International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 03 March 2022

Page No: 218-226

DOI: https://doi.org/10.47191/ijmscrs/v2-i3-05, Impact Factor: 5.276

Hyponatremia Incidence and its Association with Mortality in Patients with Pulmonary Tuberculosis Observational Study

Jeremy Javier Hernandez Rios, MD[1], Jesus Alan Guardado Vindiola, MD[1], Joaquín Cordova Erberk[1], Katya Lorena Wilhelmy Ledesma[1], Paola Alejandra Sterling Carrillo[2], Marina Estrada Rodríguez[1], Hiram Javier Jaramillo Ramirez, MD[3]

[1]Internal Medicine Department, Mexicali's General Hospital (Hospital General de Mexicali). Autonomous University of Baja California, Faculty of Medicine. Mexicali, Mexico.

[2]Internal Medicine Department, Mexicali's General Hospital (Hospital General de Mexicali). Xochicalco University, Faculty of Medicine. Mexicali, Mexico.

[3]Chairman, Internal Medicine Department, Mexicali's General Hospital (Hospital General de Mexicali). Mexicali, Mexico.

ABSTRACT

Introduction: Pulmonary tuberculosis has been of great interest for us given the high number of cases in our community at the Mexican-American border, however, this abundance of patients allows us to observe whether there is an association between the previously described development of hyponatremia and mortality in these patients.

Objective: To determine the association between mortality and hyponatremia in patients with pulmonary tuberculosis.

Material and Methods: We analyzed the electronic health record of patients with a pulmonary tuberculosis diagnosis from a 4-year period in the General Hospital of Mexicali, in México. Inclusion criteria were patients over the age of 18, a pulmonary tuberculosis diagnosis, and complete laboratory tests. The collected data was then analyzed through descriptive statistics.

Results: 116 patients with pulmonary tuberculosis were included, of which 91 (78.4%) were male. A history of past Infection with the Human immunodeficiency virus and previous tuberculosis infection were shown to correlate with higher mortality and requirement of intensive care. The logistic regression analysis showed that hyponatremia had no association with mortality or the need for intensive care. Complications such as Acute respiratory distress syndrome and Acute kidney injury were related to higher mortality and need for critical care.

Conclusions: The incidence of hyponatremia was higher than previously described, but there was no statistical association between hyponatremia and mortality in comparison to patients with normal sodium. Among this study's weaknesses, most patients were hospitalized at the time of diagnosis, implying they could already have had a complication, thus increasing the incidence.

KEYWORDS: Pulmonary, Tuberculosis, Hyponatremia, Migration, Sodium.

ARTICLE DETAILS

Published On:
18/03/2022

Available on:
https://ijmscr.org

INTRODUCTION

Tuberculosis is one of the oldest diseases known to mankind. A total of 1.4 million people died from tuberculosis in 2019 alone. Worldwide, tuberculosis is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS). In 2019, an estimated 10 million people had tuberculosis worldwide; 5.6 million men, 3.2 million women and 1.2 million children[1]. The clinical presentation of tuberculosis is usually divided into pulmonary, extrapulmonary or both. The diagnosis can be made through microbiological analysis of sputum smear or tissue pathology, however these have low sensitivity (40-60%) with a high incidence of false negatives. The skin tuberculin sensitivity test (PPD test or Mantoux test) can be used to

detect latent infection, although this test has low sensitivity and specificity. The QuantiFERON-TB Gold test measures the liberation of IFN-y by T-cells and has a lower risk of false positive test results[2].

In 1938 Winkler and Crankshaw made the association between a syndrome where patients had hyponatremia and hypochloremia, along with urinary loss of these same electrolytes in patients with pulmonary tuberculosis and no adrenal compromise[3]. Meanwhile in 1939, Westover, Stiven and Garry found low serum sodium in 55 out of 114 patients with tuberculosis and urinary loss of sodium[4].

The possible mechanism for this syndrome was studied in 10 african-american patients by Sims, et al. who concluded that renal or adrenal disease was not the cause[5]. Based on studies on bronchogenic carcinoma, Weiis and Katz describe an association between tuberculosis and hormonal involvement, proposing the hypothesis of a Syndrome of Inappropriate antidiuretic hormone (SIADH) in tuberculosis patients causing the asymptomatic hyponatremia[6]; in 1969 Shalhoub also describes this same hypothesis[7]. During that same year, Chung observed in a study of 522 patients with active pulmonary tuberculosis with no treatment, that 56 patients developed hyponatremia[8]. In contrast with the theory described by Shalhoub; De Fronzo, et al. described 3 patients with hyponatremia and normal urinary function[7,9]. And so it was until 1990 when Hill proposed to study the role un vasopressin and its association with hyponatremia in patients with active tuberculosis, showing an increase in vasopressin that responded to osmolal changes, making the hypothesis of an ectopic secretion accompanied of a osmoregulator supression linked to the tuberculosis activity itself. [10-11]

Studies by Baran and Hutchinson suggest that serum sodium is a biomarker linked to severity and mortality in any disease[12]. Bennani supports the role of serum sodium as a strong predictor for mortality; on the other hand, Sharma links hyponatremia to an increased risk of developing acute respiratory distress syndrome (ARDS) [13-14]. In 2017, Babaliche, et al. studied 100 patients who presented hyponatremia on admission to the ICU, and documented that the main cause of hyponatremia in these patients was SIADH, while tuberculosis was the main cause of SIADH and therefore hyponatremia in these patients. Jafari also reports that hyponatremia was strongly linked to advanced age in at least half of his patients with hyponatremia. [15,16]

In one cohort study in the United Kingdom, non-severe hyponatremia in patients with pulmonary tuberculosis did not appear to be related to an increase in admittance to the ICU with an OR of 0.40 (p= 0.06) [17]; which is similar to what Llamas concludes in a study on Mexican population with tuberculosis, where hyponatremia was not found to be associated with an increased mortality (p=0.48) [18]. On the other hand Sinala, et al. found 5 predictors for mortality in patients admitted with tuberculosis, with hyponatremia being among the predictors for early mortality (p=0.0067) [19]. Likewise, there's been some cases of pulmonary tuberculosis associated with SIADH reported in Japan, however, Hashimoto, et al. report a case of status epilepticus that was resolved upon correction of hyponatremia associated with pulmonary tuberculosis[20]. Given the increased association of hyponatremia with tuberculosis, which has been reported as 10.7%, we set ourselves to observe and investigate serum electrolytes in every patient with tuberculosis, even in mild cases.

The primary objective of this study is:
1- To establish whether an association between hyponatremia and increased mortality exists in patients hospitalized due to active pulmonary tuberculosis.

The secondary objectives are as follows:
1- To describe the main risk factors associated with increased mortality.
2- To find an association between hyponatremia and the requirement of intensive care.

METHODS

The present study is observational, retrospective and descriptive. We consulted the electronic health record of "Hospital General de Mexicali" for every patient with a tuberculosis diagnosis during the period between August 2014 to December 2019.

We included patients with the following ICD-9 code Z-111,Z-30, A-15, A-16, A-150, A-151, A-152, A-153, A-155, A-157,A-158, A-159, A-160, A-161, A-162, A-164, A-167 and A-168. Once selected, each file was analyzed in search of a confirmatory diagnostic test such as PCR, bacilli culture, sputum smear, or compatible chest x-ray. We excluded patients in which a different diagnosis was confirmed, as well as those without serum glucose test on admittance (since hyperglycemia can alter the "true" serum sodium levels).

The following date was recorded: biological sex, age, alcohol consumption, comorbidity status such as diabetes mellitus, hypertension, illegal drug use, tobacco use, signs and symptoms associated to hyponatremia, presence of acute kidey injury, liver failure, acute respiratory failure, pulmonary thromboembolism, clostridium difficile infection, sepsis, use of vasopressors, mechanic ventilation, admittance to the ICU, use of tuberculosis medication and reports of multi-drug resistant mycobacterium tuberculosis and whether the subject died during hospitalization. (Figure 1)

The collected data was then processed through Microsoft Windows Excel 2010, and analyzed in MiniTab 18.1. Descriptive statistics was used for quantitative variables with central tendency measurements. Chi-square test and Fisher test were used to compare variables. For qualitative variables , proportions and percentages were used.

The present study was made in accordance with the 1975 World Medical Association Declaration of Helsinki, and was approved by an independent ethics committee. All the patients included in this work have given their written consent.

RESULTS

Out of 492 patients with a compatible electronic health record, 116 were recruited; ninety one were male (78.4%). The median age was 40.01±14.70 years. With most patients either falling in the 21 to 30 year old category (28.4%) or the 41 to 50 years of age category (25.8%).

Hyponatremia was classified as mild when the serum sodium values were between 130-134 mEq/L, moderate as 125-129.9 mEq/L and severe when in the 115-124.9 mEq/L range. The mean of serum sodium level in our sample was 129.74 mEq/L. Mortality in the patients with hyponatremia was 56% (p= 0.927)

Male sex was found to have an increased risk for severe hyponatremia (OR 3.92 1.25-13.78) (p=0.03) when compared to female patients.

Seventy seven patients reported illicit drug use (63.3%), while sixty five were active tobacco smokers (56%) and fifty seven regularly drank alcohol (49.1%)

Twenty two patients (18.9%) were found to be diabetic.

Co-infection with Human-immunodeficiency-virus (HIV) as well as a previous tuberculosis infection usually increase the need for intensive care, however these two factors were not found to increase the risk for hyponatremia in our sample. (Table 2)

Fourteen cases (12.1%) presented headaches, altered neurological status, coma or seizures associated with hyponatremia and its severity. (p=<0.001).

Mechanical ventilation was needed in twenty cases (17.2%) and was strongly associated with a lethal outcome (OR 7.17 2.32-26.73)(p=<0.001) however, no apparent association with hyponatremia was found (OR 2.56 0.74-11.68)(p=0.23). Eighteen patients (15.5%) developed sepsis, which was associated with increased mortality (OR 32.61 5.54-16.29)(p=<0.001), but not to hyponatremia (OR 1.36 0.37-6.55)(p=0.36). Eleven patients (11.2%) required vasopressors, which was associated with an increase in mortality (OR 8.87 2.07-61.59)(p=<0.001) however the use of vasopressors was not related to hyponatremia (OR 1.36 0.37-6.55)(p=0.36). Deceased patients usually required intensive care prior to the lethal outcome (OR 35.75 12.05-107.15) (p=<0.001).

Figure 2 shows that the most common complication in our sample was ARDS with 43 cases (37.1%) while 22 (18.9%) developed acute kidney injury, 5 (4.3%) had liver failure and 3 (2%) developed pulmonary thromboembolism, while also 3 other patients had a Clostridium difficile infection. Table 1 shows that the development of ARDS and acute kidney injury were associated with an increased mortality. Likewise, Table 4 shows that acute kidney injury was associated with a need for intensive care. None of these complications were associated with hyponatremia.

Eighty nine (76.7%) reported the use of anti-tuberculosis drugs in a proper manner previous to hospital admittance. Twelve (10.3%) patients were infected with a multidrug resistant Mycobacterium tuberculosis strain (Resistance to Rifampicin and Isoniazid). No association between hyponatremia and resistance to treatment was found (OR 2.11 0.79-5.11)(p=0.28).

Eighty three (71.6%) patients presented with hyponatremia on admittance. Table 1 showed no association between mortality and hyponatremia (OR 1.03 0.46-2.39) (p=0.93) or between hyponatremia and the need for critical care (OR 1.38 0.59-3.32)(p=0.58) (Table 4.). Fifty three (37%) patients presented serum sodium higher than 130 mEq/L but lower than 135 mEq/L (mild hyponatremia) while twenty two (18.9%) were classified as moderate hyponatremia and only five (4.3%) had severe hyponatremia. Male sex had a higher risk of developing severe disease (OR 3.92 1.25-13.78)(p=0.03). Severity level was associated with less requirement for intensive care (OR 0.35 0.14-0.89) (p=0.025).

Thirty-six patients (31%) required critical care during their hospitalization. The use of amines, mechanical ventilation, sepsis or admission to intensive care were considered as critical care criteria. Twenty (17.2%) required mechanical ventilation support, thirteen (11.2%) required amines, and three (2.5%) were admitted to intensive care. Table 4 shows the association of the variables with the need for critical care. It was observed that having a history of pulmonary tuberculosis (OR 2.68 1.14-6.42) (p = 0.03) or being a carrier of HIV (OR 3.26 1.01-11.49) (p = 0.03) increased the probability of requiring critical care in patients with pulmonary tuberculosis hospitalized.

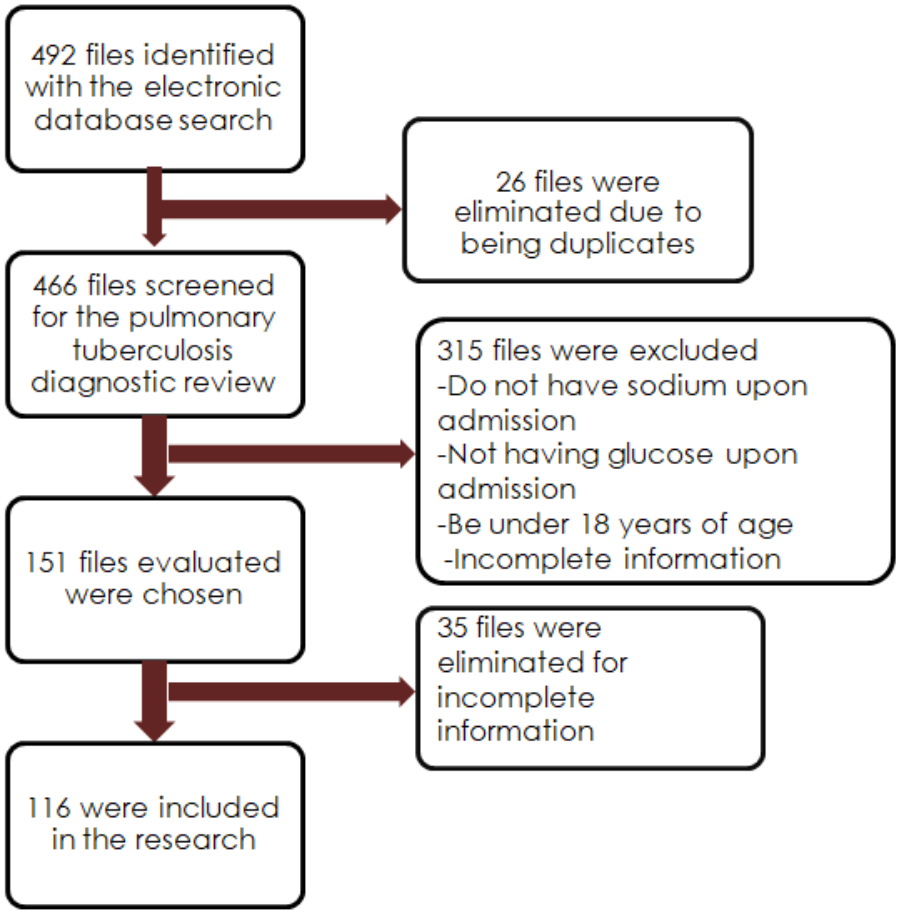

Figure 1. Selection process of clinical records for protocol

Table 1. Summary of Characteristics of Patients with Pulmonary Tuberculosis

Characteristics	Total n=116	Fatal	Non-fatal	% Letality	OR (IC95%)	P
Female	25	7	18	28	Ref	
Male	91	43	48	47.25	2.28 (0.88-6.04)	0 .09
Age	Total	Fatal	No-fatal	% Letalidad	OR	
< 60 years of age	102	43	59	42.16	Ref	
> 60 years of age	14	7	7	50	1.36 (0.43-4.37)	0.58
Diabetes Mellitus	22	6	16	27.27	0.43 (0.14-1.17)	0.097
Hypertension	14	4	10	28.57	0.49 (0.13-1.63)	0.24
Alcoholism	57	19	38	33.33	0.45 (0.21-0.96)	0.03
Drugs	77	33	44	42.86	0.97 (0.44-2.14)	0.94
Tobacco	65	26	39	40	0.75 (0.34-1.59)	0.49
Previous Tuberculosis	30	18	12	60	2.51 (1.07-6.03)	0.03

Human Immunodeficiency Virus	14	10	4	71.4	3.82 (1.14- 14.94)	0.023
Hepatitis C Virus	14	8	6	42.8	1.89 (0.59-6.24)	0.26
Hyponatremia	83	47	36	56.6%	1.03 (0.46-2.39)	0.93
Others	40	17	23	42.5	0.96 (0.44-2.09)	0.92
Antitubercular drugs	89	34	55	38.2	0.43 (0.17-1.03)	0.053
Multidrug resistance	12	6	6	50	1.36 (0.39-4.72)	0.61
Signs and symptoms	14	6	8	42.86	0.97 (0.30-3.07)	0.96
Use of vasopressor amines	13	11	2	84.62	8.87 (2.07-61.59)	<0.001
Sepsis	18	17	1	94.44	32.61(5.54-716.29)	<0.001
Mechanical Ventilation	20	16	4	80	7.17 (2.32-26.73)	<0.001
Intensive Care Unit	3	2	1	66.67	2.69 (0.19-81.02)	0.40
Acute Kidney Injury	22	18	4	81.82	8.55 (2.80-31.66)	<0.001
Acute Hepatic Failure	5	3	2	60	2.03 (0.29-17.64)	0.47
Acute Respiratory Distress Syndrome	43	38	5	88.37	36.76 (12.63124.86)	<0.001
† Pulmonary Thromboembolism	3	1	2	33.3	0.65 (0.02-8.82)	0.58
† Obtained by Fisher's Exact.						

Table 2. Factors associated with hyponatremia in patients with pulmonary tuberculosis

Characteristics	**Total**	**Hyponatremia**	**Without hyponatremia**	**OR (IC95%)**	**p**
Female	25	7	18	Ref	
Male	91	26	65	0.97 (0.34-2.58)	0.96
Age	**Total**	**Hyponatremia**	**Without hyponatremia**	**OR**	**p**
< 60 years of age	102	75	27	Ref	
> 60 years of age	14	8	6	0.48 (0.13-1.85)	0.17
†Diabetes Mellitus	22	13	4	1.99 (0.69-7.42)	0.24
Hypertension	14	10	14	0.99 (0.29-3.91)	0.99

Alcoholism	57	43	14	1.45 (0.64-3.34)	0.36
Illegal drug use	77	55	22	0.98 (0.40-2.30)	0.98
Tobacco	65	48	17	1.29 (0.57-2.93)	0.54
Previous Tuberculosis History	30	23	7	1.42 (0.54-3.73)	0.43
† Human Immunodeficiency Virus	14	13	1	5.88 (0.96-13.22)	0.06
† Hepatitis C Virus	14	12	2	2.60 (0.61-18.03)	0.17
Others	40	32	8	1.94 (0.79-5.10)	0.21
Antitubercular medication	89	65	24	1.35 (0.54-3.41)	0.52
†Multidrug resistance	12	10	2	2.11 (0.79-5.11)	0.28
† Vasopressor amines	13	10	3	1.36 (0.37-6.55)	0.36
† Sepsis	18	13	5	1.04 (0.34-3.52)	0.21
†Mechanical Ventilation	20	17	3	2.56 (0.74-11.68)	0.23
†Intensive Care Unit	3	3	0	2.69 (0.19-81.02)	0.55
Acute Kidney Injury	22	17	5	1.43 (0.49-4.75)	0.51
†Acute Hepatic Failure	5	3	2	0.58 (0.08-5.11)	0.56
Acute Respiratory Distress Syndrome	43	32	11	1.25 (0.34-3.52)	0.94
† Pulmonary Thromboembolism	3	2	1	0.79 (0.03-48.05)	0.63
† Clostridium difficile infection	4	0	4	1.64 (0.5-37.90	0.25

Table 3. Factors Associated with the Requirement of Intensive Care

Characteristics	Total	Non intensive	Intensive	OR (IC95%)	p
Female	25	8	17	Ref	
Male	91	32	59	1.39 (0.54-3.72)	0.73

Age	Total	Non intensive	Intensive	OR	p
< 60 years of age	74	65	9	Ref	
> 60 years of age	45	37	5	0.97 (0.27-3.14)	0.96
† Diabetes Mellitus	22	17	5	0.40 (0.12-1.14)	0.08
Hypertension	15	11	3	0.39 (0.083-1.41)	0.15
Alcoholism	57	37	20	0.73 (0.34-1.56)	0.42
Illegal drug use	77	48	29	0.87 (0.39-1.93)	0.72
Tobacco	65	42	23	0.72 (0.33-1.54)	0.39
Previous Tuberculosis History	30	13	17	2.68 (1.14-6.42)	0.03
† Hepatitis C Virus	14	7	7	1.67 (0.52-5.36)	0.53
†Human Immunodeficiency Virus	14	5	9	3.26 (1.01-11.49)	0.03
Others	40	25	15	0.92 (0.41-2.03)	0.83
Antituberculous drugs	89	55	34	0.90 (0.37-2.22)	0.81
† Multidrug resistance	12	5	7	2.14 (0.69-8.85)	0.14
Hyponatremia	83	49	34	1.38 (0.59-3.32)	0.49
Mild Hyponatremia	45	30	15	0.35 (0.14-0.89)	0.025
Acute Kidney Injury	22	9	13	2.77 (1.07-7.45)	0.03
†Acute Hepatic Failure	5	2	3	2.44 (0.26-30.38)	0.29
Acute Respiratory Distress Syndrome	29	14	15	0.79 (0.31-1.99)	0.61
† Pulmonary Thromboembolism	3	2	1	0.78 (0.02-10.58)	0.66
Signs and symptoms	14	9	5	0.84 (0.24-2.73)	0.39
Death	50	11	39	35.75 (12.05-107.15)	<0.001

DISCUSSION

In our study, the age range of diagnosed cases of pulmonary tuberculosis was 19 to 74 years, with a mean of 40 years and a standard deviation (SD) of 14.70. Male sex had the highest incidence with 78.4% of all cases, similar to the study done by Orozco, where it was estimated at 54.78%, with a mean age of 50.03, (older than our population) and a higher standard deviation.

The age groups of 21 to 30 years and 41 to 50 years were the ones with the highest number of cases with 56.8% of all cases

respectively; observing that the 21 to 30 years group is also the group with the highest percentage of males, representing 28.4% of the total group; while the 41 to 50 years group was 25.8%.

Seventy-seven patients (66.7%) were drug users; sixty-five (56%) admitted smoking tobacco, twenty-two (19%) claimed to have diabetes mellitus and fourteen (12%) had arterial hypertension. Less common were upper gastrointestinal bleeding, chronic kidney disease, gout and spinal cord injury, all with only one case (0.008%) [16]. According to previous studies, past tuberculosis disease was seen in 2.54% of current patients with active pulmonary tuberculosis; meanwhile 25.8% of our patients had a previous history of diagnosed tuberculosis. The difference in the prevalence of previous tuberculosis infection is probably due to the fact that Mexicali is considered an endemic area, differing from the population included by Orozco, whose work studied the migrant population in the United States[2]. Our study shows a higher prevalence of tuberculosis and HIV compared to data reported in other literature, which was 7.5%[2], while we had fourteen (12%). These risk factors were associated with a higher probability of requiring critical care and were associated with a fatal outcome compared to the group that did not have either of these two risk factors.

Fourteen patients (12%) presented symptoms related to hyponatremia. Confusion was the most common symptom found in patients with hyponatremia who received intensive care at an Indian hospital, where the patients were grouped in various etiologies, the main etiology being infectious, of which 57.70% were due to tuberculosis and only 15.3 % cases corresponded to pulmonary tuberculosis, unlike our sample that includes 116 (100%) cases studied with pulmonary tuberculosis compared to only four by Babaliche[15].

Thirty-six patients (31%) required critical care during their hospitalization. The criteria for critical care were the use of vasopressor amines, requirement of mechanical ventilation, the development of sepsis or admission to the intensive care unit. Twenty (17.2%) required mechanical ventilation support, thirteen (11.2%) required some type of vasopressor amines, and three (2.5%) were admitted to the intensive care unit. We noticed that a past history of pulmonary tuberculosis (OR 2.68 1.14-6.42) (p = 0.03) or being a HIV carrier (OR 3.26 1.01-11.49) (p = 0.03) increased the probability of requiring critical care in hospitalized patients with pulmonary tuberculosis.

The present study suggests that acute kidney failure (OR 8.55 2.80-31.66 p=<0.001) and acute respiratory distress syndrome (OR 36.76 12.63-124.86 p=<0.001) are independent risk factors for higher mortality; in addition mechanical ventilation (OR 7.17 2.32-26.73), sepsis (OR 32.61 5.54-716.29) and the need of vasopressor amines (OR 8.87 2.07-61.39) were a risk factor for mortality. Regarding adherence to treatment, it was observed that twenty-seven (23.3%) had poor adherence to their treatment, however this was not associated with higher mortality. (OR 0.43 0.17-1.03) (p = 0.53) This observed poor adherence to treatment is higher than that reported by Martínez et al, who reported 12% of patients had poor adherence to treatment[21].

Although, it has been proven that there could be different causes of hyponatremia in patients with tuberculosis[22], SIADH as an example; antituberculous treatment and immunosuppression[23], as some other comorbidities like hypertension, diabetes, and the use of diuretics, were not analyzed in the previously mentioned study[24]. Based on our findings, we conclude that hyponatremia is prevalent in patients with pulmonary tuberculosis, but it's not related with mortality or the need for intensive care. The severity of hyponatremia was related to the male gender, the choice of treatment and the presence of signs and symptoms of hyponatremia. Pulmonary tuberculosis may induce hyponatremia in several ways, such as invasion of adrenal glands, meningeal disease, SIADH (pulmonary pathway). Thus we encourage evaluating for possible hyponatremia in patients with respiratory conditions, with the goal of avoiding acute changes in serum sodium levels. The prevalence of hyponatremia in our patients is higher than previously reported in past studies, this could be due to the high incidence of pulmonary tuberculosis in our community in Baja California. Some of the limitations of this study were that most of the subjects included in our study were hospitalized at the moment of the diagnosis of pulmonary tuberculosis, meaning that they were patients with possible complications and comorbidities.

REFERENCES

I. Tuberculosis [Internet]. World Health Organization. 2021 [citado 30 agosto 2021]. Available en: https://www.who.int/es/news-room/fact-sheets/detail/tuberculosis

II. Orozco I., Acosta J, Rodriguez G. Martinez F. Enriquez A, Espinoza M, Duran O. & Orozco I. Epidemiología de tuberculosis pulmonar en población migrante. Neumol Cr Torax. 2018.

III. Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison´s principles of internal medicine. Vol 1 18th ed. New York: Mc Graw Hill; 2013; 648-661.

IV. Westwater JO, Stteven D, Garry RC. A note on the serum sodium level in patients suffering from tuberculosis. *Clin Sci* 4:73-77, 1939

V. SIMS EA, WELT LG, ORLOFF J, NEEDHAM JW. Asymptomatic hyponatremia in pulmonary tuberculosis. J Clin Invest. 1950 Jun;29(6):846-7. PMID: 15436829.

VI. Weiss H, Katz S. Hyponatremia resulting from apparently inappropriate secretion of antidiuretic hormone in patients with pulmonary tuberculosis. *Amer Rev Resp Dis* 92:609-616, 1965. doi:

10.1164/arrd.1965.92.4.609.

VII. SHALHOUB, R. J. *The Mechanism of Hyponatremia in Pulmonary Tuberculosis. Annals of Internal Medicine, 70(5), 943*. doi:10.7326/0003-4819-70-5-9

VIII. Chung D. Hyponatremia in untreated active pulmonary tuberculosis. American Review of Respiratory Disease. Vol 99: 595-596. 1969. doi: 10.1164/arrd.1969.99.4P1.595.

IX. DeFronzo RA, Goldberg M, Agus ZS. Normal diluting capacity in hyponatremic patients. Reset osmostat or a variant of the syndrome of inappropriate antidiuretic hormone secretion. Ann Intern Med. 1976 May;84(5):538-42. doi: 10.7326/0003-4819-84-5-538.

X. Hill R, Uribarri J, Mann J, Berl T. Altered water metabolism in tuberculosis. Role of Vasopressin. The American Journal of Medicine. Vol 88: 357-364. 1990. doi: 10.1016/0002-9343(90)90489-z.

XI. Vorherr H. Massry SG, Fallet R, Kaplan L. Kleeman CR. Antidruretic principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatremia. Ann Intern Med. 72: 383-387. 1970. doi: 10.7326/0003-4819-72-3-383

XII. Baran D,HutchinsonTA: The outcome of hyponatremia in general hospital population.clin nephrol. 22:72-76. 1984

XIII. Bennani SL,Abouqal R,Zeggwagh AA,Madani N,Abidi K et al. incidence,causes & prognostic factors of hyponatremia in intensive care. rev med interne 24(4):224-9. 2003. doi: 10.1016/s0248-8663(02)00811-1.

XIV. Sharma SK, Mohan A, Banga A, Saha PK, Guntupalli KK. Predictors of development and outcome in patients with acute respiratory distress syndrome due to tuberculosis. *Int J Tuberc Lung Dis*.10(4):429-35. 2006. doi: 10.1186/1471-2334-12-121

XV. Babaliche P, Madnani S, Kamat S. Clinical profile of patients admitted with hiponatremia in the medical intensive care unit. Indian J Crit Med. 21:819-24.2017

XVI. Jafari N, Izadi M, Sarrafzadeh F, Heidari A, Ranjbar R, Saburi A. Hyponatremia due to pulmonary tuberculosis: Review of 200 cases. Nephro Urol Mon. 5(1): 687-91. 2013

XVII. Underwood J, Cresswell F, Salarm A, Keely A, Clelad C & John L. Complications of miliary tuberculosis: low mortality and predictive biomarkers from UK cohort. Infectious Diseases.17:295-302. 2017

XVIII. Llamas-Lopez A, Vargas T & Maya R. Hyponatremia incidence and its Association With Mortality in Patients With Tuberculosis. Poster Abstracts OFID. Vol. 5: pg283. 2018. doi: 10.1093/ofid/ofy210.798

XIX. Singla A, Raghu B, Gupta A, Caminero J, Sethi P, Tayal O, Chakraborty A & Migliori G. Risk factors for early mortality in patients with pulmonary tuberculosis admitted to the emergency room. Pulmonol. No 8: Pg 1444-1452 2020. doi: 10.1016/j.pulmoe.2020.02.002. Epub 2020 Feb 29.

XX. Hashimoto M et all. Mild Lung Tuberculosis in a Patient Sufferin from Status Epilepticus Caused by the Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH). Intern Med 56: 429-433, 2017.

XXI. Martínez-Hernández YO, Guzmán-López F, Flores-Pulido JJ, Vázquez-Martínez VH. Factores familiares que favorecen el apego al tratamiento en casos de tuberculosis pulmonar. Aten Fam. 21(2):47-49.2014

XXII. Luies L, du Preez I. The Echo of Pulmonary Tuberculosis: Mechanisms of Clinical Symptoms and Other Disease-Induced Systemic Complications. Clin Microbiol Rev. 2020 Jul 1;33(4):e00036-20. doi: 10.1128/CMR.00036-20. PMID: 32611585; PMCID: PMC7331478.

XXIII. Olalekan A., Oluwaseun F., Oladele H. & Akeem A. (2015) Evaluation of electrolyte imbalance among tuberculosis patients receiving treatments in Southwestern Nigeria, Alexandria Journal of Medicine, 51:3, 255-260, DOI: 10.1016/j.ajme.2014.10.003

XXIV. Cerda-Esteve, Mariana, Agustín Ruiz-González, Mindaugas Gudelis, Albert Goday, Javier Trujillano, Elisa Cuadrado, y Juan Francisco Cano. «Incidencia de la hiponatremia y de sus causas en pacientes neurológicos». *Endocrinología y Nutrición* 57, n.º 5 (2010): 182-86.https://doi.org/10.1016/j.endonu.2010.02.009.