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**Tuberculosis and illicit drug use: A retrospective study in Guayaquil, Ecuador.**
**Proyecto de Investigación**


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# UNIVERSIDAD SAN FRANCISCO DE QUITO USFQ

# COLEGIO DE CIENCIAS DE LA SALUD

**HOJA DE CALIFICACIÓN**
**DE TRABAJO DE INTEGRACIÓN CURRICULAR**

**Tuberculosis and illicit drug use: A retrospective study in Guayaquil, Ecuador**.

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## RESUMEN

El objetivo de este estudio fue identificar las correlaciones entre las características médicas, socioculturales, demográficas y de consumo de drogas y el riesgo de mortalidad entre los pacientes con tuberculosis con antecedentes de consumo ilícito de drogas en una población costera urbana en Guayaquil, Ecuador, y comparar estos resultados con pacientes de la misma población con diagnóstico de tuberculosis sin antecedentes de uso ilícito de drogas.

Este fue un estudio retrospectivo que incluyó informes médicos de más de 15 años de pacientes, que fueron tratados en un hospital terciario en Guayaquil, Ecuador entre septiembre de 2008 y marzo de 2014 y que habían sido diagnosticados de acuerdo con la Clasificación Internacional de Enfermedades (ICD) ‑ 10) con TB, código A15.0. Los pacientes fueron clasificados en dos grupos: con y sin antecedentes de consumo de drogas ilícitas. Se compararon características como sexo, edad, IMC, clasificación socioeconómica, nivel educativo, entre otros, en ambos grupos. Las variables que potencialmente se correlacionan con la mortalidad se determinaron mediante regresión logística múltiple (odds ratio, OR). El coeficiente de correlación se utilizó para establecer la relación entre la duración del consumo de drogas, la dosis, la vía de administración, el tipo de droga utilizada y la mortalidad.

Se analizaron un total de 223 pacientes: 30 (13,47%) eran usuarios de drogas ilícitas y tenían un índice de masa corporal (IMC) más bajo en comparación con los no consumidores de drogas (p = 0,03). De estos 30 pacientes, 28 (93,3%) tenían un nivel socioeconómico bajo y 1 (0,03%) estaba en la indigencia (p = 0,02). 27 (90%) de los usuarios de drogas ilícitas también eran fumadores activos (p = <0.001). La cocaína fue la droga más utilizada (83,3%). El análisis multivariante mostró que el uso ilícito de drogas [OR: 1.792 (intervalo de confianza del 95%: 0.583–5.096; p = 0.287)] se asoció con una mayor mortalidad. No se observó una correlación estadísticamente significativa entre la mortalidad y la dosis, la duración del consumo de drogas, la vía de administración o el tipo de droga utilizada.

Se encontró una asociación clara entre el consumo de drogas ilícitas y una mayor tasa de mortalidad en pacientes con tuberculosis del hospital de Guayaquil. Los usuarios de drogas ilícitas tuvieron peores resultados y una tasa de supervivencia más baja en comparación con los no consumidores de drogas.


Palabras clave: Tuberculosis, drogas ilícitas, consumo, VIH, mortalidad.

Abreviaturas
TB: tuberculosis
EPTB: tuberculosis extrapulmonar
AFB: bacilos ácido-rápidos
RIF: rifampicina
VIH: virus de inmunodeficiencia humana
CIE-10: Clasificación internacional de enfermedades
OMS: Organización Mundial de la Salud
SIDA: síndrome de inmunodeficiencia adquirida
CT: tomografía computarizada
EPOC: enfermedad pulmonar obstructiva crónica

## ABSTRACT

The aim of this study was to identify correlations between medical, sociocultural, demographic, and drug use characteristics and mortality risk amongst TB patients with a history of illicit drug use in an urban coastal population in Guayaquil, Ecuador, and to compare these outcomes with TB patients of the same population without a reported history of illicit drug use.

This was a retrospective study that included medical reports of patients, aged 15 years and older, who were treated at a tertiary hospital in Guayaquil, Ecuador between September 2008 and March 2014 and who had been diagnosed in accordance with the International Classification of Diseases (ICD‑10) with TB, code A15.0. Patients were classified into two groups: with and without history of illicit drug use. Characteristics such as sex, age, BMI, socioeconomical standings, educational level, among others, were compared in both groups. The variables potentially correlating with mortality were determined using multiple logistic regression (odds ratio, OR). The coefficient of correlation was used to establish the relationship between duration of drug use, dose, route of administration, type of drug used, and mortality.

A total of 223 patients were analyzed: 30 (13.47%) were illicit-drug users and had a lower body mass index (BMI) as compared to non–drug users ($p = 0.03$). Of these 30 patients, 28 (93.3%) were of low socioeconomic status, and 1 (0.03%) was destitute ($p = 0.02$). 27 (90%) of the illicit-drugs users were also active smokers ($p = <0.001$). Cocaine was the most frequently used drug (83.3%). Multivariate analysis showed that illicit drug use [OR: 1.792 (95% confidence interval: 0.583–5.096; $p = 0.287$)] was associated with higher mortality. No statistically significant correlation was observed between mortality and dose, duration of drug use, route of administration or type of drug used.

A clear association between illicit drug consumption and higher mortality rate in TB patients of Guayaquil's hospital was found. Illicit-drug users had worst outcomes and lower survival rate as compared with non–drug users.


Keywords: Tuberculosis, illicit drugs, consumption, HIV, mortality.

Abbreviations
TB: Tuberculosis
EPTB: Extrapulmonary tuberculosis
AFB: Acid-fast bacilli
RIF: Rifampicin
HIV: Human immunodeficiency virus
ICD-10: International Classification of Diseases
WHO: World Health Organization
AIDS: Acquired immunodeficiency syndrome
CT: Computed tomography
COPD: Chronic obstructive pulmonary disease

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# INTRODUCTION

Tuberculosis (TB) is an infection caused by Mycobacterium tuberculosis that according to the World Health Organization (WHO) affected 10.4 million people worldwide in 2016; and it accounted for around 1.3 million deaths globally that year (Dombret, 2018) (Rodriguez, 2014) (World Health Organization, 2017). Nearly 95% of all deaths related to TB were in developing countries (Lönnroth & Raviglione, 2008).

Despite the decreasing incidence of TB in Ecuador between 1990 (8 243 new cases) and 2014 (5,157 new cases) (World Health Organization, 2013) (World Health Organization, 2015), TB persists as a public health issue in Ecuador. In 2016, the WHO reported 5374 new cases of TB in this country, showing a slight incidence increase in comparison to the year 2014 (World Health Organization, 2016) (World Health Organization, 2017).

Moreover, HIV and TB are closely associated, being coinfection an important risk factor in poor prognosis of both diseases, increasing the transmission, complications and mortality risks (Oprea, y otros, 2014) (Bouscaillou, y otros, 2016). Another Global TB Report by the WHO states that in 2015 there were 8,400 new cases, 51.6 per 100,000 inhabitants, of co-infection of tuberculosis and human immunodeficiency virus (TB-HIV) in Ecuador (Armas, y otros, 2018) (World Health Organization, 2016).

Drug use can cause feelings of euphoria or alter the perception of reality. Repetitive drug use drives to physical and psychological dependency. Drug addiction is a psychological disorder, characterized by drug tolerance, in which the dependency is defined as compulsive recurrence (Mayo Clinic, 2017). Addiction is determined by the combination of environmental and genetic factors, and only a fraction of drug users are prone to become addicted. Therefore, drug addiction can be defined as the phenomenon in which drug

tolerance and dependency are present (Cuevas, Rodríguez, Peraza, Pérez, & Valdivieso, 2014)

Drug addiction is another public health issue in Ecuador and has been increasing in the last couple of years, becoming one of the highest rates of drug addiction in South America. A study by the United Nations Office on Drugs and Crime and the National Council for Control of Narcotic and Psychotropic Substances identified that 51% of drug consumers in Ecuador are drug addicts, surpassing the rates of Latin American countries such as Chile (20%), Uruguay (20%) and Peru (36%) (Briones, Hidalgo, Alvarado, Noy, & Vázquez, 2018). It is important to mention that HIV-infected injection drug users face an increased probability of TB infection, having 2 to 6 times more probability to contract TB than non-HIV-Infected injection drug users (Winter, y otros, 2017). Therefore, the epidemic of TB-HIV coinfection has had a great impact worldwide, especially in Africa, central Asia and eastern Europe, increasing the mortality rate and severity of symptoms (Daniels, y otros, 2018). TB is the ninth main cause of death worldwide and is the primary cause of death by a single infectious agent, surpassing that of HIV/AIDS (World Health Organization, 2019).

Other groups with a major risk of severe TB infection are alcoholics (Przybylski, Dąbrowska, & Trzcińska, 2014) and chronic smokers (Give, y otros, 2005) (Maurya, Vijayan, & Shah, 2002) , especially if they continue consuming during their TB treatment, complicating the outcome of an otherwise potentially curable illness (Shamaei, y otros, 2009). Several studies highlight that molecular, biological, and psychosocial factors are the main reason of a complicated TB management and a more severe outcome (Silva, Gives, Aquino, & Caldas, 2017) (Nogueira, y otros, 2016).

The aim of the present article is to establish a relationship between mortality risk and several factors, such as drug consumption, sex, age, BMI, socioeconomical standings, educational

level, in TB patients with and without a reported history of illicit drug use, in an urban coastal population in Guayaquil, Ecuador.

# TOPIC DEVELOPMENT

## Material and methods

This was a retrospective descriptive study of 223 patients diagnosed with TB in accordance with the International Classification of Diseases (ICD‑10) code for TB, A15.0 (Armas, et al, 2018), at a tertiary hospital in Guayaquil, Ecuador between September 2008 and March 2014. The data collection and this study were approved by the Guayaquil Hospital Committee of Teaching and Investigation, the local equivalent of a hospital ethics committee. The study was also performed in accordance with the Declaration of Helsinki.

The data were obtained from existing clinical registry of the hospital's Department of Pneumology. There were no age limits as an inclusion criteria in the study. We obtained the demographic information, (age, race, sex, socioeconomic status, and education level), clinical data (dyspnea, cough, expectoration, hemoptysis, headache, myalgia, and thoracic pain), and imaging findings (thoracic X-ray and computed tomography [CT]) of every patient taken care of.

The patients were classified according to self-reported history of drug use. In addition, other information corresponding to the type of drug consumed, alcohol consumption, and tobacco use were compiled from the clinical records.

### *Criteria for diagnostic confirmation of active TB infection for study inclusion.*

Only patients with bacteriological and/or clinical criteria of active TB were included in the study (Mamani, Majzoobi, Torabian, Mihan, & Alizadeh, 2013). The bacteriologically confirmed cases were those with a positive acid-fast bacilli (AFB) sample by microscopy of smear, culture or molecular testing. For molecular diagnosis, we used the GeneXpert MTB/RIF (M. tuberculosis/rifampicin) system, a fully automated, cartridge-based means of nucleic acid amplification, that diagnoses TB and identifies rifampicin resistance, yielding

results in less than 2 hours after inserting the extrapulmonary sample. One of its main advantages is that it has a high accuracy and requires minimum biosecurity (Horne, et al, 2019) . The cases diagnosed clinically were those with clinical symptomatology with high suspicion of TB, patients with X-rays with high suspicion of TB-type injuries, tuberculin-positive test, TB suggestive histopathology, or positive epidemiological link (prior contact with a case of TB).

The cases with pulmonary involvement were classified as pulmonary TB. Miliary TB was included in this group, whereas pleural effusion without pulmonary involvement on radiography was classified as extrapulmonary TB (EPTB).

***Characteristics and population records***.

During this study variables such as age, sex, age group, weight, height, body mass index (BMI) were analyzed, as well as the following data:

Socioeconomic status: Socioeconomic status was assessed from information included in the clinical records and categorized as presented on the World Bank study entitled "Economic mobility and the growth of the middle class in Latin America, General Overview" where the authors defined four social classes in Latin America in function of per capita income. Based on this study patients were categorized into one of four classifications: low class (family of four people living on an average monthly income of less than USD$1,000.00), middle class (income of USD$1000.00–5000.00 per month), upper class (income higher than USD$5000.00 per month) and destitute (they do not receive remuneration and may be receiving aid from the state, i.e., a bonus of USD$30.00 monthly) (Ferreira F. , et al, 2013)

Level of education: The patients were divided in to illiterate, primary, secondary, and upper education levels.

Race: The patients were categorized into the following races based on self-reported data compiled from the clinical record: Afro-Ecuadorian, Native, Asian, Mestizo and White.

Place of origin: The patients place of residence were divided into urban or rural in order to determine if they lived in endemic zones of TB. Living in an endemic zone was qualified as a positive epidemiological link (having had contact with known TB patients).

Habits: We extracted data on alcohol consumption, hallucinogenic drug use, active smoking, passive smoking, and other habits from medical records.

Definition of clinical symptomatology and complementary evidence for TB infection: The following symptoms were extracted from medical records and analyzed: hemoptysis, cough, dyspnea, headache, myalgia, and thoracic pain; as well as the main laboratory findings: hematocrit (%), leucocytes (103/mm3), neutrophils (%), and platelets (103/mm3).

The diagnostic criteria for active TB was divided into clinical, microbiological, and pathological categories in accordance with the WHO standards (World Health Organization, 2017) (Przybylski, Dąbrowska, & Trzcińska, 2014) (Mamani, Majzoobi, Torabian, Mihan, & Alizadeh, 2013).

We also recorded the main procedures for obtaining samples that resulted in positive diagnosis, such as bronchoscopy, sputum culture, and DNA test.

During this study, the presence of different comorbidities was documented, including cancer, chronic renal illness in hemodialysis treatment, chronic obstructive pulmonary disease (COPD), type II diabetes mellitus, HIV, liver cirrhosis, collagenopathy, and other diseases (Hermosilla, et al, 2017).

***Definition of EPTB***.

EPTB was defined as any bacteriologically confirmed TB or clinically diagnosed TB involving organs other than the lungs or tracheobronchial tree, for example, the abdomen, genitourinary tract, joints and bones, lymph nodes, meninges, pleura, skin, and the

intrathoracic lymph nodes (mediastinal and/or hilar) or tuberculous lymphadenitis (World Health Organization, 2017) (Mamani, Majzoobi, Torabian, Mihan, & Alizadeh, 2013).

Pleural effusion without pulmonary involvement on radiography was classified as EPTB.

Cases with both, pulmonary and extrapulmonary involvement, were classified as pulmonary TB. Miliary TB was also included in this group.

Bronchoscopy sample collection and bronchoalveolar lavage: These procedures were performed in selected cases, i.e., difficulty with sputum expectoration, negative smears with features suggestive of TB. EPTB diagnosis was based on additional features suggestive of TB affection outside the lungs or tracheobronchial tree, with supporting evidence demonstrating AFB and/or granuloma/caseous necrosis in samples obtained from the affected site.

***Classification of radiological patterns***

The main radiographic images were reported as: cavitary lesions, interstitial infiltrates, Miliary lesions, and granulomas. Chest radiographic patterns were classified according to the United States National Tuberculosis and Respiratory Disease Association as follows (Give, et al, 2005):

Category 1: Minimum infiltration without cavities; Category 2: Moderate infiltrate expansion; Category 2A: Occasional infiltrate, unilateral or bilateral without cavities; Category 2B: Compact infiltration with expansion limited to a pulmonary lobule, and cavities with diameter < 4 cm; Category 3: Advanced with any infiltrate expansion (with or without cavities); Category 4: Miliary, miliary TB is defined as the presence of micronodules on chest radiography or high-resolution CT.

***Definition of final outcome (death attributable to TB)***

A death was attributed to TB if active TB was identified and no other cause of death was determined.

### *Definition of drug use*

Drug user patients were defined as patients who were actively consuming an illicit drug, at least one time a week, and may present a mental, physical and/or social status disorder (Mayo Clinic, 2017).

### *Type of drugs*

We recorded the use of illicit drugs as by Ecuadorian law.

### *Routes of administration*

The routes of illicit drug administration reported by the patients were documented and then divided in to two groups, intravenous and others (Routes of administration, such as chewed, snorted, orally ingested, were in this group)

### *Statistical analysis*

Statistical analysis was performed using MedCalc Statistical Software version 16.4.3 (MedCalc Software BVBA, Ostend, Belgium; https://www.medcalc.org, 2016). Continuous variables are described as the mean (SD) or median (range) depending on the statistical distribution (Kolmogorov-Smirnov test). Categorical variables are described as frequency (%). Variables potentially correlated with mortality were identified by logistic regression (odds ratio, OR). Variables with $p < 0.15$ were included in multivariate analysis.

The coefficient of correlation (r) and Spearman's coefficient of rank correlation (rho) were used as appropriate to establish the relationship between mortality and duration of drug use, dose, and route of administration (intravenous vs. non-intravenous).

## Results

The present study involved 223 patients: 32% were female, while 68% were male. 81% self-identified as Mestizo. A total of 27.8% of patients were 15–30 years old. Most of the patients (88.8%) were of low socioeconomic status. Educational background was: 57% of

the patients had completed primary education, 34.5% had attended secondary school, 6.3% were illiterate, and only 2.2% had higher education. One hundred and twenty-four patients had previous TB exposure (55.6%).

Thirty TB patients (13.47%) were active illicit drug users. In comparation to non–drug users, they had a lower BMI ($p = 0.03$), as well as lower socioeconomic status ($p = 0.02$). Twenty-seven of these 30 patients (90%) were active smokers, which resulted in a statistically significant difference in relation to the non–drug users ($p < 0.001$). Table 1 shows that 43.3% of illicit drug users were HIV-positive in contrast with 23.8% TB patients non-drug users that were HIV positive.

Multivariate analysis yielded the following results (Table 2): BMI (kg/m2, <18.5), OR: 1.711 (95% confidence interval [CI] 0.665–4.263; $p = 0.253$); drug use, OR: 1.792 (0.583–5.096; 0.287); miliary lesions, OR: 3.007 (0.684–1.1575; 0.12); comorbidities, OR: 1.426 (0.604–3.341; 0.413); microbiological diagnostic test (positive sputum smears), OR: 2.069 (0.719–7.519; 0.213); and GeneXpert MTB/RIF (DNA), OR: 2.84 (1.116–7.118; 0.026).

Several patients indicated consuming multiple drugs; the drug most often used was cocaine (83.3%).

The average drug consumption was 2719 mg (range: 0.45–5040 mg) and the average period of drug use was 7 years (range: 2–20 years) (Table 3).

The correlation coefficient showed only a weak correlation between intravenous drug use and the final outcome (Table 4).

**Discussion**

Our results show that 13.45% of patients diagnosed with TB reported illicit drug use; multivariate analysis showed that drug use was associated with mortality, regardless of the drug dose, period of time consuming drugs, drug type, and route of administration.

Other studies in Latin America have reported similar results to the ones we report. Zerbini et al. (Zerbini, et al, 2017) found in six provinces in Argentina that 9.8% of TB patients used illicit drugs; they also reported that drug use in TB patients had a higher risk of coinfection with HIV/AIDS than non-drug users. Silva et al. (Silva, et al, 2018) reported that 10% of a rural population in São Paulo, Brazil were illicit drug consumers, and from this group only the 8%, corresponding to injecting-drug users, were more likely to develop TB. In Chile, Herrera et al. (Herrera, 2015) found that 6.4% of people aged 15–64 with active TB were drug users.

The studies mentioned above agree that drug use is a major risk factor for TB infection, having a great influence in the mortality risk.

The present study clearly demonstrates an association between TB infection, illicit drug consumption, and HIV, which has also been reported in several other studies around the world and Latin America. Although the incidence of TB in Ecuador has decreased over the past two decades, there has been an increase, albeit slight, in the last 2 years, remaining as a major public health problem.

TB patients who use illicit drugs exhibit a series of signs and symptoms that differ from non-drug-users. The variety of signs and symptoms that these patients evidence, might be due to drug-induced molecular mechanisms that attenuate clinical manifestations, severity, and the perception that the patient has of the disease. This statement may also explain why the imaging findings were more varied and severe among illicit drug users, as these patients often take longer than non–drug users to seek medical care (Dhingra, Lall, Aggarwal, & Vashist, 2008).

This study has some important limitations. First, the population studied is monocentric; therefore, the results cannot be extrapolated. Being a retrospective design, there could be biases in data collection. Moreover, there is no institutional monitoring of patients who are

drug users, which could lead to underestimation of the number of deaths. As the drug use was self-reported, we can also be underestimating the number of TB patients who are actually active drug users.

## CONCLUSIONS

This study clearly demonstrates an association between TB, drug consumption and mortality risk in an urban coastal population in Guayaquil, Ecuador. Medical imaging findings are more varied and severe among Tb patients who are illicit drug users, manifesting with a lower frequency of signs and symptoms, therefore leading to a worst prognosis. Patients with active TB that consume illicit drugs have a lower survival rate and higher mortality risk compared to non–drug users, regardless of the dose, period of drug use, route of administration, and type of drug used.

## REFERENCES


Ferreira, F., Messina, J., Rigoli, J., Lopez, L., Lugo, M., & Vakis, R. (2013). *Economic mobility and the growth of the middle class in Latin America, General Overview*. Obtenido de World Bank: http://siteresources.worldbank.org/LACINSPANISHEXT/Resources/Informe_ClaseMedia.pdf

Dombret, M. (2018). *Pulmonary tuberculosis of the adult. Treated of medicine.* EMC.

Rodriguez, J. (2014). Tuberculosis. *Clinical Medical magazine Earls*, 547-552.

World Health Organization. (2017). *Global TB Report 2017*. Obtenido de WHO: http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng. Pdf?ua=1.

World Health Organization. (2013). Global Tuberculosis Report 2013. *Geneva: World Health Organization.* Geneva: WHO.

World Health Organization. (2015). Global Tuberculosis Report 2015. *Geneva: World Health Organization.* Geneva: WHO.

World Health Organization. (2016). *Global TB Report 2016*. Obtenido de WHO: http://apps.who.int/medicinedocs/documents/s23098en/s23098en.pdf.

Oprea, C., I. I., R. R., S. E., G. T., & O. N. (2014). Alarming increase in Tuberculosis and hepatitis C virus (HCV) among HIV infected intravenous drug users. *Journal Int AIDS Soc*, 19625.

Bouscaillou, J., J. E., M. P., T. I., M. K., & T. N. (2016). Prevalence and risk factors associated with HIV and tuberculosis in people who use drugs in Abidjan, Ivory Coast. *Int J Drug Policy*, 116-123.

Mayo Clinic. (26 de October de 2017). *Drogadicción (trastorno de consumo de sustancias)*. Obtenido de Mayo Clinic: https://www.mayoclinic.org/es-es/diseases-conditions/drug-addiction/symptoms-causes/syc-20365112

Cuevas, T., Rodríguez, N., Peraza, T., Pérez, R., & Valdivieso, T. (2014). *Concept of Tolerance and Addiction to drugs*. Obtenido de Health and Medicine: https://historiaybiografias.com/drogas_conceptos/

Briones, W. L., Hidalgo, H. H., Alvarado, J. M., Noy, A. G., & Vázquez, T. S. (2018). Causes of the addictions in teenagers and young in Ecuador. *Magazine File Medical of Camagüey*, 130-138.

Winter, J., Stagg, H., Smith, C., Brown, A., Lalor, M., Lipman, M., & al, e. (2017). Injecting drug use predicts activate tuberculosis in to national cohort of people living with HIV. *AIDS Lond Engl*, 2403–2413.

Daniels, C., Smyth, C., Malik, F., Creswell, J., Ayre, J., & Ditiu, L. (2018). *The Global Plan to the End of the TB and the key populations*. Obtenido de Stop TB Partnership: http://www.stoptb.org/assets/documents/resources/publications/acsm/peopleusedrugs-spa.pdf

World Health Organization. (2019). *World Health Statistics Overview 2019.* Obtenido de WHO: https://apps.who.int/iris/bitstream/handle/10665/311696/WHO-DAD-2019.1-eng.pdf

Przybylski, G., Dąbrowska, T., & Trzcińska, H. (2014). Alcoholism and other Partner-demographic risk factors for adverse TB-drug reactions and unsuccessful tuberculosis treatment – dates from have years' observation at the Regional Centre of Pulmonology, Bydgoszcz, Poland. *Med Sci Monit*, 444-453.

Give, S. B., Lill, S., Borgdorff, M., Verver, S., Bateman, E., Lombard, C., & al, e. (2005). Association between smoking and Tuberculosis infection: to population survey in to high tuberculosis incidence area. *Thorax*, 555-557.

Maurya, V., Vijayan, S., & Shah, T. (2002). Smoking and Tuberculosis: an association overlooked. . *Int J Tuberc Lung Dis.*, 942–951.

Shamaei, M., Marjani, M., Baghaei, B., Chitsaz, A., Tabar, A. R., Z. A., & al, E. (2009). Drug Abuse profile - patient delay, diagnosis delay and drug resistance pattern - among addict patients with tuberculosis. *Int J STD AIDS*, 320–323.

Silva, T., Gives, P. M., Aquino, D., & Caldas, J. (2017). Factors associated with Tuberculosis retreatment in priority districts of Maranhãor, Brazil. *Cienc Saude Coletiva*, 4095–4104.

Nogueira, C., Prim, R., Senna, S., Rovaris, D., Maurici, R., Rossetti, M., & al, E. (2016). First insight into the molecular epidemiology of Mycobacterium tuberculosis in Santa Catarina, southern Brazil. *Tuberc Edinb Scotl*, 57–64.

Mamani, M., Majzoobi, M., Torabian, S., Mihan, R., & Alizadeh, K. (2013). Latent and activate tuberculosis: evaluation of injecting drug users. *Iran Network Crescent Med J.*, 775–779.

Horne, D., Kohli, M., Zifodya, J., Schiller, I., Dendukuri, N., Tollefson, D., & Steingart, K. (2019). Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. . *The Cochrane database of systematic reviews*.

Ferreira, F., Messina, J., Rigoli, J., Lopez, L., Lugo, M., & & Vakis, R. (2013). *Economic mobility and the growth of the middle class in Latin America, General Overview.* . Obtenido de World Bank: http://siteresources.worldbank.org

Hermosilla, S., You, P., Aifah, T., Abildayev, T., Akilzhanova, T., Kozhamkulov, O., & al., e. (2017). Identifying risk factors associated with smear positivity of pulmonary Tuberculosis in Kazakhstan. . *PLOS ONE*.

Zerbini, A., Greco, T., Estrada, S., Cisneros, M., Colombo, C., Boncompain, C., & Genero, S. (2017). Factors of risk associated with the mortality by tuberculosis in adults of six provinces of Argentina. *Medicine (Buenos Aires)* , 267-273.

Silva, D., Muñoz, M., Duarte, R., Galvao, R., Bonini, A., Ferlin, F., & Carvalho Of Queiroz, F. (2018). Factors of risk for the tuberculosis: diabetes, smoke, consumption of alcohol and the use of other drugs. *Jornal Brasileiro Of Pneumologia*, 145-152.

Herrera, T. (2015). Groups of risk for tuberculosis in Chile. *Chilean Magazine of Infectología*, 15-18.

Dhingra, V., Lall, D., Aggarwal, N., & Vashist, R. (2008). DOTS in drug addicts with TB: Delhi experience. . *Indian J Tuberc.*, 122–126.

Lönnroth, K., & Raviglione, M. (2008). Global Epidemiology of Tuberculosis: Prospects for Control. *Semin Respir Crit Care Med*, 481-491.

Armas, D., León, X., Cedeño, R., Yerovi, G., Solano, D., Tátes, N., & Carriel, L. (2018). Prevention, diagnosis, treatment and control of the tuberculosis. *Guide of Clinical Practice.* I remove: National Direction of Normatization.

# ANNEXES

**Table 1.** Baseline characteristics of the study population.

| | **Total (n = 223)** | **No history of drug use (n = 193)** | **History of drug use (n = 30)** | **p-value** |
|---|---|---|---|---|
| **Age (years)**, median (range) | 42 (15–86) | 44 (15–86) | 36 (15–82) | 0.215[a] |
| 15–30 | 62 (27.8) | 51 (26.4) | 11 (36.7) | |
| 31–40 | 42 (18.8) | 36 (18.7) | 6 (20.0) | |
| 41–50 | 40 (17.9) | 34 (17.6) | 6 (20.0) | 0.455[b] |
| 51–64 | 45 (20.2) | 43 (22.3) | 2 (6.7) | |
| 65–79 | 30 (13.5) | 26 (13.5) | 4 (13.3) | |
| >80 | 4 (1.8) | 3 (1.6) | 1 (3.3) | |
| **Sex (female)**, n (%) | 73 (32.7) | 126 (65.3) | 24 (80.0) | 0.110[b] |
| **Weight (kg)**, median (range) | 51.7 (35.0–80.0) | 51.7 (35.0–80.0) | 49 (39.0–70.0) | 0.063[a] |
| **Height (cm)**, median (range) | 158 (145–174) | 158 (145–174) | 158 (145.0–172.0) | 0.412[a] |
| **BMI (kg/m$^2$)**, median (range) | 20.2 (13.49–35.6) | 20.2 (14.20–35.6) | 19.5 (13.49–26.03) | 0.031[a] |
| **Socioeconomic status**, n (%) | | | | 0.028[b] |
| Destitute | 9 (4.0) | 0 | 1 (0.03) | |
| Low Class | 198 (88.8) | 178 (92.2) | 28 (93.3) | |
| Medium Class | 16 (7.2) | 15 (7.8) | 1 (3.3) | |
| **Education level**, n (%) | | | | 0.865[b] |
| Illiterate | 14 (6.3) | 13 (6.7) | 1 (3.3) | |
| Primary school | 127 (57.0) | 109 (56.5) | 18 (60.0) | |
| Secondary school | 77 (34.5) | 67 (34.7) | 10 (33.3) | |
| College | 5 (2.2) | 4 (2.1) | 1 (3.3) | |
| **Race**, n (%) | | | | 0.617[b] |
| African-Ecuadorian | 20 (9.0) | 19 (9.8) | 1 (3.3) | |
| Native | 19 (8.5) | 15 (7.8) | 4 (13.3) | |
| Asian | 1 (0.4) | 1 (0.5) | 0 | |
| Mestizo | 181 (81.2) | 156 (80.8) | 25 (83.3) | |
| White | 2 (0.9) | 2 (1.0) | 0 | |
| **Origin**, n (%) | | | | 0.211[c] |
| Urban | 187 (83.9) | 159 (82.4) | 28 (93.3) | |
| Rural | 36 (16.1) | 34 (17.6) | 2 (6.7) | |
| **Previous contact with TB patient**, n (%) | 124 (55.6) | 107 (55.4) | 17 (56.7) | 0.900[b] |
| **Hemogram blood count,** median (range) | | | | |
| Hematocrit (%) | 30.6 (12.0–46.0) | 30.6 (16.5–46.0) | 30.6 (12.0–36.9) | 0.449[a] |
| Leucocytes ($10^3$/mm$^3$) | 11.6 (2.1–30.3) | 11.6 (2.1–30.3) | 11.6 (3.0–12.6) | 0.177[a] |

| | | | | |
|---|---|---|---|---|
| Neutrophils (%) | 37.0 (9.0–98.7) | 37.0 (9.0–98.7) | 37.0 (37.0–77.1) | 0.723[a] |
| Platelets ($10^3$/$mm^3$) | 287.1 (50.0–630.0) | 287.1 (50.0–630.0) | 287.1 (69.0–502.0) | 0.896[a] |
| **Habits,** n (%) | | | | |
| Alcohol consumption | 136/223 (61.0) | 121/193 (62.7) | 15/30 (50.0) | 0.185[b] |
| Drug use | 30/223 (13.5) | - | - | |
| Active smoking | 104/223 (46.6) | 77/193 (39.9) | 27/30 (90.0) | <0.001[c] |
| Passive smoking | 108/223 (48.4) | 90/193 (46.6) | 18/30 (60.0) | 0.173[b] |
| Other | 106/223 (47.5) | 96/193 (49.7) | 10/30 (33.3) | 0.094[b] |

**Table 1.** Baseline characteristics of the study population. *(continuation)*

| | | | | |
|---|---|---|---|---|
| **Type of drug used**, n (%) | | | | - |
| Marijuana | 5/30 (16.7) | - | 5/30 (16.7) | |
| Cocaine | 25/30 (83.3) | - | 25/30 (83.3) | |
| Crack | 9/30 (30.0) | - | 9/30 (30.0) | |
| Amphetamines | 2/30 (6.7) | - | 2/30 (6.7) | |
| Hashish | 2/30 (6.7) | - | 2/30 (6.7) | |
| Perika | 1/30 (3.3) | - | 1/30 (3.3) | |
| **Symptoms**, n (%) | | | | |
| Fever | 204/223 (91.5) | 175/193 (90.7) | 29/30 (96.7) | 0.457[c] |
| Expectoration | 176/223 (78.9) | 156/193 (80.8) | 20/30 (66.7) | 0.077[b] |
| Hemoptysis | 155/223 (69.5) | 136/193 (70.5) | 19/30 (63.3) | 0.430[b] |
| Cough | 176/223 (78.9) | 156/193 (80.8) | 20/30 (66.7) | 0.077[b] |
| Dyspnea | 176/223 (78.9) | 155/193 (80.3) | 21/30 (70.0) | 0.198[b] |
| Headache | 164/223 (73.5) | 146/193 (75.6) | 18/30 (60.0) | 0.071[b] |
| Myalgia | 164/223 (73.5) | 145/193 (75.1) | 19/30 (63.3) | 0.173[b] |
| Thoracic pain | 173/223 (77.6) | 152/193 (78.8) | 21/30 (70.0) | 0.285[b] |
| **Diagnostic test (positive)**, n (%) | | | | |
| Bacilloscopy | 165/223 (74.0) | 142/193 (73.6) | 23/30 (76.7) | 0.720[b] |
| Sputum culture | 4/223 (1.8) | 4/193 (2.1) | 0 | 1.000[d] |
| DNA | 46/223 (20.6) | 35/193 (18.1) | 11/30 (36.7) | 0.012[b] |
| **Diagnostic criteria**, n (%) | | | | 0.604[b] |
| Clinical imaging | 45 (20.2) | 41 (21.2) | 4 (13.3) | |

| | | | | |
|---|---|---|---|---|
| Microbiology | 171 (76.7) | 146 (75.6) | 25 (83.3) | |
| Pathology | 7 (3.1) | 6 (3.1) | 1 (3.3) | |
| **Imaging findings**, n (%) | | | | |
| Cavity | 179/223 (80.3) | 155/193 (80.3) | 24/30 (80.0) | 0.968[b] |
| Interstitial infiltrates | 109/223 (48.9) | 96/193 (49.7) | 13/30 (43.3) | 0.513[b] |
| Miliary lesions | 14/223 (6.3) | 12/193 (6.2) | 2/30 (6.7) | 0.925[d] |
| Granulomas | 66/223 (29.6) | 56/193 (29.0) | 10/30 (33.3) | 0.630[b] |
| **Imaging category**, n (%) | | | | 0.098[b] |
| 1 | 1 (0.4) | 0 | 1 (3.3) | |
| 2A | 40 (17.9) | 35 (18.1) | 5 (16.7) | |
| 2B | 125 (56.1) | 111 (57.5) | 14 (46.7) | |
| 3 | 51 (22.9) | 42 (21.8) | 9 (30.0) | |
| 4 | 6 (2.7) | 5 (2.6) | 1 (3.3) | |
| **Performed bronchoscopy**, n (%) | 7 (3.1) | 6 (3.1) | 1 (3.3) | 1.000[c] |
| **Comorbidities**, n (%) | 85 (38.1) | 69 (35.8) | 16 (53.3) | 0.100[b] |
| Cancer (solid tumors) | 3/85 (3.5) | 1/69 (1.4) | 2/16 (16.7) | |
| Chronic renal disease + hemodialysis | 5/85 (5.9) | 1/69 (1.4) | 1/16 (8.3) | |
| COPD | 3/85 (3.5) | 3/69 (4.1) | 0/16 | |
| Diabetes mellitus type II | 6/85 (7.1) | 6/69 (8.3) | 0/16 | |
| HIV | 53/85 (62.4) | 46/69 (63.0) | 7/16 (58.3) | |
| Hepatic cirrhosis | 5/85 (5.9) | 5/69 (6.8) | 0/16 | |
| Collagenopathy | 2/85 (2.4) | 2/69 (2.7) | 0/16 | |
| Previous lobectomies | 2/85 (2.4) | 2/69 (2.7) | 0/16 | |
| Other | 6/85 (7.1) | 5/69 (6.8) | 1/16 (8.3) | |
| **Overall survival rate**, n (%) | 192 (86.1) | 170 (88.1) | 22 (73.3) | 0.030[b] |

a. OR, Mann–Whitney test
b. Pearson's chi-square test
c. Pearson's chi-square test with the Yates continuity correction
d. Fisher's test

**Table 2.** Factors associated with mortality [OR (95% CI; p-value)].

| | |
|---|---|
| **BMI (kg/m$^2$) (<18.5)** | 1.711 (0.665–4.263; 0.253) |
| **Drug use** | 1.792 (0.583–5.096; 0.287) |
| **Diagnostic test (positive), n (%) microbiological** | |
| **Bacilloscopy** | 2.069 (0.719–7.519; 0.213) |
| **DNA** | 2.84 (1.116–7.118; 0.026) |
| **Imaging findings, n (%)** | |
| **Miliary lesions** | 3.007 (0.684–11.575; 0.12) |
| **Comorbidities** | 1.426 (0.604–3.341; 0.413) |

**Table 3.** Illicit drug use and amount used (mg).

| Drug | n | Average | Minimum | Maximum | SD |
|---|---|---|---|---|---|
| **Cocaine** | 13.0 | 0.5 | 5040 | 3121 | 2046 |
| **Crack** | 7.0 | 0.5 | 5040 | 1441 | 2459 |
| **Amphetamines** | 2.0 | 0.5 | 5040 | 2520 | 3563 |
| **Perika** | 1.0 | 2160 | 2160 | 2160 | n/To |
| **Hashish** | 2.0 | 1920 | 5040 | 3480 | 2206 |
| **Marijuana** | 5.0 | 1572 | 4527 | 3351 | 1611 |

**Table 4.** Correlation coefficients.

| Variable | n | Test | Correlation coefficient | Significance level (p-value) | 95% CI |
|---|---|---|---|---|---|
| **Drug dose (mg)** | 30 | **Correlation coefficient, r** | -0.3459 | 0.0611 | -0.6279 to 0.01640 |
| **Duration of drug use (years)** | 30 | **Correlation coefficient, r** | -0.05529 | 0.7717 | -0.4075 to 0.3112 |
| **Drug administration route (injected vs. other)** | 30 | **Spearman correlation coefficient** | 0.3182 | 0.0866 | -0.384 to 0.349 |
| **Type of drug used** | 30 | **Spearman's coefficient of rank correlation, rho** | 0.0688 | 0.7180 | -0.299 to 0.419 |