**Factors associated with death during extrapulmonary tuberculosis in adult in the Infectious and Tropical Diseases departments of CHNU de Fann and Hôpital Principal de Dakar.**

**Abstract :**

**Introduction:** Pulmonary tuberculosis remains the priority of national disease control programs, while extra-pulmonary cases are increasingly observed, often at a late stage. Additionally, in sub-Saharan Africa, data on these extra-pulmonary locations are scarce.

**Methodology:** This is a prospective, multicenter, descriptive, and analytical study including patients hospitalized for extra-pulmonary tuberculosis in the Infectious and Tropical Diseases Departments of CHNU de Fann and Hôpital Principal de Dakar, from March 1, 2019, to February 29, 2020. Data were entered into Epi Info™ version 7.2.2.6, exported to Excel, and processed using R software version 3.4.1.

**Results:** Overall, 189 patients were included. The mean age was 39 ± 16 years with a male predominance at 65.6%, representing a sex ratio of 1.9. Regarding medical history, a previous tuberculosis contact was found in 44 patients (23.3%) and a history of tuberculosis in 15 patients (7.9%). HIV infection was the most representative comorbidity in 34.4% of patients, followed by hypertension (7.9%) and diabetes (3.7%). Lymph node tuberculosis was the most frequent (54%), followed by neurological (26.2%), pleural (18.5%), and peritoneal (13.8%) locations in patients living with HIV, while in HIV-negative patients, pleural, peritoneal, and vertebral locations were more frequent than neurological involvement. The case fatality rate was 10.1%. Factors associated with death were age over 60 years: aOR: 1.07 (95% CI: 1.02–1.11), neurological location of tuberculosis: aOR: 7.05 (95% CI: 1.87–26.59), and anemia with hemoglobin level < 10 g/dl: aOR: 7.87 (95% CI: 1.62–38.1).

**Conclusion:** Tuberculosis remains a public health concern in resource-limited countries. In our series, young adult males were the most affected. Lymph node involvement was the most frequent location, followed by neurological and pleural and peritoneal serous involvement. More than a third of patients were co-infected with HIV, and factors associated with death were age over 60 years, neurological location, and the presence of anemia. Proper management of these factors could improve patient care.

**Keywords :** Extra-pulmonary tuberculosis, death, prognostic factors

1. **Introduction :**

With nearly eight million new cases each year and more than one million deaths annually, tuberculosis remains a public health concern **[1]**. According to the World Health Organization (WHO) report in 2022, it is estimated that 10.6 million people developed the disease in 2021, an increase of 4.5% compared to 2020, and that 1.6 million people died from tuberculosis (including 187,000 among HIV-positive individuals) **[1]**.

It is a disease that can affect all organs, with extra-pulmonary tuberculosis being a less common group of entities compared to pulmonary tuberculosis **[2].** Indeed, bacteriological diagnosis remains the gold standard for definitive diagnosis. It is much easier during pulmonary location and when the pathological products are rich in tubercle bacilli. However, extra-pulmonary involvement poses a real diagnostic problem because the pathological products are generally poor in tubercle bacilli **[2]** and often require invasive techniques that are rarely available in most developing countries. Additionally, many deep locations remain unknown, and severe forms of the disease (meningitis, miliary...) affecting vulnerable individuals are accompanied by high mortality even before diagnosis, partly explaining the low notification of these extra-pulmonary forms. In the literature, several factors have been identified as being associated with death in these extra-pulmonary forms, including female sex **[3]**, low education level **[4]**, neurological involvement **[5,6]**, HIV infection **[7]**, and/or extreme ages **[8,9]**.

In Senegal, in 2018, the national tuberculosis control program (PNT) recorded a total of 13,663 cases of tuberculosis of all forms **[10]**, with 9.7% for pulmonary locations and 11% for extra-pulmonary locations **[10]**. Despite progress in therapeutic success and the management of TB-HIV co-infection, the tuberculosis issue remains marked by missing cases and limited knowledge for a range of the population **[10]**. Indeed, 1/3 of the expected cases are still not detected. Apparent stigma and late recourse to care are also noted **[10]**.

It is in this context that we conducted this study on tuberculosis treatment outcomes to determine the factors associated with death in the extra-pulmonary forms of the disease.

1. **Methodology**

**2.1. Study type and period**

We conducted a prospective, multicenter, descriptive and analytical study over one year ranging from March 1, 2019, to February 29, 2020.

* 1. **Study population**

Our study included all patients aged 16ans and older with extrapulmonary tuberculosis, isolated or associated with pulmonary involvement, bacteriologically confirmed or clinically diagnosed, followed in the Infectious and Tropical Diseases Departments of CHNU de Fann and Hôpital Principal de Dakar. All patients gave their oral consent.

We didn’t include patients who were not available irrespective of the reason during the survey.

We excluded from the study patients who were initially included based on epidemiological, clinical, and/or therapeutic arguments, but whose subsequent evolution or results of paraclinical explorations did not support a diagnosis of extrapulmonary tuberculosis

 **2.3. Data collection**

The data were collected from individual structured interviews with patients, from their medical records, outpatient consultation charts, and PNT follow-up registers. The information collected included sociodemographic characteristics (age, sex, address, marital status, education level, profession; date of hospitalization, date of discharge; medical and surgical history), clinical data (functional and physical signs), paraclinical data (search for AFB and GeneXpert® in various pathological products, complete blood count, C-reactive protein, transaminases, creatinine, fasting venous blood glucose, blood ionogram and CD4 count, HIV, HCV, HBV serologies, medical imaging, pathological examination of organ specimens), therapeutic and evolutionary data (start date and anti-tuberculosis treatment regimen, other treatments, duration of hospitalization, and treatment outcome).

 **2.4. Definition of operational variables :**

For the concepts of tuberculosis management, we will refer to a new case (N) as any patient who has never been treated for tuberculosis or who has received less than one month of anti-tuberculosis treatment. Failure (E) is observed in any patient with a positive smear microscopy at the end of the 5th month of treatment or at any time between the 5th month and the end of treatment. Treatment resumption (REP) is observed when patients, lost to follow-up for two months or more, return with a positive smear microscopy on two samples. Relapse (R) is defined as any patient previously treated for active tuberculosis, declared cured at the end of treatment, and who has two positive smear microscopy results at a new consultation. Transfer (T) refers to any patient registered in the tuberculosis register at another center and sent to this one to continue their treatment. At the end of anti-tuberculosis treatment, we will refer to treatment completed (T) when a patient reaches the end of their treatment without having done the smear microscopy control of sputum at the 6th month, or a patient who never had positive AFB smears and reaches the end of their treatment. For cured patients (R), this refers to patients whose controls at the 5th month and the end of the 6th month are negative. Death (D) is any patient who dies during treatment, regardless of the cause.

 **2.5. Statistical analysis**

The data were entered into Epi Info™ version 7.2.2.6, exported to Excel, and analyzed using R software version 3.4.1. Qualitative variables were expressed in absolute and relative frequencies. Quantitative variables were expressed as mean and standard deviation or as median and extremes depending on their distribution.

The variable 'death related to extrapulmonary TB' was considered as the dependent variable with the modalities 'presence' or 'absence' of death. For the comparison of means of potentially explanatory quantitative variables, we used the Student's t-test or the Wilcoxon Mann-Whitney test according to their applicability conditions. Fisher's Chi-square test was used for the comparison of proportions of potentially explanatory qualitative variables. A univariate binary logistic regression was first performed, allowing us to obtain the crude Odds Ratios (OR) with their 95% confidence intervals (CI95%) and p-values for each explanatory variable. A multivariate binary logistic regression was then performed, and all explanatory variables with p-values less than 20% in the univariate logistic model were included in the multivariate model. At the end of this analysis, we obtained the adjusted Odds Ratios (aOR) for each explanatory variable, presented with their CI-95%. Their relationship with the variable “death” was statistically significant when the CI95% of the aOR excluded the value 1.

1. **Results**

**3.1. Description of the study population**

For this study, 282 patients with tuberculosis, in all its forms, were recorded. Our work focused only on extrapulmonary locations (189 patients), either isolated or associated with pulmonary tuberculosis, representing a proportion of 67%. Among them, 136 patients (72%) were hospitalized and 53 (28%) were followed up as outpatients. The average age was 39 ± 16 years, and the age group of 16 to 40 years represented 53.4%. There was a male predominance with a sex ratio of 1.9. HIV infection was the most representative comorbidity with 65 patients (34.4%), followed by hypertension (7.9%) and diabetes (3.7%). There was a history of tuberculosis exposure in 44 patients (23.3%), and 15 patients (7.9%) had a previous tuberculosis episode (Table I).

**Table I :** Distribution of extrapulmonary cases according to their socio-demographic characteristics, infectious and tropical Diseases Departments of CHNU de Fann and Hôpital Principal de Dakar , march 2019-february 2020

|  |  |  |
| --- | --- | --- |
| Socio-demographic characteristics | Absolute frequency (n) | Relative frequency (%) |
| Sex  |  |  |
| Male | 124 | *65.6* |
| Female | 65 | *34.4* |
| Age  |  |  |
| [16-40 years [ | 101 | *5.4* |
| [40-60 years [ | 61 | *32.3* |
| ≥ 60 years | 27 | *14.3* |
| Level of education |  |  |
| Primary | 39 | *20.6* |
| Secondary | 67 | *35.4* |
| Tertiairy | 32 | *17* |
| Non educated | 51 | *27* |
| Marital status |  |  |
| Married | 95 | *50.3* |
| Single | 66 | *34.9* |
| Divorced | 17 | *09* |
| Widowed | 11 | *05.8* |
| Comorbidities and medical history  |  |  |
| HIV infection | 65 | *34.4* |
| High blood pressure | 15 | *07.9* |
| Diabetes | 07 | *3.7* |
| CKD\* | 02 | *1.1* |
| Tuberculosis contact | 44 | *23.3* |
| Previous tuberculosis | 15 | *7.9* |
| Alcohol use | 26 | *13.8* |
| Tabacco | 40 | *21.1* |

\* : Chronic kidney disease

* 1. **Clinical and topographic patterns**

We performed a frontal chest X-ray on 135 patients (71.4%) that highlighted abnormalities in 100 of them (74.1%). These were mainly interstitial syndrome (43%), pleurisy (35%), and/or alveolo-interstitial syndrome (30%). The search for AFB was conducted in 142 patients (75.1%) and was positive in one-third of them (33.8%). The Xpert MTB/Rif test was performed on 46 patients (24.3%), of whom 29 were positive (63%). For the remaining patients, the diagnostic confirmation was based on indirect epidemiological, clinical, and paraclinical arguments (51.3%). The study population was mainly composed of new cases (91.5%, n=173). Among patients living with HIV, lymph node tuberculosis was the most frequent (54%), followed by neurological (26.2%), pleural (18.5%), and peritoneal (13.8%) locations, whereas in HIV-negative patients, pleural, peritoneal, and vertebral locations were more frequent than neurological involvement (Figure 1).

Figure 1 : Location of the tuberculosis according to the HIV status, n=189

* 1. **Factors associated with death**

The median duration of hospital stay was 17 days with extremes of et 73 days. Death occurred on 19 patients, accounting for a case fatality rate of 10.1%.

In multivariate analysis, death was associated with being older than 60 years of age, neurological location, and an anemia with an Hb levels < 10g/dl (Table 2).

**Table II:** Factors associated with death about 189 cases of extra-pulmonary tuberculosis, infectious and tropical Diseases Departments of CHNU de Fann and Hôpital Principal de Dakar , march 2019-february 2020

|  |  |  |  |
| --- | --- | --- | --- |
| **VARIABLES** |  | **UNIVARIATE** | **MULTIVARIATE** |
| **Crude OR[IC 95 %]** | ***P*** | **Ajusted OR [IC 95 %]** | ***P*** |
| **Age group** | [16-40 years [ | 1 |  |  |  |
|  | ≥ 60 years | 1.04 (1.01–1.07) | 0.005 | 1.07 (1.02–1.11) | **0.005** |
| **Sex** | Female | 1 |  |  |  |
| Male | 0.69 (0.26–1.82) | 0,45 | 0.81 (0.24–2.69) | 0.7 |
| **HIV infection** | No | 1 |  |  |  |
| Yes | 4.92 (1.77–13.65) | < 0.001 | 1.53 (0.41–5.68) | 0.5 |
| **Neurological** **location** | No | 1 |  |  |  |
| Yes | 6.75 (2.45–18.61) | < 0.001 | 7.05 (1.87–26.59) | **0.004** |
| **Hyperleukocytosis** | No | 1 |  |  |  |
| Yes | 3.51 (1.01–12.25) | 0.048 | 4.56 (0.98–21.34) | 0.054 |
| **Hb < 10 g/dl** | No | 1 |  |  |  |
| Yes | 5.62 (1.79–17.67) | < 0.001 | 7.87 (1.62–38.1) | **0.01** |

* 1. **Discussion**

We conducted this prospective, multicenter, descriptive, and analytical study to assess the factors associated with death in extrapulmonary tuberculosis cases. In the end, 189 patients were included out of a total of 282 tuberculosis cases of all forms, representing a proportional morbidity of 67%. Lymph node tuberculosis was the most frequent location (54%), followed by pleural, peritoneal, and neurological involvement. This perfectly corroborates the literature data where lymph node involvement remains the primary location of extrapulmonary tuberculosis **[11, 12, 13]**, and where a significant frequency of neurological and serous involvement is also noted **[14, 15, 16, 13]**. Diagnostic confirmation was obtained in more than a third of our patients through the search for AFB, the Xpert MTB/Rif test, histology, or culture of pathological products. However, for more than half of the patients (51.3%), diagnostic confirmation was based on indirect epidemiological, clinical, and paraclinical arguments**.** Faye A. **[15]** also in his study could only confirm about 14.2% of his cases.

On the other hand, elsewhere, particularly in the Maghreb, this diagnostic confirmation was significantly higher with 87%, 81%, and 90% respectively in the studies by Ben Mansour A. **[17]** in Tunisia, Gater N. **[14]** in Algeria, and Benchanna R. **[18]** in Morocco. This could be explained by the unavailability and inaccessibility of certain diagnostic platforms in sub-Saharan Africa, which means that the diagnosis often relies on presumptive elements. Indeed, the diagnosis of tuberculosis is all the easier when the involvement is pulmonary and the pathological products are rich in tubercle bacilli. However, extrapulmonary involvement poses a real diagnostic problem because the pathological products are generally poor in tubercle bacilli **[2]** and often require invasive techniques that are rarely practiced in most of developing countries.

In our study, we noted 19 deaths, representing a case fatality rate of 10.1%. This rate is significantly higher than the average found in the literature: Ben Mansour **[19]** 0.95% and Khedher M. in Tunisia **[19]** 4%, Morad S. in Morocco **[20]** 1.02%. This could be due to the fact that certain deep locations, such as peritoneal involvement, are often diagnosed late, and severe forms of the disease (meningoencephalitis, miliary tuberculosis) affecting individuals weakened by other conditions (HIV, diabetes, renal failure) are associated with high mortality. Indeed, immunodeficiency facilitates the expression of tuberculosis as a “disease” and its spread, with possible involvement of multiple organs simultaneously. In our study, HIV infection was the most representative comorbidity with 34.4% of patients, followed by high blood pressure and diabetes. Additionally, the apparent stigma of patients leads to delayed healthcare seeking **[10]**.

In multivariate analysis, the factors independently associated with death were age over 60 years, neurological location of tuberculosis, and anemia with a hemoglobin level below 10 g/dl. In other words, patients over 60 years old had a higher risk of dying than younger patients.

Baili L. **[8]**, in Tunisia, conducted a comparative study between two groups with extrapulmonary tuberculosis: those under 65 years old (group 1: G1) and those aged 65 and older (group 2: G2). The subsequent evolution was marked by a cure in 16% of cases for the second group (vs 78% in G1; p = 0.72) and with a death rate of 7% (vs 3% in G1; p = 0.23). In Dakar, Touré N.O. **[21]** conducted a similar study on pulmonary tuberculosis in 163 patients, with 87.2% aged 15 to 54 years, and 24 patients aged 55 and over, representing 12.8%, with extremes of 70 years for men and 72 years for women. She reported an unremarkable outcome in 83% of young patients and 50% in elderly patients. The case fatality rate was 29.2% in elderly patients and 3.7% in young patients. The average diagnostic delay was slightly higher in elderly subjects (5 months), often due to the trivialization of respiratory symptoms in this category. Horo K., **[9]** in Abidjan, in a study with 36,923 cases of pulmonary and extrapulmonary tuberculosis, found a prevalence of extrapulmonary tuberculosis of 29.68% in subjects over 65 years old, and 26.24% in subjects under 65 years old, with a higher therapeutic success rate in patients under 65 years old (61.42%) than in patients over 65 years old (52.16%). This increase in lethality with age is often due to the weakened condition of elderly subjects. Comorbidities and the particularities of the immunological profile related to age are responsible for a non-specific clinical presentation in this population group. The main problem is then to consider the diagnosis in these patients who often present with multiple pathologies.

Neuromeningeal tuberculosis is a particular form of tuberculosis characterized by clinical polymorphism and an evolutionary profile marked by complications and sequelae, which contribute to the severity of this location. It accounts for nearly 30% of extrapulmonary forms. Due to its heterogeneity in clinical and radiological presentation, the diagnosis of neuromeningeal tuberculosis is often delayed, and diagnostic errors are not uncommon. According to Hammami F. **[5]** from Tunisia, the cure rate was significantly lower in cases of neuromeningeal tuberculosis compared to other extrapulmonary TB locations (84.4% vs 92.2%; p = 0.02). The occurrence of complications (57.1% vs 15%; p < 0.001) and deaths (9.1% vs 0.7%; p < 0.001) was significantly higher in cases of neuromeningeal tuberculosis. In the literature, the lethality of neuromeningeal tuberculosis is quite variable and generally ranges between 20% and 60%. This is probably due to the availability and accessibility of diagnostic and therapeutic means, which differ depending on the study area. Most authors support that the prognosis of neuromeningeal tuberculosis is closely related to the stage of the disease and the early initiation of anti-tuberculosis treatment. Ba MD. **[6]** in Dakar found a case fatality rate of 43.5%, while Zayet S. **[22]** in Tunis estimated the case fatality rate at 19.1%. Znegui T. **[23]** in Tunisia conducted a study including only immunocompetent patients and found a case fatality rate of 20%

The involvement of hematopoietic organs in tuberculosis is rare and severe. However, hematological disorders in extrapulmonary tuberculosis are frequent, with anemia being the most common disorder. Various pathophysiologies have been demonstrated in anemia during tuberculosis, but most studies have shown suppression of erythropoiesis by inflammatory mediators as the cause of anemia. Malnutrition and malabsorption can worsen the severity of anemia **[24]**. However, other studies suggest that iron deficiency is a probable cause of anemia in tuberculosis patients **[24]**. Attoh Touré H. **[25]**, in Côte d'Ivoire, also found in his study that anemia was a risk factor for death, among other factors. Isanaka S. **[26]**, in Tanzania, reports a two to three times higher risk of death in the presence of anemia in tuberculosis patients.

Tuberculosis remains the leading opportunistic infection revealing HIV/AIDS, and extrapulmonary involvement accounts for more than half of TB/HIV co-infections **[27]**. Extrapulmonary tuberculosis is more common in severely immunocompromised individuals. In cases of HIV co-infection, the frequency of extrapulmonary tuberculosis increases as the number of CD4 T lymphocytes decreases. It has a remarkable clinical expression due to the spread of lesions with dissemination of bacilli to sites other than the lungs. Multifocal or disseminated EPT has seen its frequency increase with the advent of HIV infection [12]. Yone EWP. **[7]**, in Cameroon, found a case fatality rate of 10.5% in HIV-positive patients and 1.9% in HIV-negative patients, with a statistically significant difference and a fivefold increased risk of death during TB/HIV co-infection. However, it is important to note that in the aforementioned study, the unfavorable outcome under anti-tuberculosis treatment was only observed in patients with a CD4 T lymphocyte count below 200 cells/mm3. Kouassi B. **[28]**, in Ivory Coast, reports in his study that tuberculosis associated with HIV has atypical clinical and paraclinical manifestations, with severity varying according to the degree of immunosuppression. Patients with profound immunosuppression (CD4 < 200 cells/mm3) had a higher frequency of clinical signs and biological abnormalities. According to Wa Ilunga EN. **[29]**, the results of his study in the DRC show that HIV-positive tuberculosis patients have a 1.74 times higher risk of dying compared to HIV-negative tuberculosis patients. In Agodokpessi G.'s **[30]** study in Benin, the unfavorable outcome was higher in TB/HIV co-infection (20% vs 8.2%, p < 0.01). In our study, we did not find an association between HIV infection and death. Indeed, it is important to note that even though the majority of authors agree that HIV infection is one of the factors associated with death in tuberculosis patients; according to Lesprit P. **[31]**, in France, despite the immune deficiency, the response to anti-tuberculosis treatment in HIV-infected patients is the same as in non-HIV-infected subjects, and tuberculosis mortality and relapse rates are similar. Moreover, he noted a higher frequency of treatment-related adverse effects in HIV-positive patients.

Despite its prospective and multicenter nature, our study has certain limitations: patients are followed in reference centers for tuberculosis management, which makes the data difficult to extrapolate to the general population, especially those living in peripheral areas. We were also unable to take into account other factors that could potentially impact the risk of death, such as patient management conditions, their socio-economic status, the exact duration of symptom evolution... Additionally, data collection in reference services for the management of PLHIV could constitute a bias

1. **Conclusion :**

Tuberculosis remains a public health problem in our resource-limited countries. In our series, young adult males were the most affected. Lymph node involvement was the most frequent location, followed by neurological and pleural and peritoneal serous involvement. More than a third of the patients were co-infected with HIV, and the factors associated with death were age over 60 years, neurological involvement, and the presence of anemia. A good understanding of these factors could help improve the management of our patients.

**Consent:** The anonymity of participants and the information collected was respected during data collection.

**Ethical approval:** In accordance with international or university standards, written ethical approval was obtained and retained by the authors.

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