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Serum calcitonin gene-related peptide and inflammatory marker dynamics across the migraine attack cycle: A case-control analysis

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Abstract

Background: The role of calcitonin gene-related peptide (CGRP) and inflammatory pathways in migraine pathophysiology remains to be fully elucidated. This study addressed inconsistencies in the existing literature by comparing serum levels of CGRP and inflammatory markers in patients with migraine during (ictal) and between (interictal) attacks, relative to healthy controls.

Methods: A total of 169 individuals were enrolled: 39 patients with chronic migraine (CM), 100 with episodic migraine (EM), and 30 healthy controls matched for age and sex. Among patients with EM, 63 were assessed during a migraine attack, while 37 were assessed during an interictal phase.

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Following assessment of demographic and headache characteristics, venous blood samples were obtained. Serum levels of CGRP, cyclooxygenase-2 (COX-2), and interleukin-17 (IL-17) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

Results: The mean age of the control group and patients with migraine was 41 and 38 years, respectively. Patients with EM in the ictal phase exhibited significantly higher serum CGRP and IL-17 levels compared to interictal patients and healthy controls ($P < 0.001$). Patients with CM also had significantly higher serum concentrations of CGRP and IL-17 than both interictal EM patients and healthy controls ($P < 0.01$). Analysis of serum COX-2 levels also revealed that both the CM and ictal EM groups had significantly higher concentrations than the interictal EM group ($P < 0.001$).

Conclusion: Our findings indicate that both the ictal state in EM and the CM state are characterized by significant, similar increases in serum levels of CGRP, IL-17, and COX-2, distinguishing them from both the interictal state and healthy controls.

Introduction

Migraine, the leading cause of disability among adults under age 50, has a profound impact on approximately 11% of the adult population worldwide.[1,2] Beyond its significant societal and individual burden,[3] migraine is approximately two to three times more prevalent in women than in men. Female patients with migraine typically experience longer, more severe, and more disabling headache attacks, with an increased risk of attack recurrence, compared to male patients.[4]

According to the International Classification of Headache Disorders, 3rd Edition (ICHD-III), chronic migraine (CM) is characterized by headache occurring on ≥ 15 days per month for at least three months, with at least eight of those days meeting criteria for migraine or responding to triptan therapy. Episodic migraine (EM) is defined as headache occurring on < 15 days per month.[5,6] Longitudinal evidence indicates that EM can progress to CM over time, particularly if effective preventive therapy is not initiated.[7]

The pathogenesis of migraine is thought to originate from central neuronal hyperexcitability, which predisposes to cortical spreading depression. This depolarizing wave activates trigeminal nociceptive pathways, culminating in the peripheral release of neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP).[7-9] CGRP is a vasoactive neuropeptide densely expressed in trigeminovascular system that plays a central role in migraine pathophysiology. This is evidenced by its ability to provoke migraine upon infusion and by its increased serum concentrations during migraine attacks.[10] However, the interictal profile of CGRP, particularly in CM, remains controversial. While some studies report persistent interictal elevations in patients with CM, supporting its potential as a biomarker of migraine chronification, others have failed to replicate this finding.[11-15]

The release of vasoactive neuropeptides such as CGRP triggers trigeminovascular activation, leading to arterial vasodilation, mast cell degranulation, plasma protein extravasation, and the subsequent release of pro-inflammatory mediators, including cytokines.[8,16] Evidence indicates that pro-inflammatory cytokines may contribute to migraine pathogenesis by activating trigeminovascular nociceptors in the meninges, thereby promoting headache. Interleukin-17 (IL-17), a key pro-inflammatory cytokine derived from T helper 17 (Th17) cells, is implicated in neuroinflammation and migraine pathophysiology.[17-19] It contributes through multiple mechanisms: stimulating the production of downstream inflammatory mediators such as cyclooxygenase-2 (COX-2), promoting blood-brain barrier (BBB) disruption, and enhancing the release of nitric oxide (NO). COX-2, the rate-limiting enzyme in prostaglandin biosynthesis, mediates inflammatory responses and has been implicated in the pathogenesis of migraine.[20] Additionally, given the well-established role of NO in migraine attack initiation, this pathway could mechanistically connect IL-17-mediated inflammation with the pathogenesis of migraine headache.

Based on the identified literature gap regarding the dynamic fluctuation of these biomarkers across the migraine cycle, this study was designed to compare serum levels of key inflammatory and pain-related biomarkers between migraine phases and healthy controls. Specifically, we aimed to measure serum levels of the migraine pain biomarker, CGRP, and the pro-inflammatory mediators, IL-17 and COX-2, in CM and EM patients during and between attacks. Additionally, we sought to explore the correlations of these biomarkers with monthly headache frequency and with each other to investigate potential relationships between migraine pain intensity,

inflammatory status, and neurogenic signaling.

Materials and Methods

Study population: This cross-sectional case-control study was conducted between September 2017 and June 2020, at the tertiary headache clinic of Sina University Hospital, affiliated with Tehran University of Medical Sciences, Tehran, Iran. Cases consisted of 39 patients with CM and 100 patients with EM. Within the EM group, 63 patients were in the ictal state (during an attack), while 37 were in the interictal state (defined as having been headache-free for at least 72 hours). A control group consisting of 30 age- and sex-matched, headache-free candidates was chosen from general population. Subjects of both groups were recruited through public advertisement (flyers) on a voluntary basis to participate in this case-control study evaluating serum biomarkers in migraine.

For the case group, the migraine diagnosis was made by a neurologist specializing in headache disorders, in accordance with the ICHD-III criteria.[21] To be included, patients must have a documented history of either CM or EM for at least six months prior to recruitment. All investigated subjects had a body mass index (BMI) ranging from 18.5 to 35.0 kg/m^2, and were aged between 18 and 65 years. The individuals who had a history of inflammatory, infectious, allergic, or immune disorders, cardiovascular or endocrinological diseases, liver or kidney disorders, or other neurological or chronic diseases, such as epilepsy, Parkinson's disease (PD), multiple sclerosis (MS), or Alzheimer's disease (AD) as well as those who declined to provide informed consent were excluded from the study.

This study procedure was executed on the basis of the guidelines outlined in the 2013 version of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of National Institute for Medical Research Development (ID: IR.NIMAD.REC.1396.054) and was funded under grant no. 957537.

Headache diaries and visual analog scale (VAS): At baseline, the demographic characteristics, anthropometric indices, and clinical data of all studied subjects were collected. Then, approximately 5 ml of venous blood was collected from the study population after 8 hours of fasting.

The patients with migraine were also informed how to fill out a headache diary during the next month.[22] The length and severity of headache attack, number of headache attack, and number of abortive drugs were recorded in headache diary. The details on these features are described elsewhere.[23]

Blood samples analysis: Approximately, 5 ml fasting venous blood was taken from patients with CM (n = 39), EM subjects in the ictal phase (n = 63), and EM subjects in the interictal phase (n = 37) 72 hours after their most recent attack during their second visit after one month, when the headache diaries were collected. Then, the blood samples were centrifuged at 4 °C for 10 minutes and serum samples were kept at -80 °C until laboratory analysis. Serum levels of CGRP, IL-17, and COX-2 were evaluated using enzyme-linked immunosorbent assay (ELISA) kits (96 tests per kit; Crystal Day, China). To accurately determine the interval between the last headache attack and the time of blood sample collection, the relevant information was also recorded.

In order to verify the collected data normal distribution, a Shapiro-Wilk test was applied. Between-group differences of the variables were then determined on the basis of the independent samples t-test [in case of normally-distributed continuous variables displayed as mean ± standard deviation (SD)], the Mann-Whitney U test [in case of non-normally-distributed continuous variables displayed as median and interquartile range (IQR)], or chi-square test/Fisher's exact test (in case of categorical variables displayed as number and percentage). The Kruskal-Wallis test and Bonferroni post-hoc t-test were also conducted for making comparisons in mean values of serum antioxidant and inflammatory biomarkers between two groups of patients with migraine and the controls. The Spearman correlation test was then performed to investigate the correlations between serum levels of CGRP, IL-17, and COX-2 among all participants, as well as the correlation between headache days per month and the evaluated biomarkers in the migraineurs. Analyses were conducted applying SPSS software (version 24, IBM Corporation, Armonk, NY, USA). P-value less than 0.05 was noted as statistical significance level in all analyses.

Results

Baseline characteristics: Table 1 presents the baseline characteristics of the studied subjects. The mean age of the control group was 41 years, and the mean age of patients with migraine was 39, 38, and 37 years, in CM, ictal EM, and interictal EM groups, respectively. Women accounted for 73.3% of the control group, compared to 74.4% in the CM group, 87.3% in ictal EM group, and 78.4% in the interictal EM group.

Table 1. Baseline characteristics of the studied participants

	Control group (n = 30)	Patients with CM (n = 39)	Patients with EM (ictal phase) (n = 63)	Patients with EM (interictal phase) (n = 37)	P
Gender (women) [n (%)]	22 (73.3)	29 (74.4)	55 (87.3)	29 (78.4)	0.290*
Age (year) (mean ± SD)	41 ± 8	39 ± 8	38 ± 8	37 ± 12	0.483**

*Chi-square test; **One-way analysis of variance (ANOVA) test

The data in this table were previously published in the study by Goadsby et al.[24] in a slightly different format.

CM: Chronic migraine; EM: Episodic migraine; SD: Standard deviation

No significant differences were noted between the groups in age and gender distribution.

Between-group comparisons of BMI revealed that patients with EM who were in interictal periods had significantly lower BMI than those in the CM and ictal EM groups, with mean values of 24.24, 26.51, and 26.29 kg/m^2, respectively (Table 1).

Regarding the migraine patients' headache-related features, median days with headache were 27, 8, and 7 per month in CM, ictal EM, and interictal EM groups, respectively. More details on headache features of migraineurs are described elsewhere.[24]

Serum biochemical assessments: Table 2 depicts comparisons of serum CGRP, IL-17, and COX-2 levels between the studied groups. Regarding serum levels of CGRP and inflammatory factors, significant between-group differences were detected. Patients with EM who reported having headache attacks at the time of blood collection (ictal phase) showed significantly increased levels of serum CGRP than those in interictal phase and healthy controls [median (IQR): 189.03 (75.98), 140.02 (30.62), and 139.10 (30.31) ng/l, respectively; P < 0.001]. Patients with CM were also shown to have significantly higher CGRP serum concentrations compared to EM patients in interictal phase and healthy subjects [median (IQR): 188.58 (39.41), 140.02 (30.62), and 139.10 (30.31) ng/l, respectively; P < 0.001] (Table 2).

Likewise, patients with EM in ictal phase demonstrated significantly elevated levels of serum IL-17 compared to EM patients in interictal period and healthy individuals [median (IQR): 91.47 (52.59), 60.34 (65.06), and 59.29 (31.21) ng/l, respectively; P < 0.001]. Patients with CM were also revealed to have significantly greater IL-17 serum concentrations in comparison with interictal EM group and healthy controls [median (IQR): 81.36 (72.18), 60.34 (65.06), and 59.29 (31.21) ng/l, respectively; P = 0.009] (Table 2).

The analysis of serum levels of COX-2 revealed significant differences between EM and CM groups. As such, both CM and EM patients in ictal phase showed significantly greater levels of serum COX-2 than EM patients in interictal phase [median (IQR): 45.14 (8.60), 43.63 (24.72), and 35.40 (37.60) ng/l, respectively; P < 0.001] (Table 2).

Correlational analysis: Although very weak positive correlations were observed between serum CGRP, COX-2, and IL-17 levels and headache attacks frequency among migraineurs, none of them were statistically significant except for COX-2 (Spearman rho = 0.18; P = 0.032) (Figure 1, a-c). Furthermore, positive, though weak, correlations were documented between serum CGRP and both IL-17 and COX-2 levels (Spearman rho = 0.21 and 0.20, respectively; P < 0.01) (Figure 2, a and b).

Discussion

The present study demonstrates that both ictal EM and CM are associated with significantly elevated serum CGRP and IL-17 levels compared to interictal EM and healthy controls.

Table 2. Comparisons of serum calcitonin gene-related peptide (CGRP), interleukin-17 (IL-17), and cyclooxygenase-2 (COX-2) levels between the studied groups

	Control group (n = 30)	Patients with CM (n = 39)	Patients with EM (ictal phase) (n = 63)	Patients with EM (interictal phase) (n = 37)	P
	Median (IQR)				
CGRP (ng/l)	139.10 (30.31)$^{a, b}$	188.58 (39.41)$^{a, c}$	189.03 (75.98)$^{b, d}$	140.02 (30.62)$^{c, d}$	< 0.001
IL-17 (ng/l)	59.29 (31.21)$^{a, b}$	81.36 (72.18)$^{a, c}$	91.47 (52.59)$^{b, d}$	60.34 (65.06)$^{c, d}$	0.009
COX-2 (U/l)	41.80 (14.71)	45.14 (8.60)^{a}	43.63 (24.72)^{b}	35.40 (37.60)$^{a, b}$	< 0.001

*Using the Kruskal-Wallis and Bonferroni post-hoc t-test

Superscript letters indicate statistically significant between-group differences (P-value < 0.05); groups sharing the same superscript letter differ significantly

CM: Chronic migraine; EM: Episodic migraine; CGRP: Calcitonin gene-related peptide; IL-17: Interleukin-17; COX-2: Cyclooxygenase-2; IQR: Interquartile range

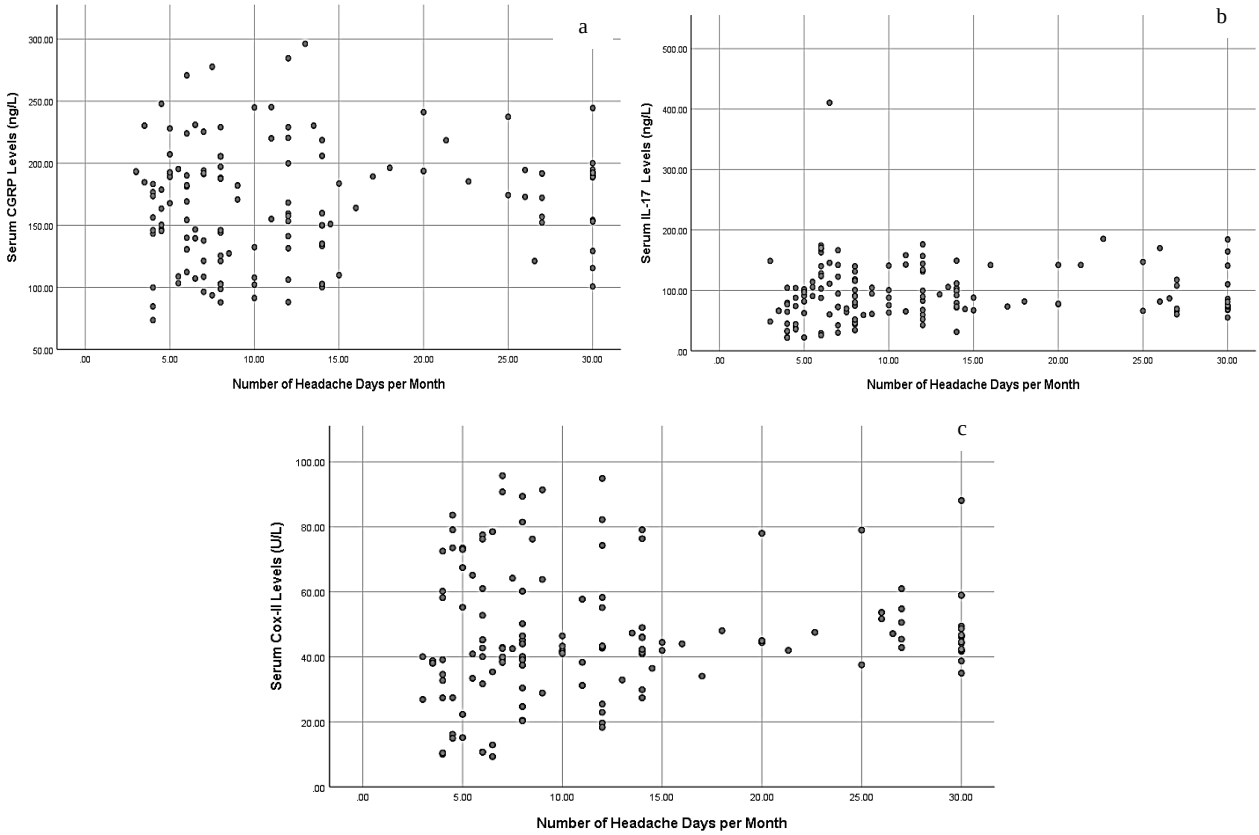

Figure 1. The correlations between migraine pain, inflammatory markers' serum levels, and number of headache days per month among patients with migraine (n = 139)
a) The correlation between calcitonin gene-related peptide (CGRP) serum levels and number of headache days per month (Spearman rho = 0.11; P = 0.206); b) The correlation between interleukin-17 (IL-17) serum levels and number of headache days per month (Spearman rho = 0.15; P = 0.079); c) The correlation between cyclooxygenase-2 (COX-2) serum levels and number of headache days per month (Spearman rho = 0.18; P = 0.032)

Similarly, serum COX-2 concentrations were higher in the CM and ictal EM groups than in the interictal EM group.

Our findings reveal a distinct peripheral inflammatory profile associated with both acute migraine attacks and CM.

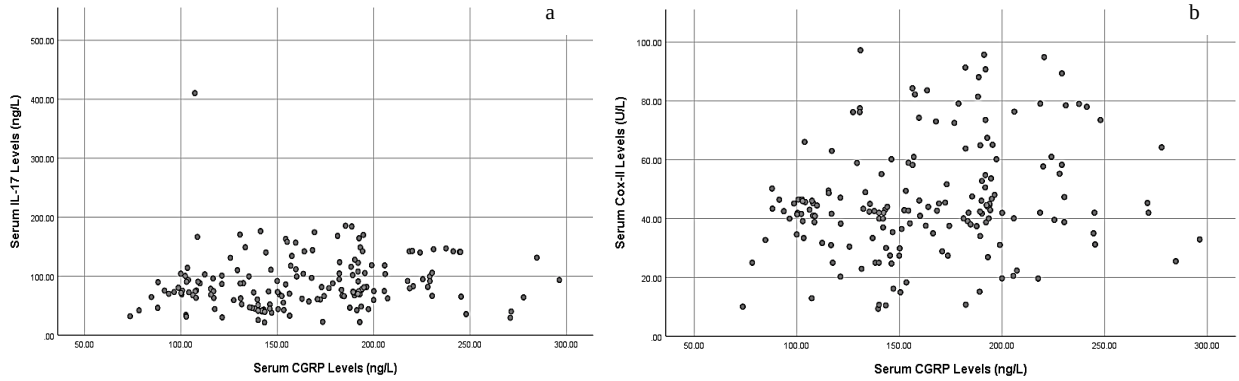

Figure 2. The correlations between migraine pain and inflammatory markers' serum levels among studied subjects (n = 169)
a) The correlation between calcitonin gene-related peptide (CGRP) and interleukin-17 (IL-17) serum levels (Spearman rho = 0.21; P = 0.006); b) The correlation between CGRP and cyclooxygenase-2 (COX-2) serum levels (Spearman rho = 0.20; P = 0.011)

Correlational analyses demonstrated very weak associations between headache frequency and each biomarker, with only COX-2 showing a statistically significant relationship. Furthermore, positive correlations among CGRP, IL-17, and COX-2 suggest interrelated pathophysiological pathways.

CGRP, a 37-amino acid vasoactive neuropeptide, is implicated in immune modulation, vasodilation, pain signal transmission, and neurogenic inflammation. While it is well established that CGRP levels increase during migraine attacks, its interictal profile, particularly in CM, remains controversial.[24,25] Lee et al. reported no elevation in interictal serum CGRP in patients with CM and found no effect of preventive medications on CGRP levels.[26] Similarly, the Danish Headache Group observed no difference in serum CGRP between patients with CM with medication overuse (MO) and healthy controls, either before or after detoxification.[27] In contrast, Cernuda-Morollón et al. demonstrated increased serum CGRP in women with CM, both with and without MO, compared to patients with EM and healthy controls, proposing a role for CGRP in migraine chronification.[13] Greco et al. found significantly higher CGRP levels in CM-MO patients compared to patients with EM, though this association was lost after adjustment for age, sex, and disease duration.[14] Notably, detoxification significantly decreased CGRP levels in these patients, suggesting that MO itself may contribute to elevated CGRP. Higher CGRP plasma levels have also been associated with the need for preventive therapy, suggesting that elevated CGRP may correlate with more frequent attacks.[28] In this context, we investigated CGRP levels across the migraine cycle and found that both ictal EM and CM were associated with significantly elevated serum CGRP levels compared to interictal EM and healthy controls.

Furthermore, considering other inflammatory and immune-related biomarkers in migraineurs, the present study also explored the serum levels of IL-17 and COX-2 in the studied participants. IL-17 is involved in a wide variety of biological activities, including stimulating macrophages to produce pro-inflammatory mediators, regulating gene expression of cell adhesion molecules, and modulating NO production – all of which could worsen inflammation and contribute to migraine pathogenesis. Chen et al. demonstrated that IL-17A could cross the BBB into the medulla oblongata, where it activates the trigeminal nucleus caudalis through microglia-mediated neuroinflammation, ultimately contributing to CM in an animal model.[18] This finding is particularly relevant to our observation of elevated IL-17 in patients with CM, as it may reflect a sustained pro-inflammatory state that promotes disease chronification. Wen et al. recently showed that blockade of IL-17A reduced CGRP levels, suppressed inflammatory mediator release, and alleviated migraine-like symptoms in CM models, suggesting a direct mechanistic link between IL-17 signaling and the trigeminovascular system.[29]

Our finding of elevated serum COX-2 in both ictal EM and CM patients aligns with evidence implicating COX-2-mediated inflammation in migraine pathogenesis. As the rate-limiting enzyme in prostaglandin E_2 (PGE_2) synthesis, COX-2 promotes vasodilation and pain sensitization. Higher COX-2 concentrations have been detected in the dura mater during migraine episodes, supporting its local involvement in neurogenic inflammation.[30] Critically, stimulation of trigeminal ganglion neurons induces COX-2 expression, leading to PGE_2 synthesis and subsequent CGRP release. The positive correlation between COX-2 and CGRP observed in our study supports an integrated model wherein prostaglandin-mediated mechanisms facilitate CGRP release and sustain trigeminovascular activation during migraine attacks.[31] Furthermore, the elevated COX-2 levels in our patients with CM may reflect a sustained pro-inflammatory state that contributes to disease chronification. This interpretation is consistent with evidence demonstrating that pro-inflammatory cytokines are frequently elevated in patients with high-frequency migraine or CM and may signal an increased risk of disease progression.[32]

Our findings align with and extend the current understanding of migraine pathogenesis, reinforcing the central role of CGRP and its association with downstream neuroinflammatory mediators, including IL-17 and COX-2. These results suggest that therapeutic strategies aimed at modulating serum levels of CGRP or these inflammatory markers may hold promise for migraine management. Furthermore, they highlight the potential importance of early intervention targeting these pathways to prevent migraine progression.

Study Strengths and Limitations: The present study has several methodological strengths, including a well-characterized sample of patients

with EM in both ictal and interictal phases, patients with CM, and age- and sex-matched healthy controls, allowing comprehensive examination of biomarker dynamics across the migraine cycle. Simultaneous measurement of multiple biomarkers (CGRP, IL-17, and COX-2) enabled exploration of interrelationships among neurogenic and inflammatory pathways. However, several limitations warrant consideration. The cross-sectional design precludes determination of causality or temporal directionality, and peripheral serum measurements may not fully reflect central nervous system (CNS) events. Variability in the timing of ictal sampling, lack of systematic adjustment for medication use, and potential confounders such as comorbid conditions or dietary factors could have influenced results. Additionally, the modest sample size limited statistical power for subgroup analyses.

Conclusion

This study demonstrates that both ictal EM and CM are characterized by significantly elevated serum levels of CGRP, IL-17, and COX-2 compared to interictal patients and healthy controls. Positive correlations among CGRP, IL-17, and COX-2 support an integrated model wherein neurogenic and immune-mediated inflammatory pathways cooperate in sustaining trigeminovascular activation. Persistent neuroinflammation and consequent central sensitization may represent key drivers of migraine chronification. These findings reinforce the rationale for therapeutic strategies targeting these interconnected mediators. Prospective longitudinal studies are warranted to determine whether baseline biomarker levels predict treatment response or risk of progression from EM to CM.

Conflict of Interests

The authors declare no conflict of interest in this study.

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