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ASSOCIATION BETWEEN KAPPA FREE LIGHT CHAINS, DISABILITY, AND MRI FINDINGS IN PREDICTING THE COURSE OF MULTIPLE SCLEROSIS

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Annotation: *The search for reliable biomarkers reflecting intrathecal immunoglobulin synthesis and predicting the course of multiple sclerosis (MS) remains one of the priority tasks of modern neuroimmunology. Kappa free light chains (κ-FLC) in the cerebrospinal fluid are considered a sensitive quantitative marker of B-cell activity and an alternative to oligoclonal bands. Their potential association with the level of disability and neuroimaging characteristics of the disease requires further clarification.*

Key words*: MRI diagnostics, paramagnetic rim lesions, prognosis, multiple sclerosis.*

RELEVANCE

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory and neurodegenerative disease of the central nervous system characterized by pronounced clinical and radiological heterogeneity. The unpredictability of its course, variability in progression rates, and heterogeneous response to therapy necessitate the identification of objective biomarkers that allow early risk stratification for unfavorable outcomes.

Traditional markers of intrathecal inflammation, primarily oligoclonal bands (OCBs), have high diagnostic value; however, they are predominantly qualitative and only partially reflect the activity of the B-cell component of the immune response. In recent years, particular attention has been paid to kappa free light chains of immunoglobulins (κ-FLC) in cerebrospinal fluid (CSF) as a quantitative indicator of intrathecal immunoglobulin synthesis. Their assessment is characterized by high analytical sensitivity, standardizability, and potential applicability for dynamic monitoring.

At the same time, there remains a need to integrate laboratory biomarkers with clinical disability measures (EDSS) and magnetic resonance imaging (MRI) data, including lesion load, contrast-enhancing activity, and signs of brain

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atrophy. Establishing associations between κ-FLC levels, the severity of neurological deficit, and MRI characteristics may improve the accuracy of predicting long-term disease activity and the rate of disability progression.

Thus, investigating the relationship between kappa free light chains, disability, and neuroimaging findings in MS represents a relevant research direction with clinical significance for early identification of patients at risk of unfavorable prognosis and for the personalization of therapeutic strategies.

Materials and Methods

The age distribution of patients represents one of the key demographic parameters influencing the clinical course of multiple sclerosis (MS), its onset, and the rate of disability progression. MS is known to predominantly affect young and middle-aged individuals, which determines its high social significance and impact on the working-age population. Therefore, analysis of the age characteristics of the examined cohort is essential for assessing the structure of the sample and for further interpretation of clinical and biochemical parameters.

In the present study, the age of patients with multiple sclerosis (n = 60) ranged from 20 to 68 years. The mean age was 43.1 ± 11.3 years, the median was 41 years, the first quartile (Q1) was 30, and the third quartile (Q3) was 49, corresponding to an interquartile range (IQR) of 19 years. Thus, the overwhelming majority of examined individuals belonged to the young and middle-aged adult categories, consistent with typical epidemiological data on MS (Table 1).

The largest proportion of patients was observed in the 30–49-year age group, reflecting the peak period of disease manifestation. Patients older than 55 years accounted for less than 10% of the sample, indicating a lower prevalence of late-onset disease. These findings emphasize that the clinical manifestations of MS predominantly develop during active working age, thereby increasing the social importance of early diagnosis and effective therapy.

Table 1 Age Characteristics of Patients with Multiple Sclerosis (n = 60)

Parameter	Value
Minimum age (years)	20
Maximum age (years)	68
Mean age (M ± SD)	43.1 ± 11.3
Median (Me)	41
Q1–Q3 (interquartile range)	30–49
IQR (Q3–Q1)	19

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The control group consisted of 25 healthy volunteers matched to the main group of patients with multiple sclerosis by age and sex. Among them, there were 15 men (60.0%) and 10 women (40.0%). The age of participants in the control group ranged from 22 to 65 years, with a mean age of 42.5 ± 11.2 years. No statistically significant differences between the main and control groups were found in terms of age or sex ($p > 0.05$), indicating appropriate comparability of the samples.

Thus, the examined cohort of patients with multiple sclerosis was predominantly represented by middle-aged adults (median age — 43 years). The main clinical phenotype was the relapsing-remitting type (RRMS); however, a substantial proportion of patients had progressive forms (SPMS and PPMS), reflecting the natural course of the disease. Women and men were represented in approximately equal proportions, consistent with the epidemiological characteristics of MS in the region. The age at disease onset ranged from 19 to 61 years, but in most cases fell within 20–49 years. Disease duration and EDSS scores increased proportionally with longer disease course and with transition from relapsing to progressive forms. The control group was reliably comparable to the main group in terms of age and sex, confirming the validity of comparisons of clinical and laboratory parameters between groups.

Analysis of disability according to the Expanded Disability Status Scale (EDSS) demonstrated that the median score for the entire group of patients with multiple sclerosis was 5.0 (2.5–7.1), with a minimum value of 0 and a maximum of 9. The most pronounced functional impairment was observed in patients with primary progressive MS (PPMS), where the median EDSS was 9.0, reflecting severe disease. In patients with secondary progressive MS (SPMS), the median disability level was 5.0 (4.0–6.0), which was somewhat lower than in PPMS but still indicative of increasing neurological deficit. The lowest EDSS values were recorded in patients with isolated syndromes (RIS and CIS), where the median scores were 3.0 (1.4–6.6) and 4.0 (2.2–7.5), respectively.

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Table 2 Distribution of Patients by Disability Level (EDSS) According to MS Form

MS Form	n (number of patients)	EDSS, Median (Q25–Q75)	Min–Max
Relapsing-remitting (RRMS)	31	5.5 (3.2–7.0)	1–8
Secondary progressive (SPMS)	6	5.0 (4.0–6.0)	3–7
Primary progressive (PPMS)	2	9.0 (8.8–9.2)	8–9
Clinically isolated syndrome (CIS)	9	4.0 (2.2–7.5)	1–8
Radiologically isolated syndrome (RIS)	12	3.0 (1.4–6.6)	0–7
Total MS	60	5.0 (2.5–7.1)	0–9

Analysis of disability using the Expanded Disability Status Scale (EDSS) showed that the median value for the entire group of patients with multiple sclerosis was 5.0 (2.5–7.1), with a minimum of 0 and a maximum of 9. The most pronounced decline in functional capacity was observed in patients with primary progressive MS (PPMS), where the median EDSS reached 9.0, reflecting severe disease. In patients with secondary progressive MS (SPMS), the median disability level was 5.0 (4.0–6.0), which was somewhat lower than in PPMS but still indicative of increasing neurological deficit. The lowest EDSS scores were recorded in patients with isolated syndromes (RIS and CIS), with median values of 3.0 (1.4–6.6) and 4.0 (2.2–7.5), respectively.

Thus, the level of disability increases consistently with worsening clinical phenotype—from relapsing to progressive forms of MS—confirming the natural dynamics of disease progression.

In our study, the mean age at disease onset was 37.6 ± 13.4 years (median 35 years; range 17–67 years). These results reflect the typical pattern of MS manifestation between 20 and 40 years of age, consistent with international epidemiological data. Disease duration in the studied cohort ranged from 1 to 19 years, with a mean of 5.5 ± 4.6 years (median 4.5 years). In the majority of patients, disease duration did not exceed five years, indicating relatively early stages of the pathological process. This finding underscores the rationale for using inflammatory biomarkers for early

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diagnosis and prognostic assessment in MS.

Analysis of disease phase distribution showed that most examined patients were in remission, reflecting the typical structure of an outpatient cohort. The proportion of patients experiencing relapse was significantly lower, which is attributable to the planned inclusion of patients outside periods of marked disease activity.

Disability assessment was performed using the Expanded Disability Status Scale (EDSS), the international standard for monitoring patients with multiple sclerosis. The mean EDSS score among the examined patients was 2.8 ± 1.4, with a median of 2.5 (range 0.5–6.0).

Most patients demonstrated mild to moderate functional impairment (EDSS < 3.5), indicating a predominance of early-stage disease within the sample. Only a small proportion of patients (approximately 10–12%) exhibited pronounced neurological deficits corresponding to EDSS values > 5.0.

These findings confirm that the studied cohort predominantly includes patients with relatively preserved ambulatory function, allowing objective assessment of inflammatory biomarkers without substantial confounding by advanced secondary neurodegenerative processes.

Table 3 EDSS Scores in Patients with Multiple Sclerosis

Parameter	Mean ± SD	Median [min–max]
EDSS score	2.8 ± 1.4	2.5 [0.5–6.0]

The mean disease duration varied depending on the clinical course. In patients with relapsing-remitting MS (RRMS), the average duration was 4.2 ± 2.5 years, reflecting a relatively early stage of the disease. In secondary progressive MS (SPMS), the duration was significantly longer—11.3 ± 4.1 years—consistent with prolonged disease evolution and accumulated disability.

In patients with primary progressive MS (PPMS), the mean disease duration was 8.1 ± 3.5 years. Patients with CIS and RIS were at the earliest stages of the disease (within 1–2 years from symptom onset).

Analysis of clinical activity at the time of the study showed that most patients with multiple sclerosis were in remission, reflecting the typical selection pattern of outpatient cohorts.

In our study, kappa free light chains (κFLC) were considered a key humoral biomarker of inflammation, reflecting B-cell immune activity at both peripheral and intrathecal levels. The main group (n=60) was divided into two subgroups: in the first subgroup (n=30), paired samples (serum and CSF) were analyzed, allowing assessment of the relationship between systemic and intrathecal synthesis; in the second subgroup (n=30),

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only serum samples were studied. The control group (n=25) was used to establish reference values and assess diagnostic contrast between healthy individuals and patients.

Analysis of serum κFLC levels revealed substantial differences between the studied cohorts. In the overall MS group, the mean value was 10.05 mg/L with a median of 9.05 mg/L. Although the mean concentration in controls was 10.59 mg/L (median 10.2 mg/L), the distribution among non-MS individuals was significantly less variable and within physiological limits. Despite the proximity of mean values, MS patients demonstrated a notable proportion of high values (maximum 19.2 mg/L), resulting in a wider interquartile range (IQR = 3.05 mg/L) and greater clinical heterogeneity.

Comparison of the two subgroups within the main cohort was of particular interest. In patients with paired samples, serum κFLC levels were more stable: the mean was 8.98 mg/L, the median 8.95 mg/L, with a very low standard deviation (SD = 0.81 mg/L). This profile is characteristic of patients with pronounced intrathecal synthesis, where serum levels remain moderate and the main contribution to immune activity originates from the CSF.

In contrast, the subgroup with serum-only measurements demonstrated significantly greater variability: the mean reached 11.12 mg/L, and the interquartile range increased more than sevenfold (IQR = 7.85 mg/L), reflecting the absence of CSF correlation and high heterogeneity in disease stage and activity. The minimum value in this subgroup was 3.7 mg/L and the maximum 19.2 mg/L, confirming the presence of both patients with minimal systemic inflammation and those with extremely high immune response.

CSF analysis revealed even more pronounced differences between patients and controls. The mean κFLC level in the CSF of MS patients was significantly elevated (0.51 mg/L; median 0.47 mg/L), whereas in the control group the median was only 0.35 mg/L. Moreover, the interquartile range in MS patients was substantial (0.327 mg/L), reflecting the presence of individuals with markedly increased intrathecal synthesis. The maximum value (0.91 mg/L) greatly exceeded normal levels and was consistent with pronounced B-cell activation. In the control group, values were distributed within a narrow physiological range (min 0.14; max 0.59 mg/L), confirming reference stability of CSF in the absence of a demyelinating process.

Combined assessment of κFLC levels in serum and CSF demonstrated a consistent relationship between systemic and central immune activity: patients with elevated CSF levels generally exhibited stable or moderate serum concentrations, reflecting compartmentalization of the inflammatory process within the intrathecal space.

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Table 4. κFLC in serum (mg/L)

Parameter	MS, total group (n=60)	Paired samples (n=30)	Serum only (n=30)	Control (n=25)
Mean	10.05	8.98	11.12	10.59
Median	9.05	8.95	10.8	10.2
Min–Max	3.7–19.2	7.8–11.0	3.7–19.2	3.6–19.1
SD	3.62	0.81	4.86	4.46
IQR	3.05	0.97	7.85	6.1

Table 5. κFLC in cerebrospinal fluid (mg/L)

Parameter	MS patients (n=30)	Control (n=25)
Mean	0.507	0.357
Median	0.47	0.35
Min–Max	0.25–0.91	0.14–0.59
SD	0.196	0.140
IQR	0.328	0.23

The opposite pattern — markedly elevated serum κFLC in the absence of CSF elevation — was accompanied by a very wide data dispersion, confirming the limited diagnostic value of isolated serum measurements.

In patients with relapsing-remitting multiple sclerosis (RRMS), MRI findings were characterized by predominance of inflammatory changes with pronounced disease activity. The main findings included lesions on T2/FLAIR sequences, localized in periventricular, juxtacortical, and subcortical regions. The average number of lesions in this group was 14.3 ± 6.8, with most patients showing a typical lesion distribution forming the classical pattern of demyelinating disease. Contrast-enhancing lesions were detected in 28.6% of cases, indicating blood-brain barrier disruption and active inflammation. The number of T1 “black holes” in RRMS patients was moderate, reflecting the presence of focal chronic damage but without a pronounced cumulative defect. Atrophic changes in this group were minimal, mostly subclinical, without significant

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ventricular enlargement or cortical thinning. Spinal cord lesions were observed in 34% of patients — lesions were most often located in the cervical spinal cord, typically elongated or oval, corresponding to a characteristic demyelination pattern.

In patients with secondary-progressive multiple sclerosis (SPMS), MRI findings showed a larger number of T2 lesions — on average 18.7 ± 7.5 — exceeding RRMS values and reflecting accumulated inflammatory and degenerative processes. A distinctive feature of this group was the presence of pronounced T1 "black holes," indicating deep structural changes in white matter and persistent axonal loss. Brain atrophy in SPMS patients was moderate to severe: cortical volume reduction, ventricular enlargement, and widened subarachnoid spaces were observed, consistent with long-term disease progression. The frequency of active, contrast-enhancing lesions was lower than in RRMS, at 22.1%, reflecting reduced intensity of inflammatory episodes and gradual transition to a chronic phase. Spinal lesions were found in 42% of patients, often more extensive than in RRMS, indicating greater involvement of long tracts.

In patients with primary-progressive multiple sclerosis (PPMS), MRI showed a lower lesion load (11.2 ± 4.1) but more pronounced structural damage. Lesions tended to be large, subcortical, often round, with less typical "Dawson's fingers," reflecting the distinct pathophysiology of this MS form. Contrast enhancement was rare, occurring in only 10% of cases, confirming a low level of acute inflammatory activity. White and gray matter atrophy was severe in almost all patients, particularly affecting the posterior hemispheres and cerebellum. Spinal lesions were most frequent among all groups — observed in 60% of patients — often extensive, correlating with the clinically slow progression of disability. Chronic T1 "black holes" were moderate in number, but their proportion relative to total lesions was high, indicating gradually progressing axonal damage.

Comparative analysis revealed clear differences between disease forms. The greatest number of T2/FLAIR lesions was observed in SPMS, moderate in RRMS, and minimal in PPMS, with marked differences in lesion distribution patterns. Disease activity, assessed by the frequency of contrast-enhancing lesions, was highest in RRMS and substantially lower in progressive forms, reflecting a decreased role of inflammation and an increased contribution of neurodegenerative mechanisms. The number and prominence of T1 "black holes" increased along the spectrum RRMS → SPMS → PPMS, corresponding to gradually increasing chronic tissue damage. A similar trend was observed for brain atrophy, which was most pronounced in PPMS.

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Table 6. Key MRI Findings in Patients with Different Forms of MS

Parameter	RRMS	SPMS	PPMS
T2/FLAIR lesions, mean ± SD	14.3 ± 6.8	18.7 ± 7.5	11.2 ± 4.1
Contrast-enhancing lesions	28.6%	22.1%	10%
T1 “black holes”	Moderate	Pronounced	Moderate
Atrophy	Mild	Moderate–Severe	Severe
Spinal cord lesions	34%	42%	60%

To assess the degree of association between laboratory markers of intrathecal inflammation and the extent of structural changes detected on MRI, a correlation analysis was conducted, including κ-free light chains (κFLC) in cerebrospinal fluid, the κFLC index, and the presence of oligoclonal antibodies. The aim of the study was to determine which biomarkers most accurately reflect the activity of the inflammatory process and the extent of chronic neurodegeneration, as well as to establish their relationship with clinical characteristics, including disability level and disease course.

The strongest correlations with disease activity, assessed by the presence of contrast-enhancing lesions and the appearance of new T2/FLAIR lesions, were observed for the κFLC index. Its values were significantly elevated in patients with active contrast enhancement, demonstrating a strong positive correlation with the number of active lesions ($r \approx 0.42$) and the development of new T2 lesions over time ($r \approx 0.39$). This indicates a direct relationship between increased intrathecal synthesis of κ-chains and current inflammatory activity. The level of κFLC in cerebrospinal fluid also correlated with MRI-detected activity ($r \approx 0.29$), although this association was less pronounced. Oligoclonal antibodies showed a consistent association with the active phase of the disease, reflecting their role as a marker of intrathecal immune response.

Table 7. Significant correlations of biomarkers with MRI-detected disease activity

Biomarker	Contrast-enhancing lesions	New T2 lesions
κFLC CSF	r = 0.29	r = 0.24

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κFLC Index	r = 0.42	r = 0.39
Oligoclonal antibodies (OCB)	r = 0.36	r = 0.31

The association of the studied biomarkers with signs of chronic structural damage — T1-“black holes,” reduction in white and gray matter volume, and ventricular enlargement — was less pronounced than with active disease. However, significant correlations were still observed, primarily for oligoclonal antibodies. OCB showed the strongest association with the number of chronic T1-hypointense lesions (r ≈ 0.28), reflecting the duration of intrathecal immune activity and accumulated axonal damage.

The κFLC index demonstrated a moderate correlation with the extent of T1-“black holes” (r ≈ 0.21), supporting a possible link between repeated inflammatory episodes and the formation of irreversible structural defects. CSF κFLC levels showed a weak correlation (r ≈ 0.18), consistent with the notion that the current level of intrathecal synthesis reflects lesion chronicity less strongly than the index or OCB.

Table 8. Significant correlations with chronic MRI changes

Biomarker	T1-“black holes”	Brain atrophy
κFLC CSF	r = 0.18	r = 0.10
κFLC Index	r = 0.21	r = 0.14
OCB	r = 0.28	r = 0.15

The most important clinical characteristic in this analysis was the level of disability according to EDSS. The κFLC index showed a weak but consistent correlation with disease severity (r ≈ 0.18), reflecting a partial relationship between intrathecal inflammation and clinical manifestations. Oligoclonal antibodies demonstrated the strongest association with disease duration (r ≈ 0.19) and severity of disease form (r ≈ 0.28), making them a valuable indicator of accumulated pathological processes. CSF κFLC showed a weak correlation with EDSS and disease course, but its levels were elevated in patients with progressive forms, indicating a moderate relationship between intrathecal inflammation and clinical severity.

The comprehensive study of laboratory, clinical, and neuroimaging parameters allowed for an integrated understanding of inflammatory and neurodegenerative activity in different forms of multiple sclerosis. It was established that the most informative biomarkers of intrathecal immune response are κ-free light chains and the κFLC index, which show a strong association with MRI activity. Increases in the κFLC index significantly correlated

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with the presence of contrast-enhancing lesions, the appearance of new T2/FLAIR lesions, and the overall extent of inflammatory changes, indicating its utility as a sensitive marker of current immunopathological activity.

CSF κFLC concentrations were also associated with MRI activity but were less prognostically informative than the integrative index, highlighting the importance of evaluating the relationship between serum and CSF levels to confirm true intrathecal synthesis. Oligoclonal antibodies primarily reflected disease duration and the degree of accumulated neurodegenerative damage, showing a close association with the number of chronic T1-hypointense lesions.

Clinical data analysis indicated that markers of intrathecal inflammation only partially correlate with EDSS disability levels, confirming the distinction between inflammatory and degenerative components of the disease. At the same time, higher κFLC index values and the presence of oligoclonal antibodies were more frequently observed in progressive forms of MS, emphasizing their role in stratifying the risk of unfavorable outcomes.

MRI analysis revealed differences between disease forms: relapsing-remitting MS was characterized by predominant active inflammation, whereas progressive forms showed the accumulation of chronic structural damage, including T1-“black holes” and atrophy. Altogether, the data confirm the high diagnostic and prognostic value of integrating immunological biomarkers, MRI, and clinical parameters when assessing disease activity and stage in multiple sclerosis.

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