



Low serum complement level is associated with higher mortality in tuberculous meningitis: a retrospective cohort study

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Purpose

We evaluated the associations between serum complement levels and tuberculous meningitis (TBM), bacterial meningitis (BM), and viral meningitis (VM), as well as the association between serum complement levels and mortality in TBM.

Methods

Background information and blood/cerebrospinal fluid analysis results were collected from 2009 to 2019. Patients who had serum complement level data collected at admission and who were diagnosed with TBM (n = 97), BM (n = 31), or VM (n = 557) were enrolled.

Results

Initial serum complement levels were significantly lower in the TBM group than the VM group in both the total population and the propensity score-matched population. In the TBM and VM groups, compared to patients with initial highest-quartile C4 level, patients in the lowest quartile (C4 < 24.3 mg/dL) had significantly greater odds of TBM diagnosis (odds ratio, 2.2; 95% confidence interval, 1.0–4.5; p = 0.038). In the TBM group, patients with the lowest-quartile C3 level (<96.9 mg/dL) experienced a significantly higher 90-day mortality rate compared to other TBM patients (hazard ratio, 19.0; 95% confidence interval, 2.1–167.4.5; p = 0.008).

Conclusion

Both serum C3 and C4 levels were significantly lower in the TBM group than in the VM group. TBM patients with lower serum C3 level had a significantly higher mortality rate than those with higher C3 level.

Keywords: Complement system proteins, Meningitis, Tuberculosis

Introduction

Tuberculosis remains a global health problem, with an estimated 10 million cases and 1.4 million deaths worldwide in 2019 [1]. Extrapulmonary tuberculosis accounts for about 16% of all tuberculosis cases, and it is estimated that 5% to 6% of

cases are tuberculous meningitis (TBM) [2]. The global burden of TBM is estimated to be $\geq 100,000$ cases per year [3]. TBM is the most lethal form of tuberculosis, resulting in death or severe disability in approximately 50% of affected patients due to devastating neurological sequelae such as tuberculo-

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ma formation, cranial nerve dysfunction, hydrocephalus, and vascular complications including stroke [4]. In contrast, most patients with aseptic viral meningitis (VM) experience a self-limiting clinical course without any neurological sequelae. Therefore, rapid diagnosis of TBM followed promptly by optimal treatment is critical, but diagnosing TBM is often challenging due to delayed or inconclusive laboratory results because of the low sensitivity and slow speed of conventional bacteriology tests. Similar cerebrospinal fluid (CSF) profiles between VM and TBM and an indolent clinical onset with nonspecific initial symptoms add to the challenge of differentiating these conditions [5].

The complement system is a major component of innate immunity and enhances antibody-triggered responses [6]. Although the complement pathway in tuberculosis infection is not fully understood, pathogens in *Mycobacterium* activate the complement pathway [7]. However, the association of the complement system with TBM has rarely been evaluated, and data on clinical implications are scarce [8].

Due to the clinical ambiguity in the differential diagnosis of TBM, as well as insufficient clinical data on the role of the complement system in TBM, we aimed to evaluate the association between serum complement levels and TBM compared to other meningitis subtypes. Moreover, we aimed to better understand the TBM mortality rate according to serum complement levels.

Methods

Participants

We used data from the Clinical Data Warehouse database, which is a large, integrated, harmonized database of five tertiary referral medical centers belonging to the College of Medicine, The Catholic University of Korea, Seoul, Korea [9,10]. The information in this database has been collected from electronic medical records and order communication systems since April 1997 via the platforms commonly shared by the five referral university hospitals. Detailed information on the database was described in a previous study [10].

The study cohort consisted of patients with TBM, bacterial meningitis (BM), or VM who were at least 18 years of age and consecutively admitted to one of the five hospitals between December 2009 and December 2019. Participants in the TBM group were enrolled when they were diagnosed with possible, probable, or definite TBM according to the uniform TBM case definition by Marais et al. [11]; all patients were using anti-

tuberculosis medications. We defined a case of BM as a patient with headache, mental status changes, and a positive CSF or blood culture, and these patients were treated with antibiotics. The VM group included patients with no evidence of other meningitis caused by *Mycobacterium tuberculosis*, bacterial infection, fungal infection, autoimmune disease, injury, cancer, or certain drugs, and these patients achieved complete recovery with only conservative treatments or had positive CSF results according to viral polymerase chain reaction (PCR). Among the study cohort, only patients who had known serum complement levels at admission were enrolled in this study (Figure 1).

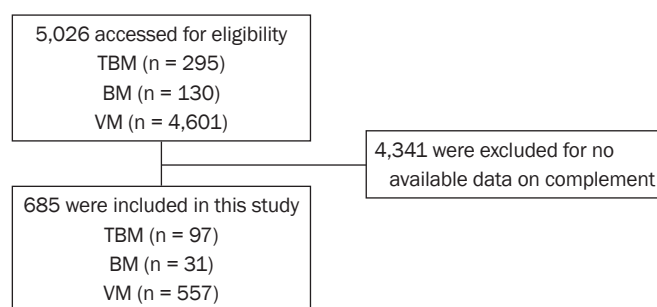
Study variables

For this study, we obtained demographic information including age at admission, sex, admission date, discharge date, medical department on admission, final diagnosis, prescribed medications and treatments, laboratory tests (blood glucose, protein, sodium, procalcitonin, lactate dehydrogenase [LDH], and white blood cell [WBC] count; CSF WBC count, glucose, protein, and LDH; varicella-zoster virus [VZV] PCR; and tuberculosis acid-fast bacillus [AFB] stain, culture, and real-time PCR in CSF). AFB stain and culture for mycobacteria were performed using Ziehl-Neelsen staining and Middlebrook 7H9 Broth/ Löwenstein-Jensen media, respectively. We obtained serum complement levels at initial admission.

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 (No. XC19WIDI0113), which waived the requirement for informed consent.

Figure 1 Flow diagram for recruitment



BM, bacterial meningitis; TBM, tuberculous meningitis; VM, viral meningitis.

Statistical analyses

All statistical analyses were performed using IBM SPSS for Windows version 27.0 (IBM Corp., Armonk, NY, USA). Independent t-tests and analysis of variance were used to compare continuous variables. Pearson chi-square tests and Fisher exact tests were used to compare categorical variables. Values are expressed as mean \pm standard deviation. In addition to analysis of absolute population numbers, we used propensity score matching for unbalanced numbers in each group to eliminate the effects of confounding variables. After adjusting for age, sex, and CSF profiles (including WBC count, glucose, and protein), two similar groups of 28 TBM or BM patients were extracted from the sample. Similarly, comparing BM versus VM, groups consisting of 28 patients with similar propensity scores were extracted, and 90 propensity score-matched patients were extracted to compare VM and TBM. A cross-sectional comparison of serum complement levels was performed using independent t-tests between propensity score-matched groups. Serum complement levels were divid-

ed by quartile distribution, and odds ratios (ORs) were calculated for diagnosis of TBM compared to VM by logistic multivariable regression analysis in the total population and the propensity score-matched population. Statistical significance was assumed at a false-detection rate less than 5% ($p < 0.05$).

Results

Baseline analysis

The baseline characteristics of the patients analyzed in this study are summarized in Table 1. In total, data from 685 participants were analyzed. For CSF VZV PCR analysis, data from 597 participants were available. For mortality at 90 days, data for 630 participants were available and included in the analysis.

Age was significantly different between the three subgroups (TBM vs. BM vs. VM, 43.6 \pm 18.2 years vs. 48.8 \pm 16.0 years vs. 40.0 \pm 15.4 years; $p < 0.001$). Serum WBC count was significantly higher in the BM group than in the TBM and VM

Table 1 Baseline clinical characteristics and laboratory findings in patients with TBM, BM, and VM

Variable	TBM	BM	VM	p-value			
				Among three groups	TBM vs. BM	BM vs. VM	VM vs. TBM
No. of participants	97	31	557				
Age (yr)	43.6 \pm 18.2	48.8 \pm 16.0	40.0 \pm 15.4	<0.001**	0.112	<0.001**	0.001**
Female sex	45 (46.4)	14 (45.2)	284 (51.0)	0.603			
Blood							
Serum WBC ($\times 10^3/\mu\text{L}$)	8.9 \pm 8.8	14.2 \pm 19.8	8.5 \pm 4.3	<0.001**	0.001**	<0.001**	0.805
LDH (U/L)	620.7 \pm 1,852.7	460.4 \pm 305.7	399.7 \pm 768.2	0.125			
Procalcitonin (ng/mL)	2.2 \pm 13.3	8.1 \pm 23.0	2.9 \pm 14.7	0.318			
HIV Ag/Ab positive	1 (1.0)	0 (0)	2 (0.4)	0.607			
C3 (mg/dL)	108.2 \pm 32.7	108.5 \pm 31.9	117.2 \pm 30.2	0.012*	0.967	0.123	0.008**
C4 (mg/dL)	28.9 \pm 11.2	29.5 \pm 13.0	32.8 \pm 11.9	0.005**	0.804	0.13	0.003**
CSF							
WBC ($/\mu\text{L}$)	261.3 \pm 544.8	512.6 \pm 751.7	198.8 \pm 1,195.3	0.299			
Neutrophil (%)	22.0 \pm 28.8	60.3 \pm 36.0	13.3 \pm 24.4	<0.001**	<0.001**	<0.001**	0.010*
Lymphocyte (%)	64.0 \pm 32.9	23.9 \pm 30.6	36.9 \pm 39.9	<0.001**	<0.001**	0.08	<0.001**
Eosinophil (%)	2.7 \pm 6.5	0.6 \pm 0.5	6.5 \pm 16.4	0.380			
Monocyte (%)	10.3 \pm 13.5	11.7 \pm 10.9	11.0 \pm 13.6	0.928			
Glucose (mg/dL)	57.8 \pm 27.1	60.7 \pm 32.6	64.6 \pm 47.6	0.386			
LDH (U/L)	150.2 \pm 342.5	160.5 \pm 247.3	92.0 \pm 563.4	0.534			
Protein (mg/dL)	275.9 \pm 677.0	206.8 \pm 201.8	101.2 \pm 337.8	0.001**	0.721	0.386	0.001**
CSF tuberculosis culture, positive rate	12 (12.4)	0 (0)	1 (0.2)				
CSF tuberculosis PCR, positive rate	11 (11.3)	0 (0)	1 (0.2)				
Xpert MTB/RIF ^a , positive rate	13 (13.4)	0 (0)	0 (0)				
CSF VZV PCR, positive rate	2/46 (4.3)	0/19 (0)	66/532 (12.4)				
Mortality at 90 days	9/88 (10.2)	4/24 (16.7)	22/518 (4.2)	0.004**			

Values are presented as number only, mean \pm standard deviation, or number (%).

TBM, meningitis; BM, bacterial meningitis; VM, viral meningitis; WBC, white blood cells; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; VZV, varicella-zoster virus.

aXpert MTB/RIF testing, Cepheid, Sunnyvale, CA, USA.

The analyses were performed by analysis of variance, independent sample t-test, Fisher exact test, or chi-square test; * $p < 0.05$, ** $p < 0.01$.

groups ($14.2 \pm 19.8 \times 10^3/\mu\text{L}$ vs. $8.9 \pm 8.8 \times 10^3/\mu\text{L}$ vs. $8.5 \pm 4.3 \times 10^3/\mu\text{L}$, $p < 0.001$). Tests for human immunodeficiency virus (HIV) antigens/antibodies were positive in one patient in the TBM group and two patients in the VM group.

In CSF analysis, the WBC profile was significantly different between groups, reflecting a neutrophil-dominant WBC population in the BM group but a lymphocyte-dominant WBC population in the TBM and VM groups ($p < 0.001$). CSF protein level was significantly higher in the TBM group than in the VM group (275.9 ± 677.0 mg/dL vs. 101.2 ± 337.8 mg/dL, $p = 0.001$).

In the TBM group, the positive rates of CSF tuberculosis cultures and PCR tests were 12.4% and 11.3%, respectively. The positive rate of Xpert MTB/RIF testing (Cepheid, Sunnyvale, CA, USA) was 13.4% in the TBM group. Among the 97 TBM patients, 14 (14.4%) were diagnosed with definite TBM, 39 (40.2%) were diagnosed with probable TBM, and 44 (45.4%) were diagnosed with possible TBM.

The CSF VZV PCR result was positive in 4.3% of patients in the TBM group compared to 12.4% of patients in the VM group.

Initial serum complement C3 and C4 levels: total population

Initial serum complement levels were significantly lower in the TBM group than in the VM group (C3: 108.2 ± 32.7 mg/dL vs. 117.2 ± 30.2 mg/dL, $p = 0.008$; C4: 28.9 ± 11.2 mg/dL vs. 32.8 ± 11.9 mg/dL, $p = 0.003$), but there were no differences between the TBM and BM groups or between the BM and VM groups.

Initial serum complement C3 and C4 levels: propensity score-matched population

We performed a propensity score-matched population analysis with adjustment for age, sex, and CSF profiles (including WBC count, glucose, and protein) (Table 2). The initial serum complement levels in the three subgroups showed the same significant difference pattern as that seen in the analysis of the total population. The initial serum complement levels were significantly lower in the TBM group than in the VM group (C3: 107.0 ± 32.4 mg/dL vs. 116.4 ± 29.2 mg/dL, $p = 0.043$; C4: 28.4 ± 11.0 mg/dL vs. 32.3 ± 11.6 mg/dL, $p = 0.023$), but no differences were found between the TBM and BM groups or between the BM and VM groups.

Associations between serum complement levels and tuberculous meningitis

In the TBM and VM groups, compared to patients in the highest initial C4 quartile (≥ 38.9 mg/dL), patients in the lowest quartile (< 24.3 mg/dL) had significantly greater odds of TBM diagnosis, with an OR of 2.2 (95% confidence interval [CI], 1.0–4.5; $p = 0.038$) (Table 3).

Association between complement level and mortality at 90 days

In the total population, the mortality rate at 90 days was 10.2% in the TBM group, 16.7% in the BM group, and 4.2% in the VM group ($p = 0.004$).

In the TBM group, patients in the lowest quartile for serum C3 level (< 96.9 mg/dL) had a significantly higher 90-day mortality rate compared to the rest of the TBM patients (28% vs. 3.2%, $p = 0.002$) (Figure 2). After adjusting for age, sex, CSF WBC

Table 2 Comparison of initial and lowest serum sodium levels in propensity-matched populations with TBM, BM, and VM

	Propensity-matched population	C3 (mg/dL)	p-value	C4 (mg/dL)	p-value
TBM vs. BM			0.795		0.159
TBM	28	105.9 ± 33.5		24.6 ± 9.8	
BM	28	108.1 ± 30.9		29.0 ± 12.8	
BM vs. VM			0.889		0.921
BM	28	108.1 ± 30.9		29.0 ± 12.8	
VM	28	107.0 ± 28.4		29.3 ± 13.2	
VM vs. TBM			0.043*		0.023*
VM	90	116.4 ± 29.2		32.3 ± 11.6	
TBM	90	107.0 ± 32.4		28.4 ± 11.0	

Values are presented as number or mean \pm standard deviation.

TBM, meningitis; BM, bacterial meningitis; VM, viral meningitis.

The propensity score was matched 1:1 between the two comparison groups controlling for age, sex, cerebrospinal fluid (CSF) white blood cell count, CSF glucose, and CSF protein.

The analyses were performed with the independent t-test; * $p < 0.05$.

Table 3 Independent association of serum complement levels with TBM compared to VM (total population of TBM and VM = 654)

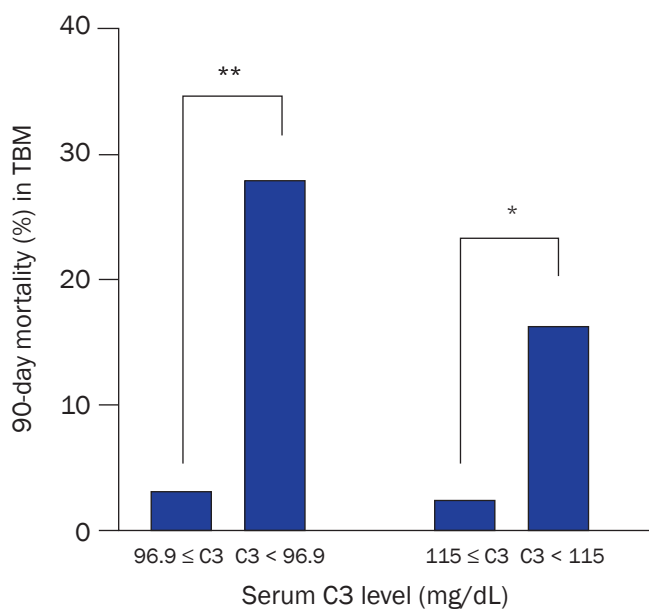
Serum complement level	C3 (mg/dL)		C4 (mg/dL)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Q1	Reference		Reference	
Q2	1.4 (0.7–2.9)	0.366	2.0 (0.9–4.2)	0.070
Q3	1.7 (0.9–3.4)	0.133	2.0 (0.9–4.1)	0.074
Q4	1.6 (0.8–3.2)	0.206	2.2 (1.0–4.5)	0.038*

TBM, tuberculous meningitis; VM, viral meningitis; OR, odds ratio; CI, confidence interval.

Serum complement levels in the first quartile (Q1; C3 of ≥ 134.4 mg/dL, C4 of ≥ 38.9 mg/dL), second quartile (Q2; C3 of < 134.4 mg and ≥ 115.0 /dL, C4 of < 38.9 and ≥ 31.0 mg/dL), third quartile (Q3; C3 of < 115.0 and ≥ 96.9 mg/dL, C4 of < 31.0 and ≥ 24.3 mg/dL), and fourth quartile (Q4; C3 of < 96.9 mg/dL, C4 of < 24.3 mg/dL).

The analyses were performed with multiple logistic regression tests, controlling for age, sex, cerebrospinal fluid (CSF) white blood cells count, CSF glucose, and CSF protein; *p < 0.05.

Figure 2 Comparison of 90-day mortality rates according to serum complement levels



TBM, tuberculous meningitis.

*p < 0.05, **p < 0.01.

count, CSF glucose level, and CSF protein level, patients in the lowest quartile (< 96.9 mg/dL) had a significantly higher hazard ratio (HR) for mortality at 3 months (19.0; 95% CI, 2.1–167.4.5; p = 0.008). Patients with serum C3 level lower than the median value (< 115 mg/dL) also had a significantly higher 90-day mortality rate compared to those with C3 level high-

er than the median value (16.3% vs. 2.6%, p = 0.040), but this result did not reach statistical significance after adjusting for confounding factors (HR, 6.5; 95% CI, 0.7–59.7; p = 0.098).

Similarly, patients with the lowest-quartile serum C4 level (< 24.3 mg/dL) had a 17.9% 90-day mortality rate, while the rest of the patients had a 6.7% 90-day mortality rate, but this difference did not reach statistical significance (p = 0.136). Patients with lower median serum C4 level (< 31 mg/dL) had a 13.7% 90-day mortality rate, whereas those with higher median level had a 5.4% 90-day mortality rate (p = 0.293).

Discussion

In this study, we evaluated the associations between serum complement levels and subtypes of infectious meningitis, including TBM, BM, and VM. Both serum C3 and C4 levels were significantly lower in the TBM group than in the VM group in both the total and the propensity score-matched populations. Patients with lower serum C4 level were more likely to have a diagnosis of TBM than of VM. Further, TBM patients with lower serum C3 level had a significantly higher 90-day mortality rate compared to TBM patients with higher serum C3 level.

The role of the complement system in tuberculosis infection has been comprehensively evaluated in many studies. The complement system plays a role in the pathogenesis of tuberculosis by opsonizing *M. tuberculosis* with specific C3 cleavage products for phagocytosis into alveolar macrophages [12]. The classical pathway is initiated by C1q, which binds to antibody-*M. tuberculosis* antigen complexes during the adaptive immune response. The binding of C1q results in cleavage of C4 and C2 to the C3 convertase (C4bC2b), which cleaves C3 to produce the opsonin C3b and promote formation of the membrane attack complex, resulting in target cell lysis [7,13,14]. The lectin-binding pathway is activated by recognition of complex sugar moieties on the *M. tuberculosis* cell surface [7], and an alternative pathway is activated by C3 convertase (C3bBb) and regulated by properdin and factor H. All three complement pathways lead to activation of C3 convertases and production of C3b, which opsonizes *M. tuberculosis* [12,13].

The alternative complement pathway is relatively unusual in the lungs compared to the classical pathway. Some researchers argue that the classical pathway plays a more active role in the pathogenesis of tuberculosis infection [12], a suggestion which was supported by the increased serum C1q level noted in active tuberculosis infection [15], as well as by the identifi-

cation of complement pathway gene activation in HIV-1-infected patients with early tuberculosis infection [16]. In our study, reductions in both serum C3 and C4 levels indicate an overactive complement system with increased complement consumption in the classical pathway, which is in line with prior studies revealing the predominant role of the classical pathway in tuberculosis infection. Also, in the formation of a tuberculous granuloma in the central nervous system, the innate immune system and specific T and B lymphocytes play a critical role [3,17]. The complement system is a major component of innate immunity and enhances antibody-triggered responses.

Serum complement level could decrease with increased complement consumption by immune complexes. Representative examples of hypocomplementemia are systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, cryoglobulinemia, and vasculitis, such as anti-neutrophil antibody-associated vasculitis. Moreover, infectious diseases with large antigenic loads, such as viral infections (e.g., by hepatitis B and C viruses, parvovirus, and flavivirus), can lead to transient hypocomplementemia as antibodies combine with viral antigens [18].

Many studies evaluating the complement system in the CSF revealed massive complement system activation in patients with BM [19-24]. However, only a few studies included blood complement measurements and correlated results with disease severity and outcomes in BM [19,25,26]. One study demonstrated a significant association between high level of C3 in serum negative for meningococcal antigens [25]. Two other studies also offered negative findings. In our study, there were no significant associations between serum complement levels and BM compared to other meningitis subtypes. As with BM, data on serum complement levels in TBM are scarce, and studies including serial blood sampling to determine complement activation profiles in acute TBM are lacking. In a study that included 23 children with TBM and 24 with non-TBM meningitis, serum complement was evaluated as a potential surrogate marker in the diagnosis of TBM, but no significant results were obtained [8]. However, our study included a much larger study population, with 97 cases of TBM and 588 cases of non-TBM meningitis, and revealed a significant decrease in serum C3 and C4 levels in TBM compared to in VM.

Delays in TBM treatment have been associated with high mortality and morbidity rates as well as complications such as vision loss, cranial nerve dysfunction, hydrocephalus, and

vascular complications including stroke and aneurysmal formation and rupture [27,28]. This study provides additional information for differentially diagnosing TBM from VM, which share similar initial clinical characteristics and CSF profiles but have contrasting clinical outcomes.

We observed a significantly increased mortality rate in TBM patients with low initial C3 level. This might be due to an overactive complement system with increased complement consumption, which could result in an uncontrolled inflammatory response and unfavorable outcomes. This is why the complement system is often regarded as a double-edged sword [29] and why complement-targeted drugs, such as eculizumab, have been developed for use in the treatment of BM [30,31].

Our study has several limitations. First, because it was a retrospective study with unbalanced numbers in the groups owing to differences in the natural prevalence of cases, there could be selection bias. To compensate for uneven patient allocation between groups and the potential risk of selection bias, we applied propensity score-matched scoring at a 1:1 ratio to eliminate the effects of selection bias and confounding variables. Second, although there was a clear significant difference in complement levels between TBM and VM patients, the average serum complement values in both groups were within the normal reference ranges. Only patients in the lowest-quartile ranges of C3 and C4 could be referred to as having hypocomplementemia. Third, the small proportion of definite TBM cases was another limitation in our study, but it also reflects the nature of clinical practice in Korea, where the sensitivity of the various bacteriology tests for TBM is very low. The positive rate of cultures in clinical practice is believed to be much lower than that measured in the literature for various reasons [32]. In addition to the paucibacillary nature of CSF in TBM diagnosis, we supposed that there is a possibility that the serous type of TBM, which is characterized by signs and symptoms of mild meningitis with spontaneous recovery, could also complicate diagnosis of TBM. There was a single case of VM with a positive CSF tuberculosis culture and PCR result in our study. This patient was diagnosed with VM because they recovered spontaneously with mild symptoms, and their CSF profile suggested VM. Whether the national bacillus Calmette-Guérin (BCG) vaccine inoculation project in Korea could influence the low sensitivity of the bacteriology tests in TBM is another hypothesis we would like to consider in future research. Finally, detailed clinical data, including those concerning symptom duration, neurologic deficits,

headache, neck stiffness, and nausea/vomiting, which are crucial factors in the differentiation of meningitis, were not provided in this study.

This study is the largest to date to evaluate serum complement levels in TBM versus other infectious meningitis subtypes. Significantly decreased serum C3 and C4 levels were observed in TBM compared to VM. We hope our results provide useful information for differentially diagnosing TBM from VM such that timely optimal treatment for TBM can be administered to improve outcomes. Further studies will be required to confirm our findings.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization, Resources: Im H, Kim T; Investigation, Data curation: Im H, Kim T, Na S, Song IU, Kim SH, Oh YS, Oh J, Kim W; Writing—original draft: Im H, Kim T; Writing—review and editing: Kim T.

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