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Analysis of prognostic factors in diffuse large B-cell lymphoma associated with rheumatic diseases

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To cite: Gorodetskiy V, Probatova N, Obukhova T, *et al*. Analysis of prognostic factors in diffuse large B-cell lymphoma associated with rheumatic diseases. *Lupus Science & Medicine* 2021;**8**:e000561. doi:10.1136/lupus-2021-000561

Received 14 August 2021
Accepted 22 October 2021

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ABSTRACT

Objective The risk of developing diffuse large B-cell lymphoma (DLBCL) is increased in many rheumatic diseases (RDs). It is possible that RD-associated DLBCL is a distinct subset within the category of 'DLBCL', exhibiting characteristic biological features and clinical behaviour. However, information on RD-associated DLBCL is limited.

Methods We searched the V.A. Nasonova Research Institute of Rheumatology (Russia) database from 1996 to 2021 for patients with RDs and coexisting DLBCL. Prognostic factors including the International Prognostic Index (IPI), bulk disease and *c-MYC/8q24* gene rearrangements were analysed. Furthermore, we stratified DLBCLs as germinal centre B-cell (GCB) subtype and non-GCB subtype based on Hans' immunohistochemical algorithm and also examined Epstein-Barr virus (EBV) status.

Results Twenty-seven patients with RD-associated DLBCL were identified. Twenty patients had primary Sjogren's syndrome, three had systemic lupus erythematosus, two had rheumatoid arthritis and two had systemic sclerosis. Secondary Sjogren's syndrome was found in four patients. The median age at the time of diagnosis of DLBCL was 59 years with a female predominance (26:1). Based on IPI, 16 patients were assigned to the intermediate-high and high-risk groups. Bulk disease was detected in 29% of patients. Of the 20 examined cases, 4 (20%) were classified as the GCB subtype and 16 (80%) were classified as the non-GCB subtype. EBV was detected in 2 of the 21 tested cases (10%), and the *c-MYC/8q24* gene rearrangement was not found in any of the 19 examined cases. After the lymphoma diagnosis, the median overall survival (OS) was 10 months (range: 0–238 months).

Conclusions Except for the more common non-GCB subtype, we did not identify any other prognostic factor that could influence the prognosis of patients with RD-associated DLBCL. We believe that short OS in our patients was predominantly associated with decreased tolerance to lymphoma treatment.

Key messages

What is already known about this subject?

- Chronic auto-antigen stimulation and inflammation, which are defining features of rheumatic diseases (RDs), represent the major drivers of specific B-cell proliferation and the increase in frequency of their transformation that may promote lymphoma development.
- Most RD-associated diffuse large B-cell lymphomas (DLBCLs), in contrast to DLBCLs in the general population, originate from non-germinal centre B-cells and are possibly a distinct subset within the 'DLBCL' category, exhibiting characteristic biological features and clinical behaviour.

What does this study add?

- RD-associated DLBCL is more common in women with primary or secondary Sjogren's syndrome.
- The *c-MYC/8q24* gene rearrangement and the Epstein-Barr virus do not appear to play a crucial role in the pathogenesis of RD-associated DLBCL.

How might this impact on clinical practice or future developments?

- It is possible that long-standing severe RDs predispose individuals to increased mortality and decreased tolerance to DLBCL treatment. Therefore, special attention regarding the management of these patients is required.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin's lymphoma with a median survival of less than 1 year in untreated patients.[1] The relative risk of developing DLBCL varies between the different rheumatic diseases (RDs) and has been reported to be about 1.8 times higher in patients with rheumatoid arthritis (RA), 2 times higher in patients with systemic sclerosis (SSc), 6.2 times higher in patients with systemic lupus erythematosus (SLE) and 11 times higher in patients with primary Sjogren's syndrome (pSS) than that in the general population.[2 3]

Chronic auto-antigen stimulation and inflammation, defining features of RDs, represent the major drivers of specific B-cell proliferation and the increase in frequency of their transformation that may promote lymphoma development.[4 5] It is possible that RD-associated DLBCLs are a distinct subset within the category of 'DLBCL', exhibiting characteristic biological features and clinical

behaviour. However, information regarding RD-associated DLBCL is limited.

The main purpose of this study was to comprehensively characterise RD-associated DLBCL and analyse its prognostic factors.

METHODS

Study design and participants

We conducted a retrospective analysis of 27 patients referred to the V.A. Nasonova Research Institute of Rheumatology (Moscow, Russia) over a 25-year period between 1996 and 2021. The inclusion criteria were as follows: age over 18 years, confirmed diagnosis of RD, histologically diagnosed DLBCL and the availability of formalin-fixed paraffin-embedded (FFPE) tissue specimens. We reviewed the medical records of the included patients to collect information on demographics, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, bulk disease (defined as a tumour diameter ≥7.5 cm), serum lactate dehydrogenase (LDH) level, DLBCL extension data (nodal and extranodal involvement), and the time elapsed between the manifestations of RDs and the diagnosis of DLBCL.

Procedures

The H&E-stained slides from each tumour block were reviewed. An immunohistochemical (IHC) study was performed on FFPE tissue sections, and antibodies against the following antigens were used: CD3 (clone F7.2.38, Dako), CD10 (clone 56C6, Dako), CD20 (clone L26, Dako), CD68 (clone PG-M1, Dako), BCL6 (clone EP278, Cell Marque), MUM1 (clone MRO-8, Cell Marque) and PAX5 (clone DAK-Pax5, Dako). Hans' IHC algorithm dichotomises DLBCL into germinal centre B-cell (GCB) and non-GCB subtypes, based on three IHC markers: CD10, BCL6 and MUM1.[6] According to Hans' algorithm, we stratified our DLBCL cases into these two subtypes.

To detect the Epstein-Barr virus (EBV) status of DLBCL, in situ hybridisation for EBV-encoded small nuclear RNA (EBER) was used on FFPE tissue sections. In accordance with the 2016 WHO classification of tumours of haematopoietic and lymphoid tissues, we classified DLBCL as EBV positive if over 80% of tumour cells exhibited EBER-positivity.[7]

Fluorescence in situ hybridisation (FISH) analysis for identifying the *c-MYC/8q24* gene locus translocation was performed on FFPE tissue sections of 19 cases using the LSI MYC Break Apart Probe (Abbott Molecular, USA) according to the manufacturer's instructions. Images were processed using Axio Imager Z2 microscope (Carl Zeiss, Germany) and Isis imaging system (MetaSystems, Germany). DLBCL was reviewed and refined according to the 2016 WHO classification of tumours of haematopoietic and lymphoid tissues.[7]

Because of poor sample quality or insufficient amounts of FFPE tissue, the EBV status was not examined in six cases, and the *c-MYC/8q24* gene rearrangement status was missed in eight cases. DLBCL was not subtyped according to the Hans' algorithm in four cases due to poor sample quality or insufficient FFPE tissue and in another three cases due to a limited number of scattered tumour cells.

Statistical analysis

Categorical variables are reported as number (%), and continuous variables are reported as median (range). Overall survival (OS) was estimated using the Kaplan-Meier method and was calculated as the time from the lymphoma diagnosis until death regardless of the cause or until the last follow-up.

RESULTS

We identified 27 patients who had an RD coexisting with DLBCL. Baseline clinical characteristics of the patients are shown in table 1. Twenty patients had pSS, three had SLE, two had RA and two had SSc. Secondary Sjogren's syndrome was found in four patients: two with SSc, one with RA and one with SLE. The median age of the patients in our cohort at the time of DLBCL diagnosis was 59 years (range: 30–83 years). The female-to-male ratio was 26:1. The median time from the onset of RD symptoms to DLBCL diagnosis was 19 years (range: 0–38 years). Based on the original International Prognostic Index (IPI),[8] 11 (41%) patients were assigned to low and low-intermediate risk groups, while 16 (59%) patients were assigned to intermediate-high and high-risk groups. Bulk disease was detected in 6 (29%) of the 21 examined patients.

The IHC results of patients with RD-associated DLBCL are shown in table 2. Based on expression patterns, according to Hans' algorithm, we classified 4 cases of DLBCL into the GCB subtype and 16 cases into the non-GCB subtype. EBV was detected in 2 (10%) of the 21 cases studied. The *c-MYC/8q24* gene rearrangement was not found in any of the 19 examined cases.

According to the 2016 WHO classification of tumours of haematopoietic and lymphoid tissues, DLBCL cases in our cohort were classified as follows: DLBCL, not otherwise specified (17 cases); EBV-positive DLBCL, not otherwise specified (two cases) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) (two cases). Six DLBCL cases could not be reclassified because of missing data.

After the lymphoma diagnosis, the median OS was 10 months (range: 0–238 months) and the 5-year OS rate was 46% (figure 1).

DISCUSSION

Autoimmune diseases (AIDs) are a heterogeneous group of more than 80 separate conditions. AIDs can be categorised widely as being mediated mainly by B-cell or T-cell responses, recognising some overlap.[9] Most of the patients in our study had autoimmune conditions mediated by B-cell responses. A large pooled analysis from the International Lymphoma Epidemiology Consortium has shown that AIDs classified as primarily mediated by B-cell

Table 1 Baseline characteristics and large B-cell lymphoma risk factors of the 27 patients with rheumatic diseases

Case no	Rheumatic diseases	Sex	Age (years) at LBCL diagnosis	Years from rheumatic disease symptoms to LBCL diagnosis	IPI	Bulk disease	c-MYC rearrangements	LBCL
1	pSS	F	52	32	Low/ intermediate	+	–	DLBCL, NOS
2	pSS	F	59	19	Intermediate/ high	NA	–	DLBCL, NOS
3	pSS	F	53	18	Low/ intermediate	–	–	DLBCL, NOS
4	pSS	F	48	38	Low	NA	–	DLBCL, NOS
5	pSS	F	83	22	Intermediate/ high	NA	–	DLBCL, NOS
6	pSS	F	59	13	Low	–	NA	DLBCL
7	pSS	F	47	26	High	–	–	DLBCL
8	pSS	F	51	22	High	NA	–	DLBCL, NOS
9	pSS	F	39	6	High	–	–	DLBCL, NOS
10	pSS	F	62	15	High	NA	NA	DLBCL, NOS
11	pSS	F	45	22	Intermediate/ high	+	NA	DLBCL
12	pSS	F	70	18	High	–	NA	DLBCL
13	pSS	F	73	18	High	+	–	DLBCL
14	pSS	F	73	24	Intermediate/ high	–	–	DLBCL, NOS
15	pSS	F	67	15	High	+	–	DLBCL, NOS
16	pSS	F	30	3	Low	–	–	DLBCL, NOS
17	pSS	F	61	20	Intermediate/ high	–	–	EBV-positive DLBCL, NOS; monomorphic
18	pSS	F	42	21	Low/ intermediate	–	NA	EBV-positive DLBCL, NOS; polymorphic
19	pSS	F	43	22	Low	NA	NA	THRLBCL
20	pSS	F	57	14	Intermediate/ high	–	NA	THRLBCL
21	SLE and sSS	F	61	25	Low/ intermediate	+	–	DLBCL, NOS
22	SLE and APS	F	58	2	Low	+	–	DLBCL, NOS
23	SLE	M	60	5	Intermediate/ high	–	–	DLBCL, NOS
24	RA	F	57	22	Intermediate/ high	–	–	DLBCL, NOS
25	RA and sSS	F	62	19	High	–	–	DLBCL, NOS
26	SSc and sSS	F	59	26	Low	–	–	DLBCL, NOS
27	SSc and sSS	F	59	0	Low/ intermediate	–	NA	DLBCL

+, positive; –, negative; APS, antiphospholipid syndrome; DLBCL, NOS, diffuse large B-cell lymphoma, not otherwise specified; EBV, Epstein-Barr virus; F, female; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; M, male; NA, not available; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SSc, systemic sclerosis; sSS, secondary Sjogren's syndrome; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma.

responses are associated with an increased risk of developing DLBCL.[10]

However, the diagnostic category of 'DLBCL' is heterogeneous in terms of genetics, morphology, virus positivity, primary localisation, biological behaviour and prognosis. The 2016 WHO classification of tumours of haematopoietic and lymphoid tissues recognises several distinct entities within this category characterised by unique clinical and pathological features, including THRLBCL, EBV-positive DLBCL, not otherwise specified, primary

Table 2 Immunohistochemical characteristics of large B-cell lymphomas associated with rheumatic diseases

Case no	CD3	CD20	CD10	BCL6	MUM1	EBV	Subtype of DLBCL according to Hans' algorithm
1	–	+	+	+	+	–	GCB
2	–	+	–	+	+	–	Non-GCB
3	–	+	–	–	+	–	Non-GCB
4	–	+	–	–	+	–	Non-GCB
5	–	+	–	+	+	–	Non-GCB
6	–	+	–	+	+	NA	Non-GCB
7	–	+	NA	NA	NA	NA	NA
8	–	+	–	–	+	–	Non-GCB
9	–	+	–	+	+	–	Non-GCB
10	–	+	–	–	+	–	Non-GCB
11	–	+	NA	NA	NA	NA	NA
12	NA	+	NA	NA	NA	NA	NA
13	–	+	–	+	–	NA	GCB
14	–	+	–	+	–	–	GCB
15	–	+	–	+	+	–	Non-GCB
16	–	+	–	+	+	–	Non-GCB
17	–	+	–	–	+	+	Non-GCB
18	–	+	NA	NA	NA	+	NA
19	–	+	NA	NA	NA	–	NA
20	–	+	NA	NA	NA	–	NA
21	–	+	–	+	+	–	Non-GCB
22	–	+	–	+	+	–	Non-GCB
23	–	+	–	–	+	–	Non-GCB
24	–	+	–	–	+	–	Non-GCB
25	–	+	–	+	+	–	Non-GCB
26*	–	–	+	+	–	–	GCB
27	–	+	NA	NA	NA	NA	NA

Case numbers 18–20 had a limited number of scattered tumour cells, making it difficult to calculate the percentage of positively stained cells.
*In this case, tumour cells were positive for CD79a and PAX5 staining.
+, positive; –, negative; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; GCB, germinal centre B-cell; NA, not available.

mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, and others.[7] Cases of DLBCLs that do not fulfil the criteria for any of these specific entities are referred to as DLBCL, not otherwise specified (formerly referred to simply as DLBCL). Most cases in our cohort of RD-associated DLBCL were DLBCL, not otherwise specified, consistent with the predominance of this variant in the diagnostic category of 'DLBCL' in the general population.

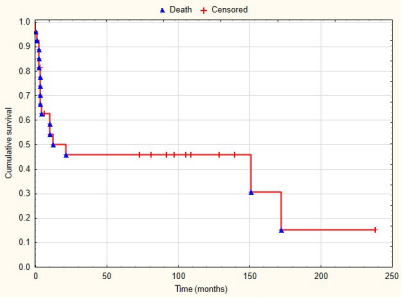

Figure 1 Overall survival among the 27 patients with rheumatic diseases and large B-cell lymphoma.

The mean age in our study corresponded to the mean age at the time of DLBCL diagnosis in the general population.[11] Although DLBCL is slightly more common in men than in women in the general population,[11] our cohort of patients with RD-associated DLBCL had a significant female predominance, which likely reflects the greater incidence of RDs identified in women. However, it cannot be ruled out that there may be sex differences in the risk of developing DLBCL in patients with RDs.

Klein *et al* hypothesised that continuing disease activity and immune stimulation were the most significant factors in the development of DLBCL in patients with RA.[12] Our findings support this hypothesis because in all of our cases, DLBCL was diagnosed after the diagnosis of RD,

and the average time from the onset of RD symptoms to the diagnosis of DLBCL was 19 years.

Prognostic factors predicting poor prognosis in DLBCL include high IPI, bulk disease and *c-MYC/8q24* gene rearrangements.[13] The addition of rituximab (R) to cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy dramatically improved the outcome in patients with DLBCL.[14 15] However, IPI based on age at lymphoma diagnosis, serum LDH concentration, ECOG performance status, Ann Arbor stage disease, and extent of extranodal involvement remain important prognostic factors in patients with DLBCL treated with rituximab and chemotherapy.[16 17] In our cohort, the percentage of patients assigned to the intermediate-high and high IPI risk groups was higher than that in the general population (59% vs 43%).[11] Since the IPI considers performance status, determining whether a poor performance state is caused by RD or DLBCL in RD-associated DLBCL cases is challenging. Perhaps the higher percentage of patients in the intermediate-high and high-risk IPI groups in our cohort can be explained by a poor performance status attributed to RD, but not to DLBCL. The incidence of bulk disease in our cohort was comparable with that in the general population of patients with DLBCL.[1] IPI and bulk disease are based solely on clinical factors that do not reflect the pathobiology of DLBCL.

Integration of the molecular features of DLBCL allows for further accurate prediction of disease outcome. Rearrangements in the *c-MYC/8q24* gene were detected in 5%–15% of DLBCL cases in the general population.[18 19] The presence of *c-MYC/8q24* gene translocation to immunoglobulin partner genes is associated with unfavourable prognosis following R-CHOP treatment.[20] To the best of our knowledge, there have been no studies on *c-MYC/8q24* gene rearrangement in RD-associated DLBCL cases. Although the FISH study revealed one to two additional signals from the *c-MYC/8q24* gene in six cases, none of the 19 examined cases in our cohort showed *c-MYC/8q24* gene translocation.

Patients with compromised immune systems are more likely to have EBV-positive DLBCL than sporadic cases.[21 22] However, the incidence of EBV-positive DLBCL varies significantly among patients with RDs (table 3).[23–27] Since all studies in the analysed literature used in situ hybridisation for the detection of EBV in tumour tissues, such variability could be explained by the different cut-off scores of EBER-positive cells used to define DLBCL as EBV positive. A meta-analysis of 13 qualified studies showed that EBV-positive DLBCL had significantly worse OS and progression-free survival.[28] In our cohort, only two (10%) cases were EBV positive, and in both cases the patients died of lymphoma progression after 1 month and 21 months from the diagnosis of DLBCL, respectively.

Although the prognostic value of DLBCL typing based on IHC algorithms has been inconsistent in patients treated with rituximab in addition to chemotherapy, the latest 2016 WHO classification of tumours of haematopoietic and lymphoid tissues recommend DLBCL typing for all cases.[7] In the pre-R-CHOP era, patients with DLBCL with the GCB subtype had better prognosis than those with the non-GCB subtype.[17 29] According to several studies, the addition of rituximab to chemotherapy has resulted in the nullification of the prognostic value of DLBCL typing based on IHC algorithms.[17 30 31] In contrast, other studies have shown that Hans' algorithm-based DLBCL typing retains predictive value in the rituximab era.[32 33] Hans' algorithm, as well as other IHC algorithms, shows a significant predominance of the GCB subtype of DLBCL in the general population.[6 34] However, our findings, as well as those of other studies, have shown a

Table 3 Review of the literature on EBV status and subtypes of diffuse large B-cell lymphoma in patients with rheumatic disease

	Vasaitis *et al*[24]	Tessier-Cloutier *et al*[35]	Löfström *et al*[25]	Baecklund *et al*[23]	Kojima *et al*[26]	Kojima *et al*[27]	Present study	Total
EBV-positive DLBCL	22%	NA	1/10 (10%)	12/139 (9%)	0/10 (0%)	0/5 (0%)	2/21 (10%)	15/185 (8%)
GCB subtype of DLBCL	13/26 (50%)	8/20 (40%)	2/10 (20%)	42/139 (30%)	0/10 (0%)	NA	4/20 (20%)	69/225 (31%)
Non-GCB subtype of DLBCL	13/26 (50%)	12/20 (60%)	8/10 (80%)	97/139 (70%)	10/10 (100%)	NA	16/20 (80%)	156/225 (69%)
Rheumatic disease (no of cases)	pSS (26)	SLE (20)	SLE (10)	RA (139)	DM (1) RA (9)	pSS (5)	pSS (14) SLE (2) SLE +sSS (1) RA (1) RA +sSS (1) SSc +sSS (1)	DM (1) RA (149) RA +sSS (1) pSS (45) SLE (32) SLE +sSS (1) SSc +sSS (1)

DLBCL, diffuse large B-cell lymphoma; DM, dermatomyositis; EBV, Epstein-Barr virus; GCB, germinal centre B-cell; NA, not available; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; sSS, secondary Sjogren's syndrome.

predominance of the non-GCB subtype in RD-associated DLBCL (table 3).[23–26 35]

The role of RDs in DLBCL prognosis is still uncertain. The 5-year survival and median OS of patients with RD-associated DLBCL in our study were significantly lower than those of patients with DLBCL in the general population: 46% (our study) vs 60%–70%[36] and 10 months (our study) vs 124 months[37], respectively. Our findings are supported in part by other studies, although the results of a small number of studies published to date are not consistent. Kleinstern *et al* reported markedly shortened relapse-free survival and OS in eight patients with DLBCL in the presence of B-cell-mediated AIDs compared with patients without AIDs.[38] Similar results were obtained by Mörth *et al* in an analysis of a cohort of 39 patients with DLBCL and primarily B-cell-mediated AIDs.[39]

In contrast, the study by Shih *et al* reported comparable OS in patients with non-Hodgkin's lymphoma with and without pre-existing AIDs.[40] However, this study reported outcomes for the entire AID group, and DLBCL represented only 18 of 34 cases of non-Hodgkin's lymphoma. Results from the Surveillance, Epidemiology, and End Results database of 5926 elderly patients with DLBCL, of whom 270 had B-cell-mediated AIDs, showed no significant difference in OS in patients with B-cell-mediated AIDs compared with patients without a history of these diseases.[4] However, this study found a tendency toward poor lymphoma-related survival in patients with DLBCL and SLE. A study using the Mayo Clinic database also showed no negative effect of autoimmune conditions mediated by B-cell responses on the prognosis of DLBCL, but there was also a trend toward inferior OS for DLBCL.[9]

The short OS in our cohort may be owing to several reasons. First, most patients in our cohort had the non-GCB subtype of DLBCL, and many of them received therapy in the pre-R-CHOP era. In a large Swedish cohort study that examined 22 patients with RA with DLBCL in the pre-R-CHOP era, the median OS was only 6 months.[41] Second, an analysis of mortality in our cohort showed that most deaths (10 of 15 cases) occurred within the first few months after DLBCL diagnosis and were attributed to complications from chemotherapy. Our findings are consistent with those in the study of Mörth *et al*, which showed that patients with DLBCL and AIDs may be more prone to neutropenic fever than patients without concomitant AIDs, and that patients with neutropenic fever after their first course of treatment had poor OS.[39] In contrast to our study findings, Mikuls *et al* showed that patients with RA and non-Hodgkin's lymphoma had a lower risk of death as a result of lymphoma or its treatment, but were more than twice as likely to die from comorbid conditions than the non-RA lymphoma controls.[42] However, in this study, DLBCL constituted only 43% of cases. Only two patients in our cohort had RA, and in both cases there was prolonged complete remission of the lymphoma.

There is a lack of knowledge in the literature regarding the biology of DLBCL arising in patients with RDs. Our findings agree with those of other researchers and suggest that DLBCL in the presence of RDs, in contrast to DLBCL in the general population, is more likely to be of the non-GCB subtype. Perhaps the poorer prognosis of patients with RD-associated DLBCL, established in some studies, is not only related solely to the biological features of DLBCL, but also to the fact that patients with long-standing severe RDs are predisposed to increased mortality and decreased tolerance to lymphoma treatment. Because the number of cases included in this study is limited, larger studies addressing this issue are needed to confirm this assumption.

Acknowledgements The manuscript was edited by Elsevier Language Editing Services.

Contributors VG was involved in the literature search, study design and writing. VG, NP, TO and VV were involved in the data collection, data analysis, and data interpretation, and edited and reviewed the manuscript. VG is author responsible for the overall content as the guarantor. All authors edited and reviewed the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval for the study's retrospective protocol was obtained from the VA Nasonova Research Institute of Rheumatology Ethics Committee. Patients provided informed consent for the collection and analysis of their data and specimens.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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