ORIGINAL ARTICLE

Prediction of pulmonary tuberculosis treatment outcome in a sub-Saharan African context

JOSEPH MAGLOIRE FOSSOKENG MOUAFO[1], ANDRÉ NANA YAKAM[1], CLAUDE SIMO[1], JULES SADEFO KAMDEM[2], SAMUEL BOWONG[1], LOUIS AIMÉ FONO[1] and JÜRGEN NOESKE[3]

[1]University of Douala, Cameroon; [2]University of Montpellier, France; [3]Independant Consultant, Yaounde, Cameroon

DOI: 10.4081/jphia.2023.2694

Abstract. Failure to treat many pathogens is a concern. Identifying a priori, patients with potential failure treatment outcome of a disease could allow measures to reduce the failure rate. The objectives of this study were to use the Scoring method to identify factors associated with the tuberculosis unsuccessful treatment outcome and to predict the treatment outcome. A total of 1,529 patients with pulmonary tuberculosis were randomly selected in the city of Douala, Cameroon, this sample was randomly split into two parts: one subsample of 1,200 patients (78%) used as the Development sample, and the remaining of 329 patients (22%) used as the Validation sample. Baseline characteristics associated with unsuccessful treatment outcomes were investigated using logistic regression. The optimal score was based on the Youden's index. HIV positive status, active smoker and non-belief in healing were the factors significantly associated with unsuccessful treatment outcomes (P<0.05). A model used to estimate the risk of unsuccessful treatment outcome was derived. The threshold probability which maximize the area under the ROC curve was 18%. Patients for whom the risk was greater than this threshold were classified as unsuccessful treatment outcome and the others as successful. HIV positive and active smoking status were associated with death; the non-belief in healing, youth and male gender associated with lost-to-follow-up, TB antecedent and not having TB contact associated with therapeutic treatment failure. To increase the tuberculosis treatment success rate, targeted follow-up could be taken during the treatment for TB patients with previous characteristics.

Correspondence to: André Nana Yakam, P O Box 4032, Douala, Cameroon
E-mail: nanayakam@yahoo.com

Key words: scoring method, logistic regression, tuberculosis, treatment failure, Cameroon

Introduction

One of the targets of the Sustainable Development Goals (SDGs) for 2030, adopted by the United Nations in 2015, is to end the global tuberculosis (TB) epidemic: The World Health Organization (WHO) End TB Strategy, approved by the World Health Assembly in 2014, calls for a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate by 2030, compared with 2015 (1). In September 2017, the WHO calls for global research and development for Mycobacterium tuberculosis as a priority pathogen (2). According to the WHO, a dollar invested in TB gives a return of US $43 (3).

Tuberculosis is the largest killer among communicable diseases in the 15 to 49 years age group, when humans are most productive. TB accounts for the highest workdays lost each year among the communicable diseases. TB is the leading cause of death among people with HIV. In 2021, there were an estimated 10.6 million new TB cases worldwide, among which an estimated 450,000 (3%) new cases of multidrug resistant (MDRTB) and rifampicin resistant (RR) TB, an estimated 1.6 million TB deaths and an additional 187,000 deaths resulting from TB disease among people living with HIV. TB remained one of the top 10 causes of death worldwide (4).

In Cameroon, despite the reduction in the case notifications between 2019 and 2020 due to the stigma associated with similarities in symptoms related to the TB and Covid-19 and the risks of going to health care facilities during the Covid-19 pandemic, there were 2% increase of the notification of new TB cases between 2020 and 2021 (from 22,492 to 22,866), the incident rate was estimated at 164/100,000 people, with a mortality rate estimate at more than 28% [95% CI:15-44] (4). The trend of the absolute number of TB cases (all forms) notified is increasing since 2006 (5). According to the list of high burden countries for the period 2016 to 2020 defined by WHO, Cameroon is among the 30 high TB/HIV burden countries, ranging among the top 20 countries with the highest estimated numbers of incident TB cases among people living with HIV (6). Could Cameroon reach the End TB strategy objectives with the current strategies of the National tuberculosis program (NTP)? The answer is negative given the too slowly decreasing trend in the incidence of annual TB cases reported in the last decade (5). What additional actions must be undertaken in

Cameroon to achieve the objectives of the End TB strategy by 2030? Among the patients notified, the treatment of 16% of them results in failure, worse on death (4). If it was possible to suspected unsuccessful treatment outcome patients before the event, additional measures could be considered to deal with them. The global TB treatment outcome data for Cameroon shows a treatment success rate of 86% for drug susceptible TB (2020 cohort) and 83% for MDRTB (2019 cohort) (4). Failure to properly treat drug susceptible tuberculosis (DSTB) can leads to the acquisition of MDRTB, and then the emergence of circulating strains of drug resistant TB. Inadequate health and TB control systems may then facilitate the creation of drug resistant TB (7). The cost per patient treated is usually in the range of US$100 to 1000 for drug susceptible TB and US$2000 to 20000 for MDRTB (6,8). Meaning that in addition to the US$2.66 to 26.57 million needed for the annual treatment of DSTB patients in Cameroon, it will cost US$0.75 to 7.44 million to treat the estimated 1.4% MDRTB patients that could result from the poor outcome treatment. Preventing treatment failures of DSTB is therefore both a health and financial issue. If there existed a decision support tool which can measure the risk of unsuccessful treatment outcome, it could enable the health field workers to implement patient management strategies based on their level of risk. This decision support tool, very popular and worldwide used in the domain of finance, is not yet available or popularized to prevent a favourite treatment outcome of infectious diseases such as tuberculosis.

The statistical models have become important technics nowadays in providing tools in analysing the spread and control of infectious diseases. In a specific context, statistical methods can be used in profiling patients, to identify risk factors associated with poor treatment outcomes and to prevent the risk of failure/death due to a disease such as TB. Statistical models, based on the Bayesian's method of scoring can be used in planning, evaluating, and preventing unfavourable treatment outcomes. In this study we intend to inform public health action by providing a decision support tool that can improve the management of tuberculosis in Sub Saharan African countries and in Cameroon in particular. More specifically, we plan to establish with the aid of scoring tool a better way to predict TB treatment outcomes. The best way to fight against failure, lost-to-follow up or death in a specific disease namely tuberculosis in sub Saharan Africa context. We plan to explore some fundamental aspect of the Scoring tool to address the following questions:

(i) What is the socioeconomic profile of a TB patients in Cameroon?
(ii) What are the risk factors associated to the poor treatment outcome of TB?
(iii) How can the tuberculosis unsuccessful treatment outcome been predicted?
(iv) What are the risk factors associated to patients lost to follow up, failure or death and how can it been predicted?

To answer these questions, we characterized TB patients in Cameroon, we analysed the profile of TB patients at risk for poor treatment outcome, and we built and validated mathematical models that could be used to estimate the treatment outcome's risk of TB patients using the scoring method, which could computerize and classify the risk of failure, lost to follow up or even death for each TB patient at the start of the treatment.

Data and methodology

Ethics approval and consent to participate. Ethics clearance for the study and administrative authorisation were granted by the Cameroon National Committee of Ethics, the National Tuberculosis Programme (NTP) and the Regional Delegation of Public Health, Littoral. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s), if subjects were below 16 years old. Decease subjects were not involved.

Data collection. The data used in this study was provided by a survey undertaken between 1st of May 2011 and 30th of April 2012 covering, Diagnostic and Treatment Centers (DTC) of the city of Douala, the region that counts for 11% of total population, but registers almost 20% of the total TB cases in Cameroon. The study population was the smear positive pulmonary tuberculosis patients. At enrolment, all study participants answered a structured questionnaire verbally administered by trained field workers. Data collected included: clinical information, socio-demographic characteristics, socio-economic information, knowledge, attitude and practice of patients. Patients enrolled were followed up until the end of their treatment. The outcomes of their treatment were registered and classified according to WHO definitions as successful (for cured or completed treatment) and unsuccessful (for lost to follow up, treatment failed or death).

Definition of variables. Standard WHO definitions were used for cure, treatment completion, death, failure, lost to follow-up. Separate Logistic regression models were used to identify risk factors for unsuccessful treatment outcomes (death, failure, or lost to follow up), loss-to-follow-up, failure, and death. The variable to be explain (dependent variable) was then Y=*Outcome*', with two modality: Successful (Y=0) or Unsuccessful (Y=1). Suspected risk factors potentially associated with treatment outcome were designated as the explanatory vector $X=(X_1,\cdots,X_{10})$ of independent variables X_i, with X_1=sex (Gender of the patient), X_2=antecedent (Previous treated TB patient), X_3=contact (Patient with a parent or household member who suffered from TB), X_4=vih (HIV status), X_5=smockA (active smoker), X_6=alcohol (patients who drink the equivalent of more than one bottle (65cl) of bier per day), X_7=feeling neglected (patients field of being neglected by their family or spouse during treatment), X_8=stigmatization (patient who felt as being stigmatized), X_9=agegrp (Age group {0='15-30 years' (reference), 1=' >30 years'}), X_{10}=heal (patient who said that he belief or not in TB healing).

Scoring method. The scoring method consists in assigning a score to an individual of a population in view of its characteristics, in order to assign him to groups defined a priori. There are several methods of constructing scores, among which we can cite discriminant analysis and logistic regression. In this

study, the score grid was constructed from logistic regression since the explained variable (outcome) was dichotomous and the explanatory variables $X=(X_1,\cdots,X_{10})$ were all qualitative.

Threshold value. The scoring method provides for establishing a threshold value: '*c*', such that $S(X) \leq c$ means that The patient is affected in the group of Successful outcome; and $S(X) > c$ means that The patient is affected in the group of Unsuccessful outcome. Where the score function $S(X)=P(Y=1|X)$), is provide by the logistic regression model (9).

In this study, the threshold was computed numerically, as being that which maximizes the sensitivity (rate of true positives) and the specificity (rate of true negatives). Indeed, using the data of the 329 patients in the Validation sample, the model chosen from the logistic regression made it possible to calculate the score for each of the patient, then we set a threshold (c_i) which allowed to assign each patient in the successful or unsuccessful group, according to the prediction of the model. The assignments predicted by the model were compared with the observe treatment results of each patient, then the sensitivity (se_i) and the specificity (sp_i) resulting from the chosen threshold were calculated. We then varied the threshold c_i in the interval]0;1[and computed the resulting se_i (sensitivity) and sp_i (sensitivity). The retained threshold (c) was the c_i which simultaneously maximizes the sensitivity and the specificity.

Statistical analysis. EpiData version 3.1 software was used for the creation of the dataform and the data entry, EpiData Analysis version 2.2 for the transformation of variables and descriptive analysis. The R version 3.6 software was used for the modelling. The Logistic regression models were used to derived the prediction models and were implemented with the *glm* function, which fits binary logistic regression models using maximum likelihood estimation. The univariate analysis was carried out individually on all of the variables suspected as risk factors, only those which were found to be significant at 5% were included as explanatory variables in the multivariate model. A backward stepwise eliminations procedures used to retain the variables in the final models as recommended by Collett (10). For this purpose, receiver-operating characteristic (ROC) curves were used to derive the optimal cut-off point score, applying the Youden's index method (11). Performance measures including the sensitivity, specificity where then estimated at this optimal threshold as well as other selected thresholds.

Results

Data available. In total, 2,545 patients with smear positive pulmonary TB (PTB+) were notified during the survey period, among them 2,132 (84%) patients permanently residing in Douala (≥3 months), consented to participate in the survey and were interviewed. Of which 1,529 patients (72%) were randomly selected for this study. The comparative characteristics of the included and excluded participants are summarized in Table I. The sample was randomly split into two parts: one subsample of 1,200 patients (78%) used as 'Development sample' and another subsample of 329 patients (22%) used as 'Validation sample'.

Treatment outcomes and sociodemographic characteristics of selected TB patients. The socio-demographic characteristics and the treatment outcomes of the 1,529 patients selected for the study are summarize in Table I: 225 (14.7%) patients were unsuccessful treatment outcome and 1304 (85.3%) were successful treatment outcome.

Characteristics of the development and the validation sample. Among the 1,200 patients included in the Development sample, 720 (60%) were men and 54.17% of patients were of age >30 years. 289 (24.08%) patients were HIV positive and 185 (15.41%) unsuccessful treatment outcome was recorded: which did not differ significantly from the whole sample.

The Validation sample included 329 patients, with 208 (63.22%) men, 53.79% of patients were of age >30 years and 67 (20.36%) were HIV positive. 40 (12.15%) unsuccessful treatment outcome was recorded among them.

Univariate analysis. A total of 15.41% unsuccessful treatment outcome were recorded (among which 9% of Lost to follow-up patients, 2.6% in of failed treatment and 3.81% of Death), 66.4% Cured and 18.9% of Treatment completed. The univariate analysis shows that variables significantly associate with unsuccessful treatment outcome (P<5%) were TB healing [OR=2.05 (95% CI: 1.05-3.76)], Active smocking [OR=2.04 (1.21-3.33)] and HIV status [OR=1.7 (1.20-2.37)] (Table II).

TB healing [OR=2.81 (1.93-6.83)], Active smocking [OR=2.34 (1.3-5.10)], HIV status [OR=5.86 (3.20-11.05)] and Age [OR=1.98 (1.06-3.87)] were associated with mortality in univariable analysis; Antecedent TB [OR=3.61 (1.67-7.48)] and Contact TB [OR=0.27 (0.06-0.78)] were associated with Failure outcome treatment while TB healing [OR=2.16 (1.16-4.36)] and Age [OR=0.57 (0.38-0.85)] were associated with Lost to follow-up.

Multivariate analysis

Model estimation. The HIV status, active smoker and healing remained significantly associated with the outcome treatment and were retained in the final model (Table III part A). The risk of unsuccessful treatment outcome was derived from the following estimated model:

$$risk = \frac{1}{1 + e^{-(-1.96+0.55.vih+0.77.smockA+0.68.heal)}}$$

Validation of the model using the Test sample. The Table IV summarizes the incremented process which allowed to compute the optimal threshold value derived from the model. This optimal threshold was compute as 18%. The corresponding performance measures were 50% for sensitivity and 69% for specificity.

Risk factors associated to patients lost to follow-up. A defeatist (patient who asset not belief in TB cure), youth and male gender were significantly associated with Lost to follow-up (P-value ≤0.05), in a multivariate logistic regression model (Table III part B). Estimation of the risk of Lost to follow-up is provided by the following equation:

$$risk = \frac{1}{1 + e^{-(-2.4+0.8.heal-0.6.agegrp+0.5.sex)}}$$

Table I. Characteristics of smear positive pulmonary TB patients.

Variables	Included patient N=1529 (%)	Excluded patients N=60 (%)
Sex		
Male	928 (60.69)	43 (71.67)
Female	601 (39.31)	17 (28.33)
Belief in healing		
Belief	1461 (95.55)	57 (95)
No belief	68 (4.45)	3 (5)
Antecedent TB No	1310 (85.68)	50 (83.33)
Yes	219 (14.32)	10 (16.67)
Contact TB No	1097 (71.75)	38 (63.33)
Yes	432 (28.25)	22 (36.67)
HIV status		
Negative	1173 (76.72)	37 (61.67)
Positive	356 (23.28)	23 (38.33)
Active smoker		
No	1401 (91.63)	49 (81.67)
Yes	128 (8.37)	11 (18.33)
Alcoolic1		
No	1183 (77.37)	46 (76.67)
Yes	346 (22.63)	14 (23.33)
Feeling neglected Yes	1502 (98.23)	54 (90)
No	27 (1.77)	6 (10)
Stigmatization		
Yes	1524 (99.67)	50 (83.33)
No	5 (0.33)	10 (16.67)
Age		
15-30 years	702 (45.91)	27 (45)
>30 years	827 (54.09)	33 (55)

Model validation using the Test sample. The Test sample contained 329 patients, of whom 23 (7%) Lost to follow-up. The optimal threshold for predicting a lost to follow-up was 0.130 (13%) using the Youden index. The corresponding performance measures were set at 35% for sensitivity and 71% for specificity.

Risk factors associated with failure outcome treatment. The variables significantly associated with the failure outcome treatment were: antecedent TB, gender and contact with TB patients (Table III part C). The Male patients and those having a TB contact were positively associate to Cure, whereas an antecedent TB was positively associate to failure outcome. The risk of Failure outcome treatment was derived from the following estimated model:

$$risk = \frac{1}{1 + e^{-(-3.3+1.4.antecedent-1.3.contact-0.7.sex)}}$$

Risk factors associated to death. The variables significantly associated to death during TB treatment were HIV status and active smoker (P-value ≤0.05) (Table III part D). The risk of Death was derived from the following estimated model:

$$risk = \frac{1}{1 + e^{-(-4.1+1.8.vih+1.1.smockA)}}$$

Model validation with the test sample. The test sample contained 329 patients including 13 (3.9%) death patients. The optimal threshold for predicting death was 0.091 (9.1%). The corresponding performance measures were 77% for sensitivity and 82% for specificity.

The ROC curve of the death model. The ROC curve of the model is presented in the Fig. 1, with the AUC=0.7965.

Discussion

An extensive literature review revealed the importance of the demographic, socio economic, cultural, and environmental risk factors associated with the spread of TB and the treatment outcome of TB patients in different countries worldwide, but few studies addressed the risk measurement linked to unsuccessful treatment outcomes. A Sudanese study shows that the socio demographic risk factors determining defaulting of TB treatment were unemployment, low income, alcohol use, traveling when under treatment, feeling neglected, experience of losing hope and bad perception towards medication (12). In

Table II. Univariate logistic regression analysis of potential predictors of tuberculosis treatment outcome.

Predictors	Overall (%)	Unsucces (%)	Success (%)	Crude OR (95% CI)	P-value
Sex					
Female	480 (40)	71 (38.38)	409 (40,30)	1	
Male	720 (60)	114 (61.62)	606 (59.7)	1.08 (0.78-1.50)	0.6245
Belief in healing					*
Belief	1147 (95.6)	171 (92.43)	976 (96.16)	1	
No belief	53 (4.4)	14 (7.57)	39 (3.84)	2.05 (1.05-3.76)	0.02609
Antecedent TB No	1014 (84.5)	152 (82.16)	862 (84.92)	1	
Yes	186 (14.5)	33 (17.83)	153 (15.8)	1.22 (0.79-1.83)	0.34
Contact TB No	869 (72.42)	137 (70.05)	732 (72.12)	1	
Yes	331 (27.58)	48 (29.95)	283 (27.88)	0.9 (0.62 1.28)	0.588
HIV status					**
Negative	911 (75.92)	124 (67.03)	787 (77.54)	1	
Positive	289 (24.08)	61 (32.97)	228 (22.46)	1,7 (1.20-2.37)	0.00228
Active smoker					**
No	1111 (92.58)	162 (87.57)	949 (93.5)	1	
Yes	89 (7.42)	23 (12.43)	66 (6.5)	2.04 (1.21-3.33)	0.005421
Alcoolic1					
No	944 (78.67)	144 (77.84)	800 (78.82)	1	
Yes	256 (21.33)	41 (22.16)	215 (21.18)	1.06 (0.71-1.53)	0.7648
Feeling neglected					
Yes	1181 (98.42)	181 (97.84)	1000 (98.52)	1	
No	19 (1.58)	4 (2.16)	15 (1.48)	1.47 (0.41-4.11)	0.4955
Stigmatization					
Yes	1196 (99.67)	184 (99.46)	1012 (99.7)	1	
No	4 (0.33)	1 (0.54)	3 (0.3)	1.83 (0.09-14.40)	0.6005
Age					
15-30 years	550 (45.83)	89 (48.11)	461 (45,42)	1	
>30 years	650 (54.17)	96 (51.89)	554 (54.58)	0.9 (0.65-1.22)	0.4997

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1.

South Africa, significant risk factors associated with defaulting TB treatment were poor health care worker attitude, retreatment, changing residence during TB treatment, having no formal education, feeling ashamed to have TB, not receiving adequate counselling about treatment, drinking any alcohol and seeing a traditional healer during TB treatment (13). In Ethiopia, unsuccessful treatment outcome was higher among patients older than 40 years of age, family size greater than 5 persons, unemployed and among retreatment (14). In an India study, factors associated with TB treatment defaulting were alcoholism, illiteracy, having other commitments during treatment, inadequate knowledge of TB, poor patient provider interaction, lack of support from health staff, having instances of missed doses, side effects to anti TB drugs and dissatisfaction with services provided (15). None of these study seeker for healing in cure as risk factor.

The scoring system was used for the first time in the epidemiology of tuberculosis in 2013, to estimate the prognosis of tuberculosis patients (16). This retrospective cohort study conducted in Japan computed a tuberculosis prognostic score among patients with newly diagnosed smear positive pulmonary tuberculosis. Significant variables for the prediction of TB death were age, respiratory condition, malnutrition and activity of daily living. Among the limits of this study, the authors mentioned its validity for patients in other countries such as developing countries. According to the authors, patients in these countries may have a prognosis that differs from that calculated using their scoring system due to different medical systems. They concluded that further investigations were required in other cohorts to establish external validity. Moreover, the samples of population used for both development and validation cohorts were hospitalized elderly patients (>64 years).

A simple score was derived and validated in Cameroon to predict mortality during tuberculosis treatment in high TB endemic areas (17). The authors investigated the characteristics associated with mortality. Clinical form of tuberculosis, age, body mass index and HIV status were significant predictors in the final model. The sensitivity and specificity of the model were 81 and 67% respectively. The authors conclude that their

Table III. Model estimation, using the multivariate logistic regression.

Part	Predictors	βcoefficient	Standard error	Crude OR (95% CI)	P	Signif. Codes
	(Intercept)	-1.9613	0.1044	0.14 (0.11-0.17)	<2e-16	***
A	Hiv	0.5476	0.1753	1.73 (1.22-2.42)	0.00178	**
	SmockA	0.7699	0.2594	2.16 (1.27-3.54)	0 .00299	**
	Heal	0.6804	0.3262	1.97 (1.01-3.65)	0.03697	*
	(Intercept)	-2,3792	0,1957	0.09 (0.06-0.13)	<2e-16	***
B	Heal	0.7944	0,3847	2.21 (1.93-4.51)	0.03893	*
	Agegrp	-0.6047	0,2065	0.54 (0.36-0.82)	0.00341	**
	Sex	0.4882	0,2187	1.63 (1.07-2.53)	0.02558	*
	(Intercept)	-3,3499	0,2875	0.03 (0.01-0.06)	<2e-16	***
C	Antecedent	1.4068	0.3889	4.08 (1.86-8.67)	0.000298	***
	Contact	-1.3253	0.6141	0.26 (0.06-0.76)	0,030926	*
	Sex	-0.7521	0.3769	0.47 (0.22-0.99)	0,045965	*
	(Intercept)	-4,1089	0,2607	0.02 (0.01-0.03)	<2e-16	***
D	VIH	1,8310	0,3173	6.24 (3.38-11.86)	7,91e-09	***
	SmockA	1,0981	0,4443	2.99 (1.16-6.82)	0,0134	*

Signif. codes: 0 '***' 0,001 '**' 0,01 '*' 0,05 '.' 0,1 ' ' 1.

Table IV. Sensitivity and specificity according to the threshold on the test sample of the model.

Threshold	Sensitivity	Specificity	Youden index
0.5	0	1	0
0.33	0.13	0.99	0.12
0.31	0.15	0.98	0.13
0.23	0.23	0.89	0.12
0.21	0.25	0.85	0.1
0.18	0.5	0.69	0.19
0.13	1	0	0

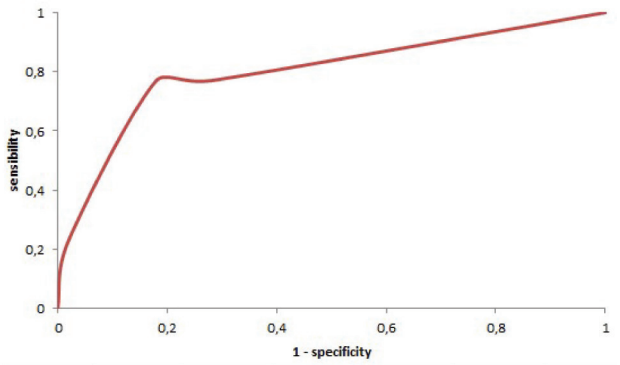

Figure 1. ROC curve of death.

study require confirmation through independent external validation studies to facilitate the stratification of TB patients for mortality risk and implementation of additional monitoring and management measures in vulnerable patients. Among the weakness of this mono centre study was the poorness of data; socio demographic and cultural characteristics of TB patients data were lacking.

In the current study, unsuccessful treatment outcomes were more common among men: with a prevalence of 61.62% of cases compared to 38.38% of female cases, which corroborates with the results of other works, such as those of Enarson *et al* (18). This vulnerability of men towards this pathogen can be explained by exposure to risk factor such as alcoholism, smoking, drug use and promiscuity (19,20). It was found that subjects older than 30 were the least affected by unsuccessful treatment outcomes (13%) compared to (14%) in subjects younger than 30 years. Although patients >30 years old represent a vulnerable group at risk for several infections, which could be explained by the weakened immune system and the various associated chronic diseases, these elderly patients follow their treatment apparently with caution and are, thus, less concern by being lost-to-follow-up, unlike young people. Elderly patients were most concern with death, which corroborates with the results of several other authors, who reported high proportions of treatment failure in this population category (>30 years) (16,19).

Our study proved that TB healing, active smoker and HIV status were strongly associated with unsuccessful treatment outcome of TB. These risk factors have been established by prior cohort studies (21-27) the new interesting predictor assessed in this study was the belief in healing. Another high risk of unsuccessful treatment outcome is the belief or not in cure. A defeatist (patient who asset not belief in TB cure) has low morale and will not be able to take his treatment seriously. Just as patients can be cured after taking a placebo in clinical trials, this discovery proves that patients, even after taking their medication properly may not be cured if they don't believe in it. The final model developed in the current study was based on four predictors that are routinely assessed in most tuberculosis control programs in high endemic areas. Interestingly,

data on those predictors can be accurately collected event by lay people, meaning that the model can be applicable even in remote and under equipped primary care settings.

Active smoking and HIV status were mainly associated with death due to TB. A patient with HIV has 06 (six) times more chance of dying during treatment, compare to others, whereas an active smoker patient was 03 (three) times more likely to die during treatment compared to a non-smoker. Smoking increases the risk of active tuberculosis: it is involved in 8% of tuberculosis cases worldwide (28). A normal lung is elastic, the formation of granulomas which causes the presence of cavities causes the lung to lose this elasticity which is essential for breathing. This property of the lungs is regained only gradually after complete recovery (29). A tuberculosis patient being on treatment and regularly absorbing toxic smoke will blacken his lung and have less chance of regaining its elasticity and thus will not be able to regain recovery. The patient's HIV status is known to be a major risk of the TB outcome treatment, which corroborates with the results of other studies, such as those of Pefura *et al* (17). The prognosis for tuberculosis-HIV co-infection is significantly poorer; while tuberculosis responds favourably to anti-tuberculosis treatment. The excess mortality in HIV-positive tuberculosis patients is due to the progression of the HIV infection itself. In the natural history of HIV infection, tuberculosis occurs at a relatively early stage, before other opportunistic infections. A history of tuberculosis is often found, which is in favour of endogenous re-infection. Tuberculosis is a major cause of death in HIV positive people (30).

The variables significantly associated with lost-to-follow-up were: the non-belief in the cure, gender and age. The results show that a defeatist has 02 (two) times more chance of abandoning treatment compared to one who believes in a cure. Lost to-follow-up patients were common in men with age range between 15-30 years. This vulnerability of men and young people to treatment dropout can be explained by the lack of awareness. Which corroborates with the results of other authors, such as Enarson *et al* (18).

The variables significantly associated with therapeutic treatment failure were: the patient's past history on TB, the presence of a household member who suffered from TB. Our results showed that a re-treatment TB patient was 04 (four) times more likely to fail treatment, compared to a subject newly diagnosed and started the treatment for the first time. In addition, treatment failure is more common in women than men. Patients with the presence of a household member who suffered from tuberculosis are the least affected by failure; it could be due to the fact that these patients benefited from the prodigious advice given by their family member who suffered from this diseases before (13).

An additional study was carried out in the Development sample database. Indeed, the age variable has been split into 4 modalities (0='15-24 years', 1='25-34 years', 2='35-44 years, 3='45 years and over') and we note the identical results. Subsequently, patients with a history of TB were excluded from the database and the same analysis carry on. The results revealed a slight difference: The final model was globally significant with the same variables but slight difference with the coefficients and a higher Youden index 0.26 with a threshold of 0.115 (against 0.19 in the initial model). The risk factors linked to death remain identical in both cases, but the presence of a high Youden index value 0.73 with a threshold of 0.047 in the analysis without antecedent TB (against 0.59 and threshold of 0.043 of the former model). The model better explains newly diagnosed patients. On the other hand, the risk factors related respectively to failure and loss to follow-up with the analysis of data without antecedent TB patients do not present any significant variable at 5% in the overall model. This implies that failure and loss to follow-up are more observed in patients with a previous history of TB.

Our models presents some limits: The ROC curve approaches the first bisector with the area under the curve (AUC) not close enough to unity.

Conclusions

The main objectives of this study were to use the scoring method to identify the factors associated with the unsuccessful treatment outcome and to construct a score scale to predict the outcome of treatment for new TB patients before they start treatment. Using the mathematical theory of multivariate logistic regression and scoring, as well as a database of Tuberculosis patients collected in the city of Douala-Cameroon, we built and validated our models. In total, 1,589 patients with pulmonary confirm tuberculosis were included in the sample considered in our study, of whom 225 (14.7%) unsuccessful treatment outcome were notified. This sample was split into two parts: a sub-sample consisting of 1200 (78%) patients used as the Learning set to build the model and the other sub-sample of 329 (22%) patients was used for the model evaluation. The result of the study shows that HIV status, smoking (active smoker) and belief in cure were the variables significantly associated with the treatment outcome ($P \leq 0.05$). The threshold probability of unsuccessful treatment outcome which maximize the area under the ROC curve was 18%. This threshold was used to predict the treatment outcome: A patient for whom the a priori probability of unsuccessful treatment outcome was greater than this threshold was classified as unsuccessful and the remainder as successful. The corresponding performance metrics were 50% for sensitivity and 69% for specificity. The model's ability to detect true unsuccessful and true successful treatment outcome was deemed acceptable, although the ROC curve approximates the first bisector with the area under the curve AUC=0.606 (*AUC* <70).

A specific study was carried out on each of the three variables which were used to construct the' unsuccessful treatment outcome' modality, namely: lost-to-follow up, therapeutic treatment failure and death. Our analysis led to the following results:

• Gender (male) and age (youth) of the patient were significantly associated with Lost-to-follow-up. The optimal threshold was 13% and the corresponding performance measures were 35% for sensitivity and 71% for specificity;
• Patient's history of TB, the presence in the household of a member who suffered from TB, and gender were significantly associated with therapeutic treatment failure. The optimal threshold was 0.9% and the corresponding performance measures were 100% for sensitivity and 18% for specificity;

• HIV status and active smoking were significantly associated with death. The optimal threshold was 9.1% and the corresponding performance measures were 77% for sensitivity and 82% for specificity.

Additional measures, such as specific and targeted follow-up, should be taken before initiation of treatment and during treatment of patients with HIV, active smokers, defeatists, youth and antecedent TB patients to increase the success rate in treatment for TB.

Acknowledgments

Thanks to the German International Cooperation (GIZ) who funded the survey. This work was carried out under the research grand FR21-333RG/MATHS/AF/AC_G-FR3240319514 from UNESCO-TWAS and the Swedish international Development Cooperation Agency (SIDA). The authors sincerely thank TWAS. The views expressed herein do not necessarily represent those of UNESCO-TWAS, SIDA, or its Board of Governors.

Funding

None.

Availability of data and materials

Data used for this paper is available on demand to the corresponding author.

Contributions

JMFM, ANY, CS, JSK, SB, LAF, JN, draft the manuscript; JMFM, ANY, performed the data analysis.

Ethical approval and consent to participate

Ethical clearance for the study and administrative authorization were granted by the Cameroon National Committee of Ethics, the National Tuberculosis Programme (NTP) and the Regional Delegation of Public Health, Littoral. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s), if subjects were below 16 years old. Decease subjects were not involved.

Conflict of interest

The authors declare no potential conflict of interest.

Accepted: 4, July 2023; submitted: 12, May 2023.

References

1. World Health Organization, Global tuberculosis report, 2014, WHO/HTM/TB/2015.22. Geneva, Switzerland: WHO, 2015.
2. WHO, Antibacterial agents in clinical development an analysis of the antibacterial clinical development pipeline, including tuberculosis; 2017. http://www.who.int/medicines/news/2017.
3. Bending the curve ending TB: Annual report 2017. India: World Health Organization, Regional Office for South East Asia; 2017. Licence: CC BYNCSA 3.0 IGO.
4. W.H.O., Global tuberculosis report 2022: Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0.
5. IGO. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022 (accessed on 10 May 2022).
6. Noeske J, Nana Yakam A and Abena Foe JL: Epidemiology of tuberculosis in Cameroon as mirrored in notification data, 2006-2014. Int J Tuberc Lung Dis 20: 1489-1494, 2016.
7. World Health Organization: Global tuberculosis report 2016.
8. Pablos Mendez A, Paviglione MC, LaszLo A, Binkin N, Rieder HL, Bustreo F, Cohn DL, Lambregts-van Weezenbeek CS, Kim SJ, Chaulet P and Nunn P: Global surveillance for antituberculosis drug resistance 1994-1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 338: 1641-1649, 1998.
9. World Health Organization: Revised TB recording and reporting forms and registers: version 2006.WHO/HTM/TB/2006.373. Geneva, Switzerland: WHO, 2006. https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf.
10. Hosmer D and Lemeshow S: Applied logistic regression. 2nd ed. New York: Willey; 2000.
11. Collett D: Modelling binary data. 2nd ed. New York: Chapman & Hall/CRC; 2003.
12. Youden WJ: Index for rating diagnostic tests. Cancer 3: 32-35, 1950.
13. Elnazeer H and Elsadig YM: Risk factors for default from tuberculosis (TB) treatment in patients attending a rural sudanese hospital. EC Pulmonol Respir Med 6: 177-182, 2017.
14. Finlay A, Lancaster J, Holtz TH, Weyer K, Miranda A and van der Walt M: Patient- and provider-level risk factors associated with default from tuberculosis treatment, South Africa, 2002: A case control study. BMC Public Health 12: 56, 2012.
15. Berhe G, Enquselassie F and Aseffa A: Treatment outcome of smear positive pulmonary tuberculosis patients in Tigray Region, Northern Ethiopia. BMC Public Health 12: 537, 2012.
16. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP and Rao SG: Risk factors associated with default among new smear positive TB patients treated under DOTS in India. PLoS One 5: e10043, 2010.
17. Horita N, Miyazawa N, Yoshiyama T, Sato T, Yamamoto M, Tomaru K, Masuda M, Tashiro K, Sasaki M, Morita S, *et al*: Development and validation of a tuberculosis prognostic score for smear-positive in patients in Japan. Int J Tuberc Lung Dis 17: 54-60, 2013.
18. Pefura-Yone EW, Balkissou AD, Poka-Mayap V, Fatime-Abaicho HK, Enono-Edende PT and Kengne AP: Development and validation of a prognostic score during tuberculosis treatment. BMC Infect Dis 17: 251, 2017.
19. Enarson DA, Wang JS and Dirks JM: The incidence of active tuberculosis in a large urban area. Am J Epidemiol 129: 1268-1276, 1989.
20. Touré NO, Dia Kane Y, Diatta A, Ba Diop S, Niang A, Ndiaye EM, Thiam K, Mbaye FBR, Badiane M and Hane AA: [Tuberculosis in elderly persons]. Rev Mal Respir 27: 1062-1068, 2010 (In French).
21. Abdallah TM and Ali AA: Epidemiology of tuberculosis in Eastern Sudan. Asian Pac J Trop Biomed 2: 999-1001, 2012.
22. Yen YF, Yen MY, Shih HC, Hu BS, Ho BL, Li LH, Hsiao JC and Deng CY: Prognostic factors associated with mortality before and during anti-tuberculosis treatment. Int J Tuberc Lung Dis 17: 1310-1316, 2013.
23. Babalik A, Kilicaslan Z, Sevkan Caner S, Gungor G, Ortakoylu MG, Gencer S and McCurdy SA: A registry-based cohort study of pulmonary tuberculosis treatment outcomes in Istanbul, Turkey. Jpn J Infect Dis 66: 115-120, 2013.
24. Yen YF, Yen MY, Shih HC and Deng CY: Risk factors for unfavorable outcome of pulmonary tuberculosis in adults in Taipei, Taiwan. Trans R Soc Trop Med Hyg 106: 303-308, 2012.
25. Horne DJ, Hubbard R, Narita M, Exarchos A, Park DR and Goss CH: Factors associated with mortality in patients with tuberculosis. BMC Infect Dis 10: 258, 2010.
26. Pardeshi G: Survival analysis and risk factors for death in tuberculosis patients on directly observed treatment-short course. Indian J Med Sci 63: 180-186, 2009.
27. Alobu I, Oshi SN, Oshi DC and Ukwaja KN: Risk factors of treatment default and death among tuberculosis patients in a resource-limited setting. Asian Pac J Trop Med 7: 977-984, 2014.

28. Choi H, Lee M, Chen RY, Kim Y, Yoon S, Joh JS, Park SK, Dodd LE, Lee J, Song T, *et al*: Predictors of pulmonary tuberculosis treatment outcomes in South Korea: A prospective cohort study, 2005-2012. BMC Infect Dis 14: 360, 2014.
29. Aubry P and Bernard-Alex G: Tuberculose Actualit'es 2018, M'edecine Tropicale 2018, http://www.medecinetropicale.com.
30. Franz JL, Veronique D and Thomas D: A color Atlas of comparative pathology of pulmonary tuberculosis. CRC: 236, 2010.
31. Török ME and Farrar JJ: When to start antiretroviral therapy in HIV-associated tuberculosis. N Engl J Med 365: 1538-1540, 2011.