The Incidence and Risk Factors of Hyponatremia in Pulmonary Tuberculosis

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Abstract
Context: The syndrome of inappropriate antidiuresis (SIAD) with euvolemic hyponatremia may occur in patients with pulmonary tuberculosis (PTB), but little is known about the clinical characteristics of SIAD-associated hyponatremia in PTB patients.

Objective: This study aimed to investigate the frequency and risk factors of hyponatremia in PTB patients.

Methods: In this retrospective chart review, we examined the incidence and severity of hyponatremia in PTB patients. Multivariate analysis was conducted to identify risk factors for hyponatremia in PTB patients.

Results: Of the 161 patients who were screened, after excluding patients with hyperglycemia and renal failure, we enrolled and analyzed data from 113 participants. Hyponatremia occurred in 40.7% patients (<135 mEq/L). Univariate analysis revealed that the presence of hyponatremia was associated with old age, female sex, low body mass index, high glycosylated hemoglobin, C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide. Multivariable analysis indicated that hyponatremia was strongly associated with old age (odds ratio, 1.06; 95% CI, 1.03-1.09 for every 1-year age increase) and CRP values (odds ratio, 1.15; 95% CI, 1.03-1.30 for every 1-mg/dL increase in CRP). For 86 patients with blood cortisol measurements, the cortisol level was significantly high in the hyponatremia group.

Conclusions: Hyponatremia was less frequently associated with hyperglycemia, heart failure, renal failure, and other diseases that cause euvoletic hyponatremia; thus, PTB patients may have euvoletic hyponatremia due to SIAD. Administration of hypertonic saline or fluid restriction should be considered in PTB patients with hyponatremia.

Key Words: pulmonary tuberculosis, hyponatremia, syndrome of inappropriate antidiuresis

The syndrome of inappropriate antidiuresis (SIAD) arises from an imbalance between sodium and water due to insufficient water diuresis, and results in hyponatremia (1). Patients with respiratory diseases, such as pneumonia, can precipitously present with SIAD-induced hyponatremia (2, 3). In many patients with pneumonia, the diagnosis is often limited to mild hyponatremia. However, severe hyponatremia may occur in some cases, leading to neurological symptoms, such as disorientation, headache, and even life-threatening cerebral edema.

Patients with pulmonary tuberculosis (PTB) may develop SIAD (4), and previous studies have shown an association between hyponatremia and increased mortality risk in PTB patients (5, 6). A major concern in SIAD is that the administration of isotonic saline infusion may worsen hypertonic hyponatremia via the “desalination” phenomenon (7, 8). Hypertonic saline is preferred, and the patient’s fluid intake should be limited. Therefore, understanding the frequency and risk factors for hyponatremia in PTB patients is a crucial factor for improving their clinical outcomes. In particular, the extent to which pneumonia may exacerbate hyponatremia in PTB patients remains unclear. Therefore, this study aimed to investigate the incidence and risk factors of hyponatremia in PTB patients.

Materials and Methods
Study Design
We conducted a retrospective chart review at the International University of Health and Welfare Ichikawa Hospital, which had 45 allocated beds for PTB cases in 2019, to identify and enroll PTB patients who were hospitalized because of persistent productive cough and were subsequently discharged and treated as outpatients between January 1 and December 31, 2019, regardless of the admission date. The PTB diagnosis in all participants were confirmed by a positive result for tuberculosis in the sputum smear culture or on the polymerase chain reaction test. PTB patients are always admitted to a specialized hospital for a more extended period (on average, 2-3 months) to prevent the spread of tuberculosis. Of the 161 patients with PTB in 2019, the following patients were excluded from the analysis: (i) patients using antidiabetes
medication, (ii) those with nonfasting blood glucose level \( \geq 200 \, \text{mg/dL} \) or glycosylated hemoglobin (HbA1c) \( \geq 6.5\% \) on admission, and (iii) those with chronic kidney disease with estimated glomerular filtration rate (eGFR) \(< 30 \, \text{mL/min/1.73 m}^2\). In addition, we excluded patients without N-terminal pro-brain natriuretic peptide (NT-proBNP) test results on admission, as this value is necessary to evaluate the association with heart failure (Fig. 1).

We extracted data for the minimum blood sodium concentration during hospitalization, C-reactive protein (CRP) concentration, baseline test values of eGFR, HbA1c, NT-proBNP on admission, age, body mass index (BMI), and the medicines used. The CRP value that was selected was aligned with the lowest blood sodium level that was recorded.

First, we defined hyponatremia and severe hyponatremia as a blood sodium concentration \(< 135 \, \text{mEq/L} \) and \( \leq 125 \, \text{mEq/L} \), respectively, and determined the frequency of hyponatremia. Subsequently, we subgrouped the patients according to the presence or absence of hyponatremia. We assessed the difference of each parameter in the univariate analysis, which was followed by multivariate analysis using 3 parameters that were selected as the most relevant variables by Lasso regression analysis. Finally, we investigated whether there was a difference in blood cortisol levels depending on the presence or absence of hyponatremia in patients whose blood cortisol levels were measured at the time of admission.

This study was approved by the local ethics committee of the International University of Health and Welfare Ichikawa Hospital (approval no. 126), which follows the principles of the Declaration of Helsinki.

### Outcome Measures

The following independent variables that are considered to be associated with hyponatremia were investigated: sex (a dichotomous variable); BMI (kg/m\(^2\)); CRP (mg/dL) at the same time the patient had their lowest blood sodium concentration; age at admission; the number of current medications used that are known to cause hyponatremia, including angiotensin-converting enzyme inhibitors, aldosterone receptor blockers (ARBs), thiazide diuretics, psychotropic drugs, and proton-pump inhibitors (PPIs); eGFR (mL/min/1.73 m\(^2\)); HbA1c (\%); NT-proBNP (pg/mL); and cortisol (µg/dL).

### Statistical Analysis

For the statistical analysis, we used R version 4.1.3 (The R Foundation for Statistical Computing Platform, https://www.r-project.org).

We evaluated whether there were significant intergroup differences for each of the study variables. In the univariate analysis, the significance of categorical variables (number of current medications related to hyponatremia and sex) was tested using Pearson’s chi-square test with Yates’ continuity correction. For continuous variables, the normal distribution of data was first confirmed using the Shapiro-Wilk test, and then homoscedasticity was examined by the F-test. We used the student’s t-test for parameters with normal distribution and intergroup homoscedasticity (eg, eGFR) and the Mann-Whitney U test for parameters without normal distribution (eg, age, BMI, CRP, HbA1c, and NT-proBNP). The variables were selected using the least absolute shrinkage and operator (Lasso) regression analysis in the multivariable analysis. The log (lambda) that achieves the minimal binomial deviance was estimated by cross-validation for selecting the most relevant variables.

### Antibodies and Immunoassays

Elecsys Cortisol II (Roche Diagnostics Asia Pacific, Singapore, antibody ID: AB_2802131) for cortisol measurement and an AVP kit (Yamasa, Chiba, Japan, antibody ID: AB_2801274) for vasopressin were used in this study.

### Results

From a review of the medical records, we selected 161 patients who were discharged in 2019 from the International University of Health and Welfare Ichikawa Hospital (Fig. 1). We excluded 37 patients who were receiving diabetes medication or had hyperglycemia with random blood glucose \( \geq 200 \, \text{mg/dL} \) or HbA1c \( \geq 6.5\% \) on admission. Subsequently, patients in renal failure (eGFR \(< 30 \, \text{mL/min}; \, n = 4\) and patients without NT-proBNP measurements (n = 7) were excluded. The remaining 113 patients were enrolled and their data were included in the analysis.

We examined the distribution of the lowest serum sodium concentration during hospitalization in the study patients (Fig. 2). Of the 113 participants, 46 (40.7\%) had a blood sodium concentration of less than 135 mEq/L and 3 (2.65\%) had severe hyponatremia (125 mEq/L or less).

Table 1 summarizes the patients’ information, including the total number of patients selected (113), with 70 men (61.9\%) and 43 women (38.1\%). The median age was 71 years, and the interquartile range was 50 to 85 years. The average BMI was 19.37 \pm 2.98, and the concomitant use of drugs associated with hyponatremia was observed in 34.5\%. One patient used 3 types of medicines: a PPI, an aldosterone antagonist, and a psychotropic drug. PPIs and ARBs were more frequently used in patients who were on 2 types of drugs that are associated with hyponatremia (n = 6 each, for ARB and PPI). The mean eGFR in the selected patients was 84.47 mL/min/1.73 m\(^2\) (SD = 28.00). The median and the interquartile ranges for NT-proBNP, HbA1c, and CRP were 203.00 pg/mL (50.00-844.00), 5.80% (5.50-6.10), and 2.50 mg/dL (0.32-6.39), respectively. The median and interquartile range for the lowest blood sodium concentration during the hospitalization was 136.00 mEq/L (132.00-138.00).

Table 2 shows the univariate and multivariate analyses for each predictor of hyponatremia. We divided the study participants into groups with serum sodium levels \(< 135 \, \text{mEq/L} \) (hyponatremia, n = 46) and no hyponatremia (n = 67). In the univariate analysis, the participants in the hyponatremia group were significantly older (hyponatremia vs no hyponatremia; 84 vs 58 years, \( P < 0.001 \)), were more likely to be female (50% vs 29.9%, \( P = 0.049 \)) and had lower BMI (18.74 vs 19.54, \( P = 0.019 \)).

In the multivariate analysis, we investigated the parameters involved in the onset of hyponatremia. As there were only 46 participants in the hyponatremia group, we could choose only 4 parameters as the explanatory variables. Therefore, we performed a variable selection using Lasso regression analysis. As shown in Figure 3, the log (λ) that achieves the minimal binomial deviance was estimated by cross-validation, resulting in the \( λ = 0.0604705 \). Using this λ, the best combination of variables, age, CRP, and HbA1c were selected by
Lasso logistic regression analyses (Table 3). We found that hyponatremia was significantly associated with age and CRP levels (Table 2). For the age parameter, the odds ratio was 1.06 (95% CI, 1.03-1.09; \( P < 0.001 \)) for every 1-year of age increase. For CRP, the odds ratio was 1.15 (95% CI, 1.03-1.30; \( P = 0.019 \)) for every 1-mg/dL CRP increase.

Next, we investigated the involvement of adrenal insufficiency in hyponatremia in patients with PTB. Unfortunately, of the 113 participants, cortisol measurements were available for only 86. Therefore, we assigned the 86 patients with serum cortisol measurements at admission into the hyponatremia (\( n = 34 \)) and no hyponatremia (\( n = 52 \)) groups (Table 4). In univariate analysis, the hyponatremia group had a significantly high number of current medication associated with hyponatremia and included those who were old, had low BMI, and had high CRP, HbA1c, and NT-proBNP levels. The blood cortisol levels were unexpectedly high in the hyponatremia group (Table 4 and Fig. 4). Conversely, there was no significant difference according to sex and eGFR.

On evaluating the case with the lowest blood sodium level, a 73-year-old woman with a BMI of 18.5 kg/m^2 and on antihypertensive medication (azilsartan) and a PPI (vonoprazan) for

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**Table 1. Patient characteristics**

| Factor                          | Group Overall |
|--------------------------------|---------------|
| n                              | 113           |
| Sex, %                         |               |
| Male                           | 70 (61.9)     |
| Female                         | 43 (38.1)     |
| Age, median (IQR)              | 71 (50, 85)   |
| BMI, kg/m^2, mean (SD)         | 19.37 (2.98)  |
| Medicines, n (%)               |               |
| 0                              | 74 (65.5)     |
| 1                              | 27 (23.9)     |
| 2                              | 11 (9.7)      |
| 3                              | 1 (0.9)       |
| eGFR, mL/min/1.73 m^2, mean (SD)| 84.47 (28.00) |
| NT-proBNP, pg/mL, median (IQR) | 203.00 (50.00, 844.00) |
| HbA1c, %, median (IQR)         | 5.80 (5.50, 6.10) |
| CRP, mg/dL, median (IQR)       | 2.50 (0.32, 6.39) |
| Lowest sodium value, mEq/L, median (IQR) | 136.00 (132.00, 138.00) |

For the categorical variable, such as sex and number of medicines, the total number and the percentage of each group are shown. The continuous variables with a normal distribution (BMI, eGFR) are expressed as mean and SD. For continuous variables that exhibit a nonnormal distribution, the median and the IQR (Q1, Q3) are presented.

Abbreviations: BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide.
### Table 2. Univariable and multivariable predictors of hyponatremia

| Variable                                   | Univariable predictors | P-value | Multivariable predictors |
|--------------------------------------------|------------------------|---------|--------------------------|
|                                            | Hyponatremia (n = 46)  |         |                          |
|                                            | No hyponatremia (n = 67)|         |                          |
| Demographic characteristics               |                        |         |                          |
| Age, years, median (IQR)                   | 84 (71, 89)            | <0.001  | 1.06 (1.03-1.09)         |
|                                            | 58 (45, 79.5)          |         | <0.001d                  |
| Female sex, %                              | 50.0                   |         |                          |
|                                            | 29.9                   | 0.049a  |                          |
| BMI, kg/m², median (IQR)                   | 18.74 (16.85, 20.26)   |         | 0.019b                   |
|                                            | 19.54 (18.17, 21.88)   |         |                          |
| Medicines used associated with hyponatremia, |                        |         |                          |
| n, (%)                                     | 24 (52.2)              |         |                          |
|                                            | 50 (74.6)              |         |                          |
|                                            | 15 (32.6)              |         |                          |
|                                            | 4 (6.0)                |         |                          |
|                                            | 0 (0.0)                |         |                          |
| Blood chemistry                            |                        |         |                          |
| Lowest sodium value, median (IQR)          | 131 (128, 132)         | <0.001c |                          |
|                                            | 138 (136, 139)         |         |                          |
| HbA1c, %, median (IQR)                     | 5.85 (5.70, 6.20)      | 0.013d  | 1.94 (0.51-7.85)         |
|                                            | 5.70 (5.40, 6.05)      |         | 0.3d                     |
| CRP, mg/dL, median (IQR)                   | 3.81 (2.07, 8.86)      | <0.001c | 1.15 (1.03-1.30)         |
|                                            | 1.07 (0.13, 3.79)      |         | 0.019d                   |
| NT-proBNP, pg/mL, median (IQR)             | 545.50 (208.00, 1113.25)| <0.001c |                          |
|                                            | 80.00 (24.00, 300.00)  |         |                          |
| eGFR, mL/min/1.73 m², mean (SD)            | 80.22 (31.81)          |         | 0.182b                   |
|                                            | 87.39 (24.89)          |         |                          |

Patients were divided into those with blood sodium levels < 135 mEq/L (hyponatremia) and others (no hyponatremia). For the categorical variable, such as sex and number of medicines, the total number and the percentage of each group are shown. The continuous variables with a normal distribution (BMI, eGFR) are expressed as mean and SD. For continuous variables that exhibit a nonnormal distribution, the median and the IQR [Q1, Q3] are presented. Abbreviations: BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide.

*In the univariable analysis, the categorical variables (number of drugs in use related to hyponatremia and sex) were tested using the chi-squared test with Yates’ continuity correction.*

*We used the Mann-Whitney U test for continuous variables that did not show a normal distribution and used the median, minimum, and maximum values to describe their distribution.*

*Since eGFR showed a normal distribution in each group and determined homoscedasticity, we used the student’s t-test and its mean and SD to show the distribution.*

*In the multivariate analysis, because the smaller group (hyponatremia) had only 46 patients, logistic regression analysis was performed using 4 explanatory variables with a lower P-value in the univariate analysis, including age, HbA1c, CRP, and NT-proBNP.*

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**Figure 3.** Cross-validated log-likelihood deviance. The horizontal and the vertical axes show the log ($\lambda$) and the binomial deviance, respectively. The figures on the upper row indicate the number of variables to be selected corresponding to each log ($\lambda$).
reflux esophagitis, we found that the patient was delirious at the onset of hyponatremia and was given the antipsychotic drug haloperidol, which can also cause SIADH (9). When the blood sodium level decreased to 115 mEq/L, her plasma osmolality was 234 mOsm/kg/H₂O. However, her urinary osmolality was inappropriately elevated to 506 mOsm/kg/H₂O, and her vasopressin level was inappropriately elevated to 1.3 pg/mL (Table 5). In addition, we found that the patient drank a large amount of water because her low urinary output was misconstrued as arising from dehydration, for which she was administered a normal saline infusion that worsened her hyponatremia.

Discussion

This study found that hyponatremia developed in 40.7% of PTB patients. This is comparable to the incidence of hyponatremia in patients hospitalized for severe coronavirus disease (COVID-19; 45.8%) (10). In addition, 3 patients (2.7%) presented with severe hyponatremia (<125 mEq/L) and, in 1 case, the blood sodium concentration decreased to 115 mEq/L. As shown in Table 2, the univariate analysis demonstrated that age, HbA1c, CRP levels at the time of hyponatremia, and NT-proBNP values were significantly high and BMI was significantly low in the hyponatremia group. However, multivariate analysis indicated that HbA1c and NT-proBNP levels were not associated with worsening hyponatremia. This illustrates that older adults and those with high CRP levels are more likely to have hyponatremia. However, since eGFR decreases and NT-proBNP increases with higher age in general (11), the eGFR and NT-proBNP effects on hyponatremia could have been diluted by the age factor in multivariable analysis. Therefore, they might not have been detected as significant explanatory variables. The following 4 mechanisms are considered the leading causes of hyponatremia in older adults: (i) Medicines associated with hyponatremia, such as thiazide diuretics, are more commonly used (12); (ii) they tend to have

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Table 3. Variable selection by Lasso regression analysis using the estimated λ

| Factors          | Regression coefficient |
|------------------|------------------------|
| Intercept        | 3.72149559             |
| Age              | -0.03623420            |
| CRP              | -0.06482085            |
| HbA1c            | -0.09957772            |
| Sex              | -                      |
| BMI              | -                      |
| No. of Medicines | -                      |
| eGFR             | -                      |
| NT-proBNP        | -                      |

When Lasso regression analysis was performed using \( \lambda = 0.064705 \) estimated from Figure 3, 3 variables, such as age, CRP, and HbA1c, were selected as the best combination. Abbreviations: BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 4. The univariable analysis in patients with serum cortisol

| Factor                              | Univariate predictors | P-value |
|-------------------------------------|-----------------------|---------|
|                                    | Hyponatremia (n = 34) | No hyponatremia (n = 52) |         |
| Lowest sodium value, mEq/L, median (IQR) | 130.50 (127.25, 132.00) | 138.00 (136.00, 139.00) | <0.001\(^a\) |
| Medicines used associated with hyponatremia, n (%) | 0 17 (50.0) | 43 (82.7) | 0.002\(^a\) |
|                                      | 1 11 (32.4) | 8 (15.4) |
|                                      | 2 6 (17.6) | 1 (1.9) |
| Sex, %                              | F 17 (50.0) | 15 (28.8) | 0.068\(^a\) |
|                                      | M 17 (50.0) | 37 (71.2) |
| eGFR, mean (SD)                     | 81.65 (31.71) | 90.13 (24.36) | 0.165\(^c\) |
| Age, median (IQR)                   | 84.50 (71.00, 90.00) | 51.00 (43.00, 69.25) | <0.001\(^b\) |
| BMI, kg/m², median (IQR)            | 18.81 (16.89, 20.26) | 9.39 (18.18, 22.41) | 0.035\(^b\) |
| CRP, mg/dL, median (IQR)            | 3.91 (2.07, 8.86) | 1.12 (0.17, 3.87) | 0.001\(^b\) |
| HbA1c, %, median (IQR)              | 5.95 (5.70, 6.20) | 5.70 (5.40, 6.00) | 0.003\(^b\) |
| NT-proBNP, pg/mL, median (IQR)      | 545.50 (230.75, 1113.25) | 63.50 (21.75, 205.75) | <0.001\(^b\) |
| Cortisol, µg/dL, median (IQR)       | 17.85 (14.10, 21.78) | 12.20 (10.29, 15.70) | <0.001\(^b\) |

Eighty-six patients with blood cortisol levels measured at admission were divided into blood sodium levels <135 mEq/L (hyponatremia) and others (no hyponatremia). For the categorical variable, such as sex and number of medicines, the total number and the percentage of each group are shown. The continuous variables with a normal distribution (BMI, eGFR) are expressed as mean and SD. For continuous variables that exhibit a nonnormal distribution, the median and the IQR [Q1, Q3] are presented. Abbreviations: BMI, body mass index; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide.

\(^a\)Categorical variables (number of drugs in use and sex) were tested using the chi-squared test with Yates’ continuity correction.

\(^b\)The Mann-Whitney U test examined variables that did not show a normal distribution.

\(^c\)Since eGFR showed a normal distribution in each group and the 2 groups revealed homoscedasticity, we used student’s t-test to determine the significant difference between groups.
may occur in those with low glomerular filtration rate (GFR) when they are taking a diet low in sodium and high in liquid, such as tea and coffee. Decreased GFR and chronic salt deficiency increase water reabsorption, and if concomitant water intake exceeds the renal water excretion capacity, it will result in diluted hyponatremia (15).

As some studies have attributed SIAD to hyponatremia associated with pneumonia (2, 3), we investigated the relationship between tuberculous pneumonia and hyponatremia due to SIAD. In general, SIAD is a diagnosis of exclusion (16–18). First, it is essential to rule out pseudohyponatremia, such as hypertonic and isotonic hyponatremia. Isotonic hyponatremia is typically seen in patients with severe hypertriglyceridemia and increased gamma-globulin levels in patients with multiple myeloma, which were not present in our review of medical records. Hypertonic hyponatremia includes hyperglycemic conditions and the use of sugar alcohols, including mannitol or glycerol, which are generally used to reduce brain edema. This study excluded patients with pronounced hyperglycemia and those taking diabetic medications to exclude hypertonic hyponatremia (Fig. 1). In addition, we did not see a significant difference in HbA1c between groups in the multivariable analysis, although HbA1c levels were higher in the hyponatremia group in the univariate analysis (Table 2), suggesting that hyperglycemia is less associated with hyponatremia in PTB patients. The medical records confirmed that no other complications were present that could lead to pseudohyponatremia.

In hypotonic hyponatremia (true hyponatremia), it is essential to differentiate hypovolemic and hypervolemic conditions from euvolemma. Hypovolemic hyponatremia involves dehydration, vomiting, diarrhea, and the use of antihypertensives, including thiazide diuretics (17), angiotensin-converting enzyme inhibitors (19–22), ARBs (22, 23), and mineralocorticoid receptor blockers (24, 25), although in some cases these medications may cause euvolemic-hypotonic hyponatremia. Regarding the use of drugs related to hyponatremia, there was no significant difference between the hyponatremia and no-hyponatremia groups in the univariate analysis (Table 2). The proportion of drug use associated with hyponatremia was higher in the hyponatremia group (47.8%) than in the no-hyponatremia group (25.4%). Among the medicines used, ARBs and PPIs were the most frequent. However, no statistically significant difference was found in the overall comparison in the univariate analysis (Table 2). Nevertheless, the analysis is based on the assumption that the effect of each drug on hyponatremia is equivalent; therefore, the possibility that 1 medication is significantly more effective in causing hyponatremia than the other cannot be ruled out. In addition, we had an insufficient number of patients to evaluate the independent risk of each drug in inducing hyponatremia.

Moreover, exclusion of hypervolemic hyponatremia is crucial for the diagnosis of SIAD. Hypervolemic hyponatremia includes heart failure, liver cirrhosis with ascites retention, nephrotic syndrome, and renal failure. None of the patients had liver cirrhosis in the medical records in this study. We excluded patients with an eGFR <30 mL/min and performed univariate and multivariable analyses using eGFR and NT-proBNP as surrogate markers for renal function and heart failure, respectively. We did not observe a significant difference in these parameters between the groups (Table 2).

In general, SIAD must be distinguished from other causes that induce euvolemic-hypotonic hyponatremia.
Euvoletic-hypotonic hyponatremia includes adrenal insufficiency, psychogenic polydipsia, beer potomania, and exercise-associated hyponatremia other than SIAD. Furthermore, adrenal failure may often be a problem in patients with severe PTB if the adrenal glands are bilaterally impaired (26). The tuberculosis drug rifampicin can cause an adrenal crisis by altering cortisol metabolism (27, 28). Therefore, it is essential to rule out adrenal insufficiency in the diagnosis of SIAD in patients with PTB. Unfortunately, we could only measure cortisol levels in 86 patients among a total of 113 patients, but we analyzed the difference in cortisol levels between groups. Although we only had baseline cortisol levels recorded at admission, the univariate analysis showed significantly high cortisol levels in the hyponatremia group (Table 3 and Fig. 3), suggesting the negligible involvement of adrenal insufficiency in PTB-associated hyponatremia; instead, the cortisol levels might have been high as a result of stressful conditions in the hyponatremia group.

Moreover, multiple drugs such as PPIs and psychotropic drugs can induce SIAD (29-32). The reason that PPIs cause SIAD is unclear. In contrast, it has been suggested that increased expression of water channel aquaporin-2 in the inner medullary collecting duct cells, via vasopressin V2-receptor/cAMP/protein kinase A signaling, may cause SIAD in psychotropic drug-treated animals (33). As mentioned, assuming that the effects of each drug on hyponatremia were equivalent, we did not observe any difference in the number of medications related to hyponatremia between the groups (Table 2).

This study has some limitations. First, this cross-sectional study describes the significant characteristics of PTB patients who develop hyponatremia; however, the causal relationship between elevated CRP, increased age, and hyponatremia remains unclear, because a longitudinal study would be required to ascertain this relationship. Second, factors such as cardiac and renal functions, which generally worsen with age, or the number of medicines used, which typically increase with age, may be underestimated because age was a confounding factor. Third, there may have been selection bias as this study was conducted at a facility specializing in PTB patients requiring hospitalization. We excluded patients with apparent diabetes and renal failure, and we limited the study to patients who underwent NT-pro BNP and cortisol tests. Fourth, it is possible that measurement errors may have occurred, especially in regard to blood test items, such as sodium and CRP levels, because this study was based on a single measurement of these items. Finally, it is unclear whether the results of this study can be generally applied to patients with PTB, given the aforementioned limitations.

In summary, patients with PTB who are older and have an increased CRP level are likely to have hyponatremia. Patients with infectious diseases, such as PTB, generally have neutrophilia and fever before their CRP increases (34). Therefore, it is essential to focus on the drugs that have a high risk of causing hyponatremia and the administration of relatively hypotonic infusion in older patients with inflammation. Blood glucose, cardiac, renal, and adrenocortical function and the number of medications in use are less associated with hyponatremia, suggesting that these patients most likely have euvoletic hyponatremia due to SIAD. Other reports have shown that older people are more likely to develop SIAD (12, 35), and SIAD is more likely to occur in pneumonia, including PTB (2-4). Our results are consistent with these reports. However, in the case where the blood sodium level declined to 115 mEq/L (CRP = 3.69 mg/dL at that time), the 73-year-old woman was diagnosed with SIAD despite having only slight consolidation on the chest X-ray and without exacerbation of pneumonia requiring oxygen supply. This suggests that the systemic inflammation, rather than the lung lesion itself, might have exacerbated her SIAD. Furthermore, it has been reported that the inflammatory cytokine interleukin-6 promotes vasopressin secretion in an osmolality-independent manner (36). However, in this case, various other factors, such as the use of ARBs, PPIs, psychotropic drugs, psychogenic polydipsia, concomitant vomiting, and saline infusion, may have aggravated hyponatremia. Regardless, we need special care to treat hyponatremia associated with SIAD, and in that case, administration of normal saline may have worsened the condition. Fluid restriction (generally 15-20 mL/kg/day) or treatment with hypertonic saline is a safer method for treating hyponatremia. Therefore, we need to pay more attention to the onset of hyponatremia, especially in older patients and those with exacerbated inflammation and PTB.

Acknowledgments
We would like to thank Editage (www.editage.com) for English-language editing.

Funding
This research was supported by the Ministry of Health, Labour, and Welfare of Japan (grant no. H30-nanchippan-009; recipient: Minoru Takemoto).

Disclosures
The authors declare that they have no competing interests.

Data Availability
Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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