as factors positively associated with the death of patients, did not emerge in multivariate analysis. It is necessary to note the serious consequences of anemia with a hemoglobin level < 7 g/dl on an extensive respiratory infection. Both situations result in a state of respiratory failure. Moreover, the association of asthma with TB is not a situation commonly described in the medical literature. Even less, asthma has not been described as a factor in the death of patients with TB. It is a chronic inflammatory disease of the bronchi [34]. In pulmonary TB [33], there is often inflammation of the respiratory mucosa. TB-related inflammation could be an aggravating factor or a factor promoting the severity of bronchial obstruction. Extensive lesions are already known as factors in the severity of lower respiratory infections.

4.3. Mortality and Relevance of the Predictive Score for Death from Tuberculosis

The negative predictive value (NPV) of the predictive score for death during TB varied between 94.9% and 100%. The specificity of the score to predict death from TB was 99.78% with a PPV of 94.9% for a score ≥3. This predictive score is accessible and acquired based on routine elements. It is reproducible at will. It is relatively easy to integrate into our practices due to the data necessary for patient care. Like other diagnostic scores in pathology (pneumonia, pulmonary embolism, etc.), this score could help avoid abusive hospitalizations. Beyond the parameters, health workers will have to give a prognostic value to each sign. The integration of the score into practices will simplify and rationalize decisions on the orientation of care for patients with TB.

4.4. Strategy for Reducing Mortality in Outpatient Tuberculosis Patients

There are many strategies in the management of TB. We propose a rare strategy in decision support for practitioners. In the field, the monitoring of confirmed pulmonary TB is the work of paramedical agents. It is then appropriate to offer them medical decision support tools. The decision tree or diagnostic score has the particularity of transforming complex situations into a situation for optimizing patient care. The analytical results of our data made it possible to identify the independent variables influencing patient death. Overall, these variables are divided into 2 groups:

A first group relates to socio-demographic variables: illiteracy and the fact that TB is considered witchcraft. Interventions on these variables are possible through education, information and awareness of the patient and his entourage [35]. Tuberculosis is not only a somatic disease; but, it also has a social and cultural dimension. The aim of education, information and awareness actions is to create an environment conducive to care in order to obtain the patient's adherence to therapeutic compliance. Compliance is the key to the success of any chronic disease, especially for tuberculosis which is a perfectly curable disease.

A second group relates to pathological situations: Asthma, Creatinemia ≥ 28 mg/L, Hemoglobin ≤ 7 g/dl), bilateral lung involvement, HIV infection. It is important to manage these co-mobilities which are factors of death. Certainly, it is the management of co-morbidity factors [36] at risk of death which will reduce mortality. In this case, the management actions consist of starting in a hospital environment sometimes specialized like the management of renal failure.

In the presence of three risk factors, death seems inevitable during outpatient care. The implementation of this strategy requires a subsidy for routine check-ups. In addition to systematic HIV screening, the performance of a CBC and the measurement of serum creatinine should be included in the initial assessment of the management of patients with TB.

5. Conclusion

The mortality of patients followed in outpatient for TB remains a biomedical and social concern. It varies greatly from one health center to another. The independent risk factors for death (IFID) during TB on the national level are classified into two groups. The first group is composed of illiteracy and the false beliefs that coincide that TB is witchcraft. The second group of independent factors inducing death by TB is continued morbid situations that worsen the prognosis of patients. These are asthma, the extension of pulmonary lesions to all pulmonary territories witnessing a chronic evolution, renal failure, severe anemia and HIV infection. TB remains a mode of discovery of HIV infection. The presence of renal failure and severe anemia could be the result of a late discovery of HIV infection. The implementation of the predictive score contributes to a better selection for a rational management of resources and a reduction in the mortality of tuberculosis patients. The strategy based on this score is possible; because the constitutive criteria are accessible and available.

Abbreviations

HTA	High Blood Pressure
HIV	Human ImmunoVirus
IFID	Independent Factors Inducing Death
TB	Tuberculosis

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Author Contributions

Amenan Kouame: Co- Writing original draft

Kouadio Patrick A Don: Co- Writing original draft, review & editing, supervision of article

Elodie Michelle Claudia Adombi: Review & editing

Jacquemin Kouakou: Technical support of the National Tuberculosis Control Program (PNLT)

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix

Appendix tables (Table A1 and Table A2) cited in the text.

Table A1. *Sociodemographic characteristics of tuberculosis patients.*

Variables		Become		p	OR, 95% CI
		Death	Success		
Sex	Man	4.9% (30/618)	95.1% (588/618)	0.064	0.637
	Women	7.6% (23/302)	92.4% (279/302)		0.377 – 1.078
Age ≥ 45 years	Yes	10.3% (19/184)	89.7% (165/184)	0.004	2,254
	No	4.6% (34/742)	95.4% (708/742)		1,316 – 3,858
CAT Residence	Commune	5% (35/701)	95% (666/701)	0.049	0.580
	Out of town	8.6% (16/186)	91.4% (170/186)		0.329 – 1.090
Type of habitat	Villa	4.3% (7/163)	95.7% (156/163)	0.841	----------
	Studio	6.9% (15/217)	93.1% (202/217		
	Apartment	5.4% (23/425)	94.6% (402/425)		
	Hut	6.2% (5/81)	93.8% (76/81)		
	homeless	0% (0/2)	100% (2/2)		
Common courtyard	Yes	6.5% (35/539)	93.5% (504/539)	0.182	1,352
	No	4.8% (17/354)	95.2% (337/354)		0.770 – 2.376
Professional sector	Public service	0 (0 %)	100% (19/19)	0.382	----------
	Private sector	4.3% (7/161)	95.7% (154/161)		
	Informal sector	5.7% (22/389)	94.3% (367/389)		
	Unemployed	7.4% (20/270)	92.6% (250/270)		

Variables		Become		p	OR, 95% CI
		Death	Success		
Monthly income	Regular	4.6% (7/151)	95.4% (144/151)	0.674	----------
	Irregular	4.7% (15/317)	95.3% (302/317)		
	No income	6.1% (22/361)	93.9% (339/361)		
Level of education	Primary	5.9% (14/236)	94.1% (222/236)	0.012	----------
	Secondary	4.5% (13/292)	95.5% (279/292)		
	Superior	0.9% (1/108)	99.1% (107/108)		
	Not in school	9% (25/278)	91% (253/278)		

Table A2. *History and comorbidities of tuberculosis patients.*

Variables		Become		p	OR, 95% CI
		Death	Success		
Tuberculosis infection	Yes	5.2% (15/286)	94.8% (271/286)	0.363	0.852
	No	6.2% (29/471)	93.8% (442/471)		0.465 – 1.561
Hypertensive (HTA)	Yes	21.4% (6/28)	78.6% (22/28)	0.003	4,237
	No	5.1% (44/870)	94.9% (826/870)		1,971 – 9,110
Diabetes	Yes	0% (0/14)	100% (14/14)	0.465	1,057
	No	5.4% (47/875)	94.6% (828/875)		1,040 – 1,074
UGD	Yes	5.7% (5/88)	94.3% (83/88)	0.515	1,071
	No	5.3% (42/792)	94.7% (750/792)		0.435 – 2.637
Sickle cell disease	Yes	12.5% (1/8)	87.5% (7/8)	0.357	2,364
	No	5.3% (47/889)	94.7% (842/889)		0.370 – 15.103
Known HIV infection	Yes	15.4% (21/136)	84.6% (115/136)	<0.001	3,160
	No	4.9% (28/573)	95.1% (545/573)		1,852 – 5,390
Asthma	Yes	17.4% (4/23)	82.6% (19/23)	0.029	3,516
	No	4.9% (41/829)	95.1% (188/829)		1,374 – 8,996
Psychiatric disorders	Yes	5.9% (1/17)	94.1% (16/17)	0.635	1,031
	No	5.7% (49/859)	94.3% (810/859)		0.151 – 7.039
Alcoholism	Yes	3.3% (8/239)	96.7% (231/239)	0.033	0.493
	No	6.8% (44/648)	93.2% (604/648)		0.236 – 1.032
Smoking	≥ 1 cigarette/day	4.1% (6/147)	95.9% (141/147)	0.621	----------
	Weaned	5.6% (6/107)	94.4% (101/107		
	Never	6.2% (37/600)	93.8% (563/600)		

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Biography

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Research Field

Amenan Kouame: health management; health program; health financing; universal health coverage; chronic disease.

Kouadio Patrick Adon: health program evaluation, education for health, gender equity and rights; medical prevention, immunization, sexual and reproductive health, workforce health, disability, chronic diseases (cancers, tuberculosis, etc.).

Elodie Michelle Claudia Adombi: sexual and reproductive health; maternal and child health; midwife; contraception; maternal deaths; nutrition, child and women diseases, midwife training.

Jacquemin Kouakou: public health; health management; health program; medicines; health financing; universal health coverage; chronic disease.