

Relevance of complement immunity with brain fog in patients with long COVID

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Abstract

Introduction: This study aimed to elucidate the prevalence and clinical characteristics of patients with long COVID (coronavirus disease 2019), especially focusing on 50% hemolytic complement activity (CH50).

Methods: This retrospective observational study focused on patients who visited Okayama University Hospital (Japan) for the treatment of long COVID between February 2021 and March 2023. CH50 levels were measured using liposome immunometric assay (Autokit CH50 Assay, FUJIFILM Wako Pure Chemical Corporation, Japan); high CH50 was defined as ≥ 59 U/mL. Univariate analyses assessed differences in the clinical background, long COVID symptoms, inflammatory markers, and clinical scores of patients with normal and high CH50. Logistic regression model investigated the association between high CH50 levels and these factors.

Results: Of 659 patients who visited our hospital, 478 patients were included. Of these, 284 (59.4%) patients had high CH50 levels. Poor concentration was significantly more frequent in the high CH50 group (7.2% vs. 13.7%), whereas no differences were observed in other subjective symptoms (fatigue, headache, insomnia, dyspnea, tiredness, and brain fog). Multivariate analysis was performed on factors that could be associated with poor concentration, suggesting a significant relationship to high CH50 levels (adjusted odds ratio [aOR], 2.70; 95% confidence interval [CI], 1.33–5.49). Also, high CH50 was significantly associated with brain fog (aOR, 1.66;

95% CI, 1.04–2.66).

Conclusions: High CH50 levels were frequently reported in individuals with long COVID, indicating a relationship with brain fog. Future in-depth research should examine the pathological role and causal link between complement immunity and the development of long COVID.

Keywords: Long COVID; Complement immunity; Complement system; Coronavirus disease 2019; Inflammation

Introduction

With the advancement of vaccines and treatments, preventive strategies and clinical management of coronavirus disease 2019 (COVID-19) have been established. However, chronically prolonged symptoms that persist beyond the acute phase of the disease, which are called either long COVID or post-acute sequelae of COVID-19, remain a growing public health concern and affect a significant proportion of individuals following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1,2]. Long COVID definitely has considerable physical, cognitive, and psychological impacts on patients [3,4], especially among young populations [5], and an urgent need for further research to understand its underlying mechanisms and elaborate therapeutic options has been addressed.

An extensive overview of long COVID in its clinical features, potential mechanisms, and recommended management is provided in a recent study [6]. Briefly, hypothesized mechanisms underlying long COVID include a range of potential etiologies such as immune dysregulation (persistent viral infection), microbiota dysbiosis, autoimmunity and immune priming, blood clotting and endothelial abnormalities, and dysfunctional neurological signaling. More than 200 symptoms associated with multiple organ systems have been reported, which require multidisciplinary care and tailored approaches for individual symptoms. More than three years have passed since the global COVID-19 pandemic and enormous efforts have been made

internationally, but we still have not succeeded in developing reliable care based on solid evidence for patients suffering from long COVID [7].

In this context, we initiated specialized outpatient services at our university hospital to see such patients and understand their pathophysiology in response to societal requirements. Through data analysis of our patients, for example, we have proposed that hormonal disorders, including hypogonadism and thyroidal or adrenal dysfunction, may underlie the development of long COVID [8–14].

The complement system constitutes the innate immune system that reacts to SARS-CoV-2 and provokes a dysregulated immune response in infected patients [15,16]. The essential role of complement activation in the pathogenesis of acute SARS-CoV-2 infection has been demonstrated in clinical [17], post-mortem [18], and proteomic studies [19]. In contrast, the potential involvement of complement immunity with long COVID was not mentioned in the previous review [6]. Only recently, the role of the complement system in the development of long COVID has been discussed in the literature [20], potentially sowing the seeds for further research. We hypothesized that the regulation of the complement system will lead to the prevention and treatment of long COVID. This study aimed to elucidate the prevalence and clinical characteristics of long COVID patients with elevated CH50, with a particular focus on brain fog.

Materials and methods

Study design and data source

This retrospective observational study included patients visiting the COVID-19 aftercare clinic (CAC) of the Department of General Medicine at Okayama University Hospital in Japan between February 2021 and March 2023. Any persistent symptoms that lasted for more than four weeks after the onset of COVID-19 were regarded as long COVID [21]. The clinical symptoms of long COVID were evaluated and reported through in-person medical interviews and physical examinations. Age, sex, height, weight, body mass index (BMI), COVID-19 severity during the acute phase, duration from COVID-19 onset to the first visit to the CAC, clinical symptoms, vaccine history before onset, laboratory data (inflammatory parameters such as white blood cell count, erythrocyte sedimentation rate, and serum levels of ferritin, lactate dehydrogenase, and CH50), and self-reporting scale scores were all collected. We applied the criteria established by the Japanese Ministry of Health, Labor, and Welfare to classify the acute phase of COVID-19 severity [22]. Individual interviews were carefully conducted to determine the presence of "brain fog" symptoms, which were based on complaints of subjective feelings of concentration difficulty and impaired ability to concentrate and/or think; specifically, being mentally slow, fuzzy, or spaced out, affecting the patient's ability to think or concentrate with a dull headache [23]. At the

first visit, all patients completed self-assessment questionnaires, including self-rating depression scale (SDS) scoring to assess the respondent's depressive status [24], frequency scale for the symptoms of gastroesophageal reflux disease (FSSG) [25], Japanese version of the Fatigue Assessment Scale (FAS) scoring to assess fatigue status [26], and Japanese version of the EuroQOL 5-dimensions 5-levels (EQ-5D-5L) scoring to measure health-related QOL [27]. The poorest QOL is indicated by a score of "-0.025" on the EQ-5D-5L, and the best QOL is indicated by a score of "1". In this study, a QOL impairment was determined as a score of less than 0.8 points [28].

Laboratory testing

Each doctor ordered blood tests for the patients with long COVID as needed to help them rule out differential diagnoses. In late morning or early afternoon, blood was drawn while patients were comfortably seated and was analyzed using the auto-analyzer device in our facility's central laboratory. CH50 was mostly measured in purpose of evaluating autoimmune disease secondary to COVID-19, using an in-house liposome immunometric assay (Autokit CH50 Assay, FUJIFILM Wako Pure Chemical Corporation, Japan) immediately after the blood samples were delivered to the laboratory. The normal range for the assay was defined as 32–58 U/mL. Due to technical instability, CH50 values over ≥ 60 U/mL were quantitatively not measurable.

Data processing and statistical analyses

We categorized patients with high CH50 (≥ 59 U/mL) into the high CH50 group, while those not as the normal CH50 group. We first compared the clinical backgrounds, symptoms, inflammatory markers, and clinical scores between the two groups using univariate analysis. For categorical variables and non-normally distributed continuous variables, the Fisher's exact test and the Mann–Whitney U test were applied, respectively. Based on the results of univariate analysis, the association between high CH50 and long COVID symptoms, including brain fog, was analyzed using a logistic regression model. EZR version 4.2.2, a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria), was used to perform all statistical analyses [29]. Statistical significance was defined as $p < 0.05$.

Ethical approval

The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975 (as revised in 2008) as well as the ethical standards of the relevant national and institutional committees on human experimentation. We posted details about the study methodology on our website and on the clinic wall for opt-outs. Informed consent was not required owing to the retrospective nature of the study.

Results

During the study period, 659 patients visited the CAC clinic. Of these, 119 patients were excluded, including 3 patients under 10 years old, 4 patients without visiting, 5 patients visiting us within 30 days after COVID-19 onset, 44 patients without a definitive diagnosis of COVID-19 by laboratory testing, and 68 patients without CH50 data. We included only adult patients aged ≥ 18 years, and 478 patients were eligible for the analysis.

Of these patients, 284 (59.4%) had high CH50 levels (≥ 59 U/mL) and were categorized into the high CH50 group (**Table 1**). Data of one patient in the normal CH50 group was below the reference range of CH50 levels (30 U/mL). The median patient age was higher in the high CH50 group (41 years vs. 44.5 years; $p=0.005$). There were no significant differences between the two groups in sex proportion, days from COVID-19 onset to the first visit, body temperature at the visit, severity in the acute phase of COVID-19, and vaccine history. Inflammatory parameters, including white blood cell count, erythrocyte sedimentation rate, and serum ferritin and lactate dehydrogenase levels, were significantly higher in the high CH50 group, although all were within normal ranges and were clinically insignificant (**Table 2**).

The clinical manifestations of the patients are summarized in **Table 3**, which compares

normal and high CH50 groups. The most frequent chief complaint was fatigue (61.3%, 293 cases), followed by headache (21.8%, 104 cases), dysosmia (20.9%, 100 cases), and insomnia (20.1%, 96 cases). Brain fog was diagnosed in 28.2% of patients (135 cases). Univariate analysis showed that the frequency of poor concentration was significantly higher in the high CH50 group (7.2% vs. 13.7%; $p=0.03$). There were no differences in other symptoms between the two groups. Clinical scoring results were also evaluated. As shown in **Table 4**, no significant differences were observed in any of the scores between the two groups.

Multivariate analysis was applied to evaluate the association of high CH50 and poor concentration with predictors of patient background (age, sex, and severity in the acute phase of COVID-19), clinical symptoms (fatigue, headache, insomnia, and tiredness), and laboratory parameters (white blood cell count, erythrocyte sedimentation rate, and serum levels of ferritin and lactate dehydrogenase) (**Table 5**). Consequently, a high CH50 and the presence of clinical symptoms of fatigue and insomnia were significantly associated with poor concentration. Finally, we performed the multivariate analysis using brain fog as a response variable (**Table 6**). Similar to the above results, high CH50, male sex, fatigue, and insomnia were significantly associated with brain fog.

Discussion

Up to 60% of the patients visiting our CAC showed abnormally high levels of CH50. This is noteworthy in that more than half of the patients with long COVID were proven to have involvement of the complement system, even though it was measured three months after the onset of COVID-19. While other inflammatory markers remained within normal ranges, they exhibited slight yet statistically significant elevations in the high CH50 group. This observation implies a potential association between the activation of inflammatory pathways, including the complement system, and the development of long COVID. Recent research has progressively elucidated the hypothetical mechanisms underlying long COVID pathogenesis. Notably, pathophysiological alterations in dysregulated immunity, changes in microbiota composition, abnormal autoimmune responses, coagulation disturbances, microvascular endothelial damage, and dysfunction in neurological signaling have all been proposed as potential underlying factors [6]. The chronic inflammatory state resulting from the persistence of SARS-CoV-2 in the body is presumed to be a triggering factor in these conditions [30]. Our current data support the hypothesis that the complement system may be implicated in the development of long COVID.

Among the various manifestations, poor concentration was significantly more common in the high CH50 group. Remarkably, high CH50 was selected as a predictor of poor concentration when analyzed with those possibly related to it, such as fatigue and insomnia. Although the involvement of brain fog appeared to be higher in the high CH50 group (24.2% vs. 31.0%), there

was no statistically significant difference in the univariate analysis. However, the multivariate regression model demonstrated a significant association between high CH50 levels and brain fog. Despite the absence of definitive diagnostic criteria, the symptoms of brain fog include various cognitive impairments such as poor concentration. Therefore, we conclude that high CH50 levels are associated with brain fog in patients with long COVID. According to recent findings, the term “brain fog” refers to not a single experience alone, but complicated, heterogeneous, subjective experiences that are rich in descriptions of distinct and overlapping phenomena, such as dissociation, fatigue, forgetfulness, and excessive cognitive effort [31]. Thus, establishing clear criteria for an unresolved entity based on symptomatology is difficult. We hope that future studies will explore the usefulness of complement measurements, such as a prognostic marker for the development of the long COVID in the acute or subacute phase, a laboratory parameter to evaluate treatment efficacy, or one of the reference criteria for the long COVID diagnosis.

There is an urgent need to elucidate the etiology of brain fog and develop treatment strategies. According to recent studies, the damage to and influence of SARS-CoV-2 infection on neurocognitive function have been considered as relevant factors. For example, such patients were shown to have an increased risk of various post-acute neurological disorders, especially cognition and memory disorders (hazard ratio, 1.77) and Alzheimer’s disease (hazard ratio, 2.03), after one year compared to uninfected individuals [32]. Compared to other respiratory infections, the risks

of psychotic disorder, cognitive deficit, dementia, and epilepsy or seizures were also demonstrated to be increased in an international, long-term, retrospective cohort study using electronic health record networks [33]. However, neurological sequelae reportedly continue longer than somatic symptoms [34]. Recent efforts have suggested that early viral treatment, as well as a prior history of vaccination, reduce the risk of the long COVID [35–37]. Based on these facts, it can be deduced that reduced involvement of complement immunity by appropriate therapy or prevention may prevent the onset of brain fog. This needs to be carefully investigated by future researches.

The complement pathway, which consists of the classical complement pathway, alternative complement pathway, and lectin pathway, is very complicated and is not highly specific to a disease. In the acute phase of COVID-19, excessive complement activation with substantial amplification of the inflammatory response, known as a cytokine storm, potentially hastens disease progression and commences complement-dependent cytotoxic tissue damage, triggering the coagulation cascade, resulting in thrombotic microangiopathy and end-organ damages [38]. Of the various complement components, C5 and C5a inhibitors appear to be the most promising for suppressing the cytokine release and reduce the severity of COVID-19 [39]. Based on our data, we inferred that complement inhibitors may possibly mitigate long COVID.

The frequencies of physical symptoms, such as fatigue, headache, dysosmia, insomnia, dyspnea, tiredness, and low-grade fever, including the scoring data, were almost identical between

the normal and high CH50 groups. Fatigue, the most representative somatic symptom of long COVID, reportedly affects nearly 60% of patients [2], as indicated in our data. However, the proportion of patients with fatigue in the high CH50 group was similar to that in the normal CH50 group. This may indicate that a high CH50 does not influence the somatic manifestations of long COVID, although this should be further investigated in subsequent studies.

Unexplained post-acute infection syndromes, similar to those in long COVID, have been a matter of debate. A recent review article presented the current understanding and challenges of long COVID and similar persistent syndromes developing after other infections such as Lyme disease, Epstein-Barr virus, and Q fever [40]. Cutting-edge scientists have examined the possible pathophysiology of these inexplicable conditions, including central sensitization, dysautonomia, immunological dysfunction, and residual viral fragments. They highlighted the importance of securing patients' QOL under a specifically organized healthcare system, as well as the necessity of diagnostic criteria and promising therapies for such syndromes. Another emerging disease will appear sooner or later, and administrative and scientific platforms for such fastidious syndromes should be developed.

The limitations of this study should be addressed. First, all the included patients were referred from neighboring clinics or hospitals, and thus, the aggregated data could be biased. Second, a causal relationship between long COVID symptoms and high CH50 could not be firmly

determined because of the study design. Third, the presence of inflammatory pathologies other than long COVID at the visit was not fully excluded and adjusted for. Fourth, the presence of potential confounding factors must be considered in the multivariate analysis. Also, the case numbers included in the multivariate analysis might be insufficient, leaving the possibility of statistical inaccuracy and a need of further analysis for validity. Fifth, the CH50 was not quantitatively tested in the range of ≥ 60 U/mL, and further detailed analysis was impossible. In addition, the timing of CAC visits and CH50 measurements from disease onset differed among patients, which could have influenced the laboratory data. Despite these points, the data provided in this study were suggestive of the relevance of complement immunity in developing long COVID, especially brain fog.

In conclusion, high CH50 levels were frequently observed in patients with long COVID, approximately 60%, which could underscore the pathogenesis of poor concentration, or possibly brain fog. Still, due to a lack of data, we do not emphasize a need of routinely measuring CH50 values in patients with long COVID. Diagnostic criteria for long COVID are yet to be established, but pathological involvement and causal relationship of complement immunity in such a complexity of somatic and mental disorders should be further investigated by continuous, large surveillance and comprehensive data collection. Hopefully, randomized controlled trials to evaluate the efficacy and safety of complement inhibitors for the long COVID should be

considered.

Author Contributions:

H.H. (Hagiya) conceived and designed the study; K.T., Y.O., N.S., Y.N., and H.H. (Honda) collected the data; M.F. was responsible for laboratory testing; H.H. (Hagiya) analyzed the data and drafted the manuscript; F.O. supervised the study. All authors read and agreed to the publication of the final version of the manuscript.

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Institutional Review Board Statement:

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Okayama University Hospital (No. 2105-030).

Informed Consent Statement:

Informed consent from the patients was not necessary due to the anonymization of the data.

Information about the current study was posted on our hospital's walls and website, and patients who wanted to opt out were given the option.

Data Availability Statement:

Detailed data will be available if requested to the corresponding author.

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Conflicts of Interest:

The authors declare no conflict of interest.

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- 99

100 **Table 1. Baseline characteristics of patients with long COVID aged ≥ 18 years, in total and by CH50 values**

Patient groups	Overall (n=478)	Normal CH50 (n=194, 40.6%)	High CH50 (n=284, 59.4%)	<i>p</i> value
Age (years), median [IQR]	43 [33–52]	41 [26.25–51]	44.5 [35.75–52.25]	0.005
Sex, Female, n (%)	256 (53.6%)	102 (52.6%)	154 (54.2%)	0.78
Days from onset to visit [IQR]	87.5 [59–133.75]	91 [62–142]	86.5 [56.75–130.25]	0.28
Body temperature at visit [IQR]**	36.7 [36.5–37.0]	36.7 [36.4–36.9]	36.7 [36.5–37.0]	0.15
Severity of COVID-19				
Mild, n (%)	404 (84.5%)	166 (85.6%)	238 (83.8%)	0.29
Moderate, n (%)	29 (6.1%)	14 (7.2%)	15 (5.3%)	
Severe, n (%)	45 (9.4%)	14 (7.2%)	31 (10.9%)	
Vaccination***				
None	173 (36.2%)	64 (33.3%)	109 (38.4%)	0.40
1-2 doses	192 (40.2%)	78 (40.6%)	114 (40.1%)	
≥3 doses	111 (23.2%)	50 (26.0%)	61 (21.5%)	

101 Number of missing data: * 1 patient, ** 4 patients, and *** 3 patients. A high CH50 was defined as ≥ 59 U/mL.

102 CH50, 50% hemolytic complement activity; COVID-19, coronavirus disease 2019, IQR, interquartile range

103

104 **Table 2. Comparison of laboratory data for inflammatory parameters between patients with normal and high CH50 values**

Patient groups	Overall (n=478)	Normal CH50 (n=194, 40.6%)	High CH50 (n=284, 59.4%)	<i>p</i> value
White blood cell counts (/μL) [IQR]	6,200 [4,980–7,503]	5,565 [4,793–6,812]	6,620 [5,395–7,970]	<0.001
ESR [IQR]*	8 [4–14]	6 [2–11]	9 [6–15]	<0.001
Ferritin [IQR]	126 [51.075–250.75]	114.5 [42.9–210.75]	138 [56.825–276.25]	0.03
LDH [IQR]*	169 [151–191]	161 [147–182]	173.5 [155.75–194.25]	<0.001

105 Number of missing data points: 1 patient *

106 CH50, 50% hemolytic complement activity; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactate dehydrogenase

107

108 Table 3. Numbers and proportions of chief complaints and brain fog between patients with normal and high CH50 values.

Chief complaints	Overall (n=478)	Normal CH50 (n=194, 40.6%)	High CH50 (n=284, 59.4%)	<i>p</i> value
Fatigue	293 (61.3%)	114 (58.8%)	179 (63.0%)	0.39
Headache	104 (21.8%)	44 (22.7%)	60 (21.1%)	0.74
Dysosmia	100 (20.9%)	39 (20.1%)	61 (21.5%)	0.73
Insomnia	96 (20.1%)	35 (18.0%)	61 (21.5%)	0.42
Dysgeusia	102 (21.3%)	38 (19.6%)	64 (22.5%)	0.50
Dyspnea	89 (18.6%)	31 (16.0%)	58 (20.4%)	0.23
Hair loss	66 (13.8%)	23 (11.9%)	43 (15.1%)	0.35
Poor concentration	53 (11.1%)	14 (7.2%)	39 (13.7%)	0.03
Dizziness	41 (8.6%)	14 (7.2%)	27 (9.5%)	0.41
Tiredness	35 (7.3%)	14 (7.2%)	21 (7.4%)	1.00
Low-grade fever	25 (5.2%)	11 (5.7%)	14 (4.9%)	0.84
Brain Fog	135 (28.2%)	47 (24.2%)	88 (31.0%)	0.12

109 Brain fog was clinically determined by each physician according to patient's symptoms.

110 **Table 4. Comparisons of clinical scorings between patients with normal and high CH50**

	Overall (n=478)	Normal CH50 (n=194, 40.6%)	High CH50 (n=284, 59.4%)	<i>p</i> value
FAS*	33 [25–41]	32 [23–41]	34 [26–41]	0.32
FAS_Physical*	19 [14–22]	18 [13–21]	19 [15–22]	0.13
FAS_Mental**	15 [10–19]	15 [9–20]	15 [11–19]	0.61
EQ-5D-5L***	0.711148 [0.5813667–0.844124]	0.739871 [0.5983498–0.844124]	0.708480 [0.5745885–0.825748]	0.12
EQ-5D-VAS****	60 [40–70]	60 [45–75]	60 [40–70]	0.09
FSSG*****	8 [4–15]	8 [4–14.25]	8 [4–15]	0.85
SDS*****	49 [43–55]	49 [41–55]	49 [44–55]	0.45

111 FAS, Fatigue Assessment Scale; EQ-5D, EuroQOL Five-dimensional Questionnaire; EQ-5D-5L, Five levels of the EQ-5D; EQ-5D-VAS, Visual

112 Analog Scale of the EQ-5D, FSSG, Frequency Scale for the Symptoms of GERD; SDS, Self-rating Depression Scale.

113 Number of missing data points: * 3 patients, ** 4 patients, *** 16 patients, **** 15 patients, and ***** 4 patients.

114

115 **Table 5. Logistic regression analysis of factors potentially associated with poor concentration.**

Predictors	Adjusted odds ratio [95% confidence intervals]	<i>p</i> value
Patient background		
Age, years	1.01 [0.98–1.03]	0.64
Sex, male	2.16 [0.97–4.82]	0.06
Severity in the acute phase		
mild vs. moderate	0.34 [0.04–2.70]	0.30
mild vs. severe	0.62 [0.17–2.25]	0.47
Symptoms		
Fatigue	2.35 [1.09–5.08]	0.03
Headache	1.10 [0.55–2.22]	0.79
Insomnia	2.08 [1.07–4.04]	0.03
Tiredness	1.61 [0.58–4.50]	0.36
Laboratory parameters		
High CH50	2.70 [1.33–5.49]	0.006
WBC	0.88 [0.73–1.06]	0.17
ESR 1hour	0.96 [0.90–1.01]	0.11
LDH	0.99 [0.98–1.00]	0.18
Ferritin	1.00 [0.99–1.00]	0.78

116 CH50, 50% hemolytic complement activity; ESR, erythrocyte sedimentation rate, LDH, lactate dehydrogenase WBC, white blood cell count.

117 Explanatory variables of the multivariate logistic analysis include age, sex, severity, clinical symptoms (fatigue, headache, insomnia, and tiredness),
118 and laboratory parameters (CH50, WBC, ESR, and serum levels of ferritin and LDH).

119

120 **Table 6. Logistic regression analysis of factors potentially associated with brain fog**

Predictors	Adjusted odds ratio [95% confidence intervals]	<i>p</i> value
Patient background		
Age, years	1.01 [0.99–1.03]	0.41
Sex, male	1.80 [1.06–3.07]	0.03
Severity in the acute phase		
mild vs. moderate	1.36 [0.53–3.50]	0.52
mild vs. severe	0.73 [0.32–1.69]	0.47
Symptoms		
Fatigue	3.20 [1.91–5.36]	<0.001
Headache	1.34 [0.81–2.23]	0.25
Insomnia	2.04 [1.23–3.99]	0.006
Tiredness	1.80 [0.84–3.85]	0.13
Laboratory parameters		
High CH50	1.66 [1.04–2.66]	0.04
WBC	0.96 [0.85–1.08]	0.47
ESR 1hour	0.97 [0.94–1.00]	0.06
LDH	0.99 [0.99–1.00]	0.64
Ferritin	0.99 [0.99–1.00]	0.19

121 CH50, 50% hemolytic complement activity; ESR, erythrocyte sedimentation rate, LDH, lactate dehydrogenase WBC, white blood cell count.

122 Explanatory variables of the multivariate logistic analysis include age, sex, severity, clinical symptoms (fatigue, headache, insomnia, and tiredness),
123 and laboratory parameters (CH50, WBC, ESR, and serum levels of ferritin and LDH).

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