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Performance evaluation of CXCL10 ELISA "cosmic" kit to measure CXCL10 in cerebrospinal fluid of patients with HTLV-1-associated myelopathy

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Abstract

Objectives: This study aimed to validate the clinical utility of cerebrospinal fluid (CSF) CXCL10 measurements in HTLV-1-associated myelopathy (HAM) using a CXCL10 ELISA "Cosmic" kit, a more widely applicable method than cytometric bead array (CBA).

Methods: CSF CXCL10 levels were measured in 165 samples from 111 patients with HAM and 18 controls using a CXCL10 ELISA "Cosmic" kit. We assessed the following: (1) CSF CXCL10 concentrations by HAM activity level (high, moderate, and low) versus controls; (2) correlation with CBA; (3) cutoff values, sensitivity, and specificity for differentiating among HAM activity levels; (4) changes in HAM activity after steroid therapy; and (5) relationship between HAM activity and prognosis in patients undergoing steroid therapy. A correlation coefficient of ≥0.9 with CBA was the primary endpoint.

Results: The median CSF CXCL10 levels in the high, moderate, low, and control groups were 4016.0, 841.0, 112.8, and 102.5 pg/mL, respectively. The ELISA findings were highly correlated with the CBA findings ($r = 0.99$). Cutoff values were set at 2500 pg/mL (sensitivity, 93.3%; specificity, 100%) to distinguish between high and moderate activity and 180 pg/mL (sensitivity, 81.8%; specificity, 100%) for low to moderate activity comparable to CBA. The new cutoffs enabled the detection of HAM activity changes and prediction of motor disability progression under steroid therapy.

Conclusion: CXCL10 ELISA "Cosmic" kit findings were strongly correlated with CBA findings, meeting the primary endpoint and demonstrating comparable sensitivity and specificity for distinguishing HAM activity. This product shows a promising ability to determine the therapeutic strategy.

KEYWORDS
CSF, CXCL10, ELISA, HTLV-1, HTLV-1-associated myelopathy

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1 | INTRODUCTION

HTLV-1-associated myelopathy (HAM) is a chronic inflammatory neurological disease caused by human T-cell leukemia virus type 1 (HTLV-1).[1,2] Its main symptoms include gait disturbance, bladder and rectal dysfunction, and sensory impairment, and its pathology is attributed to chronic inflammation of the spinal cord caused by HTLV-1-infected cells.[3,4] It is known that CXCL10, a chemokine, is involved in the chronic spinal cord inflammation of HAM. The mechanism is thought to involve CXCL10 produced by astrocytes, which induces CXCR3-positive infected and inflammatory cells to infiltrate the spinal cord.[5,6] Cerebrospinal fluid (CSF) CXCL10 levels indicate involvement in its disease pathology and reflect HAM disease activity,[7,8] assist in assessing steroid treatment efficacy,[9] and can be useful for predicting post-treatment prognosis.[10] Given that CSF CXCL10 levels correlate with disease activity, as does CSF neopterin, another activation marker of cellular immunity, CSF CXCL10 has been incorporated into the HAM clinical guidelines' criteria for disease activity classification (Table 1) to aid in treatment decision-making.[11]

The clinical utility of CXCL10 was initially demonstrated based on measurements using a cytometric bead array (CBA) (BD Biosciences, San Jose, CA, USA). However, CBA requires specialized equipment and analytical software, making it complex and less widely applicable for clinical testing. This study aimed to verify whether the more widely applicable CXCL10 ELISA "Cosmic" kit, which is based on ELISA principles, can distinguish disease activity, assess steroid treatment efficacy, and predict prognosis similar to CBA.

2 | METHODS

2.1 | Overall study design

This retrospective study analyzed stored CSF samples and clinical data. We evaluated the clinical utility of the CXCL10 measurement system using a CXCL10 ELISA kit in patients with HAM using five test items. The measurements were compared with those of CBA, the current gold standard. The Pharmaceuticals and Medical Devices Agency (PMDA) reviewed the study protocol.

2.2 | Tests conducted

The following tests were conducted:

- Test 1: CSF CXCL10 levels across the high, moderate, and low disease activity groups as well as in the control group;
- Test 2: Correlation assessment with CBA;
- Test 3: Determination of cutoff values, sensitivity, and specificity for classifying disease activity;
- Test 4: Changes in disease activity after steroid treatment; and
- Test 5: Association between disease activity at a single timepoint during steroid treatment and prognosis.

2.3 | Participants and samples

This study included 111 patients with HAM and 18 controls. The HAM diagnosis was based on the criteria established by the Ministry of Health, Labour and Welfare Research Group.[12] Controls consisted of 10 HTLV-1 carriers and eight noninflammatory neurological disease patients without HTLV-1 infection. Among the 111 patients with HAM, 59 had presteroid treatment CSF samples, 36 had presteroid treatment and on-treatment CSF samples, and 16 had on-treatment CSF samples. Of these, 59 patients with pretreatment samples and 27 of 36 with pretreatment and on-treatment samples, for a total of 86 patients, divided into high ($n = 15$), medium ($n = 60$), and low ($n = 11$) disease activity based on the disease activity classification criteria (Table 1).

2.4 | Measurement of CXCL10 in CSF

CSF CXCL10 was measured using CBA (BD Biosciences) and CXCL10 ELISA "Cosmic" (manufacturing/marketing authorization holder: Cosmic Corporation, Tokyo, Japan) kits following the manufacturers' instructions. The operators were blinded to the original sample identifiers. The CXCL10 ELISA kits were provided by Cosmic Corporation.

TABLE 1 Classification criteria for HAM disease activity.[11]

Disease activity	Classification criteria based on biomarkers		Classification criteria based on onset pattern	Classification criteria based on clinical course	MRI findings
	CSF neopterin (pmol/mL)	CSF CXCL10 (pg/mL)			
High	≥44	≥4400	Rapid progression: OMDS ≥5 within 2 y of motor impairment onset	OMDS progression by ≥2 within past 2 y	Spinal cord swelling or high-signal area on T2-weighted imaging
Moderate	6–43	320–4399	Slow progression: neither rapid progression nor stable course		
Low	≤5	<320	Stable course: OMDS ≤3 after 10 y from onset of motor impairment		

Abbreviations: CSF, cerebrospinal fluid; HAM, HTLV-1-associated myelopathy; MRI, magnetic resonance imaging; OMDS, Osame Motor Disability Score.

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2.5 | Specific test methods

The specific test methods were as follows:

- Test 1: CXCL10 levels were measured in patients with untreated high, moderate, and low HAM disease activity ($n = 86$) as well as controls ($n = 18$). Medians, quartiles, means, and standard deviations were calculated. The Kruskal–Wallis test followed by Dunn's post-hoc test was used for the intergroup comparisons;
- Test 2: Correlation analysis between CXCL10 ELISA and CBA measurements was conducted on the CSF CXCL10 levels in 111 patients with HAM. Pearson's correlation coefficient and a linear regression analysis were used to determine the primary regression equation;
- Test 3: Using patients with untreated HAM, cutoff values for distinguishing between high and low disease activity with CBA versus CXCL10 ELISA were established. The 90% confidence intervals (CIs) for sensitivity and specificity were calculated using the Clopper-Pearson method;
- Test 4: Disease activity changes before and during steroid treatment were determined in 36 patients using the cutoff values established in Test 3. The proportion of patients with improved disease activity was calculated, and an exact (two-tailed) test of a binomial proportion with the null hypothesis of "H_0: Improvement proportion = 10%" was performed. The significance level was set at $P < .05$; and
- Test 5: In 52 patients, disease activity at one timepoint during steroid treatment was evaluated for its association with prognosis using Kaplan–Meier analysis and Cox regression.

2.6 | Endpoints

The primary endpoint was the correlation between CBA and CXCL10 ELISA results in Test 2, with a Pearson correlation coefficient ≥0.9 set as the success criterion. The secondary endpoints included the cutoff values for distinguishing disease activity in Test 3 and evaluating the association between disease activity during steroid treatment and prognosis in Test 5.

3 | RESULTS

3.1 | CSF CXCL10 concentrations in each disease activity group (high, moderate, and low) and control group (Test 1)

The median CSF CXCL10 concentrations in patients with untreated HAM ($n = 86$) and controls ($n = 18$) were 853.0 pg/mL and 102.5 pg/mL, respectively (upper part of Table 2). Patients with untreated HAM were further categorized into high, moderate, and low disease activity groups based on their clinical presentation or disease course (Table 1). The median CSF CXCL10 levels in these groups were 4016.0, 841.0, and 112.8 pg/mL, respectively (lower part of Table 2, Figure 1). As shown in Figure 1, significant differences were noted among all group combinations except the low disease activity and control groups.

3.2 | Correlation assessment with CBA (Test 2)

Using data from 111 patients with HAM, a strong correlation was observed between CSF CXCL10 concentrations measured by CXCL10 ELISA and CBA (Figure 2; $r = 0.99$, $P < .0001$). However, CXCL10 concentrations measured by ELISA were approximately 0.56 times those measured by CBA (Figure 2; $Y = 0.5616X$).

3.3 | Cutoff values, sensitivity, and specificity for disease activity levels (high, moderate, and low) (Test 3)

To determine whether CXCL10 ELISA could distinguish disease activity with similar sensitivity and specificity as CBA, we calculated these metrics based on the ELISA results. First, in patients with HAM classified as having high (test group) and moderate/low (control group) activity levels, we applied the established CBA cutoff for high versus moderate activity (4400 pg/mL), yielding a sensitivity of 100.0% (90% CI, 81.9%–100.0%) and specificity of 95.8% (90% CI, 89.4%–98.8%) (upper part of Table 3). Based on the regression formula ($Y = 0.5616X$) from Test 2, the CBA cutoff of 4400 pg/mL

TABLE 2 CSF CXCL10 concentrations in patients with untreated HAM versus controls and in patients with untreated HAM by disease activity level (high, moderate, and low) (all units in pg/mL)

	Minimum	1st quartile	Median	3rd quartile	Maximum	Mean	SD
Group							
Patients with untreated HAM ($n = 86$)	60.2	356.5	853.0	1646.0	7612.0	1418.0	1587.2
Controls ($n = 18$)	48.6	83.7	102.5	164.5	238.0	121.5	54.2
Disease activity							
High ($n = 15$)	2212.0	3613.0	4016.0	5207.0	7612.0	4401.6	1357.5
Moderate ($n = 60$)	196.0	406.0	841.0	1233.0	2364.0	909.6	594.2
Low ($n = 11$)	60.2	94.2	112.8	153.1	201.8	122.7	46.4

Abbreviations: CSF, cerebrospinal fluid; HAM, HTLV-1-associated myelopathy; SD, standard deviation.

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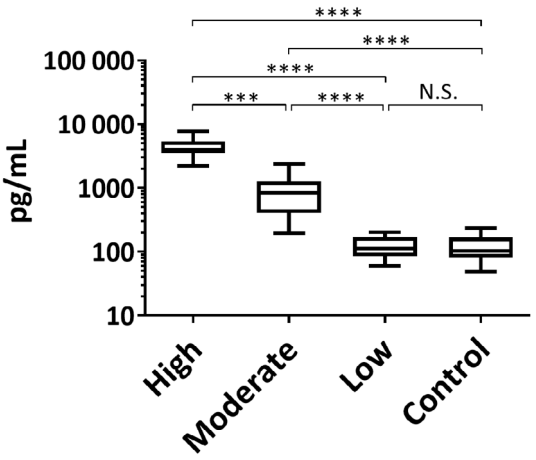

FIGURE 1 Distribution of CSF CXCL10 concentrations by disease activity (high, moderate, and low) and control groups. CSF CXCL10 concentrations measured using the CXCL10 ELISA kit were compared among the high, moderate, and low disease activity and control groups. Data are shown as boxplots, with values presented as the median (IQR) and whiskers representing 1.5 times the IQR. The statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's post-hoc test. CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; N.S., not significant. ***P < .001; ****P < .0001.

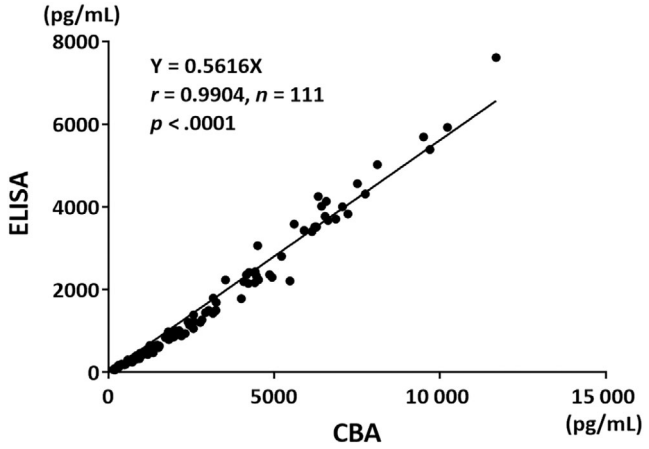

FIGURE 2 Correlation between CXCL10 ELISA kit and CBA findings. The correlation between cerebrospinal fluid CXCL10 concentrations measured using a CXCL10 ELISA kit and CBA was examined in 111 patients with HTLV-1-associated myelopathy. The statistical analyses were performed using Pearson's correlation analysis. The linear regression line is represented by a straight line with an intercept of zero. CBA, cytometric bead array; ELISA, enzyme-linked immunosorbent assay.

corresponded to 2471 pg/mL on the CXCL10 ELISA. Using this cutoff or rounded value of 2500 pg/mL yielded the same sensitivity of 93.3% (90% CI, 72.1%–99.7%) and specificity of 100.0% (90% CI, 95.9%–100.0%) (lower part of Table 3). CXCL10 ELISA sensitivity fell within the 90% CI of that of CBA, while the specificity was higher, at 100%.

TABLE 3 Sensitivity and specificity of CBA cutoff value (4400 pg/mL) and CXCL10 ELISA cutoff value (2500 pg/mL) for distinguishing between high and moderate/low disease activity.

	High disease activity	Moderate/low disease activity	Total
≥4400 pg/mL	15	3	18
<4400 pg/mL	0	68	68
Total	15	71	86
Sensitivity (90% CI)	100.0% (81.9%–100.0%)		
Specificity (90% CI)	95.8% (89.4%–98.8%)		
≥2500 pg/mL	14	0	14
<2500 pg/mL	1	71	72
Total	15	71	86
Sensitivity (90% CI)	93.3% (72.1%–99.7%)		
Specificity (90% CI)	100.0% (95.9%–100.0%)		

Abbreviations: CBA, cytometric bead array; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

TABLE 4 Sensitivity and specificity of CBA cutoff value (320 pg/mL) and CXCL10 ELISA cutoff value (180 pg/mL) for distinguishing between low and moderate/high disease activity.

	Low disease activity	Moderate/high disease activity	Total
<320 pg/mL	8	0	8
≥320 pg/mL	3	75	78
Total	11	75	86
Sensitivity (90% CI)	72.7% (43.6%–92.1%)		
Specificity (90% CI)	100.0% (96.1%–100.0%)		
<180 pg/mL	9	0	9
≥180 pg/mL	2	75	77
Total	11	75	86
Sensitivity (90% CI)	81.8% (53.0%–96.7%)		
Specificity (90% CI)	100.0% (96.1%–100.0%)		

Abbreviations: CBA, cytometric bead array; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

Similarly, when the low disease activity group was classified as the test group and the high/moderate group as the control group, use of the CBA low-to-moderate cutoff of 320 pg/mL provided a sensitivity of 72.7% (90% CI, 43.6%–92.1%) and specificity of 100.0% (90% CI, 96.1%–100.0%) (upper part of Table 4). Based on the regression formula, this CBA cutoff corresponded to 180 pg/mL for CXCL10 ELISA, which resulted in a sensitivity of 81.8% (90% CI, 53.0%–96.7%) and specificity of 100.0% (90% CI, 96.1%–100.0%) (lower part

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TABLE 5 Disease activity classification criteria based on CSF CXCL10 concentration measured by CXCL10 ELISA.

Disease activity	CSF CXCL10 concentration
High	≥2500 pg/mL
Moderate	180 to <2500 pg/mL
Low	<180 pg/mL

Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay.

TABLE 6 Disease activity before versus during steroid treatment.

		Disease activity during treatment			
		High	Moderate	Low	Total
Disease activity before treatment	High	1	9	0	10
	Moderate	0	25	1	26
	Low	0	0	0	0
Total		1	34	1	36

of Table 4). The sensitivity of CXCL10 ELISA was within the 90% CI of CBA, with an identical specificity of 100%. Based on these findings, we defined the CSF CXCL10 cutoff values for CXCL10 ELISA as ≥2500, 180–2500, and <180 pg/mL for high, moderate, and low disease activity, respectively (Table 5).

3.4 | Changes in disease activity after steroid treatment (Test 4)

Using the CXCL10 ELISA cutoff values determined in Test 3, we assessed the disease activity before and during steroid treatment in 36 patients (Table 6). Improvement was observed in 10 of 36 patients (27.8%), with a two-sided 95% CI of 14.2%–45.2%. Conversely, no improvement was noted in 26 of 36 cases (72.2%), with a two-sided 95% CI of 54.8%–85.8%. An exact test of the binomial proportion yielded a value of $P = .0044$, which allowed us to reject the null hypothesis and conclude that the improvement proportion was significantly higher than 10%.

3.5 | Association between disease activity at one timepoint during steroid treatment and prognosis (Test 5)

Using the CXCL10 ELISA cutoff values determined in Test 3, disease activity was assessed in 52 cases at one timepoint during steroid treatment and was high ($n = 5$), medium ($n = 45$), and low ($n = 2$). A significant difference was found in the time to worsening by one Osame Motor Disability Score (OMDS) between the high and moderate disease activity groups (Figure 3; $P < .0001$). Patients with high disease activity showed a higher risk of worsening OMDS than those in the moderate disease activity group (hazard ratio, 15.32; 95% CI, 0.0832–2821). Meanwhile, the two patients with low disease activity were followed for 0.9 and 4.6 y, respectively, with no OMDS progression observed during the observation period.

4 | DISCUSSION

This study demonstrated that the CXCL10 ELISA "Cosmic" kit can classify disease activity in patients with HAM as effectively as CBA. First, in this study it was confirmed that CBA, which has been used to measure CSF CXCL10 concentrations as a disease activity classification, could reliably classify disease activity with high sensitivity and specificity, as previously established (upper part of Tables 3 and 4). Additionally, the same samples were tested using CBA and CXCL10 ELISA "Cosmic" kits, each of which was performed by different blinded operators. Despite this, the two methods exhibited a very high correlation ($r = 0.99$), surpassing the primary endpoint threshold of 0.9. Furthermore, one of the secondary endpoints was that the sensitivity and specificity of the CXCL10 ELISA should fall within 90% CI of the CBA values. Although the 90% CI was narrower than the commonly used 95% CI, the CXCL10 ELISA results met this standard. Thus, the CXCL10 ELISA "Cosmic" kit can classify HAM disease activity as well as the CBA kit. This conclusion was further supported by significant differences in CSF CXCL10 concentrations among the three disease activity groups (Figure 1). CSF neopterin levels, like CSF CXCL10 levels, can be used to assess disease activity (Table 1). However, the measurement of neopterin requires high-performance liquid chromatography, and if CXCL10 can be measured by ELISA, CSF CXCL10 measurement would be superior in terms of versatility.

The study findings also suggest that the CSF CXCL10 levels measured with a CXCL10 ELISA "Cosmic" kit are similar to those measured by a CBA kit to assess steroid treatment efficacy and predict patient prognosis. The former is supported by the findings of Test 4, which evaluated changes in disease activity based on CSF CXCL10 levels during steroid treatment. Known to improve disease activity,[9] the effect of steroid treatment was confirmed using CXCL10 ELISA (Table 6). Prognostic predictions after steroid treatment were supported by Test 5, which examined the association between disease activity during steroid therapy and outcomes. On CXCL10 ELISA, patients with high post-treatment CSF CXCL10 levels demonstrated faster progression of their motor disability, consistent with previous findings (Figure 3).[10] Thus, CXCL10 ELISA demonstrated a clinical utility comparable to that of CBA. CSF CXCL10, measured using a CBA method, has been shown to have potential as a surrogate marker,[9] and in fact, CSF CXCL10 has been used as a marker to infer the therapeutic efficacy of a new drug candidate.[13] This suggests that the CSF CXCL10 assay will continue to be useful in drug development, even after the assay is converted to ELISA.

One limitation of this study is that the absolute CSF CXCL10 concentration remains uncertain. The values measured using CXCL10 ELISA were approximately 0.56 times lower than those obtained using CBA (Figure 2). Because neither method showed issues on the

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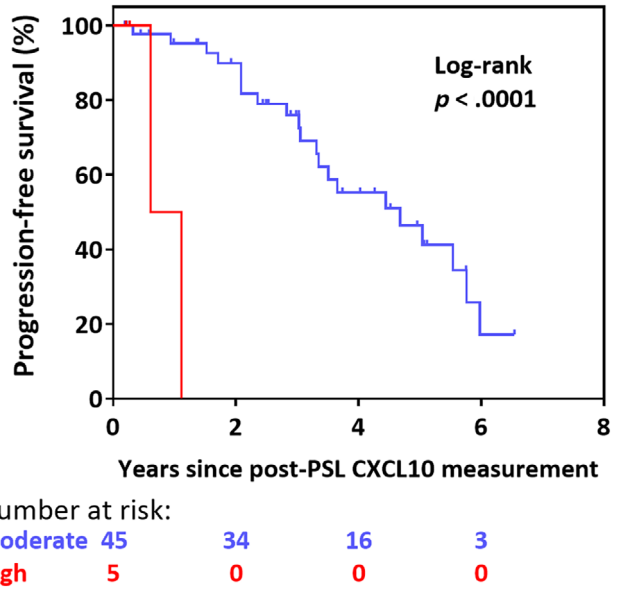

FIGURE 3 Association between disease activity classification based on CSF CXCL10 levels measured by CXCL10 ELISA and worsening OMDS. The Kaplan–Meier method was used to analyze the rate of OMDS worsening by one grade from the time of CSF CXCL10 measurement during steroid treatment. The disease activity levels were determined based on the classification criteria listed in Table 5. The high (red) and moderate (blue) disease activity groups were compared using log-rank tests. CSF, cerebrospinal fluid; OMDS, Osame Motor Disability Score.

calibration curves, the discrepancy may be attributed to the different CXCL10 concentrations of their respective standards. However, in clinical practice, absolute CSF CXCL10 values are less critical and relative quantification is more significant.

5 | CONCLUSION

This study showed that the CXCL10 ELISA "Cosmic" kit can measure CSF CXCL10 as effectively as a CBA kit. Moreover, it established cut-off values for classifying disease activity using CXCL10 ELISA measurements (Table 5). In Japan, if the CXCL10 ELISA kit becomes insurance-approved and widely available in the future, this classification standard could assist in treatment planning, the evaluation of therapeutic effects, and the prediction of prognosis.

AUTHOR CONTRIBUTIONS

R. Ko, T. Sato, and Y. Yamano contributed to the conception and design of the study; K. Takahashi and Y. Kunitomo conducted the analysis; K. Tanabe and T. Sato conducted the statistical analysis; R. Ko, T. Sato, and Y. Yamano analyzed and interpreted the results; R. Ko, T. Sato, and Y. Yamano drafted the article; and R. Ko, N. Yagishita, J. Yamauchi, N. Araya, M. Nakashima, T. Shimizu, and Y. Yamano critically revised the article. All authors have read and approved the final version of the article.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DISCLOSURE OF ETHICAL STATEMENTS

Approval of the research protocol: This retrospective study was approved by the Ethics Committee of the St. Marianna University School of Medicine using the opt-out method. All participants provided written informed consent for the HAM research prior to the CSF sampling (approval IDs: 1646, 2560, 4983, or 5472).
Informed Consent: Informed consent was obtained from all subjects.
Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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