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Paraproteinemias in Sjögren disease: cryoglobulinemia and serum monoclonal gammopathy identify distinct clinical phenotypes and differential lymphoma susceptibility

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ABSTRACT

Objective: Sjögren disease (SjD) is a systemic autoimmune disease characterized by increased risk of B-cell non-Hodgkin lymphoma. Although cryoglobulinemia and serum monoclonal component (MC) are well-recognized paraproteinemias in SjD, no large-scale study has directly compared their isolated and combined impact on phenotype and lymphoproliferative risk.

Methods: A retrospective, multicenter, cross-sectional study was conducted within the Italian GRISS registry. Patients with SjD were stratified into four groups: isolated monoclonal gammopathy (MC-alone), isolated cryoglobulinemia (CRYO-alone), both (MC+CRYO), or neither (controls). Demographics, lymphoma history, ever-documented ClinESSDAI domains, and laboratory lymphoproliferative risk-related markers were analyzed. Primary and secondary outcomes assessed lymphoma diagnosis and the distribution of laboratory lymphoproliferative risk-related markers and ClinESSDAI domains across groups, with associations tested using logistic regression adjusted for confounders.

Results: 1202 SjD patients were enrolled: 58 (4.83%) in the MC-alone, 32 (2.66%) in the CRYO-alone, 35 (2.91%) in the MC+CRYO, and 1077 (89.60%) controls. Compared with controls, only the MC+CRYO group showed significant association with lymphoma (OR 6.30, 95%CI 2.66–14.92; $p < 0.001$), while MC-alone and CRYO-alone were not associated. Cryoglobulinemia, alone or combined with MC, correlated with laboratory lymphoproliferative risk-related markers such as rheumatoid factor ($p < 0.001$) and low C4 ($p < 0.001$), and with

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ClinESSDAI vasculitic features (cutaneous [$p < 0.001$], renal [$p < 0.05$], PNS [$p < 0.001$]). The MC+CRYO group additionally displayed a lymphoproliferative phenotype correlating with constitutional ($p < 0.05$), glandular ($p < 0.05$), hematological ($p < 0.001$), and lymphadenopathy ($p < 0.001$) domains.
Conclusion: Cryoglobulinemia in SjD associates with vasculitic disease activity, whereas the coexistence of serum MC and cryoglobulins identifies a distinct, high-risk subset characterized by advanced B-cell expansion and increased lymphoma susceptibility.

Introduction

Sjögren disease (SjD) is a systemic autoimmune epithelitis primarily affecting the exocrine glands, characterized by B-cell hyperactivity, lymphocytic infiltration of salivary and lacrimal tissues, and progressive glandular dysfunction [1,2]. One of the most severe long-term complications of SjD is the development of B-cell non-Hodgkin lymphoma, particularly mucosa-associated lymphoid tissue (MALT) lymphoma of the salivary glands [2–5]. The pathogenetic hallmark of this evolution is the persistence of polyclonal B-cell activation and subsequent clonal expansion within glandular tissue eventually leading to the emergence of one or more malignant clones [6,7].

Several clinical and serological factors have been associated with an increased risk of lymphoma in SjD, including persistent glandular swelling, purpura, lymphadenopathy, leuko-lymphopenia, low serum C4 levels, anti-La/SSB positivity, rheumatoid factor (RF) positivity, cryoglobulinemia, and the presence of serum monoclonal components (MC) [8–16]. Among these, cryoglobulinemia and monoclonal gammopathy are two paraproteinemic conditions that directly reflect B-cell clonal activity and have been extensively linked to an increased risk of lymphoproliferative complications [8–12].

Both cryoglobulinemia and monoclonal gammopathy have been independently associated with lymphoproliferative complications, whereas their combined or comparative impact on the disease phenotype has not been fully elucidated. Cryoglobulinemia occurs in 3–7% of patients with SjD and it is typically associated with an increased risk of salivary gland MALT lymphoma. Moreover, it defines a distinct vasculitic phenotype, characterised by constitutional symptoms, skin lesions, renal disease, and peripheral nervous system (PNS) involvement [8,17]. On the other hand, monoclonal gammopathy is detectable in approximately 7–22% of patients with SjD, with IgG being the most frequently observed isotype, followed by IgM clonal bands. Although monoclonal gammopathy—particularly of the IgM isotype—has been regarded in SjD as a strong risk factor for hematologic malignancies (e.g., B-cell lymphomas), emerging evidence indicates that this association is not universal. In particular, the more common IgG isotype often remains clinically silent in SjD and it is not necessarily linked to an increased lymphoproliferative risk or higher disease activity [10–12,14]. In rare cases, however, it may represent a precursor to hematologic disorders such as multiple myeloma, a condition not typically associated with SjD [12].

The distinction between these two paraproteinemias is clinically relevant not only for risk stratification but also to tailor monitoring strategies and guide early therapeutic decisions in SjD [18,19]. Despite overlapping features, it is plausible that isolated monoclonal gammopathy and cryoglobulinemia reflect divergent B-cell clonal pathways, with different predisposition toward systemic activity and lymphoproliferative transformation. The assessment of their individual and synergistic associations with clinical activity scores and established lymphoproliferative risk markers may provide a more nuanced understanding of B-cell dysregulation in SjD.

To date, no large-scale study has systematically compared patients with isolated monoclonal gammopathy, isolated cryoglobulinemia, a combination of the two, and patients without any of these markers in terms of disease activity, immunologic risk profile, and lymphoma development. This study aims to fill this gap by evaluating whether monoclonal gammopathy and cryoglobulinemia, alone or in combination, delineate distinct clinical phenotypes in terms of lymphoproliferation and disease activity and different lymphoproliferative risk profiles in patients with SjD.

Materials and methods

Study design and population

This retrospective, multicenter, cross-sectional study was conducted between November 2024 and June 2025 in ten Italian hub centers for the diagnosis and management of SjD, all affiliated with the Italian Sjögren disease Research Group (GRISS) network. The study included patients from the GRISS cohort who fulfilled either the 2002 AECG or the 2016 ACR/EULAR classification criteria for SjD [20,21]. The GRISS cohort is a national, multicenter, prospective registry that anonymously collects longitudinal clinical and laboratory data from patients with SjD followed at each participating center from the time of diagnosis to last follow-up. The study was conducted in accordance with the principles of the Declaration of Helsinki (1975/83), and ethics approval was obtained at the coordinating center (CE-1713/2025; University of Perugia) and at each participating center. Written informed consent was obtained at each center in accordance with the requirements of the respective ethics committees.

Study variables

The following variables were extracted from the GRISS database: (a) demographic characteristics, including biologic sex, age at SjD diagnosis, and disease duration; (b) clinical characteristics, including coexisting systemic autoimmune diseases, disease activity assessed through the presence of one or more ever-documented ClinESSDAI domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, muscular, pulmonary, PNS, central nervous system (CNS), hematological) from diagnosis to last follow-up, and history of lymphoma; (c) ever-documented laboratory parameters, including anti-Ro/SSA antibodies and laboratory lymphoproliferative risk-related markers (RF, anti-La/SSB antibodies, low C4 levels, cryoglobulins, and presence and type of serum monoclonal component), assessed from diagnosis to last follow-up. Laboratory variables, including serum cryoglobulins, were considered positive only if confirmed twice, at least 12 months apart. Patients with a documented diagnosis of type I cryoglobulinemia, or with cryoglobulinemia considered likely to be type I, namely associated with an overt hematologic lymphoproliferative disorder diagnosed prior to SjD onset, lacking RF activity or showing no evidence of low C4, were excluded, as this represents a distinct entity compared with SjD associated mixed cryoglobulinemia. Disease activity was evaluated using the ClinESSDAI, with the biological domain excluded to avoid redundancy with separately analysed laboratory variables. For the hematological domain, only patients fulfilling the criteria for this domain prior to therapeutic interventions (e.g., B-cell depleting agents) were considered positive.

Study procedure and outcomes

Patients enrolled were stratified into four mutually exclusive groups according to the presence of detectable serum cryoglobulinemia, detectable serum MC, or both. The groups were: (1) isolated monoclonal

gammopathy (MC-alone) group; (2) isolated cryoglobulinemia (CRYO-alone) group; (3) concomitant monoclonal gammopathy and cryoglobulinemia (MC+CRYO) group; (4) control group with neither of the two conditions. MC was identified by serum protein electrophoresis and immunofixation, whereas cryoglobulins were detected by cryoprecipitation. No standardized GRISS-wide analytical protocol for cryoglobulin measurement was available across participating centers. Moreover, given the retrospective multicenter design, and the long-time span of data collection, detailed reconstruction of center-specific pre-analytical and analytical procedures for cryoglobulin testing was not feasible. The primary outcome was to assess differences in lymphoma frequency across the four groups and to determine whether any group exhibited a stronger association with lymphoma compared with controls. Among patients with SjD and a history of lymphoma, secondary outcomes included evaluating potential differences across the four groups in lymphoma histotype, age at lymphoma diagnosis, and the latency interval between SjD diagnosis and lymphoma onset. Other secondary outcomes included assessing differences in the frequency of specific ClinESSDAI domains and the other laboratory lymphoproliferative risk-related markers (RF, low C4 levels, anti-La/SSB) across the four groups and identifying whether any group showed a stronger association with each variable compared with controls. When more than one group demonstrated a significant association with a given variable relative to controls, additional post-hoc analyses were performed to identify the group with the strongest association. Analyses were performed considering potential confounders, including sex, age at SjD diagnosis, disease duration, presence of concomitant systemic autoimmune diseases, and anti-Ro/SSA antibody positivity. Anti-Ro/SSA and anti-La/SSB antibodies were assessed using routine immunological assays (e.g., ELISA, chemiluminescent, or fluorescence enzyme immunoassays) according to local laboratory procedures. Because no standardized analytical protocol was implemented across centers and the study was retrospective with data collected over a long-time span, it was not possible to reliably reconstruct the specific assay used for each individual determination.

Statistical analysis

Statistical analyses were conducted using RStudio (*Posit Software, PBC, Boston, MA)*. Descriptive statistics are presented as medians with interquartile ranges (IQR) for continuous variables and as absolute frequencies and percentages for categorical variables. Between-group differences in descriptive analyses were first assessed using omnibus tests (Chi-squared or Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables). Univariate logistic regression analyses were performed to assess associations, adjusting for potential confounders that showed statistically significant differences across the four groups. Patients with missing data for a given variable were excluded from analyses involving that variable. The primary hypothesis of an overall difference in lymphoma frequency across the four groups was assessed using a chi-square test of independence. Results of logistic regression analyses were expressed as odds ratios (OR) with 95% confidence intervals (CI), and p-values$<$0.05 were considered statistically significant.

Results

Cohort characteristics

A total of 1202 patients with SjD were included in the analysis, of whom 1144 (95.17%) were females and 58 (4.83%) males. The median age at diagnosis was 53 years (IQR 43–63), and the median disease duration from diagnosis to the last follow-up was 10 years (IQR 5–17).

Anti-Ro/SSA antibodies were detected in 873/1202 patients (72.63%). All patients positive for anti-La/SSB antibodies (443/1202; 36.86%) showed also anti-Ro/SSA positivity. Overall, 67/1202 patients (5.57%) had cryoglobulinemia and 93/1202 (7.74%) had a detectable serum monoclonal component. **Supplementary Table S1** reports the rate of cryoglobulinemia across the different centres.

Concomitant systemic autoimmune diseases were recorded in 114/1202 individuals (9.48%), most commonly rheumatoid arthritis (50.87%), followed by systemic lupus erythematosus (28.07%), systemic sclerosis (14.04%), and myositis (7.02%). Lymphoma developed during follow-up in 57/1202 patients (4.74%). Non-Hodgkin B-cell MALT lymphoma represented the predominant histotype (80.70%), followed by diffuse large B-cell lymphoma (12.28%), with single cases of Hodgkin lymphoma, lymphoplasmacytic lymphoma, splenic B-cell lymphoma, and B-cell lymphoblastic lymphoma.

Based on the presence of detectable serum cryoglobulinemia or a detectable serum MC, the cohort was stratified as it follows: 58 patients (4.83%) in the MC-alone group, 32 (2.66%) in the CRYO-alone group, 35 (2.91%) in the MC+CRYO group, and 1077 (89.60%) in the control group (Fig. 1).

Demographic and general SjD-related characteristics across groups

As detailed in **Supplementary Table S2**, the four groups did not differ significantly in sex distribution ($p = 0.975$), age at diagnosis ($p = 0.652$), prevalence of concomitant systemic autoimmune diseases ($p = 0.721$), or anti-Ro/SSA antibody positivity ($p = 0.066$). Disease duration, however, showed a highly significant variation across groups ($p < 0.001$). In particular, patients in the CRYO-alone and MC+CRYO groups had a notably longer disease duration at last visit compared with the other groups. Given the potential influence of disease duration on the diagnosis of lymphoma, lymphoproliferative risk markers, and disease activity patterns, all subsequent univariate logistic regression analyses were adjusted for this variable.

Lymphoma diagnosis across groups

The primary outcome analysis revealed significant heterogeneity in lymphoma diagnosis across the four groups ($p < 0.001$). The MC+CRYO group exhibited by far the highest prevalence (25.71%), followed by the CRYO-alone (9.38%) and MC-alone (8.62%) groups, with the lowest prevalence observed in controls (3.71%) (**Supplementary Table S3**). These differences were substantiated by logistic regression models adjusted for disease duration. Compared with controls, coexisting MC+CRYO were independently associated with lymphoma (OR 6.30, 95%CI 2.66–14.92, $p < 0.001$), whereas this independent association was not observed for MC-alone and CRYO alone (Fig. 2). When focusing exclusively on patients with a lymphoma diagnosis ($n = 57$), no significant between-group differences emerged regarding lymphoma histotype ($p = 0.350$), age at lymphoma diagnosis ($p = 0.380$), or latency from SjD diagnosis to lymphoma onset ($p = 0.526$) (**Supplementary Table S4**).

Laboratory lymphoproliferative risk-related markers across groups

The distribution of several laboratory markers, including RF, low C4 levels, and anti-La/SSB antibodies, markedly differed across the four groups, with higher prevalence observed in patients with cryoglobulinemia, particularly when concomitant with a serum detectable MC (MC+CRYO group) (**Supplementary Table S5**).

For RF, prevalence progressively decreased from the MC+CRYO group to the CRYO-alone group, the MC-alone group, and finally controls. This trend was supported by univariate logistic regression adjusted for disease duration, which revealed the strongest association in the MC+CRYO group (OR 10.65, 95%CI 3.69–30.62, $p < 0.001$), followed by CRYO-alone (OR 9.88, 95%CI 3.41–28.59, $p < 0.001$) and MC-alone (OR 2.07, 95%CI 1.21–3.55, $p = 0.008$) compared with controls (Fig. 3). Significant associations were also observed for both MC+CRYO and CRYO-alone groups versus the MC-alone group (MC+CRYO: OR 5.14,

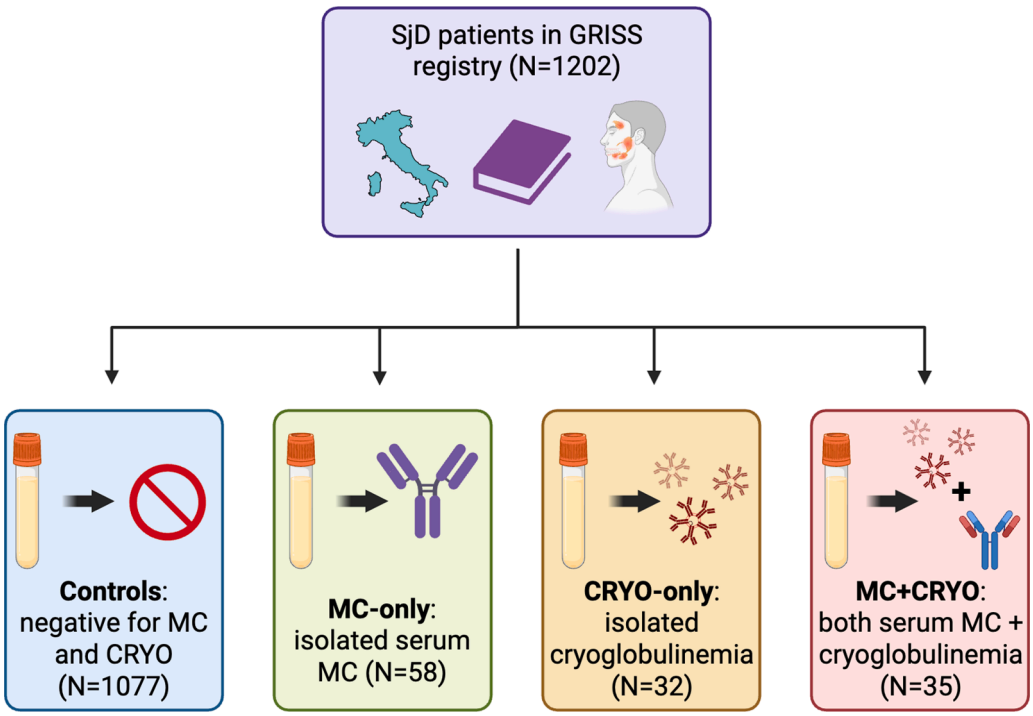
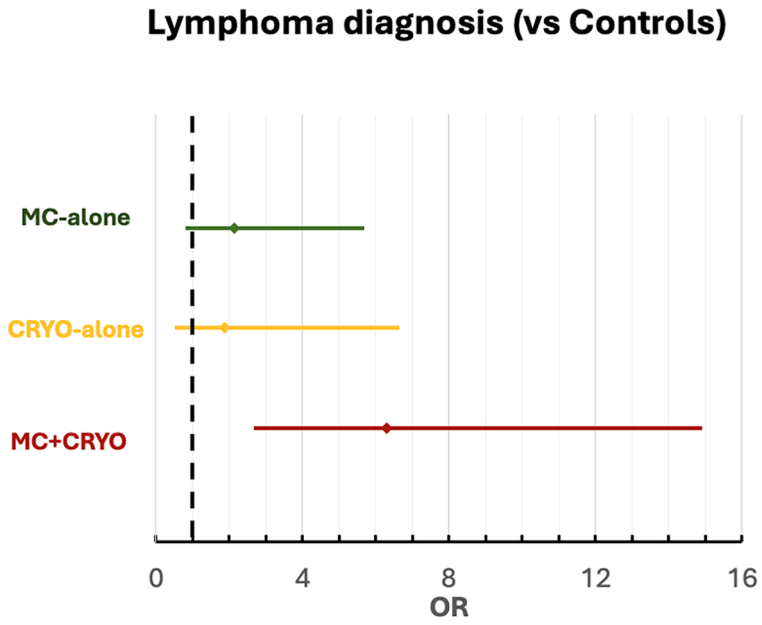


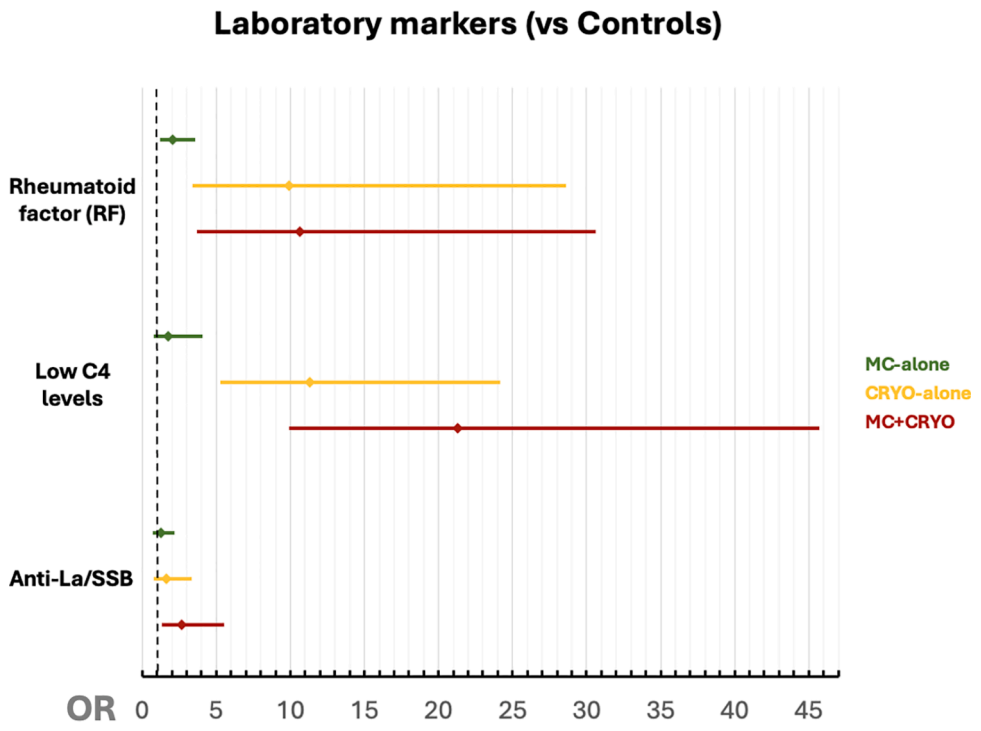
Fig. 1. Stratification of SjD patients according to serum monoclonal component and cryoglobulinemia. Legend: SjD= Sjögren disease; GRISS= Italian Research Group on Sjögren disease; MC= monoclonal component; CRYO=cryoglobulinemia.



Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Lymphoma	MC-alone	2.13	0.80	5.67	0.131
Lymphoma	CRYO-alone	1.86	0.52	6.63	0.340
Lymphoma	**MC+CRYO**	**6.30**	**2.66**	**14.92**	**<0.001**

Fig. 2. Forest plot showing odds ratios with 95% confidence intervals for lymphoma diagnosis in MC-alone, CRYO-alone, and MC+CRYO groups compared to controls. Legend: MC= monoclonal component; CRYO=cryoglobulinemia; OR=Odds Ratio; CI=Confidence Interval.

95%CI 1.60–16.53, p = 0.006. CRYO-alone: OR 4.77, 95%CI 1.47–15.44, p = 0.009, respectively), whereas no significant difference emerged between MC+CRYO and CRYO-alone (**Supplementary Figure S1**). A similar pattern was found for low C4 levels, which were strongly associated with both MC+CRYO (OR 21.29, 95%CI 9.92–45.69, p < 0.001) and CRYO-alone groups (OR 11.29, 95%CI 5.28–24.15, p <



Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
RF	**MC-alone**	**2.07**	**1.21**	**3.55**	**0.008**
RF	**CRYO-alone**	**9.88**	**3.41**	**28.59**	**<0.001**
RF	**MC+CRYO**	**10.65**	**3.69**	**30.62**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Low C4	MC-alone	1.76	0.77	4.05	0.183
Low C4	**CRYO-alone**	**11.29**	**5.28**	**24.15**	**<0.001**
Low C4	**MC+CRYO**	**21.29**	**9.92**	**45.69**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Anti-La	MC-alone	1.26	0.73	2.17	0.400
Anti-La	CRYO-alone	1.62	0.78	3.33	0.193
Anti-La	**MC+CRYO**	**2.68**	**1.30**	**5.53**	**0.008**

Fig. 3. Forest plot showing odds ratios with 95% confidence intervals for laboratory markers such as rheumatoid factor, low C4 levels and anti-La/SSB in MC-alone, CRYO-alone, and MC+CRYO groups compared to controls. Legend: MC= monoclonal component; CRYO=cryoglobulinemia; OR=Odds Ratio; CI=Confidence Interval; RF= Rheumatoid Factor.

0.001) versus controls, with no significant difference between MC+CRYO and CRYO-alone. Anti-La/SSB antibodies were significantly associated only with the MC+CRYO group compared with controls (OR 2.68, 95%CI 1.30–5.53, p = 0.008) (Fig. 3 and **Supplementary Figure S1**).

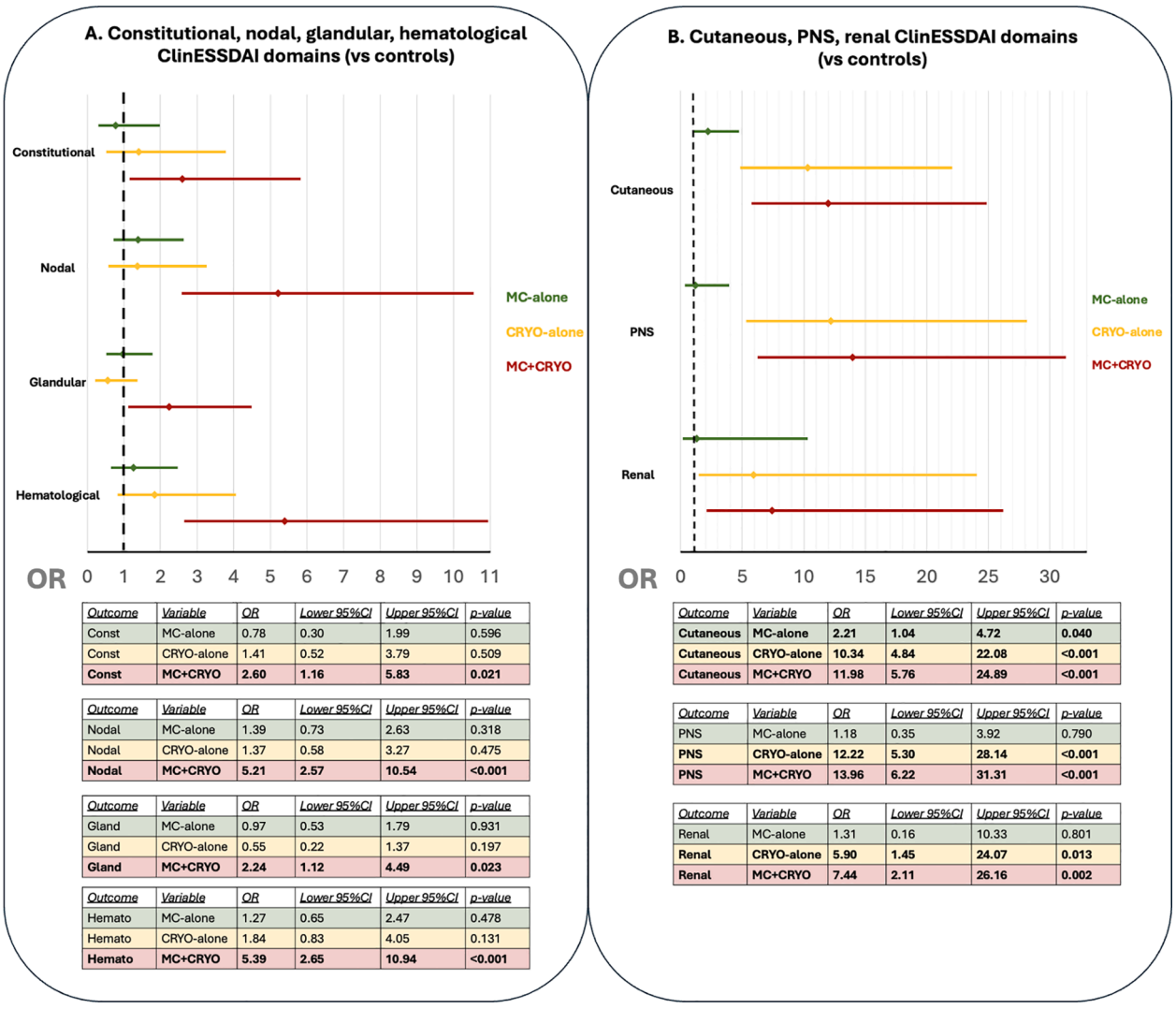
Finally, a significant difference emerged in the type of clonal immunoglobulin between MC-alone and MC+CRYO patients; IgG components predominated in MC-alone, whereas IgM components were more frequent in MC+CRYO (**Supplementary Table S5**). This was confirmed by strong reciprocal associations: IgG with MC-alone versus MC+CRYO (OR 6.49, 95%CI 2.55–16.52, p < 0.001) and IgM with MC+CRYO versus MC-alone (OR 6.40, 95%CI 2.46–16.63, p < 0.001) (**Supplementary Figure S2**). No significant difference was observed for IgA clonal components (p = 0.361).

Disease activity (ClinESSDAI) across groups

Ever-documented activity in several ClinESSDAI domains differed significantly across the four groups, namely the constitutional, glandular, cutaneous, lymphadenopathy, PNS, renal, and hematological domains (**Supplementary Table S6**).

Constitutional domain activity occurred predominantly in MC+CRYO patients and were significantly associated with this group compared with controls (OR 2.60; 95%CI 1.16–5.83; p = 0.021), with no significant associations observed for either the MC-alone or CRYO-alone groups. Activity in the glandular domain followed a similar pattern, being more common in MC+CRYO patients and significantly associated with this group versus controls (OR 2.24; 95%CI 1.12–4.49; p = 0.023), while no such association emerged for the other two groups. Lymphadenopathy and hematological domains showed analogous trends, with the highest frequency of ever-documented activity in MC+CRYO patients and significant associations limited to this group when compared with controls (lymphadenopathy: OR 5.21, 95%CI 2.57–10.54, p < 0.001; hematological: OR 5.39, 95%CI 2.65–10.94, p < 0.001). Neither the MC-alone nor the CRYO-alone groups demonstrated significant associations with these latter domains. Forest plots for constitutional, glandular, lymphadenopathy, and hematological domains are presented in Fig. 4A.

Regarding the cutaneous, PNS, and renal domains, ever-documented activity was significantly more frequent in patients with cryoglobulinemia, both in those with isolated cryoglobulinemia and, most notably, in those with concomitant monoclonal component and



Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Const	MC-alone	0.78	0.30	1.99	0.596
Const	CRYO-alone	1.41	0.52	3.79	0.509
Const	**MC+CRYO**	**2.60**	**1.16**	**5.83**	**0.021**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Nodal	MC-alone	1.39	0.73	2.63	0.318
Nodal	CRYO-alone	1.37	0.58	3.27	0.475
Nodal	**MC+CRYO**	**5.21**	**2.57**	**10.54**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Gland	MC-alone	0.97	0.53	1.79	0.931
Gland	CRYO-alone	0.55	0.22	1.37	0.197
Gland	**MC+CRYO**	**2.24**	**1.12**	**4.49**	**0.023**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Hemato	MC-alone	1.27	0.65	2.47	0.478
Hemato	CRYO-alone	1.84	0.83	4.05	0.131
Hemato	**MC+CRYO**	**5.39**	**2.65**	**10.94**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Cutaneous	**MC-alone**	**2.21**	**1.04**	**4.72**	**0.040**
Cutaneous	**CRYO-alone**	**10.34**	**4.84**	**22.08**	**<0.001**
Cutaneous	**MC+CRYO**	**11.98**	**5.76**	**24.89**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
PNS	MC-alone	1.18	0.35	3.92	0.790
PNS	**CRYO-alone**	**12.22**	**5.30**	**28.14**	**<0.001**
PNS	**MC+CRYO**	**13.96**	**6.22**	**31.31**	**<0.001**

Outcome	Variable	OR	Lower 95%CI	Upper 95%CI	p-value
Renal	MC-alone	1.31	0.16	10.33	0.801
Renal	**CRYO-alone**	**5.90**	**1.45**	**24.07**	**0.013**
Renal	**MC+CRYO**	**7.44**	**2.11**	**26.16**	**0.002**

Fig. 4. Forest plot showing odds ratios with 95% confidence intervals for constitutional, lymphoadenopathy, glandular, hematological (A) and for cutaneous, PNS, renal (B) ClinESSDAI domains in MC-alone, CRYO-alone and MC+CRYO groups compared to controls. Post-hoc analyses were conducted to determine which group showed the strongest association with these ClinESSDAI domains among those that had demonstrated a significant association compared with controls. Legend: MC=monoclonal component; CRYO=cryoglobulinemia; OR=Odds Ratio; CI=Confidence Interval; PNS=peripheral nervous system; Hemato=hematological; Gland=-glandular; Nodal=Lymphoadenopathy; Const=constitutional.

cryoglobulins. All cutaneous manifestations in cryoglobulinemia-associated groups presented as purpura. The strongest association with cutaneous domain activity was observed for MC+CRYO versus controls (OR 11.98, 95%CI 5.76–24.89, $p < 0.001$), followed by CRYO-alone (OR 10.34, 95%CI 4.84–22.08, $p < 0.001$) and MC-alone (OR 2.21, 95%CI 1.04–4.72, $p = 0.040$). Both cryoglobulinemia-associated groups also showed significantly higher odds of cutaneous domain activity compared with MC-alone (OR 5.41; 95%CI 2.02–14.48; $p < 0.001$ and OR 4.67; 95%CI 1.71–12.77; $p = 0.003$, respectively for MC+CRYO and CRYO-alone group), whereas no difference emerged between MC+CRYO and CRYO-alone. Similarly, activity in the PNS and renal domains was markedly more frequent in the MC+CRYO and CRYO-alone groups, whereas activity in the MC-alone group was comparable to that of controls. This pattern was supported by statistically significant associations for both MC+CRYO and CRYO-alone groups versus controls in the PNS domain (MC+CRYO: OR 13.96, 95%CI 6.22–31.31, $p < 0.001$. CRYO-alone: OR 12.22, 95%CI 5.30–28.14, $p < 0.001$) and renal domain (MC+CRYO: OR 7.44, 95%CI 2.11–26.16, $p = 0.002$. CRYO-alone: OR 5.90, 95%CI 1.45–24.07, $p = 0.013$). No significant associations were observed for the MC-alone group compared with controls, nor between MC+CRYO and CRYO-alone groups for activity in either the PNS or renal domains. **Supplementary Figure S3** and Fig. 4B summarize the forest plots for the cutaneous, PNS, and renal domains. Finally, no statistically significant differences emerged across groups for the articular, muscular, or pulmonary domains, either in overall frequency of ever-documented activity or in pairwise comparisons (**Supplementary Table S6**). The CNS domain was excluded from comparative analyses due to its very low frequency in the cohort (6/1202 patients [0.49%]).

Discussion

In this large multicenter cohort, we systematically compared the clinical and immunological profiles of SjD patients stratified into four groups based on the presence or absence of detectable serum monoclonal gammopathy and cryoglobulinemia, two paraproteinemias well recognized in the context of SjD [8,11,22]. By jointly evaluating these two clinically accessible biomarkers in a multicenter setting, we aimed to clarify their individual and combined clinical significance in defining distinct SjD phenotypes and informing the risk of systemic activity and lymphoproliferative progression. The combination of detectable serum MC and cryoglobulins (MC+CRYO) emerged as the most distinctive

profile. This group showed the highest lymphoproliferative activity and was the only one significantly associated with overt lymphoma after adjusting for disease duration. Lymphoma histotype (mainly MALT), sex, age at SjD diagnosis and at lymphoma diagnosis, antiRo/SSA antibody positivity, presence of other concomitant systemic autoimmune diseases and latency from SjD onset to lymphoma were similar across groups, excluding these as possible confounding factors.

Cryoglobulinemia is a well-recognized risk factor for lymphoma in SjD, with MALT proliferation representing a common biological substrate [22–24]. Nevertheless, it remains unclear whether all SjD patients with a history of cryoglobulinemia carry the same degree of lymphoproliferation and lymphoma risk. Cryoglobulinemia is conventionally classified according to Brouet into type I, type II, and type III, based on the immunochemical composition of the cryoprecipitate [25]. Patients with a diagnosis of type I cryoglobulinemia or with clinical or laboratory features suggestive of type I cryoglobulinemia were excluded a priori from the cohort, given that cryoglobulinemia in SjD is typically mixed, most commonly type II and less frequently type III, whereas type I forms are distinctly uncommon and usually associated with overt lymphoproliferative hematologic disorders rather than with SjD itself [26,27]. Accordingly, based on available literature, patients in our isolated cryoglobulinemia group would be expected to fall predominantly within the mixed cryoglobulinemia spectrum rather than the type I category, with type II likely representing the most common subtype. This is supported by SjD-specific cohorts: in the GISC (Italian Group for the Study of Cryoglobulinaemias) study, 65% of SjD patients had type II and 35% type III cryoglobulinemia [28]. Additional evidence suggests that type II cryoglobulinemia is the form more closely linked to cryoglobulinemic vasculitis, with IgMκ monoclonal RF representing a major pathogenic driver of this phenotype [29,30]. Brouet classification and our stratification should therefore be regarded as complementary rather than overlapping frameworks, since the former describes the immunochemical composition of cryoglobulins, whereas the latter better captures the clinical-serological profile associated with lymphoproliferative risk in SjD. In this context, type II cryoglobulinemia does not necessarily coincide with the presence of a serum-detectable monoclonal band. Serum detectability of the monoclonal component may reflect, at least in part, its circulating burden rather than simply its presence within the cryoprecipitate, although this aspect could not be directly assessed in the present study. Importantly, this distinction proved clinically relevant, as the subgroup with both cryoglobulinemia and a serum-detectable monoclonal component showed the strongest lymphoproliferative profile and an independent association with lymphoma. In this setting, our stratification may provide complementary clinical value for risk stratification in SjD, alongside the Brouet classification, by capturing features associated with lymphoproliferative risk that are not directly addressed by immunochemical subclassification. In fact, it identifies the subgroup in whom cryoglobulinemia coexists with a serum-detectable monoclonal component, which in our cohort was associated with the most marked lymphoproliferative features and the highest lymphoma frequency. Multivariable studies have shown that other factors, such as RF, disease activity, or low serum complement, emerge as independent predictors for lymphoma in SjD, attenuating the apparent contribution of cryoglobulins [14,15]; furthermore, preliminary evidence suggests that in SjD not all forms of cryoglobulinemia carry the same risk of lymphoma, with persistent cryoglobulinemia appearing to be associated with lymphoma, unlike fluctuating forms [31]. In our cohort cryoglobulinemia, whether isolated or in combination with serum MC was strongly associated with laboratory markers of lymphoproliferative risk, including RF and low C4 levels. This aligns with the known interplay between autoreactive immune responses, immune complex–driven inflammation, and B-cell clonal expansion in SjD [32,33]. However, such immune activation does not inevitably result in lymphomagenesis; progression to overt lymphoproliferative disease may be associated with more extensive clonal expansion, although this relationship cannot be directly inferred from the present cross-sectional data. In this sense, the MC+CRYO profile may serve as a pragmatic enrichment criterion to identify, among cryoglobulin-positive patients, those in whom immune complex activation is accompanied by more advanced clonal features. Notably, total serum gammaglobulin levels were not analysed in this study. Although hypergammaglobulinemia may reflect the overall burden of B-cell activation in SjD and could theoretically relate to the presence of monoclonal gammopathy or cryoglobulinemia, it has not consistently been identified as an independent predictor of lymphoproliferative complications. Therefore, to avoid unnecessary multiple comparisons, we prioritized serological markers more robustly associated with lymphoma risk in SjD, including RF activity, low C4 levels, and anti-La/SSB antibodies [9,13].

On the other hand, although generally considered a weaker predictor than cryoglobulinemia, serum MC has also been proposed as a potential independent risk factor for lymphoma in SjD, as it may reflect ongoing B-cell clonal expansion [5,14,34]. However, this association is not universally observed, and MC may represent a lymphoproliferation not necessarily driven by SjD or prone to malignant evolution. Our results align with the serological pattern reported in previous studies on SjD: monoclonal IgG is predominantly associated with isolated MC, whereas monoclonal IgM is closely linked to cryoglobulinemia [10,11]. IgM monoclonality, often coupled with RF activity, has been significantly associated with lymphoma in previous evidence and is thought to arise from B cells engaged in immune complex formation [10,35–37]. In contrast, serum IgG monoclonal bands are less frequent in SjD patients who develop lymphoproliferative disease, despite tissue-based studies consistently identifying IgG-restricted clones in MALT lymphomas [38]. This discrepancy likely reflects compartmentalization: serum monoclonal bands indicate systemic secretion, whereas tissue detection reflects localized clonal expansion at the site of lymphomagenesis. Thus, IgG monoclonality in tissue may represent a localized phenomenon not mirrored by detectable serum MC, as occurred in cutaneous AL amyloidosis, a very rare localized lymphoproliferative manifestation in SjD [39].

Concerning systemic involvement of SjD, distinct clinical patterns emerged with respect to disease activity. Cryoglobulinemia alone, or in combination with serum detectable MC, was associated with a vasculitic phenotype, characterized by renal, cutaneous (particularly purpura) and PNS involvement, irrespective of MC status. Cutaneous involvement was more frequent in MC-only patients than in controls, however it lacked association with PNS or renal disease, suggesting that purpura in MC-only cases may be gammopathy-related, probably in the context of oligo-polyclonal hypergammaglobulinemia, rather than indicative of systemic vasculitis [40]. By contrast, the more extensive vasculitic features seen in CRYO-alone and MC+CRYO groups align with the systemic immune complex–driven phenotype described in previous studies [8,29,30]. Conversely, a lymphoproliferative phenotype, encompassing glandular, constitutional, hematological, and lymphadenopathy domains, was predominantly observed in MC+CRYO patients. Glandular involvement, frequently associated with persistent parotid swelling and early lymphoid proliferation, was almost twice as prevalent in MC+CRYO patients compared with either the MC-alone or CRYO-alone groups alone. Indeed, the only significant association with the glandular domain emerged in the MC+CRYO group. Constitutional symptoms, lymphadenopathy, including lymphoma complications, and hematological abnormalities were likewise most common in MC+CRYO, with significantly higher odds than all other groups when compared with controls. Articular, pulmonary, and muscular domains showed no between-group differences, supporting the view that these manifestations may be not primarily B-cell–driven but instead relate to other pathways namely type I/II interferon–mediated responses and T-cell–predominant inflammation [41,42].

These observations have clear clinical implications, briefly summarized in Fig. 5. While cryoglobulinemia should prompt thorough evaluation for vasculitic complications, the co-occurrence of serum

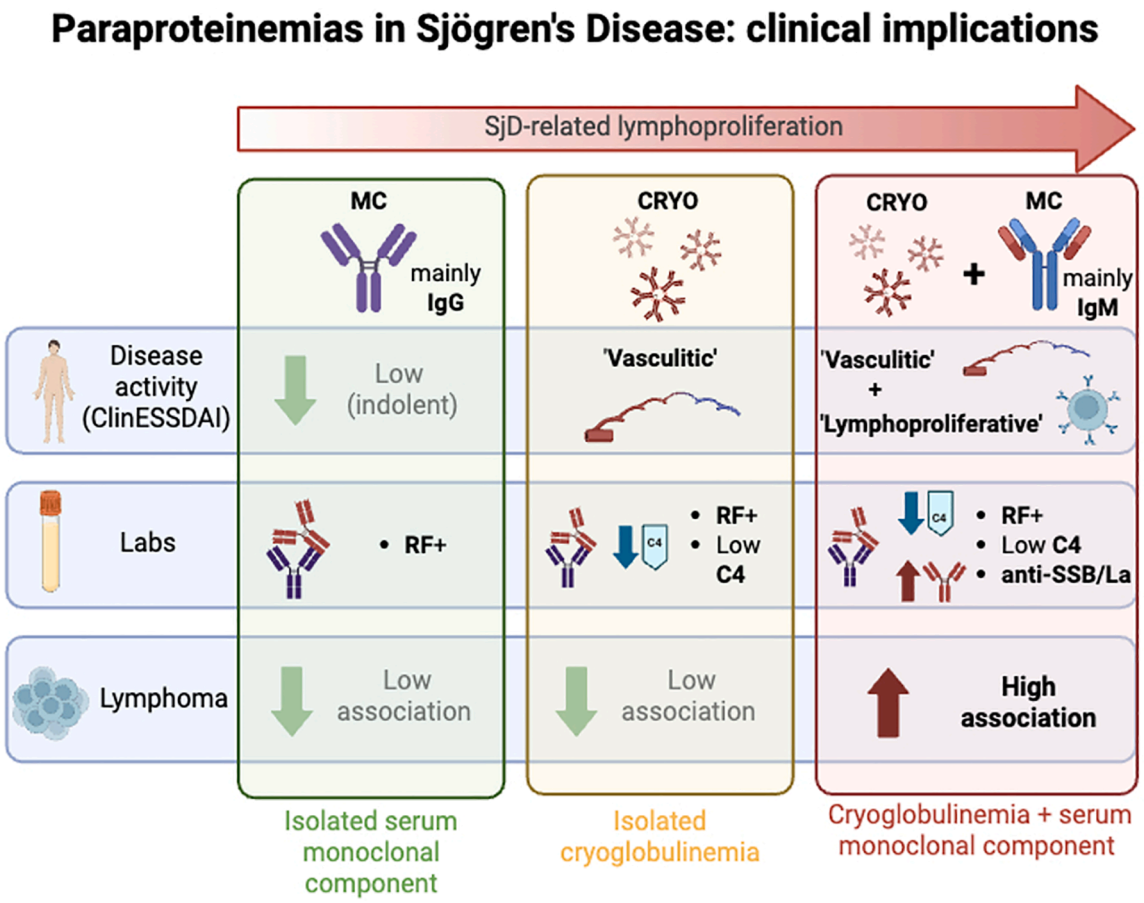


Fig. 5. Clinical implications of serum MC and cryoglobulins in Sjögren disease. Patients with isolated serum MC (predominantly IgG-type) generally exhibit an indolent disease course, characterized by higher rheumatoid factor (RF) positivity compared with controls and a low association with lymphoma. Patients with isolated cryoglobulinemia display a more vasculitic disease phenotype, with higher RF positivity compared with both controls and patients with isolated MC, as well as lower C4 levels compared with controls, yet still with a low association with lymphoma. In contrast, patients with concomitant serum MC and cryoglobulinemia demonstrate a disease phenotype combining vasculitic and lymphoproliferative features, with marked RF positivity, low C4 levels, and anti-La/SSB antibody positivity, together with a stronger association with lymphoma. Legend: MC= monoclonal component; CRYO=cryoglobulinemia; RF= Rheumatoid Factor; SjD= Sjögren disease.

detectable MC marks a later-stage state, with concurrent immune complex–driven inflammation and advanced B-cell clonal expansion. Identifying the MC+CRYO phenotype is therefore crucial for risk stratification, as this dual marker combination may reflect a more advanced stage of B-cell clonal expansion, characterized by the coexistence of immune complex–mediated inflammation and features associated with increased lymphoma susceptibility. In contrast, isolated MC was associated with a clinical, immunological, and lymphoproliferative profile similar to that of patients without either marker, with lower systemic involvement, fewer lymphoproliferative activity, and not increased lymphoma risk, suggesting that MC alone was not associated with a higher prevalence of vasculitic or lymphoproliferative complications.

Some limitations must be acknowledged. Firstly, the retrospective cross-sectional design precludes causal or temporal inferences, as variables were captured across patients' disease histories rather than prospectively, and we could not consistently reconstruct the time lag between the first documentation of paraproteinemias and lymphoma diagnosis; therefore, we cannot establish whether MC and/or cryoglobulins preceded, accompanied, or followed lymphomagenesis. Accordingly, our findings should be interpreted as associations, aligned with our primary aim of identifying a readily detectable serological combination that flags higher lymphoproliferative burden and systemic activity regardless of when it is recorded during follow-up, to support risk stratification in routine care.

Secondly, some data were missing in our cohort, particularly regarding cryocrit levels and cryoglobulin typing, which were not consistently assessed, especially in patients with older clinical records. In a multicenter real-world setting, subtype determination (type II vs III) could not be uniformly available across centers, and the immunochemical characterization of the cryoprecipitate remains variably standardized and potentially affected by pre-analytical factors, limiting the reliability and comparability of subtype information. Furthermore, regarding cryoglobulin measurement in serum no standardized GRISS-wide protocol was available, and the retrospective design precluded detailed reconstruction of pre-analytical and analytical procedures at each center. Consistent with this, detection rates of cryoglobulinemia varied across participating centers. This variability may partly reflect differences in pre-analytical sample handling, as cryoglobulin testing is highly sensitive to collection and processing conditions. In addition, referral patterns may have contributed, as some centers may follow a higher proportion of patients with systemic or vasculitic manifestations. However, while these factors may influence the observed prevalence of cryoglobulinemia across centers, any misclassification related to laboratory handling would most likely result in false-negative rather than false-positive findings, thereby potentially attenuating—rather than artificially generating—the associations observed in our study; accordingly, this variability is more likely to have attenuated the observed associations rather than generated spurious ones, although its impact cannot be completely excluded. Therefore, despite these limitations, we

adopted a pragmatic approach based on the most consistently documented information across sites, namely the presence of cryoglobulins and/or a serum-detectable MC, focusing on CRYO alone versus MC+CRYO rather than on cryoglobulin subtype.

Thirdly, treatment exposure varied across patients, and detailed information, particularly on B-cell–depleting therapies such as anti-CD20 agents, was not incorporated in the present analyses. However, because our analyses relied on ever-documented domains and abnormalities across the disease course, they were less sensitive to short-term treatment-related fluctuations. It should nonetheless be acknowledged that different therapeutic strategies may have influenced the likelihood of detecting paraproteinemias or documenting selected complications in some patients. These limitations are partly mitigated by the large sample size, the multicenter design study, the standardized assessment of systemic activity using the ClinESSDAI, and the harmonized immunological profiling across patients.

Future multicenter prospective studies will require standardized pre-analytical and analytical procedures for cryoglobulin testing in order to minimize false-negative results and improve patient classification. Such studies will also be needed to confirm whether the MC+CRYO phenotype independently predicts lymphomagenesis, and whether early identification of vasculitic-predominant versus lymphoproliferative-predominant subgroups can guide therapy, as suggested by a preliminary retrospective study with rituximab [43]. In-depth immunophenotypic and molecular studies could further clarify B-cell pathways and support the development of targeted B-cell–modulating strategies.

In conclusion, to our knowledge, this is one of the largest multicenter studies in SjD to date evaluating, both individually and in combination, the impact of characteristic paraproteinemias on patient stratification, disease phenotype, and lymphoma risk, an approach consistent with the principles of precision medicine in this heterogeneous condition. Our findings help disentangle the respective contributions of these two markers: cryoglobulinemia primarily delineates a systemic, immune complex–driven vasculitic phenotype, whereas the additional detection of serum MC identifies a distinct subset with the greatest lymphoproliferative burden and the strongest association with overt lymphoma. The MC+CRYO combination therefore captures a convergent biology, ongoing immune complex–mediated inflammation alongside more advanced B-cell clonal expansion, consistent with a late-stage, high-risk profile. Clinically, this dual-marker signature may support closer monitoring and could inform clinical decision-making, including consideration of B-cell–targeted strategies in selected cases, pending prospective validation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Luca Quartuccio reports was provided by University of Udine. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.152986.

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