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The association between serum sodium levels and tuberculous meningitis compared to viral and bacterial meningitis: Multicenter retrospective cohort study

Seunghee Na
Incheon St. Mary's Hospital
Taewon Kim (kimtaewon79@gmail.com)
Incheon St. Mary's Hospital
In-Uk Song
Incheon St. Mary's Hospital
Sung-Woo Chung
Incheon St. Mary's Hospital
Seong-Hoon Kim
Uijeongbu St. Mary's Hospital
Yoon-Sang Oh
Yeouido St. Mary's Hospital
Juhee Oh
St. Vincent's Hospital
Woojun Kim
Seoul St. Mary's Hospital

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Abstract

We evaluated the association between hyponatremia and tuberculous meningitis (TBM) in hopes of providing additional information for the differential diagnosis of TBM from other types of infectious meningitis, especially from viral meningitis (VM). Cross-sectional and longitudinal data involving 5,026 participants more than 18 years of age were analyzed in the total population and the propensity-matched population. The initial and lowest sodium levels and longitudinal changes in TBM, VM, and bacterial meningitis (BM) patients were compared. The initial serum sodium levels were significantly lower in the TBM patients than in the VM and BM patients (136.9 ± 5.9 vs. 139.0 ± 3.1, $p < 0.001$ for TBM vs. VM, and 138.3 ± 4.7 mmol/L and $p < 0.001$ for TBM vs. BM) and it dropped significantly more steeply to lower levels in both the TBM and BM patients compared to the VM patients. Consequently, the lowest serum sodium levels were in the order of the TBM < BM < VM patients, which were also statistically significant in all subgroups. (131.8 ± 6.4, 133.1 ± 5.1, 137.4 ± 3.7, respectively, $p < 0.001$). The participants with lower serum sodium levels were more likely to have a diagnosis of TBM rather than VM, and this association was more pronounced for the lowest sodium levels than the initial sodium levels (OR 8.4 (95% CI: 4.5–15.8, $p < 0.001$)). The baseline and longitudinal evaluation of serum sodium levels can provide supportive information for the differential diagnosis of TBM from VM or BM.

Introduction

Tuberculosis remains a global health problem, with an estimated 10.4 million cases and 1.8 million deaths in 2015 [1]. Tuberculous meningitis (TBM) accounted for 6% of the 57,217 extrapulmonary tuberculosis cases in a large epidemiology study [2]. Even considering that a diagnosis of TBM is difficult to ascertain and, therefore, the incidence rate might be underestimated, the global burden of TBM is estimated to be at least 100,000 cases per year [3]. TBM is the most lethal form of tuberculosis, resulting in death or severe disability in around 50% of the affected patients [4], whereas most of the aseptic viral meningitis (VM) patients have a self-limiting, good prognosis without any neurological sequelae. Therefore, the rapid differential diagnosis of TBM from other types of infectious meningitis and prompt optimal treatment are crucial in preventing the devastating neurological sequelae of TBM including tuberculoma formation, cranial nerve dysfunction, hydrocephalus, and vascular complications including stroke. However, the diagnosis of TBM is often challenging and delayed by inconclusive laboratory results due to the low sensitivity and slow speed of conventional bacteriology tests, similar cerebrospinal fluid (CSF) profiles between VM and TBM, as well as the indolent clinical onset with initial non-specific symptoms [5], which are indistinguishable from the early symptoms of VM.

Hyponatremia is a common finding in acute brain disease [6]. It is common in patients with traumatic brain injury, subarachnoid hemorrhage, and brain tumors, and patients who underwent intracranial procedures [7]. Hyponatremia has been also reported to be associated with septic meningitis including bacterial meningitis (BM) and TBM [8–10].

We aimed to evaluate the association between hyponatremia and TBM in hopes of providing additional information for the differential diagnosis of TBM from other types of infectious meningitis, especially from VM.

Results

Baseline analysis

The baseline characteristics are summarized in Table 1. In total, the data from 5,026 participants were analyzed. In the analysis of blood test results, the data from 4,963 participants were available for the analysis of WBC counts, 4,925 participants for the analysis of LDH levels, 1028 participants for the analysis of procalcitonin levels, and 4,962 participants for the analysis of sodium levels. In the CSF analysis, 3,147 participants were included in the analysis of the glucose, 3,076 participants in the analysis of LDH levels, 3,193 participants in the analysis of protein levels, 1,339 participants in the analysis of tuberculosis cultures, 1,852 participants in the analysis of tuberculosis PCR results, and 434 participants in the analysis of VZV PCR results.

Age was significantly different between the three subgroups (VM vs. BM vs. TBM, 35.6 ± 14.2 vs. 52.1 ± 18.8 vs. 44.7 ± 18.6 years, $p < 0.001$). There were more females in the VM group than the TBM group (49.9% vs 40%, $p = 0.001$). Serum WBC counts were significantly higher in the BM group than in the VM and TBM groups (13.2 ± 11.5 vs. 8.7 ± 4.1 vs. 9.0 ± 6.1 x 10^3/μL, respectively, $p < 0.001$). Serum LDH levels were significantly higher in the TBM group than in the VM group (503.8 ± 1078.0 vs. 387.2 ± 627.9 U/L,

p = 0.013). Serum procalcitonin levels had a strong trend to be higher in the BM group than in the VM group (7.1 ± 19.0 vs. 1.5 ± 9.0 ng/ml, p = 0.056). In the CSF analysis, glucose levels were significantly lower in the TBM group than in the VM group (51.9 ± 23.5 vs. 62.2 ± 24.8 mg/dL, p < 0.001), the VM group had lower LDH levels than the BM group (61.5 ± 249.0 vs. 225.0 ± 389.9 U/L, p < 0.001), and the protein levels were significantly lower in the VM group than in the BM and TBM groups (78.8 ± 244.0 vs. 240.1 ± 266.9 vs. 306.6 ± 795.7 mg/dl, respectively, p < 0.001). In the TBM group, the positive rate of CSF tuberculosis cultures and PCR tests were 12.0% and 11.4%, respectively. VZV PCR in the CSF was positive in 12.5% of the VM group compared to 3.6% of the TBM group (p = 0.049).

Initial and lowest serum sodium levels: Cross-sectional analysis

In the total population, the initial serum sodium levels were significantly lower in the TBM group compared to the VM and BM groups (136.9 ± 5.9 vs. 139.0 ± 3.1 and 138.3 ± 4.7 mmol/L, p = 0.041 and p < 0.001, respectively), but there was no difference between the VM and BM groups. In respect to the lowest serum sodium levels, the significant difference between the TBM and VM groups was maintained (131.8 ± 6.4 vs. 137.4 ± 3.7 mmol/L, p < 0.001), and those between BM and VM became significantly different at lower sodium levels in the BM group (133.1 ± 5.1 vs. 137.4 ± 3.7 mmol/L, p < 0.001) (Table 1). The average interval days from the initial to the lowest serum sodium levels were 4.9 ± 6.0, 0 ± 3.1, and 4.5 ± 7.0 days in the TBM, VM, and BM groups, respectively.

In the propensity-matched population analysis (Table 2), the initial serum sodium levels in the three subgroups showed the same significant difference pattern as the analysis of the total population. It was significantly lower in the TBM group compared to the VM and BM groups (TBM vs. VM, 136.9 ± 5.9 vs. 138.7 ± 4.0, p < 0.001; TBM vs. BM, 136.2 ± 6.6 vs. 138.3 ± 5.0 mmol/L, p = 0.013), but no difference was found between the VM and BM groups. The lowest serum sodium levels were in the order of TBM < BM < VM. All of the comparisons between three subgroups were statistically significant (TBM vs. VM, 131.7 ± 6.4 vs. 135.6 ± 5.0 mmol/L, p < 0.001; TBM vs. BM, 130.3 ± 7.1 vs. 132.7 ± 5.3 mmol/L, p = 0.013; BM vs. VM, 132.7 ± 5.3 vs. 135.0 ± 5.5 mmol/L, p = 0.004).

Analysis of changes in serum sodium levels by repeated-measures ANOVA

The group x time interactions (reflecting whether there was a significant influence of the meningitis subtype on interval changes in serum sodium levels) were analyzed (Fig. 1). In both the total and propensity-matched populations, there were significant group x time interactions between meningitis subtypes and interval changes in serum sodium levels, which significantly decreased more steeply to a lower level in both the TBM and BM groups compared to the VM group. However, no group x time effect was found between the TBM vs. BM groups (in the total population, the p-value of the group x time effect was p < 0.001, p = 0.959, and p < 0.001 for TBM vs. VM, TBM vs. BM, and VM vs. BM, while in the propensity-matched population analysis, they were p < 0.001, p = 0.676, and p < 0.001, respectively).

Association between serum sodium levels and TBM

In the total population, when compared to patients in the highest initial sodium quartile group (≥ 141 mmol/L), patients in the lowest quartile (< 137 mmol/L) had significantly higher odds of a TBM diagnosis with an OR of 1.8 (95% CI: 1.3 – 2.4, p < 0.001) (Table 3). This association was maintained in the propensity-matched population with an OR of 2.1 (95% CI: 1.3 – 3.2, p < 0.001).

Regarding the lowest sodium levels, when compared to the patients in the highest quartile (≥ 140 mmol/L), the patients in the lower three quartiles had significantly higher odds of a TBM diagnosis both in the total population and the propensity-matched population. In the lowest quartile (< 135 mmol/L), the OR for TBM was 11.9 (95% CI: 7.3 – 19.4, p < 0.001) in the total population and 8.4 (95% CI: 4.5 – 15.8, p < 0.001) in the propensity-matched population.

Discussion

In this study, we evaluated the association between hyponatremia and each subtype of infectious meningitis, TBM, VM, and BM. The initial serum sodium level was significantly lower in the TBM group than in the VM and BM groups, and it dropped significantly more steeply to lower levels in both the TBM and BM groups compared to the VM group. Consequently, the lowest

serum sodium levels were lower in the order of TBM < BM < VM, which were also statistically significant between all subgroups. The participants with lower serum sodium levels were more likely to have a diagnosis of TBM rather than VM, and this association was more pronounced for the lowest sodium levels than the initial sodium levels.

The association between hyponatremia and TBM has already been elucidated and is well-known [5,11]. In one study including 76 cases of TBM, hyponatremia was observed in approximately 45% of the cases [9]. The syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting are considered the most likely causes of hyponatremia in patients with TBM and could overlap [9]. Hyponatremia can develop anytime during TBM [8], and worsens cerebral edema, headache, confusion, seizures, and coma [12], and predicts increased mortality in patients particularly with human immunodeficiency virus (HIV) infections and TBM [13]. However, to the best of our knowledge, the cross-sectional or longitudinal comparison according to various infectious meningitis etiologies has not been previously performed, although diagnosing TBM is one of the most challenging differential diagnoses and the cost of a false-negative diagnosis is fatal.

Subacute clinical onset of TBM, typically with a prodromal period of 2 – 4 weeks with non-specific symptoms such as fatigue, malaise, myalgia, and fever, often makes the diagnosis of TBM challenging, differentiating it from VM in the early stage [5,14]. Only about 10% of the patients with TBM have a history of tuberculosis disease [15]. Furthermore, the CSF profile of TBM typically shows lymphocytic pleocytosis with an average cell count of around 200 cells/μL and elevated protein content [5], which is similar to the profile of aseptic meningitis including VM. Microbiological tests are insensitive and laborious in TBM. The use of microscopy and Ziehl–Neelsen staining to detect acid-fast bacilli has a 50% sensitivity for high bacterial burden tuberculosis, such as cavitary pulmonary tuberculosis, and is 10 – 20% sensitive in paucibacillary diseases such as TBM [3]. Although cultures for Mycobacterium tuberculosis are more sensitive than microscopy, they usually take 2 – 3 weeks and require a biosafety level 3 laboratory. The culture sensitivity for TBM is still low at 5% to 58% depending upon the kind of media used and the testing facility [16,17], and in particular, the sensitivity of the conventional Lowenstein-Jensen culture is quite low at 10.9% [18]. However, the positive rate of culture in clinical practice is believed to be much lower for various reasons [19]. Our study also showed very low positive tuberculosis culture and PCR rates in the CSF of the TBM group, reflecting the paucibacillary CSF samples in clinical practice.

In comparison to BM, the meningismus symptoms of TBM including headache, fever, vomiting, photophobia, and stiffness of the neck evolve slower, usually taking more than a week to manifest [20], whereas BM typically shows initial devastating and rapid neurological deterioration with altered consciousness. The CSF profile of TBM also substantially differs from that of BM in that BM typically shows a polymorphonuclear pleocytosis with a cell count of more than 1,000 cells/μL.

Because of the suboptimal sensitivity and specificity of diagnostic tests, treatment may often be started based on a presumptive diagnosis of TBM in the setting of relevant clinical and epidemiologic factors and typical CSF findings. Delays in the treatment of TBM, which are often attributable to these clinical and laboratory diagnostic pitfalls and uncertainty have been associated with high mortality and morbidity including tuberculoma formation, vision loss, cranial nerve dysfunction, hydrocephalus, or vascular complications including stroke and aneurysmal formation and rupture [21-23].

Serum sodium level evaluation is relatively fast, widely used, low cost, and easy to perform and follow-up, and does not need any special facility. Given that TBM is the major disease in developing countries, this easy accessibility could be a major advantage for the evaluation in the differential diagnosis of the meningitis. We clearly demonstrated the significant association between hyponatremia and TBM compared to other infectious meningitis subtypes. Nevertheless, because hyponatremia is merely a secondary epiphenomenon of TBM and cannot confirm the presence of *M. tuberculosis*, it is not reasonable to consider serum sodium level evaluation as a diagnostic method for TBM. Rather, we hope hyponatremia could provide supportive information for the diagnosis of TBM as a surrogate marker.

Our study requires a cautious interpretation based on the following limitations. First, because of the retrospective study design with data extraction from an integrated big data platform, there were some limitations to the data acquisition. For instance, data regarding the number and differential WBC counts in the CSF and adenosine deaminase were not available. In contrast, because the data was based on the OCS and its subsequent results, we could obtain accurate laboratory results such as serial serum sodium levels. Second, although we included TBM patients diagnosed with TBM who were taking anti-tuberculosis medications, it

is not certain whether suspected TBM was confirmed or highly probable or probable or possible according to clinical categorizations [17].

We showed a significant association between hyponatremia and TBM compared to VM and BM, both cross-sectionally and longitudinally. We hope the results can provide more useful information in the differential diagnosis of TBM from VM or BM so that prompt optimal treatment can be applied in a timely manner.

Patients And Methods

A. Participants

We used data from the Clinical Data Warehouse (CDW) database, which is a large, integrated harmonized database of five tertiary referral medical centers belonging to The Catholic University of Korea, College of Medicine, Seoul, Korea [24]. The information in this database has been collected from the electronic medical records (EMR) and order communication system (OCS) since April 1997, the platforms of which are commonly shared by these five hospitals. Briefly, the CDW database is a relational database composed of a demographics database; a diagnosis database including the participant age and the date at diagnosis; an admission database including admission dates, discharge dates, and information on inpatients and outpatients; a surgery database; a prescription database including the prescribed medications and ordered laboratory tests; a laboratory database with the results of ordered test such as serum sodium levels and the date of the test; and a histology database including cultures and polymerase chain reaction (PCR) analysis of the samples. The data extraction is processed through anonymization and researchers are not able to identify and access the participants' personal information.

The study cohort consisted of patients with VM, BM, and TBM more than 18 years of age who were consecutively admitted to the five hospitals from December 2009 to December 2019. The participants in the TBM group were enrolled when they were diagnosed with TBM and took anti-tuberculosis medications.

B. Study Variables

For this study, we obtained demographic information including the age at admission for meningitis, the sex of the participants, admission date, discharge date, the medical department for admission, the final diagnosis (by the International Classification of Diseases code), the prescribed medications and treatments, the results of various laboratory tests available in the database (blood glucose, protein, sodium, procalcitonin, and lactate dehydrogenase (LDH) levels, and white blood cell (WBC) count; and CSF glucose, protein, and LDH levels, and varicella-zoster virus (VZV) polymerase chain reaction (PCR), and tuberculosis culture and PCR in the CSF). We obtained serial serum sodium levels from the initial admission to hospital discharge and the initial and the lowest sodium levels.

C. Standard protocol approvals, registrations, and patient consent

All aspects of this retrospective study were approved by the Institutional Review Board of The Catholic University of Korea (XC19WIDI0113). The requirement for informed consent was formally waived by the Institutional Review Board of The Catholic University of Korea.

D. Statistical analyses

All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Independent t-tests and analysis of variance (ANOVA) were used to compare the continuous variables. Pearson's chi-squared tests and Fisher's exact test were used to compare the categorical variables. The values are expressed as means ± standard deviations. In addition to the analysis of absolute population numbers, we used propensity score matching for the unbalanced numbers in each group and to eliminate the effect of confounding variables. By balancing according to age, sex, and CSF profiles, two similar groups of 279 TBM and VM patients were extracted from the sample. Similarly, when comparing TBM versus BM, each group consisting of 105 patients with similar propensity scores were extracted, and 105 propensity-matched patients were extracted when comparing VM versus BM. A cross-sectional comparison of the initial and lowest serum sodium levels was performed using paired t-tests between the propensity-matched groups. To assess temporal longitudinal changes in the serum sodium levels in each meningitis

subgroup, repeated-measures ANOVA was performed for the total patients and the propensity-matched population. The initial and lowest serum sodium levels were divided by quartile distribution and the odds ratios (ORs) were calculated for the diagnosis of TBM compared to VM using logistic multivariable regression analysis in the total population and the propensity-matched population, respectively. Statistical significance was assumed at a false detection rate of less than 5% (i.e., $p < 0.05$).

Declarations

Author contributions statement

S.N. and T.K. conceived and designed the study, performed data acquisition/interpretation, and provided substantial input to the manuscript. I.S., S.C., SH.K., YS.O., J.O. and W.K. performed data acquisition/interpretation. T.K. approved the final version.

Additional information

Conflicts of Interest/Disclosures: None

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Ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Data availability

The de-identified data supporting the findings of this study are available upon reasonable request to the corresponding author.

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Potential conflict of interest: Nothing to report.

Ethical standards: The authors declare that this single case report has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Tables

Table 1 Baseline clinical characteristics and laboratory findings in patients with viral and tuberculosis meningitis

	VM	BM	TBM	*p*-value			
	n=4601	n=130	n=295	Among three groups	Viral vs. Bacterial	Bacterial vs. tuberculosis	Tuberculosis vs viral
Age (yr.), mean ± SD	35.6±14.2	52.1±18.8	44.7±18.6	<0.001**	<0.001**	<0.001**	<0.001**
Female, No. (%)	2295 (49.9)	56 (43.1)	118 (40.0)	<0.001**	0.126	0.552	0.001**
Blood							
Serum WBC, $x10^3$/μL (n)	8.7±4.1 (4538)	13.2±11.5	9.0±6.1	<0.001**	<0.001**	<0.001**	0.728
LDH, U/L (n)	387.2±627.9 (4505)	460.1±268.2 (125)	503.8±1078.0 (295)	0.007**	0.473	0.823	0.013*
Procalcitonin, ng/ml (n)	1.5±9.0 (843)	7.1±19.0 (63)	3.5±16.2 (122)	<0.001**	0.056	0.404	0.360
Initial Na level, mmol/L (n)	139.0±3.1 (4537)	138.3±4.7 (130)	136.9±5.9 (295)	<0.001**	0.264	0.041*	<0.001**
Lowest Na level, mmol/L (n)	137.4±3.7 (4537)	133.1±5.1 (130)	131.8±6.4 (295)	<0.001**	<0.001**	0.061	<0.001**
CSF							
Glucose, mg/dL (n)	62.2±24.8 (2762)	55.8±40.9 (105)	51.9±23.5 (280)	<0.001**	0.114	0.363	<0.001**
LDH, U/L (n)	61.5±249.0 (2706)	225.0±389.9 (98)	229.8±1262.9 (272)	<0.001**	<0.001**	1.000	0.085
Protein, mg/dl (n)	78.8±244.0 (2798)	240.1±266.9 (112)	306.6±795.7 (283)	<0.001**	<0.001**	0.516	<0.001**
CSF tuberculosis culture, positive rate, n (%)	1/1112 (0.1)	0/61 (0)	20/166 (12.0)				
CSF tuberculosis PCR, positive rate, n (%)	1/1515 (0.1)	0/75 (0)	30/262 (11.4)				
CSF VZV PCR, positive rate, n (%)	45/359 (12.5)	0/19 (0)	2/56 (3.6)				

Abbreviations: BM = bacterial meningitis; CSF = cerebrospinal fluid; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; TBM = tuberculous meningitis; VM = viral meningitis; VZV = varicella-zoster virus; WBC = white blood cells.

All scores are shown as percent, n values, or mean (SD).

(n): number of patients who underwent the test

Analyses were performed by the analysis of variance (ANOVA), independent sample t-test, Fisher's exact test, or $\chi 2$ test.

*P < 0.05, **P < 0.01

Table 2 Comparison of the initial and lowest serum sodium levels in propensity-matched populations with tuberculous, viral, and bacterial meningitis

	Tuberculous vs. viral meningitis			Tuberculous vs. bacterial meningitis			Bacterial vs. viral meningitis		
	TBM	VM	*p*-value	TBM	BM	*p*-value	BM	VM	*p*-value
Propensity-matched population	n=279	n=279		n=105	n=105		n=105	n=105	
Initial Na level (mmol/L)	136.9±5.9	138.7±4.0	<0.001**	136.2±6.6	138.3±5.0	0.013*	138.3±5.0	138.9±4.0	0.277
Lowest Na level (mmol/L)	131.7±6.4	135.6±5.0	<0.001**	130.3±7.1	132.7±5.3	0.003**	132.7±5.3	135.0±5.5	0.004**

Abbreviations: BM = bacterial meningitis; TBM = tuberculous meningitis; VM = viral meningitis.

All scores are shown as percent, n values, or mean (SD).

The propensity score was matched 1:1 between the two comparison groups controlling for age, sex, cerebrospinal fluid (CSF) glucose, CSF lactate dehydrogenase (LDH), and CSF protein. The analyses were performed with the paired t-test.

*P < 0.05, **P < 0.01

Table 3 Independent association of serum sodium levels with tuberculosis meningitis compared to viral meningitis

Initial sodium level (mmol/L)			Lowest sodium level (mmol/L)		
Total population of VM and TBM (n=4896)					
	OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
141≦Na (Q1)	Reference		140≦Na (Q1)	Reference	
139≦Na<141 (Q2)	0.7 (0.5-1.0)	0.061	138≦Na<140 (Q2)	1.7 (1.0-3.1)	0.058
137≦Na<139 (Q3)	0.8 (0.5-1.1)	0.177	135≦Na<138 (Q3)	2.7 (1.6-4.5)	<0.001**
Na<137 (Q4)	1.8 (1.3-2.4)	<0.001**	Na<135 (Q4)	11.9 (7.3-19.4)	<0.001**
Propensity-matched Population of VM and TBM (n=558)					
	OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
141≦Na (Q1)	Reference		140≦Na (Q1)	Reference	
139≦Na<141 (Q2)	0.8 (0.5-1.2)	0.281	138≦Na<140 (Q2)	2.1 (1.0-4.3)	0.039*
137≦Na<139 (Q3)	1.0 (0.6-1.6)	0.920	135≦Na<138 (Q3)	2.8 (1.5-5.4)	0.002**
Na<137 (Q4)	2.1 (1.3-3.2)	<0.001**	Na<135 (Q4)	8.4 (4.5-15.8)	<0.001**

Abbreviations: BM = bacterial meningitis; OR = odds ratio; TBM = tuberculous meningitis; VM = viral meningitis.

Serum sodium levels in the first quartile (Q1), second quartile (Q2), third quartile (Q3), and fourth quartile (Q4).

Analyses were performed with multiple logistic regression tests, controlling for age, sex, cerebrospinal fluid (CSF) glucose, and CSF protein. Propensity was matched controlling for age, sex, CSF glucose, CSF lactate dehydrogenase (LDH), and CSF protein.

*P < 0.05, **P < 0.01

Figures

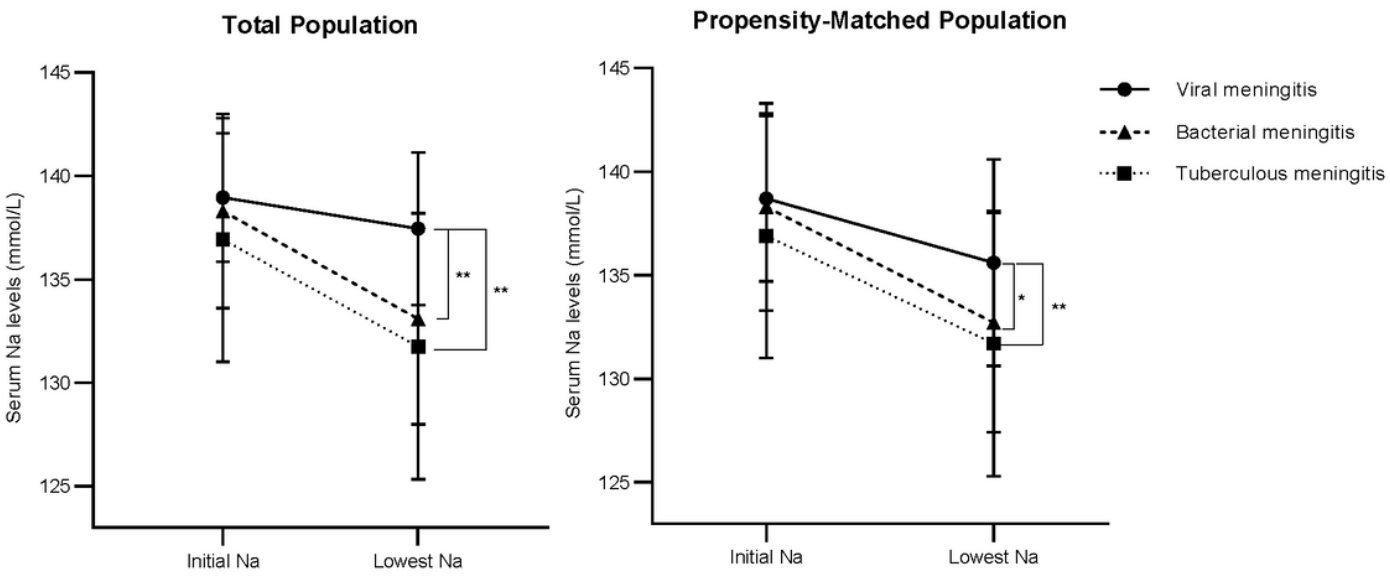

Figure 1

Changes in serum sodium levels in VM, BM and TBM, respectively. P values for the group x time interactions are demonstrated. *P < 0.05, **P < 0.01.