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# Role of Chitinase 3–like 1 as a Biomarker in Multiple Sclerosis

## A Systematic Review and Meta-analysis

Stefano Floro, MD, Tiziana Carandini, MD, Anna Margherita Pietroboni, MD, Milena Alessandra De Riz, MD, Elio Scarpini, and Daniela Galimberti

**Correspondence**
Dr. Floro
stefano.floro@unimi.it

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## Abstract

### Background and Objectives

Multiple sclerosis (MS) is an autoimmune disease confined in the CNS, and its course is frequently subtle and variable. Therefore, predictive biomarkers are needed. In this scenario, we conducted a systematic review and meta-analysis to evaluate the reliability of chitinase 3–like 1 as a biomarker of MS.

### Methods

Research through the main scientific databases (PubMed, Scopus, Web of Science, and Cochrane Library) published from January 2010 to December 2020 was performed using the following keywords: "chitinase 3-like 1 and multiple sclerosis" and "YKL40 and multiple sclerosis." Articles were selected according to the 2020 updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines by 2 authors independently, and data were extracted; 20 of the 90 studies screened were included in the meta-analysis. The main efficacy measure was represented by the standardized mean difference of CSF and blood CHI3L1 levels; Review Manager version 5.4 and R software applications were used for analysis.

### Results

Higher levels of CHI3L1 were found in CSF of 673 patients with MS compared with 336 healthy controls (size-weighted mean difference [SMD] 50.88; 95% CI = 44.98–56.79; $p < 0.00001$) and in 461 patients with MS than 283 patients with clinically isolated syndrome (CIS) (SMD 28.18; 95% CI = 23.59–32.76; $p < 0.00001$). Mean CSF CHI3L1 levels were significantly higher in 561 converting than 445 nonconverting CIS (SMD 30.6; 95% CI = 28.31–32.93; $p < 0.00001$). CSF CHI3L1 levels were significantly higher in patients with primary progressive MS (PPMS) than in patients with relapsing-remitting MS (RRMS) (SMD 43.15; 95% CI = 24.41–61.90; $p < 0.00001$) and in patients with secondary progressive MS (SMD 41.86 with 95% CI = 32.39–51.33; $p < 0.00001$). CSF CHI3L1 levels in 407 patients with MS during remission phase of disease were significantly higher than those in 395 patients with MS with acute relapse (SMD 10.48; 95% CI = 08.51–12.44; $p < 0.00001$). The performances of CHI3L1 in blood for differentiating patients with MS from healthy controls were not significant (SMD 0.48; 95% CI = −1.18 to 2.14; $p$: 0.57).

### Discussion

CSF levels of CHI3L1 have a strong correlation with the MS pathologic course, in particular with the mechanism of progression of the disease; it helps to distinguish the PPMS from the RRMS. The potential role of CHI3L1 in serum needs to be further studied in the future.

From the Fondazione IRCCS Ca' Granda (S.F., T.C., A.M.P., M.A.D.R., E.S., D.G.), Ospedale Policlinico; and University of Milan (S.F., E.S., D.G.), Milan, Italy.

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## Glossary

**BBB** = blood-brain barrier; **CDMS** = clinically definite MS; **CHI3L1** = chitinase 3–like 1; **CIS** = clinically isolated syndrome; **EDSS** = Expanded Disability Status Scale; **ELISA** = enzyme like immunosorbent assay; **HC** = healthy control; **IQR** = interquartile range; **MS** = multiple sclerosis; **NfL** = neurofilament light chain; **NOS** = Newcastle-Ottawa Scale; **PPMS** = primary progressive MS; **RRMS** = relapsing-remitting MS; **SMD** = size-weighted mean difference; **SPMS** = secondary progressive MS.

MRI is the reference standard to diagnose and monitor inflammatory activity over time in patients with multiple sclerosis (MS). However, imaging data are difficult to standardize and are retrospective. Therefore, both in clinical trials and clinical practice, there is an urgent need to find less costly and easier-to-perform biomarkers, which can be suitable for longitudinal monitoring of the disease.[1]

Among several CSF/serum biomarkers of tissue damage,[2-4] chitinase 3–like 1 (CHI3L1) has been recently proposed as having a potential role in MS. Also known as YKL-40, it belongs to the chitin glycoside hydrolase 18 family, a large group of protein, some of which without enzymatic activity,[5] produced by several cell types, mainly macrophages and astrocytes.[6-9] Its elevated levels have already been demonstrated in some inflammatory conditions such as rheumatoid arthritis[10] and system lupus erythematosus.[11] Within the CNS, CHI3L1 is linked to neuroinflammatory processes and reactive gliosis; however, its mechanism of action remains poorly understood, and its role in MS pathogenic mechanisms has not been fully elucidated yet. Herein, we conducted a systematic review of the literature and a quantitative meta-analysis aimed at evaluating the diagnostic performance of CHI3L1 levels in CSF and blood in MS and its subtypes and establishing its utility to define the stage of the disease activity and its response to treatment.

## Methods

### Search Strategy

A systematic review and meta-analysis was performed according to the new 2020 update of the PRISMA Statement[12] and Cochrane Handbook.[13] We searched on PubMed, Scopus, Web of Science, and Cochrane Library databases the following terms: "chitinase 3-like 1 and multiple sclerosis" and "YKL40 and multiple sclerosis." The search was restricted to articles published after 2010 and last updated on December 31, 2020. To complete the research of all the studies potentially relevant to the analysis, review articles and all the reference lists of the already included publications were also used.

### Selection Criteria

We included all original studies that compared CSF and/or serum levels of CHI3L1 between patients with MS and a group of healthy controls (HCs) and among the several MS subtypes. Studies were included if they fulfilled the following criteria: (1) quantification of CSF and serum CHI3L1 levels with enzyme like immunosorbent assay (ELISA) (2) MS diagnosis made according to the 2010[14] and the revised 2017 diagnostic criteria[15]; and (3) data of CHI3L1 concentration reported as either mean and SD or median and interquartile range (IQR). No restrictions on duration of the disease, pathologic history, or treatment were adopted, and no language limit was applied.

The following exclusion criteria were formulated: (1) case reports, reviews, and studies with fewer than 2 patients included; (2) published abstracts only; (3) animal or in vitro studies; (4) no clear control groups; and (5) pediatric MS.

### Data Extraction

Two authors (S.F. and T.C.) extracted and double checked the following data independently: (1) article information (title of the study, year of publication, and first author); (2) main demographic and clinical data (number of samples, age, sex, disease duration, and disability assessed with the mean Expanded Disability Status Scale [EDSS] score); and (3) quantitative levels of biomarker in CSF and serum (expressed as mean/median with SD/IQR). Corresponding authors of the studies were contacted if the data requested were not given in the manuscript. In case of disagreement, a consensus was reached after discussion between the 2 authors.

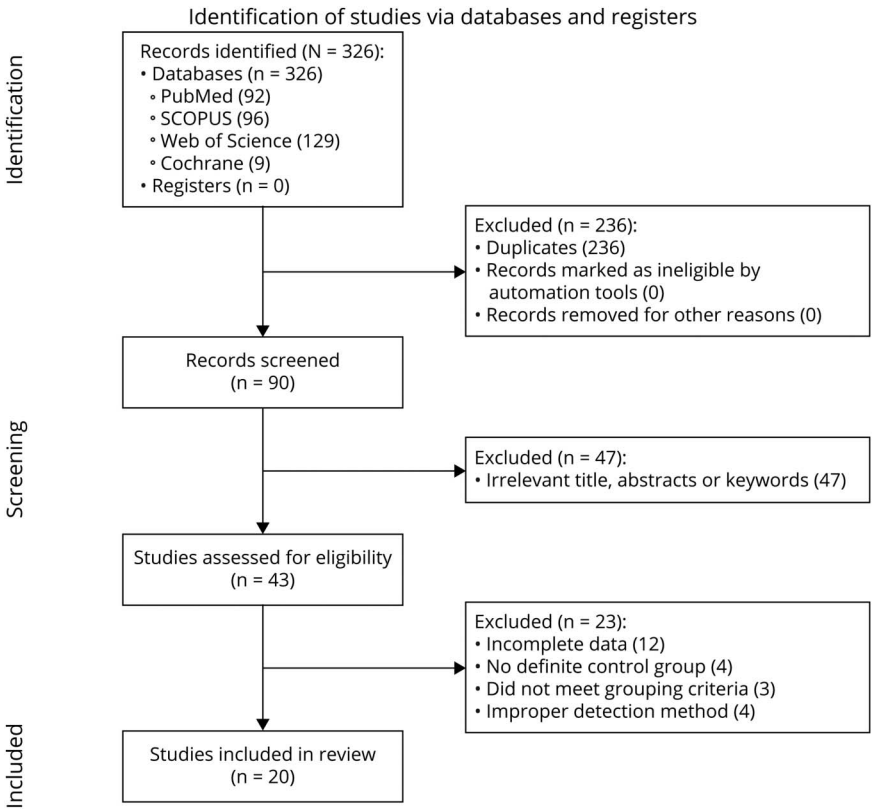
### Quality Assessment

The Newcastle-Ottawa Scale (NOS)[16] was used to assess the quality of the studies included in the analysis. Each study receives from 0 to 9 stars, according to the requirements of sample selection, comparability of cases and controls, and assessment of outcome. For comparability of cases and controls, the matching of the main demographic features (e.g., age and sex) was considered. Disagreements were discussed until the achievement of consensus.

### Statistical Analysis

Review Manager (RevMan software version 5.4.1) was used to perform the meta-analysis and forest plots of those studies that fulfilled the criteria reported above. As several of them reported valuable data of different study comparators, they were used in multiple analyses. The mean, SD, and 95% CIs were calculated for each group in every study. Levels of CHI3L1 in CSF/serum were quantified in ng/mL. Median and IQR were converted as mean and SD according to Hozo et al.[17] statistical methods. For continuous data, the sample size-weighted mean difference (SMD) was calculated using a weighted fixed or random-effect model, according to,

**Figure 1** Selection of the Studies Included in the Analysis




Study selection process according to the new 2020 update of the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) statements.

respectively, the low or the high heterogeneity among the studies (with 95% CI and corresponding *p* value). For proportions, the OR was calculated using the Mantel-Haenszel test. The I squared ($I^2$) test was used to estimate the heterogeneity across studies, $I^2$ >50% indicating substantial heterogeneity.[18,19] In cases where $I^2$ exceeded 50%, subgroup analyses were performed based on the type of control groups in different studies. To further assess the causes of heterogeneity—when present—we conducted influential analysis and Baujat statistical methods[20] to identify influential cases. Several parameters for each study were extracted (externally standardized residuals [rstudent], DFFITS values, Cook distances [cook.d], covariance ratios [cov.r], leave-one-out estimates of the amount of heterogeneity [tau2.del], leave-one-out values of the test statistics for heterogeneity [QE.del], hat values, and weight) to identify the outliers; the Baujat plot showed the contribution of each study to the overall Q-test statistic for heterogeneity (defined as Squared Pearson Residual) related to its influence. Then, we recalculated the effect size using sensitivity analysis. In the sensitivity analysis, weight percentage of the studies excluded was not reported by RevMan software, and mean difference was reported as not applicable. We also conducted meta-regressions to estimate the effect of the main demographic and clinical data on overall effect size and heterogeneity. Influence plots, Baujat plots, and meta-regressions were performed using Meta and Metafor packages on R software.

# Results

## Study Characteristics

Of the 326 records initially identified, 236 were removed because of being duplicated. Forty-seven of 90 studies screened were then removed after their titles, abstracts, or keywords were read. Forty-three records were assessed for eligibility, from which 23 were removed because of the following reasons: (1) incomplete data; (2) no definite control group; (3) not meeting the inclusion criteria; and (4) improper detection method. Finally, 20 studies were included in this systematic review. The flow diagram used for the search strategy is shown in Figure 1. Table shows the main features of the included studies.

## Difference of CSF Levels of CHI3L1 in Patients With MS vs Healthy Controls

Differences in CSF CHI3L1 levels between patients with MS and HCs were reported by 13 studies, involving 673 patients and 336 controls.[5,6,8,21-30] The results of the meta-analysis showed that the mean difference in CSF CHI3L1 levels between patients with MS and controls was 70.67 (95% CI = 53.35–88.00; $p < 0.00001$). Because of the high heterogeneity among the studies, the predictive value of the difference of age between MS and HC groups to the effect size was examined through a meta-regression, which was not significant (*p*: 0.12). The bubble plot is shown in eFigure 1, links.lww.com/NXI/A711. A sensitivity analysis

**Table** Characteristics of the Studies Included in the Systemic Review and Meta-analysis

| Author | Year | Country | Study design | Patients with CIS/MS (N°) | Healthy controls (N°) | Patients with CIS/MS (age) | Healthy controls (age) | Patients with CIS/MS (male sex) | Healthy controls (male sex) | Patients with CIS/MS (EDSS score) | Patients with CIS/MS (disease duration) | Sample source | Methods | Quality (NOS) | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Barkay et al.** | 2010 | United States | Retrospective | 10 | 12 | 48 | 40 | N(A | N/A | N/A | N/A | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 4* | 6 |
| **Correale et al.** | 2010 | Argentina | Retrospective | 48 | 24 | 37.9 | 38.4 | 33 | 33 | 4 | 7 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 6* | 21 |
| **Comabella et al.** | 2010 | Spain | Prospective | 60 | 0 | 28 | N/A | 23 | N/A | N/A | 5.7 | CSF | ELISA METRA, kit (Quidel Corporation, San Diego, USA) | 7* | 33 |
| **Stoop et al.** | 2013 | Germany | Retrospective | 13 | 0 | 37 | N/A | 23 | N/A | 3.5 | 8.4 | CSF | ELISA Quantikine kit R&D Systems (Abingdon, UK) | 4* | 49 |
| **Modvig et al.** | 2013 | Denmark | Prospective | 56 | 27 | 36 | 33 | 23 | 22 | N/A | N/A | CSF | ELISA Quantikine kit R&D Systems (Abingdon, UK) | 4* | 22 |
| **Cantò et al.** | 2015 | Multicentric (Europe) | Prospective | 813 | 0 | 32 | 32 | 27 | 50 | N/A | 5.8 | CSF | ELISA METRA kit (Quidel Corporation, San Diego, USA) | 8* | 34 |
| **Manè-Martinez et al.** | 2015 | Spain | Prospective | 301 | 0 | 34 | N/A | 35 | N/A | 2 | 3.6 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 7* | 35 |
| **Manè-Martinez et al.** | 2016 | Spain | Prospective | 324 | 0 | 34 | N/A | 36 | N/A | 2 | 3.8 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 6* | 31 |
| **Burman et al.** | 2016 | Sweden | Prospective | 62 | 30 | 45 | 40 | 37 | 73 | 3 | 12.4 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, USA) | 6* | 8 |
| **Hakansson et al.** | 2016 | Sweden | Retrospective | 44 | 23 | 30 | 32 | 20 | 22 | 2 | 1.1 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, USA) | 6* | 23 |
| **Novakova et al.** | 2016 | Sweden | Retrospective | 59 | 39 | 37 | 34 | 39 | 64 | 2.5 | N/A | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, USA) | 6* | 24 |
| **Novakova et al.** | 2017 | Sweden | Prospective | 43 | 39 | 39 | 33 | 37 | 64 | 2.5 | N/A | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 6* | 25 |
| **Sellebjerg et al.** | 2017 | Denmark | Prospective | 52 | 24 | 48 | 42 | 44 | 50 | 4.5 | 10 | CSF | ELISA Quantikine kit R&D Systems (Abingdon, UK) | 7* | 26 |

Continued

**Table** Characteristics of the Studies Included in the Systemic Review and Meta-analysis *(continued)*

| Author | Year | Country | Study design | Patients with CIS/MS (N°) | Healthy controls (N°) | Patients with CIS/MS (age) | Healthy controls (age) | Patients with CIS/MS (male sex) | Healthy controls (male sex) | Patients with CIS/MS (EDSS score) | Patients with CIS/MS (disease duration) | Sample source | Methods | Quality (NOS) | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **De Fino et al.** | 2019 | Italy | Prospective | 71 | 11 | 36 | 39 | 70 | 73 | 1.5 | 1.5 | CSF/serum | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 6* | 27 |
| **Gil-Perotin et al.** | 2019 | Spain | Prospective | 157 | 0 | 44 | N/A | 39 | N/A | 4 | 3.9 | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, USA) | 6* | 28 |
| **Thouvenot et al.** | 2019 | France | Retrospective | 169 | 42 | 37 | 37.2 | 25.5 | 31 | N/A | N/A | CSF | ELISA MicroVue YKL-40 kit (Quidel Corporation, San Diego, CA) | 5* | 29 |
| **Christensen et al.** | 2019 | Denmark | Prospective | 27 | 0 | 48 | N/A | 44 | N/A | N/A | 5.5 | CSF | ELISA Quantikine kit R&D Systems (Abingdon, UK) | 6* | 50 |
| **Sellebjerg et al.** | 2019 | Denmark | Prospective | 177 | 0 | 31 | N/A | 62 | N/A | 2 | 1.3 | CSF | ELISA MicroVue YKL-40 kit (Quidel, San Diego, CA) | 7* | 32 |
| **Kusnierovà et al.** | 2020 | Czech Republic | Retrospective | 56 | 15 | 39 | 41 | N/A | N/A | N/A | N/A | CSF | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 6* | 5 |
| **Huss et al.** | 2020 | Germany | Retrospective | 86 | 20 | 44 | 44 | 58 | 65 | 4 | N/A | CSF/serum | ELISA Quantikine kit R&D Systems (Minneapolis, MN, USA) | 5* | 30 |

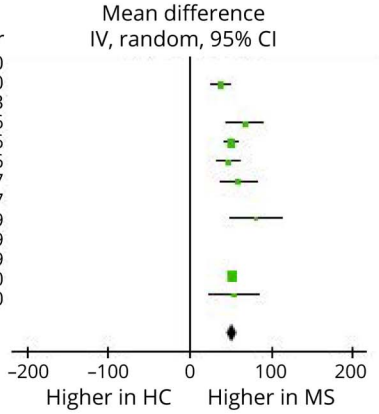
Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; ELISA = enzyme like immunosorbent assay; MS = multiple sclerosis; NOS = Newcastle-Ottawa Scale.
Age is expressed as mean years; male sex is expressed as percentage (%) of male subjects; disease duration is expressed as mean years.

**Figure 2** Comparison Between Multiple Sclerosis vs Healthy Controls

A

| Study or subgroup | Multiple sclerosis Mean | SD | Total | Healthy controls Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Ref. #36 | 359.925 | 90.833 | 10 | 137.437 | 31.500 | 12 | | Not estimable | 2010 |
| Ref. #21 | 111.000 | 21.000 | 24 | 73.700 | 21.700 | 24 | 15.0 | 37.30 (25.22, 49.38) | 2010 |
| Ref. #22 | 99.751 | 10.917 | 56 | 72.941 | 7.850 | 27 | | Not estimable | 2013 |
| Ref. #8 | 148.794 | 108.115 | 117 | 81.980 | 29.840 | 30 | 6.0 | 66.81 (44.50, 89.13) | 2016 |
| Ref. #23 | 127.720 | 18.712 | 22 | 77.560 | 6.608 | 23 | 22.5 | 50.16 (41.89, 58.43) | 2016 |
| Ref. #24 | 132.000 | 35.000 | 33 | 85.000 | 22.500 | 39 | 12.5 | 47.00 (33.13, 60.87) | 2016 |
| Ref. #25 | 144.000 | 67.000 | 43 | 85.000 | 31.000 | 39 | 6.0 | 59.00 (36.74, 81.26) | 2017 |
| Ref. #26 | 182.269 | 18.000 | 26 | 106.906 | 13.500 | 24 | | Not estimable | 2017 |
| Ref. #27 | 148.000 | 91.100 | 46 | 67.800 | 29.500 | 11 | 3.2 | 80.20 (48.63, 111.77) | 2019 |
| Ref. #28 | 143.567 | 20.333 | 157 | 60.013 | 5.000 | 30 | | Not estimable | 2019 |
| Ref. #29 | 266.399 | 42.533 | 50 | 129.082 | 14.933 | 42 | | Not estimable | 2019 |
| Ref. #30 | 124.587 | 12.283 | 47 | 73.035 | 8.100 | 20 | 31.3 | 51.55 (46.56, 56.55) | 2020 |
| Ref. #5 | 139.350 | 68.800 | 42 | 85.840 | 42.240 | 15 | 3.6 | 53.51 (23.68, 83.34) | 2020 |
| **Total (95% CI)** | | | **374** | | | **201** | **100.0** | **50.88 (44.98, 56.79)** | |

Heterogeneity: $\tau^2 = 22.55$; $\chi^2 = 11.05$, df = 7 ($p = 0.14$); $I^2 = 37\%$
Test for overall effect: z = 16.89 ($p < 0.00001$)




B

| Study or subgroup | Multiple sclerosis Mean | SD | Total | Healthy controls Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| **1.1.1 HC vs RRMS only** | | | | | | | | | |
| Ref. #21 | 111.000 | 21.000 | 24 | 73.700 | 21.700 | 24 | 8.3 | 37.30 (25.22, 49.38) | 2010 |
| Ref. #23 | 127.720 | 18.712 | 22 | 77.560 | 6.608 | 23 | 8.4 | 50.16 (41.89, 58.43) | 2016 |
| Ref. #24 | 132.000 | 35.000 | 33 | 85.000 | 22.500 | 39 | 8.1 | 47.00 (33.13, 60.87) | 2016 |
| Ref. #25 | 144.000 | 67.000 | 43 | 85.000 | 31.000 | 39 | 7.5 | 59.00 (36.74, 81.26) | 2017 |
| Ref. #27 | 148.000 | 91.100 | 46 | 67.800 | 29.500 | 11 | 6.7 | 80.20 (48.63, 111.77) | 2019 |
| Ref. #29 | 266.399 | 42.533 | 50 | 129.082 | 14.933 | 42 | 8.2 | 137.32 (124.69, 149.94) | 2019 |
| Ref. #30 | 124.587 | 12.283 | 47 | 73.035 | 8.100 | 20 | 8.5 | 51.55 (46.56, 56.55) | 2020 |
| **Subtotal (95% CI)** | | | **265** | | | **198** | **55.8** | **65.63 (42.78, 88.48)** | |

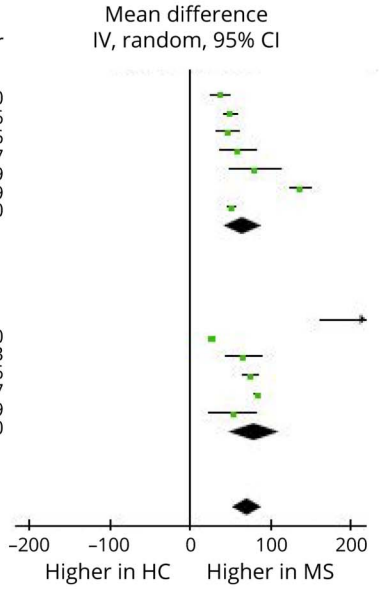
Heterogeneity: $\tau^2 = 880.38$; $\chi^2 = 176.96$, df = 6 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: z = 5.63 ($p < 0.00001$)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.1.2 HC vs RRMS + PMS** | | | | | | | | | |
| Ref. #36 | 359.925 | 90.833 | 10 | 137.437 | 31.500 | 12 | 4.3 | 222.49 (163.44, 281.54) | 2010 |
| Ref. #22 | 99.751 | 10.917 | 56 | 72.941 | 7.850 | 27 | 8.6 | 26.81 (22.69, 30.93) | 2013 |
| Ref. #8 | 148.794 | 108.115 | 117 | 81.980 | 29.840 | 30 | 7.5 | 66.81 (44.50, 89.13) | 2016 |
| Ref. #26 | 182.269 | 18.000 | 26 | 106.906 | 13.500 | 24 | 8.4 | 75.36 (66.59, 84.14) | 2017 |
| Ref. #28 | 143.567 | 20.333 | 157 | 60.013 | 5.000 | 30 | 8.6 | 83.55 (79.90, 87.20) | 2019 |
| Ref. #5 | 139.350 | 68.800 | 42 | 85.840 | 42.240 | 15 | 6.8 | 53.51 (23.68, 83.34) | 2020 |
| **Subtotal (95% CI)** | | | **408** | | | **138** | **44.2** | **79.17 (48.46, 109.88)** | |

Heterogeneity: $\tau^2 = 1308.46$; $\chi^2 = 451.09$, df = 5 ($p < 0.00001$); $I^2 = 99\%$
Test for overall effect: z = 5.05 ($p < 0.00001$)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **673** | | | **336** | **100.0** | **70.67 (53.35, 88.00)** | |

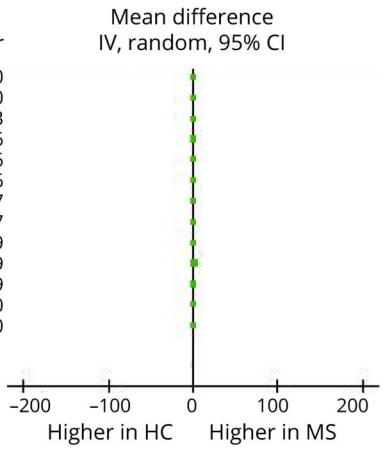
Heterogeneity: $\tau^2 = 908.83$; $\chi^2 = 629.88$, df = 12 ($p < 0.00001$); $I^2 = 98\%$
Test for overall effect: z = 8.00 ($p < 0.00001$)
Test for subgroup differences: $\chi^2 = 0.48$, df = 1 ($p = 0.49$); $I^2 = 0\%$




C

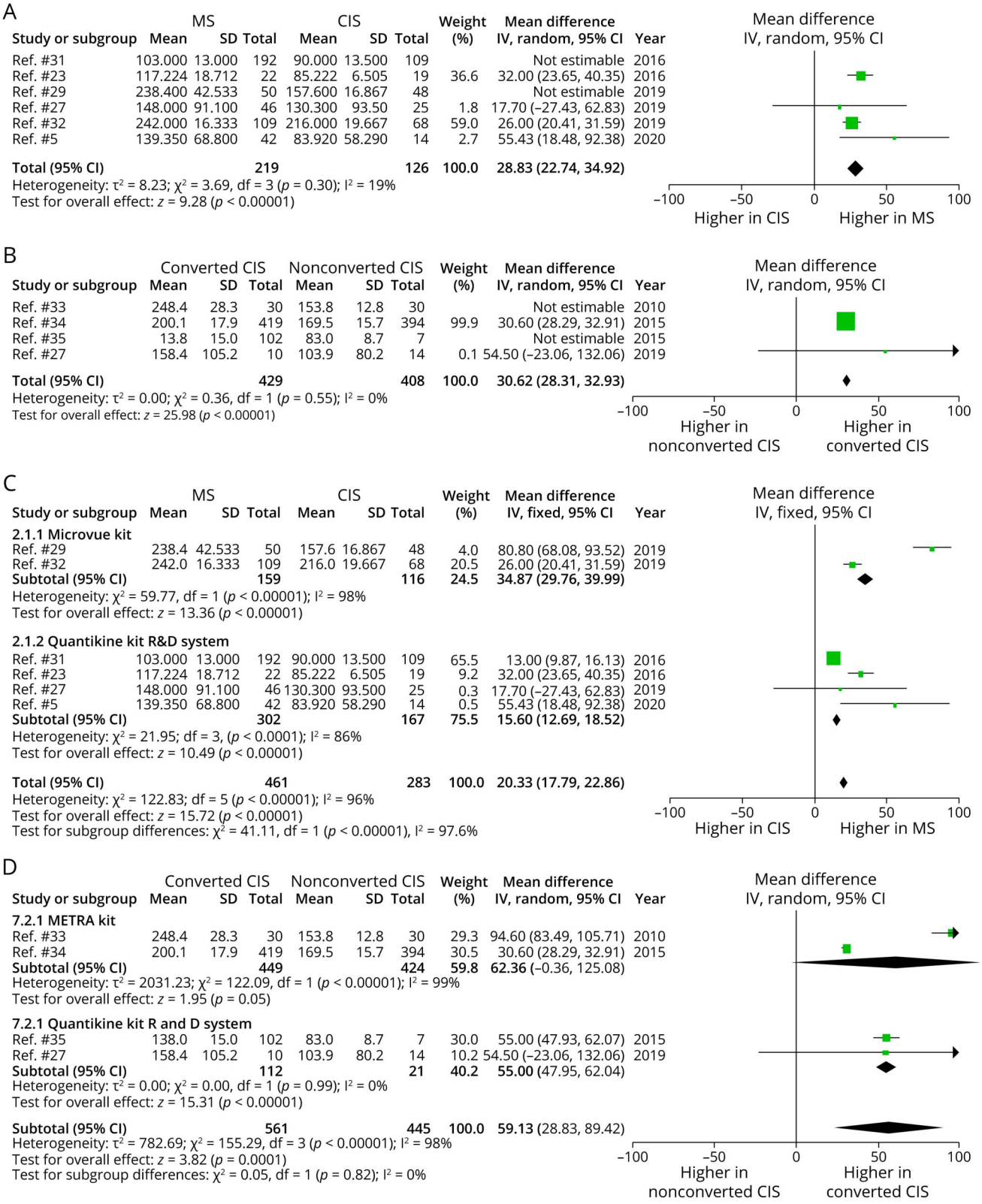
| Study or subgroup | Multiple sclerosis Mean | SD | Total | Healthy controls Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Ref. #36 | 3.0 | 1 | 10 | 2.3 | 1 | 12 | 5.2 | 0.70 (−0.14, 1.54) | 2010 |
| Ref. #21 | −0.7 | 1 | 24 | −0.6 | 1 | 24 | 7.3 | −0.10 (−0.67, 0.47) | 2010 |
| Ref. #22 | −0.8 | 1 | 56 | −0.6 | 1 | 27 | 8.3 | −0.20 (−0.66, 0.26) | 2013 |
| Ref. #8 | −0.1 | 1 | 117 | −0.1 | 1 | 30 | 8.8 | 0.00 (−0.40, 0.40) | 2016 |
| Ref. #23 | −0.4 | 1 | 22 | −0.4 | 1 | 23 | 7.2 | 0.00 (−0.58, 0.58) | 2016 |
| Ref. #24 | −0.4 | 1 | 33 | −0.1 | 1 | 39 | 8.2 | −0.30 (−0.76, 0.16) | 2016 |
| Ref. #25 | −0.2 | 1 | 43 | −0.1 | 1 | 39 | 8.5 | −0.10 (−0.53, −0.33) | 2017 |
| Ref. #26 | 0.3 | 1 | 26 | 0.9 | 1 | 24 | 7.4 | −0.60 (−1.15, −0.05) | 2017 |
| Ref. #27 | −0.1 | 1 | 46 | −0.8 | 1 | 11 | 6.6 | 0.70 (0.04, 1.36) | 2019 |
| Ref. #28 | −0.2 | 1 | 157 | −1.2 | 1 | 30 | 8.9 | 1.00 (0.61, 1.39) | 2019 |
| Ref. #29 | 1.6 | 1 | 50 | 1.9 | 1 | 42 | 8.7 | −0.30 (−0.71, 0.11) | 2019 |
| Ref. #5 | −0.3 | 1 | 42 | 0.0 | 1 | 15 | 7.1 | −0.30 (−0.89, 0.29) | 2020 |
| Ref. #30 | −0.5 | 1 | 47 | −0.6 | 1 | 20 | 7.7 | 0.10 (−0.42, 0.62) | 2020 |
| **Total (95% CI)** | | | **673** | | | **336** | **100.0** | **0.03 (−0.23, 0.29)** | |

Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 42.33$, df = 12 ($p < 0.0001$); $I^2 = 72\%$
Test for overall effect: z = 0.22 ($p = 0.82$)



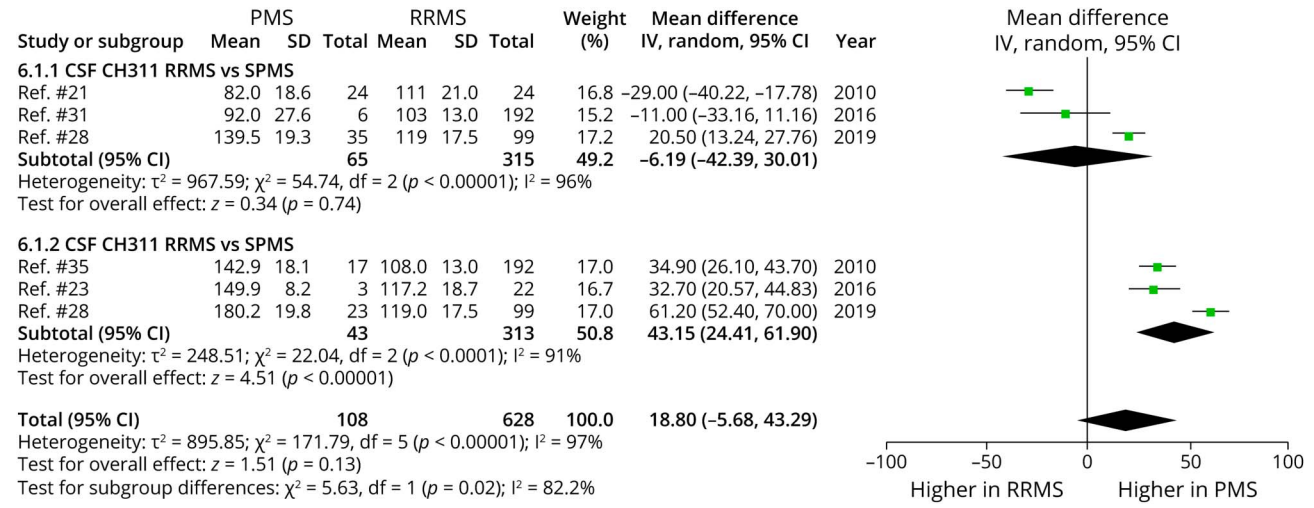

Forest plot of meta-analysis (with sensitivity analysis) (A) CHI3L1 levels in CSF in patients with MS vs healthy controls (HC); (B) subgroups analysis comparing CHI3L1 levels in CSF in HC vs relapsing-remitting + progressive forms (RRMS+PMS) and in HC vs RRMS only. Random-effects model was used. Outcomes are expressed as standardized mean difference (SMD) with 95% CI. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients. Subgroup differences are expressed through score. The SMD of the studies excluded from the analysis compared in the forest plot as "not estimable." (C) Standardization of absolute value of CSF levels of CHI3L1 with Z-scores extraction.

**Figure 3** Comparison Between Multiple Sclerosis vs Clinically Isolated Syndrome




Forest plot of meta-analysis (with sensitivity analysis) showing: (A) CHI3L1 levels in CSF in patients with clinically definite MS (MS) vs clinically isolated syndrome (CIS) (B) CHI3L1 levels in CSF in patients with converted vs non-converted CIS. The two meta-analysis were further performed with a subgroup analysis according to the specific ELISA kit used for the extraction of CSF levels of CHI3L1 ([C] Quantikine kit R&D system vs MicroVue kit in MS vs CIS; [D] Quantikine kit R&D system vs METRA kit in converting vs non converting CIS). For all the analysis, random-effects model was used. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients. Subgroup differences are expressed through score. The SMD of the studies excluded from the analysis compared in the forest plot as "not estimable"

**Figure 4** Comparison Between Relapsing-Remitting vs Progressive Multiple Sclerosis




Forest plot of meta-analysis showing CHI3L1 levels in CSF in patients with relapsing remitting MS (RRMS) vs progressive MS (PMS). Random-effects model was used. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients. Subgroup differences are expressed through score. PPMS = primary progressive MS; SPMS = secondary progressive MS.

was performed to eliminate the outliers, showing that the mean difference in CSF CHI3L1 levels between patients with MS and controls remained significant (50.88 with 95% CI = 44.98–56.79; $p < 0.00001$; Figure 2A) with low heterogeneity ($I^2$ 37%). A subgroup analysis was also performed showing persistence of a significant effect size comparing HC vs relapsing-remitting + primary progressive MS forms (RRMS + PPMS) and HC vs RRMS only (Figure 2B). All data were standardized, and Z-scores were extracted, which were quite similar among the studies in both patients with MS and HCs (Figure 2C).

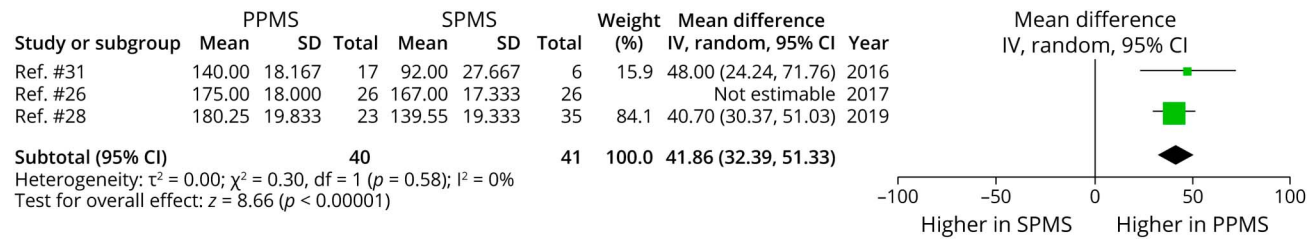
## Difference of CSF Levels of CHI3L1 in Patients With Clinically Definite MS vs CIS

Differences in CSF CHI3L1 levels between patients with clinically definite MS (CDMS) and patients with CIS were reported by 6 studies, involving 461 CDMS and 283 CIS.[5,23,27,29,31,32] The meta-analysis showed higher levels of CSF CHI3L1 in patients with CDMS than patients with CIS with SMD of 20.73 (95% CI = 17.79–22.86; $p < 0.00001$). The heterogeneity among the studies was high ($I^2$ 96%), so an influence analysis and a Baujat plot were performed (eFigure 2A, B, links.lww.com/NXI/A711). After that, sensitivity analysis was conducted without the outlier studies, which showed persistence of a significant effect size (mean difference 28.18 with 95% CI = 23.59–32.76; $p < 0.00001$; Figure 3A) with very low heterogeneity ($I^2$ 19%). A subgroup analysis was also performed; it showed the same significant results independently to the different ELISA kit used for the extraction of CSF levels of CHI3L1 (SMD 34.87 with 95% CI = 29.76–39.99; $p < 0.00001$ with the MicroVue kit; SMD 15.60 with 95% CI = 12.69–18.52; $p < 0.00001$ with the Quantikine kit R&D Systems [Figure 3C]).

## Difference of CSF Levels of CHI3L1 in Patients With Converted vs Nonconverted CIS

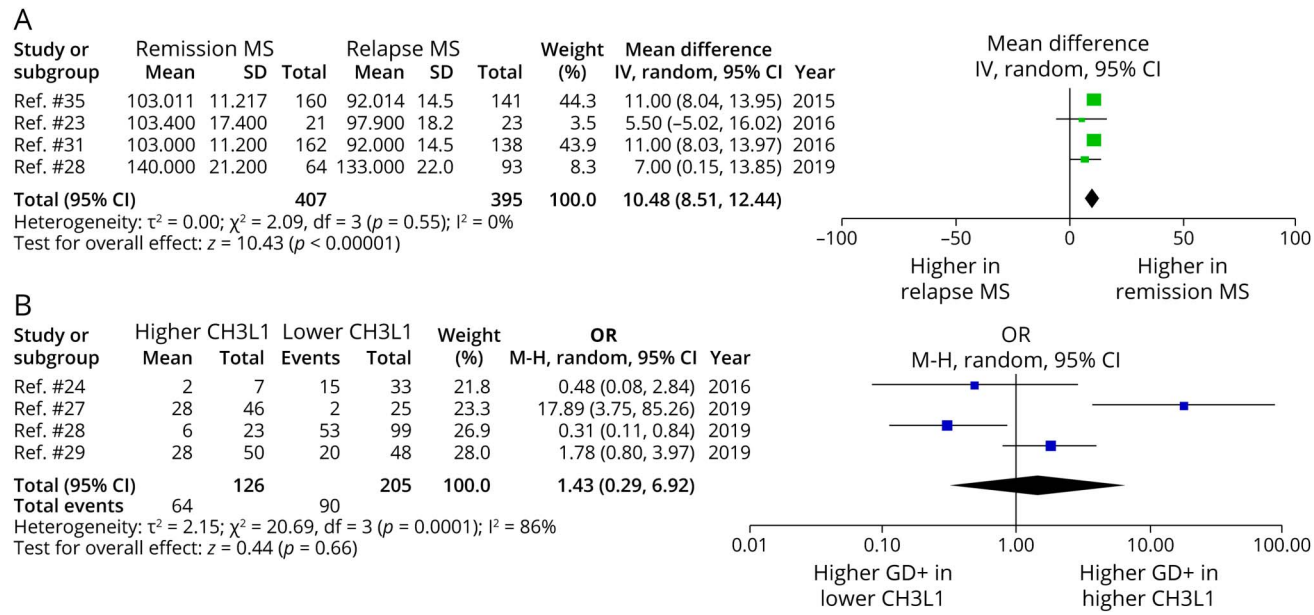
CSF CHI3L1 levels between patients with converted and nonconverted CIS were reported by 4 studies, for a total of

**Figure 5** Comparison Between Primary vs Secondary Progressive Multiple Sclerosis




Forest plot of meta-analysis (with sensitivity analysis) showing CHI3L1 levels in CSF in patients with primary progressive MS (PPMS) vs secondary progressive MS (SPMS). Random-effects model was used. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients. The SMD of the studies excluded from the analysis compared in the forest plot as "not estimable."

**Figure 6** Comparison Between Relapse vs Remission Stage of Disease




Forest plot of meta-analysis showing: (A) CHI3L1 levels in CSF in patients with acute relapse vs remission stage of the disease; (B) proportions of patients with gadolinium enhancing lesion (GD+) on MRI in those with higher vs lower CHI3L1 levels in CSF. To compare the proportions, the Mantel-Haenszel model was used. Outcomes are expressed as Odds-Ratio, with 95% CI. Random-effects model was used for all the analysis. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients.

561 converted and 445 nonconverted CIS.[27,33-35] The meta-analysis showed significant higher levels of CSF CHI3L1 in patients with converted CIS compared with those with non-converted CIS (SMD 59.13; 95% CI = 28.83–89.42; $p$: 0.0001). Because of the high heterogeneity among studies, we performed sensitivity analysis, which showed persistence of a significant effect size (SMD 30.60; 95% CI = 28.31–32.93; $p$ < 0.00001, Figure 3B) with no heterogeneity ($I^2$ 0%). A subgroup analysis according to the different ELISA kit used for the extraction of CSF levels of CHI3L1 was performed, showing that levels of CHI3L1 were significantly higher in converting CIS for those studies that used the Quantikine kit R&D Systems (SMD 55.00; 95% CI = 47.95–62.04; $p$ < 0.00001, $I^2$ 0%) but not for those that used the METRA kit (SMD 62.36; 95% CI = −0.36 to 125.08; $p$ = 0.05, $I^2$ 99%). Results are shown in Figure 3D.

## Difference of CSF Levels of CHI3L1 in Patients With Relapsing-Remitting MS vs Progressive MS

To assess whether CSF levels of CHI3L1 were significantly different between patients with RRMS and PPMS, we compared data from 628 patients with RRMS and 108 patients with PPMS by 5 studies.[21,23,28,31,35] The results of the meta-analysis showed no significant differences of mean levels of CSF CHI3L1 between patients with PPMS and those with RRMS (SMD 18.82 95% CI = −5.66 to 43.30; $p$ = 0.16). However, because of the high heterogeneity among studies, a subgroup analysis was performed to compare each form of progressive MS (primary and secondary progressive) with RRMS. Of interest, the analysis showed significantly higher levels of CSF CHI3L1 in patients with primary progressive MS (PPMS) (SMD 43.15; 95% CI = 24.41–61.90; $p$ < 0.00001) but not in patients with secondary progressive MS (SPMS) compared with patients with RRMS (SMD −6.15; 95% CI = −42.43 to 30.12; $p$: 0.74; Figure 4). Considering the comparison between patients with PPMS and those with RRMS, meta-regression showed a positive correlation between the difference of baseline EDSS score and the SMD of the levels of CHI3L1 in CSF ($p$: 0.000091); this could explain the high heterogeneity among studies ($I^2$ 91%). No correlation was found between levels of CHI3L1 in CSF and age ($p$: 0.614), duration of disease ($p$: 0.325), and previous disease-modifying treatment ($p$: 0.507) between the 2 subgroups. Bubble plots are shown in eFigure 3A–D, links.lww.com/NXI/A711.

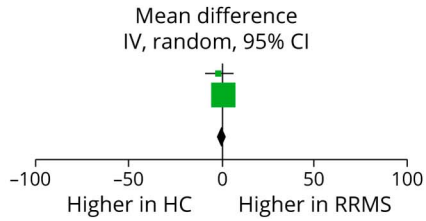
## Difference of CSF Levels of CHI3L1 in Patients With PPMS vs Those With SPMS

Differences in CSF CHI3L1 levels between PPMS and SPMS were reported by 3 studies, involving 66 patients with PPMS and 67 patients with SPMS.[26,28,31] The meta-analysis showed significant higher levels of CSF CHI3L1 in PPMS than SPMS with SMD of 31.08 (95% CI = 5.05–57.12; $p$: 0.02). Because of the high heterogeneity across studies ($I^2$ 92%), an influence analysis and a Baujat plot were performed (eFigure 4A, B, links.lww.com/NXI/A711), showing Sellebjerg study as an inflectional case. Removing it by sensitivity analysis, a significant effect size (SMD 41.86 with 95% CI = 32.39–51.33; $p$ < 0.00001; Figure 5) persisted with no heterogeneity ($I^2$ 0%). Meta-regression showed that SMD of

**Figure 7** Comparison Between Serum Levels of CHI3L1 Between Relapsing-Remitting Multiple Sclerosis vs Healthy Controls

| Study or subgroup | Serum CH3L1 in RRMS Mean | SD | Total | Serum CH3L1 in HC Mean | SD | Total | Weight (%) | Mean difference IV, random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Ref. #27 | 14.9 | 8.9 | 46 | 16.4 | 10.8 | 11 | 5.8 | −1.50 (−8.38, 5.38) | 2019 |
| Ref. #30 | 26.4 | 2.3 | 47 | 25.8 | 3.6 | 20 | 94.2 | 0.60 (−1.11, 2.31) | 2022 |
| **Total (95% CI)** | | | **93** | | | **31** | **100.0** | **0.48 (−1.18, 2.14)** | |

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.34$, df = 1 ($p = 0.56$); $I^2 = 0\%$
Test for overall effect: $z = 0.56$ ($p = 0.57$)




Forest plot of meta-analysis showing CHI3L1 levels in serum in patients with relapsing-remitting MS (RRMS) vs healthy controls (HC). Random-effects model was used for all the analysis. Overall effect is expressed with Z score; heterogeneity is expressed with Tau and coefficients.

CH3L1 negatively correlated with the difference of age ($p$: 0.435), disease duration ($p$: 0.947), EDSS ($p$: 0.435), and previous disease-modifying treatment ($p$: 0.435) (eFigure 5A–D, links.lww.com/NXI/A711).

### Difference of CSF Levels of CHI3L1 in Relapsing vs Remission MS

To assess whether CSF levels of CHI3L1 were significantly different during acute relapsing activity (defined as the presence of at least one clinical relapse and/or new/enlarging lesion on T2 MRI sequences and/or gadolinium-enhancing lesion on T1 + gadolinium MRI sequences in the last 2 months before lumbar puncture) and remission stage of the disease, we compared data from 395 patients with acute relapse and 407 patients with remission phase by 4 studies.[23,28,31,35] The results of the meta-analysis showed that the levels of CSF CHI3L1 were significantly higher in patients during the remission stage of the disease than patients with an acute relapse (SMD 10.48; 95% CI = 08.51–12.44; $p < 0.00001$; Figure 6A), with no heterogeneity ($I^2$ 0%). Besides, there were no significant differences in the proportions of patients with at least one gadolinium-enhancing lesion (Gd+) on MRI at the time of lumbar puncture by comparing data from 126 patients with MS with higher levels of CSF CHI3L1 and 205 patients with MS with lower levels of CSF CHI3L1 by 4 studies (OR 1.43; 95% CI = 0.29–6.92; $p = 0.66$; Figure 6B).[24,27-29]

### Serum Levels of CHI3L1 in Patients With RRMS vs Healthy Controls

Serum CHI3L1 levels between patients with RRMS and HCs were reported by 2 studies, for a total of 93 RRMS and 31 HC.[27,30] The meta-analysis showed no significant difference in levels of serum CHI3L1 in RRMS and HC (SMD 0.48; 95% CI = −1.18 to 2.14; $p$: 0.57; Figure 7) with no heterogeneity among studies ($I^2$ 0%).

## Discussion

Our systematic review clarified the potentiality of CHI3L1 marker for the characterization of disease progression in patients with MS[36,37] and the relationship between CHI3L1 levels and the different subtypes of MS. The meta-analysis showed that CHI3L1 levels in CSF were significantly elevated in patients with MS compared with HCs. Moreover, CHI3L1 levels in CSF were found to be significantly associated with conversion from CIS to MS. This body of evidence supports the hypothesis that CHI3L1 sustains, in some way, disease activity in CNS since the earliest phases of the disease, in accordance with a few studies that demonstrated the expression of CHI3L1 both in macrophages and astrocytes.[34,38,39]

To complicate this scenario, other studies demonstrated that the pattern associated with the production of CHI3L1 in vivo differs from that in vitro. In vivo astrocytes are the main responsible of the release of CHI3L1, and this process is sustained by macrophages through cytokine crosstalk. In vitro, CHI3L1 seems instead to be produced by macrophages themselves.[5] Similar to the more studied glial fibrillar acidic protein marker,[40] CHI3L1 provides evidence of the importance of the role of astrocytes in the modulation of inflammatory activity in the different phases of MS disease.[41,42]

Of interest, our meta-analysis showed that CHI3L1 CSF levels were significantly higher in patients with PPMS compared with both patients with RRMS and those with SPMS. This is in contrast with the hypothesis that RRMS/SPMS and PPMS histopathologic differences are more quantitative rather than qualitative.[43] Recent evidence suggests that in the 2 subtypes of the disease, different inflammatory patterns develop independently.[44] The first is the transmigration of T and B lymphocytes from a pathologically permeable blood-brain barrier (BBB), which predominately affects the white matter and forms the well-known active demyelinated plaques. The other type of inflammatory process does not involve the immune system outside the CNS; without substantial BBB leakage, brain-derived T cells and B cells accumulate in the connective tissue, forming a sort of lymph follicles, which stabilize a subtle chronic immune response over time.[45] Characteristic signs of chronic active disease, such as subpial demyelinated lesions in the cerebral and cerebellar cortex, slow-evolving lesions in the white matter, and degeneration of neurons in the normal-appearing white or gray matter, seem to be mostly associated with this type of inflammatory pattern. The first type of histopathologic subset characterizes the acute and relapsing MS. The second type of

inflammation is already present in early stages of MS and becomes more evident in the PPMS subtype.[44] CHI3L1 seems to be more associated with the second subset, and this is further supported by existing literature, such as the independent correlation between CSF CHI3L1 levels and the albumin CSF/serum ratio, which is a well-noticed index of blood-CSF barrier dysfunction[46]; moreover, other studies demonstrated the relevant difference observed in CHI3L1 levels between CSF and serum samples.[33] Together, the findings strongly suggest a primarily local CNS origin of CSF CHI3L1 levels.

The results of our analysis show higher levels of CHI3L1 in the remission stage of the disease rather than during the relapse activity. Moreover, considering imaging biomarkers, the proportion of patients with gadolinium + lesions on MRI was found to be not significantly different between those with higher and lower levels of CHI3L1 in CSF. This observation supports the hypothesis that the role of the protein in the inflammatory environment could be not only limited to the acute phase of the disease, but chronic over time. It has previously been demonstrated that CHI3L1 can interfere with the development of axonal processes in the hippocampus by blocking blood fibroblast growth factor signaling. Thus, it is reasonable to hypothesize that CHI3L1 protein can, in some way, influence the molecular pattern associated with synaptic plasticity and neuronal regeneration.[47] Our study demonstrated also a strongly significant correlation between higher levels of CSF CHI3L1 and the EDSS score, especially in patients with PPMS vs RRMS, supporting a possible connection between CHI3L1 and the disability progression (see supplementary materials). Besides, our supplementary analysis showed that CH3L1 is independent from normal aging and disease duration; this represents an important difference from other more studied markers such as glial fibrillar acidic protein or neurofilament light chain (NfL). This evidence encourages a possible reliability of CHI3L1 in clinical practice in monitoring the course of MS disease even in the later stages. However, further research that investigates the correlation of CHI3L1 levels in CSF and the main clinical and imaging measures of disease progression, e.g., changes in the EDSS score over time and estimation of brain atrophy, is warranted in the future.

Results from our meta-analysis show no significant difference between levels of CHI3L1 in patients with RRMS and HCs within the serum. This can be due to the predominant intrathecal production of CHI3L1 in CNS inflammatory processes, as argued above. However, the small number of studies included in the analysis and the restricted size of the groups of comparison may have affected the results. Therefore, larger studies are warranted.

The availability of many prospective studies in our analysis strongly supports the reliability of our results. Moreover, the high heterogeneity we found among some of the studies depends mainly on the presence of outliers, in which the dosage of CSF/serum CHI3L1 could be justified by clinical and radiologic data not available for all of them. One example is the amount of brain or spinal cord atrophy, which, according to the last findings, seems to correlate well with the levels of CHI3L1 in CSF. Schneider et al.[48] recently supported the reliability of CHI3L1 to differentiate progressive from relapsing form of disease and demonstrated a different correlation between CHI3L1 and NfL with brain and spinal cord atrophy. CHI3L1 seemed to best correlate with spinal cord involvement, and, in agreement with our results, it was less influenced by age and disease duration than NfL. However, more studies are needed to better evaluate the correlation between the levels of CHI3L1 and the topographic distribution of the lesion load in CNS. Another possible explanation to the heterogeneity found in some results is purely methodological; e.g., the subgroup analysis investigating the different levels of CSF CHI3L1 in converting vs nonconverting CIS was found to be significant for those studies that used the Quantikine kit R&D Systems but not for those that used the METRA kit; more importantly, the heterogeneity between the studies was largely significant only for the METRA kit. We suggest further investigations about the accuracy and reproducibility of the different ELISA techniques used for quantification of CHI3L1 in CSF and serum.

However, the largest part of the studies selected for the meta-analysis used the same ELISA kit for the extraction of data. Moreover, the performed influence and sensitivity analysis confirmed the persistence of the high significance of the results obtained. In the end, the statistical standardization of each absolute value of CSF levels of CHI3L1 in HCs showed no significant difference from each other, excluding the hypothesis of a center-dependent bias.

Our study has some limitations. Despite the high number of articles selected, the majority of studies reported have been carried out is small cohorts. There is also heterogeneity in the quality assessment, with few studies with low NOS scores (Table). As mentioned before, data about some imaging features (e.g., the number of brain and spinal cord lesions on T2 MRI sequences or quantification of brain atrophy), correlations with other serum/CSF biomarkers (e.g., neurofilament light chain), and the estimation of CHI3L1 levels over disease course and in response to the several disease modifying treatments are not available in this meta-analysis.

The context of use of CHI3L1 in clinical practice is still indecisive. However, our results suggest a high potential of CHI3L1 for the identification of patients with MS at baseline, especially for what concerns the primary progressive subtype, and for monitoring the severity of progression over time. Further investigations in the future to confirm its reliability in the follow-up of patients with MS, especially on serum, are warranted.

In summary, the results of our meta-analysis showed that CSF levels of CHI3L1 are higher in patients with MS compared with HCs and those with CIS and in converting CIS in comparison with nonconverting CIS. More importantly, higher levels of CHI3L1 in the CSF best correlated with

PPMS than the other subtypes, and consistently CHI3L1 levels better correlated with MS remission stages than with acute relapses. In addition, the EDSS score significantly correlates with higher CSF levels of CHI3L1 in PPMS vs RRMS. These results suggest a potential role of CSF CHI3L1 levels as a reliable biomarker to characterize MS disease activity and its phenotypes and indicate a possible connection with measures of progression. More studies are needed to establish its utility in clinical practice, especially for what concerns the identification of high probable-converting CIS, the distinction of PPMS from RRMS at baseline and the correlation with other measurement of disease progression (e.g., brain atrophy). We also suggest further research in the future to establish the potential role of CHI3L1 in serum for monitoring the disease activity and its response to the main therapies.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## Appendix Authors

| Name | Location | Contribution |
|---|---|---|
| **Stefano Floro, MD** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy; University of Milan, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data |
| **Tiziana Carandini, MD** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content |
| **Anna Margherita Pietroboni, MD** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content |
| **Milena Alessandra De Riz, MD** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content |
| **Elio Scarpini** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy; University of Milan, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content |
| **Daniela Galimberti** | Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy; University of Milan, Milan, Italy | Drafting/revision of the manuscript for content, including medical writing for content |

## References


1. Stefano NDe, Sormani MP. News & VIews Combining biomarkers to profile multiple sclerosis patients. *Nat Rev Neurol.* 2020;16(9):463-464.
2. Ebrahimkhani S, Vafaee F, Young PE, et al. Exosomal microRNA signatures in multiple sclerosis reflect disease status. *Sci Rep.* 2017;7(1):14293-14310.
3. Paul A, Comabella M, Gandhi R. Biomarkers in multiple sclerosis. *Cold Spring Harb Perspect Med.* 2019;9(3):a029058.
4. Ziemssen T, Akgün K, Brück W. Molecular biomarkers in multiple sclerosis. *J Neuroinflammation.* 2019;16(1):272.
5. Kušnierová P, Zeman D, Hradílek P, Zapletalová O, Stejskal D. Determination of chitinase 3-like 1 in cerebrospinal fluid in multiple sclerosis and other neurological diseases. *PLoS One.* 2020;15(5):e0233519.
6. Bonneh-Barkay D, Wang G, Starkey A, Hamilton RL, Wiley CA. In vivo CHI3L1 (YKL-40) expression in astrocytes in acute and chronic neurological diseases. *J Neuroinflammation.* 2010;7:34.
7. Matute-Blanch C, Calvo-Barreiro L, Carballo-Carbajal I, et al. Chitinase 3-like 1 is neurotoxic in primary cultured neurons. *Sci Rep.* 2020;10(1):7118.
8. Burman J, Raininko R, Blennow K, Zetterberg H, Axelsson M, Malmeström C. YKL-40 is a CSF biomarker of intrathecal inflammation in secondary progressive multiple sclerosis. *J Neuroimmunol.* 2016;292:52-57.
9. Querol-Vilaseca M, Colom-Cadena M, Pegueroles J, et al. YKL-40 (Chitinase 3-like I) is expressed in a subset of astrocytes in Alzheimer's disease and other tauopathies. *J Neuroinflammation.* 2017;14(1):118.
10. Lee YH, Song GG. YKL-40 levels in rheumatoid arthritis and their correlation with disease activity: a meta-analysis. *J Rheum Dis.* 2019;26:257-263.
11. Vos K, Steenbakkers P, Miltenburg AM, et al. Raised human cartilage glycoprotein-39 plasma levels in patients with rheumatoid arthritis and other inflammatory conditions. *Ann Rheum Dis.* 2000;59(7):544-548.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
13. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev.* 2019;10:ED000142.
14. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302.
15. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173.
16. Wells GA, Shea B, O'Connel D et al. The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses. 2009. Accessed February 1, 2009. www.ohca/programs/clinical_epidemiology/oxford.asp.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.
18. Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect.* 2013;20(2):123-129.
19. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods.* 2006;11(2):193-206.
20. Baujat B, Mahé C, Pignon JP, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med.* 2002;21(18):2641-2652.
21. Correale J, Fiol M. Chitinase effects on immune cell response in neuromyelitis optica and multiple sclerosis. *Mult Scler.* 2011;17(5):521-531.
22. Modvig S, Degn M, Horwitz H, et al. Relationship between cerebrospinal fluid biomarkers for inflammation, demyelination and neurodegeneration in acute optic neuritis. *PLoS One.* 2013;8(10):e77163.
23. Håkansson I, Tisell A, Cassel P, et al. Neurofilament light chain in cerebrospinal fluid and prediction of disease activity in clinically isolated syndrome and relapsing-remitting multiple sclerosis. *Eur J Neurol.* 2017;24(5):703-712.
24. Novakova L, Axelsson M, Khademi M, et al. Cerebrospinal fluid biomarkers of inflammation and degeneration as measures of fingolimod efficacy in multiple sclerosis. *Mult Scler.* 2017;23(1):62-71.
25. Novakova L, Zetterberg H, Sundström P, et al. Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. *Neurology.* 2017;89(22):2230-2237.
26. Sellebjerg F, Börnsen L, Ammitzbøll C, et al. Defining active progressive multiple sclerosis. *Mult Scler.* 2017;23(13):1727-1735.
27. De Fino C, Lucchini M, Lucchetti D, et al. The predictive value of CSF multiple assay in multiple sclerosis: a single center experience. *Mult Scler Relat Disord.* 2019;35(-June):176-181.
28. Gil-Perotin S, Castillo-Villalba J, Cubas-Nuñez L, et al. Combined cerebrospinal fluid neurofilament light chain protein and chitinase-3 like-1 levels in defining disease course and prognosis in multiple sclerosis. *Front Neurol.* 2019;10:1008.
29. Thouvenot E, Hinsinger G, Demattei C, et al. Cerebrospinal fluid chitinase-3-like protein 1 level is not an independent predictive factor for the risk of clinical conversion in radiologically isolated syndrome. *Mult Scler.* 2019;25(5):669-677.
30. Huss A, Senel M, Abdelhak A, et al. Longitudinal serum neurofilament levels of multiple sclerosis patients before and after treatment with first-line immunomodulatory therapies. *Biomedicines.* 2020;8(9):312.
31. Mañé-martínez MA, Olsson B, Bau L, et al. Glial and neuronal markers in cerebrospinal fluid in different types of multiple sclerosis. *J Neuroimmunol.* 2016;299:112-117.
32. Sellebjerg F, Royen L, Soelberg Sørensen P, Oturai AB, Jensen PEH. Prognostic value of cerebrospinal fluid neurofilament light chain and chitinase-3-like-1 in newly diagnosed patients with multiple sclerosis. *Mult Scler.* 2019;25(11):1444-1451.

33. Comabella M, Fernández M, Martin R, et al. Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis. *Brain.* 2010;133(pt 4):1082-1093.
34. Cantó E, Tintoré M, Villar LM, et al. Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. *Brain.* 2015;138(pt 4):918-931.
35. Martínez MA, Olsson B, Bau L, et al. Glial and neuronal markers in cerebrospinal fluid predict progression in multiple sclerosis. *Mult Scler.* 2015;21(5):550-561.
36. Bonneh-Barkay D, Zagadailov P, Zou H, et al. YKL-40 expression in traumatic brain injury: an initial analysis. *J Neurotrauma.* 2010;27(7):1215-1223.
37. Yeo IJ, Lee CK, Han SB, Yun J, Hong JT. Roles of chitinase 3-like 1 in the development of cancer, neurodegenerative diseases, and inflammatory diseases. *Pharmacol Ther.* 2019;203:107394.
38. Bonneh-Barkay D, Bissel SJ, Kofler J, Starkey A, Wang G, Wiley CA. Astrocyte and macrophage regulation of YKL-40 expression and cellular response in neuroinflammation. *Brain Pathol.* 2012;22(4):530-546.
39. Chen A, Jiang Y, Li Z, et al. Chitinase-3-like 1 protein complexes modulate macrophage-mediated immune suppression in glioblastoma. *J Clin Invest.* 2021;131(16):e147552.
40. Sun M, Liu N, Xie Q, et al. Review article A candidate biomarker of glial fibrillary acidic protein in CSF and blood in differentiating multiple sclerosis and its subtypes: a systematic review and. *Mult Scler Relat Disord.* 2021;51(November):102870.
41. Touil H, Kobert A, Lebeurrier N, et al. Human central nervous system astrocytes support survival and activation of B cells: implications for MS pathogenesis. *J Neuroinflammation.* 2018;15(1):114.
42. Li K, Li J, Zheng J, Qin S. Reactive astrocytes in neurodegenerative diseases. *Aging Dis.* 2019;10(3):664-675.
43. Kuhlmann T. Relapsing-remitting and primary progressive MS have the same cause(s): the neuropathologist's view: 2. *Mult Scler.* 2013;19(3):268-269.
44. Lassmann H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. *Front Immunol.* 2019;9:3116.
45. Negron A, Stüve O, Forsthuber TG. Ectopic lymphoid follicles in multiple sclerosis: centers for disease control? *Front Neurol.* 2020;11:607766.
46. Brettschneider J, Claus A, Kassubek J, Tumani H. Isolated blood-cerebrospinal fluid barrier dysfunction: prevalence and associated diseases. *J Neurol.* 2005;252(9):1067-1073.
47. Bonneh-Barkay D, Bissel SJ, Wang G, et al. YKL-40, a marker of simian immunodeficiency virus encephalitis, modulates the biological activity of basic fibroblast growth factor. *Am J Pathol.* 2008;173(1):130-143.
48. Schneider R, Bellenberg B, Gisevius B, et al. Chitinase 3-like 1 and neurofilament light chain in CSF and CNS atrophy in MS. *Neurol Neuroimmunol Neuroinflamm.* 2020;8(1):e906.
49. Stoop MP, Singh V, Stingl C, et al. Effects of natalizumab treatment on the cerebrospinal fluid proteome of multiple sclerosis patients. *J Proteome Res.* 2013;12(3):1101-1107.
50. Romme Christensen J, Komori M, von Essen MR, et al. CSF inflammatory biomarkers responsive to treatment in progressive multiple sclerosis capture residual inflammation associated with axonal damage. *Mult Scler.* 2019;25(7):937-946.