Review

Seasonal prevalence of myositis-associated and myositis-specific autoantibodies in a Greek patient cohort over a period of 8 years

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ABSTRACT

Objective. *Idiopathic inflammatory myopathies (IIMs) are a group of rare systemic autoimmune diseases primarily characterised by immune-mediated myocyte destruction and skeletal muscle inflammation. The recent introduction of myositis-associated and -specific autoantibodies (MAAs/MSAs) in clinical practice has revolutionised the early diagnosis and stratification of patients with IIMs. Environmental factors such as seasonal changes can influence the occurrence of specific autoantibodies or the onset of IIMs. Here, we aimed to investigate the seasonal prevalence of MAAs and MSAs in a Greek patient cohort.*

Methods. *Serological data were collected from 1896 patients referred for MAA/MSA detection between February 2017 and January 2025 via line immunoassays. Seasonality was evaluated by performing the Rayleigh test (for circular data) and the Chi-squared test (for ratios of positive tests).*

Results. *Of 1896 LIAs performed for the detection of MAAs and MSAs, 888 were positive for at least one autoantibody. The prevalence of positive MAAs was significantly higher compared to MSAs (χ^2 test, $p<0.001$). Among MAAs, anti-PM-Scl100 and anti-PM-Scl75 autoantibodies were significantly more frequent in the fall-winter seasons (χ^2 test; $p=0.008$ and $p=0.026$, respectively). Among MSAs, no significant seasonal associations were observed. Finally, the analysis of autoantibodies positivity rates between spring-summer and fall-winter seasons before COVID-19 (2017-2019) and during COVID-19 (2020-2024) did not show statistically significant differences.*

Conclusion. *The findings on seasonal prevalence of anti-PM-Scl100 and anti-PM-Scl75 autoantibodies suggest that various environmental factors present in different seasons of the year may trigger distinct immune responses and clinical manifestations in IIM.*

Introduction

Idiopathic inflammatory myopathies (IIMs) are heterogeneous systemic autoimmune diseases primarily characterised by immune-mediated myocyte destruction and inflammation of skeletal muscle. IIMs are reported with incidence rates of 0.2 to 2 per 100,000 person-years and prevalence rates of 2 to 25 per 100,000 people (1). Apart from muscle involvement, IIMs are often characterised by multi-systemic manifestations involving the skin, lungs, and vasculature, further underscoring their complexity. According to clinical and histopathological features, IIMs can be classified into several subgroups: dermatomyositis (DM) and juvenile dermatomyositis (JDM), antisynthetase syndrome (ASyS), immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM), and overlap myositis (OM) (2).

The pathogenesis of IIMs involves a complex interplay between genes, immune cells, muscle cells, as well as environmental factors such as infections, geoclimatic factors, toxins, and drugs (3, 4). Enhancing clinical outcomes for IIM subgroups requires a thorough understanding of the molecular pathways driving pathogenesis, as well as identifying the autoantigens involved in immune responses. Numerous mechanisms are believed to contribute to and

cause the breakdown of immune tolerance in IIMs, but the exact cascade remains largely unknown. Genetic susceptibility plays a crucial role in the breakdown of immune tolerance. Genetic variation at certain loci of human leukocyte antigens (HLA) class II is linked to distinct autoantibody-defined subtypes of IIM (5, 6). In addition, mutations and polymorphisms in non-HLA genes such as signal transducer and activator of transcription (STAT4), TNF receptor associated factor 6 (TRAF6), ubiquitin conjugating enzyme E2 L3 (UBE2L3), and protein tyrosine phosphatase non-receptor type 22 (PTPN22) are identified as shared autoimmune-risk loci affecting T-cell and B-cell signalling pathways contributing to the breakdown of self-tolerance in IIM (5). Environmental factors are also strongly associated with the development of autoimmune diseases. Extrinsic and intrinsic triggers, such as infections, toxins, and stress, can alter immune dysregulation in genetically predisposed individuals. Over the past few decades, an increasing amount of evidence has highlighted the role of viral infections such as human immunodeficiency virus (HIV), human T-lymphotropic virus type 1 (HTLV-1), hepatitis C virus (HCV), human cytomegalovirus (CMV), Epstein-Barr virus (EBV), and more recently severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) as key external factors triggering autoimmunity in IIM through different mechanisms, including molecular mimicry, epitope spreading, and bystander activation (4, 6-10). Distinct autoantibody reactivities identified in up to 70% of individuals with IIMs are increasingly recognised for their profound impact on early diagnosis, stratification, and prognosis, altogether rendering their implementation in clinical practice transformative (11). These autoantibodies are typically classified into two categories: myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs) (12). Different MAAs and MSAs target various cellular components and are associated with distinct clinical features and subtypes of IIM (13). MAAs are autoantibodies associated with myositis and other autoimmune diseases, generally indicating overlap syndromes such as the polymyositis-scleroderma (PM/Scl) overlap syndrome(11). MSAs are considered highly specific for IIMs and are particularly useful as they have been linked to increased risk of interstitial lung disease (ILD), necrotising myopathy, malignancy, and higher mortality rates (14).

Previous studies have shown that different seasons, as well as various ethnic and environmental factors, influence the occurrence of specific autoantibodies or the onset of IIMs (15-17). For instance, the occurrence of anti-melanoma differentiation-associated protein 5 (MDA-5), which is associated with vasculopathic lesions and ILD, has been predominantly observed in cases of exposure to respiratory infectious agents, especially in the winter season (3, 14). Additionally, the presence of transcription intermediary factor 1-gamma (anti-TIF1γ) autoantibody, which is typically associated with DM and an increased risk of malignancy, is also linked to viral infections (variola virus or SARS-CoV-2 virus) through the mechanism of molecular mimicry (3, 13). Prevalence of autoantibodies presentation and clinical manifestations can vary significantly based on the cohort, ethnicity, geographical region, and season under investigation (15, 17, 18).

This retrospective study aimed to investigate the seasonal prevalence of MAAs and MSAs positivity in a Greek patient cohort presenting with IIM symptomatology.

Patients and methods

Study population and MAA/MSA serological detection

To determine the seasonal prevalence of MAA and MSA positivity we retrospectively examined the serological data collected from 1896 patients referred to the Molecular and Applied Physiology Unit at the Medical School of National and Kapodistrian University of Athens for the evaluation of MAAs and MSAs between February 2017 and January 2025. Patients were referred from multiple centres around Greece for MAA/MSA detection due to a suspected underlying IIM diagnosis based on the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile IIM and their subtypes (19). Detection of MAAs and MSAs during the years 2017-2021 was performed with the EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) EUROIMMUN line immunoassays (LIA), with 16 antigens (Mi-2α, Mi-2β, TIF-1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52), during 2022-2025, detection was performed with the same LIA and the addition of cN-1A and HMGCR, for a total of 18 antigens (Supplementary Table S1). Prepared LIA were scanned using a flatbed scanner and evaluated using the EUROLineScan (EUROIMMUN) software. Results were interpreted by signal intensity, with a signal intensity value of 11 or greater being considered positive, according to the manufacturer's instructions.

Ethics committee approval was not necessary because this retrospective study used anonymised data.

Statistical analysis

For data reported as absolute numbers of positive tests per month and year (circular data), statistical analysis was performed using the Rayleigh test, whereas for data reported as ratios (frequencies) calculated between positive and total tests performed, statistical analysis was conducted using the Chi-squared test (χ^2 test). Data analysis and figure generation were performed using the Python programming language (version 3.13). Statistical significance was considered for a p-value <0.05.

Results

During the studied period, we conducted 1896 LIAs for the detection of MAAs and MSAs, out of which 888 were positive for at least one autoantibody. The prevalence of positive MAAs during this period was significantly higher compared to MSAs (χ^2 test, p<0.001) (Fig. 1). In the following sections, we present the findings of

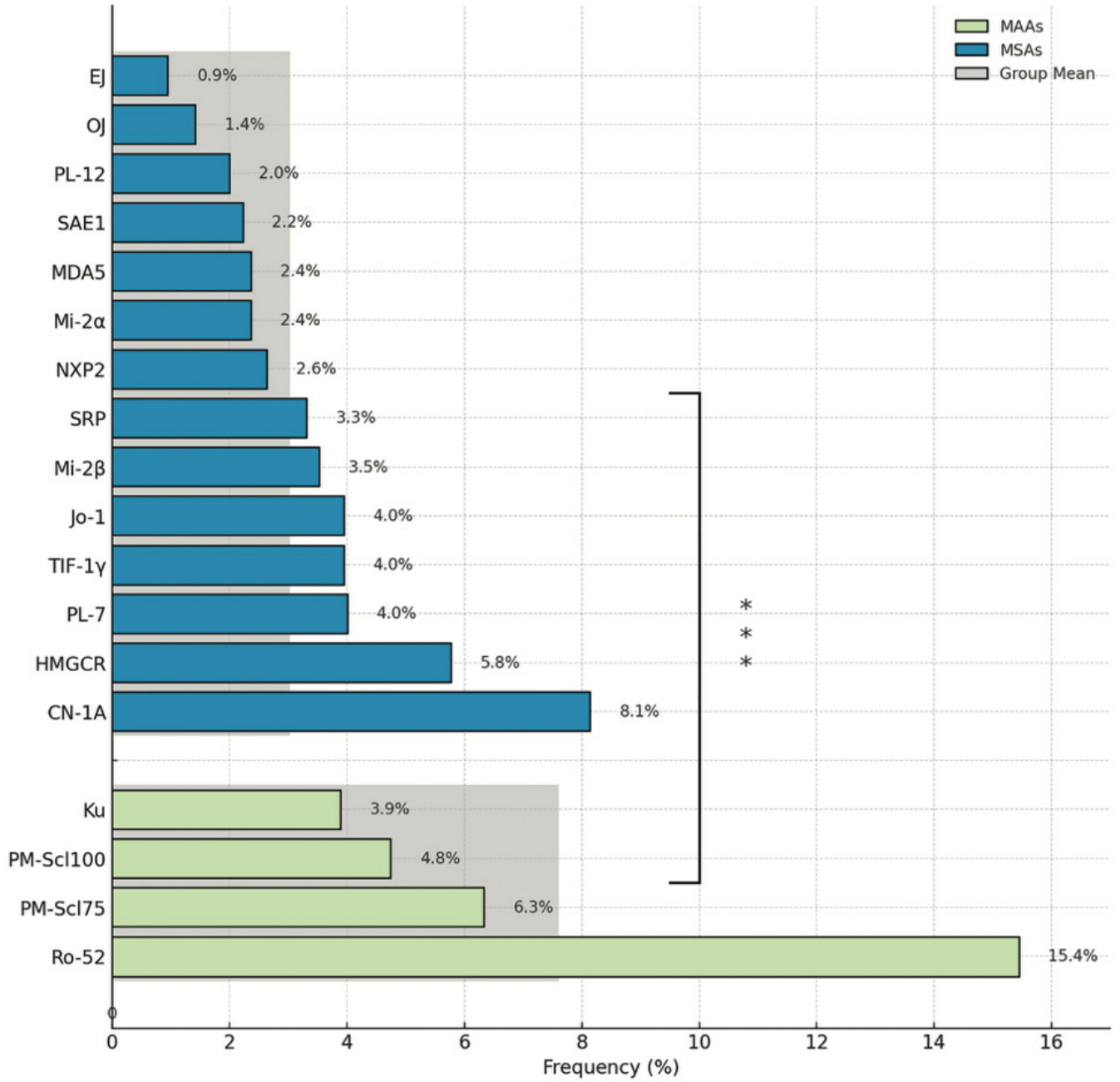

Fig. 1. Bar plot illustrating positive autoantibody frequencies by group (MAAs *vs*. MSAs, $p<0.001$).

our analysis focusing on the seasonal prevalence and clustering of MAAs and MSAs, as well as the prevalence of MAAs/MSAs before and during COVID-19 pandemic.

Seasonality of MAAs

As displayed in Figure 2, among the MAAs (anti-PM-Scl75, anti-PM-Scl100, anti-Ro52, and anti-Ku), anti-PM-Scl100 was detected more frequently in the fall-winter seasons (of 1039 tests conducted in the fall-winter period, 62 (5.97%) were positive; of 857 tests conducted in the spring-summer period, 28 (3.27%) were positive; χ^2 test, $p=0.008$). Anti-PM-Scl100 seasonality was further supported by the Rayleigh test (circular mean: December, $p=0.006$) (Supplementary Fig. S1). Along the same lines, anti-PM-Scl75 autoantibodies were also significantly more frequent in fall-winter seasons (of 1039 tests conducted in the fall-winter period, 78 (7.51%) were positive; of 857 tests conducted in the spring-summer period, 42 (4.90%) were positive; χ^2 test, $p=0.026$) (Fig. 2). No other significant seasonal associations of MAAs were detected (Table I, Fig. 2, Supplementary Fig. S1).

Seasonality of MSAs

Among the MSAs (anti-Mi2a, anti-Mi2b, anti-MDA5, anti-TIF1-γ, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti-Jo1, anti-NXP2, anti-SAE1, anti-SRP, anti-CN-1A, and anti-HMGCR), no significant seasonal associations were observed in either the frequency of positive tests (Fig. 2) or the absolute number of those tests (Supplementary

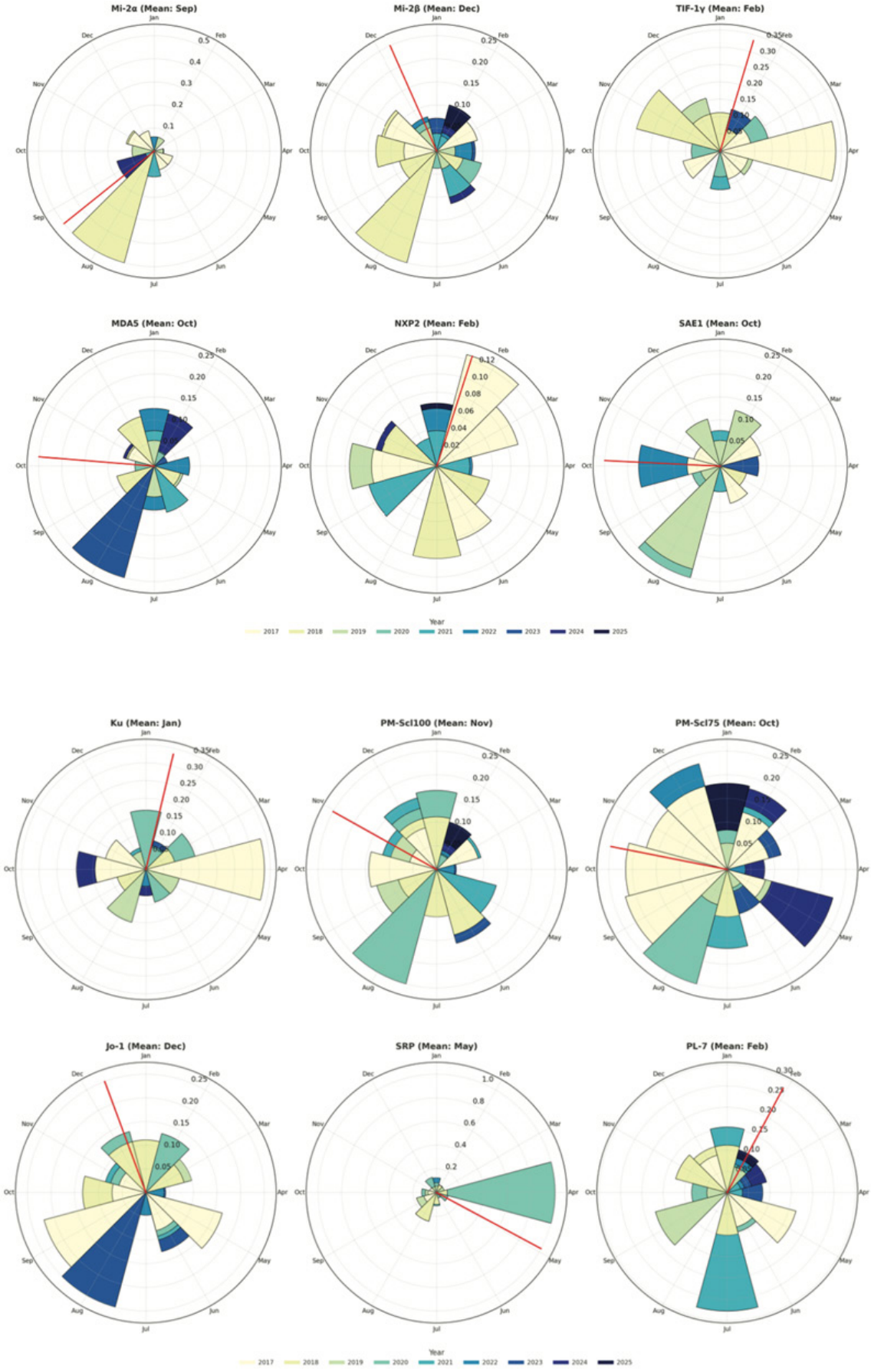
Mi-2α (Mean: Sep)
Mi-2β (Mean: Dec)
TIF-1γ (Mean: Feb)
MDA5 (Mean: Oct)
NXP2 (Mean: Feb)
SAE1 (Mean: Oct)
Ku (Mean: Jan)
PM-Scl100 (Mean: Nov)
PM-Scl75 (Mean: Oct)
Jo-1 (Mean: Dec)
SRP (Mean: May)
PL-7 (Mean: Feb)
Jan
Feb
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Fig. 2. Rose plots illustrating the monthly distribution of positive LIAs for the 18 autoantibodies. Data are presented as ratios of positive results per total test, color-coded by year as presented in the legend. The circular mean is indicated by the red line on the plots.

Fig. S1). Chi-squared test and Rayleigh test revealed only a trend of seasonality for distinct MSAs. Specifically, anti-HMGCR autoantibody showed a trend of being more frequent during the spring-summer seasons (of 474 tests conducted in the fall-winter period, 21 (4.43%) were positive; of 410 tests conducted in the spring-summer period, 30 (7.32%) were positive; χ^2 test, p=0.066) (Fig. 2). Additionally, anti-TIF-γ and anti-OJ autoantibodies demonstrated a distribution trend clustered in the fall-winter seasons, with a circular mean in January and March, respectively (Rayleigh test, p=0.076 and p=0.078, respectively) (Supplementary Fig. S1).

Seasonal prevalence of MAAs/MSAs stratified by positivity titre

The significance of the seasonal model for frequencies (ratios) was examined separately for medium-positive titres (11≤x≤25) and strong-positive titres (x≥26), according to the manufacturer's stratification. Analysis for the medium-positive titres revealed that anti-PM-Scl100 was more frequent during fall-winter seasons (p=0.006), anti-PM-Scl75 autoantibody showed a trend of being more frequent in fall-winter seasons (p=0.079), and anti-HMGCR autoantibody was found to be more frequent during the spring-summer seasons (p=0.027) (Supplementary Fig. S2). No statistically significant seasonality was detected when analysing strong-positive titres of autoantibodies (Supplementary Fig. S3).

COVID-19 and MAAs/MSAs prevalence

In light of the fact that COVID-19 has been associated with the activation of polyclonal autoreactive B cells reflected by autoantibody production (20, 21), we aimed to leverage this unique opportunity to assess the MAAs/MSAs prevalence before and during the COVID-19 pandemic. A comparative analysis of myositis autoantibodies' rates identified in spring-summer and fall-winter seasons before COVID-19 (2017-2019) and during COVID-19 (2020-2024) revealed no statistically significant differences (Fig. 3). Similarly, no significant differences were observed in autoantibody positivity rates across the two periods for all titres (Supplementary Fig. S4), as well as for medium-positive and strong-positive titres (Supplementary Fig. S5).

Discussion

The findings of our study provide significant insight into the possible seasonality of MAAs and MSAs in a Greek patient cohort. Statistical analysis of autoantibody positivity revealed that MAAs anti-PM-Scl100 and anti-PM-Scl75, were significantly more prevalent in the fall-winter seasons compared to spring-summer seasons. Moreover, the results of the analysis for medium-positive antibodies confirmed the seasonal prevalence of anti-PM-Scl100 and anti-PM-Scl75 autoan-

Table I. Seasonal variation of autoantibody positivity among 1896 LIAs between Fall-Winter and Spring-summer season groups.

Autoantibody	Season	Number of positive tests	% of positive tests	Number of negative tests	% of negative tests	Total tests	Chi-squared *p*-value	Rayleigh *p*-value
Mi-2α	Fall-Winter	26	2.50%	1013	97.50%	1039	0.798	0.452
	Spring-Summer	19	2.22%	838	97.78%	857		
Mi-2β	Fall-Winter	34	3.27%	1005	96.73%	1039	0.579	0.380
	Spring-Summer	33	3.85%	824	96.15%	857		
TIF-1γ	Fall-Winter	48	4.62%	991	95.38%	1039	0.129	0.076
	Spring-Summer	27	3.15%	830	96.85%	857		
MDA5	Fall-Winter	24	2.31%	1015	97.69%	1039	0.961	0.871
	Spring-Summer	21	2.45%	836	97.55%	857		
NXP2	Fall-Winter	29	2.79%	1010	97.21%	1039	0.751	0.740
	Spring-Summer	21	2.45%	836	97.55%	857		
SAE1	Fall-Winter	28	2.69%	1011	97.31%	1039	0.159	0.204
	Spring-Summer	14	1.63%	843	98.37%	857		
Ku	Fall-Winter	46	4.43%	993	95.57%	1039	0.238	0.149
	Spring-Summer	28	3.27%	829	96.73%	857		
PM-Scl100	Fall-Winter	62	5.97%	977	94.03%	1039	0.008	0.006
	Spring-Summer	28	3.27%	829	96.73%	857		
PM-Scl75	Fall-Winter	78	7.51%	961	92.49%	1039	0.026	0.184
	Spring-Summer	42	4.90%	815	95.10%	857		
Jo-1	Fall-Winter	40	3.85%	999	96.15%	1039	0.887	0.244
	Spring-Summer	35	4.08%	822	95.92%	857		
SRP	Fall-Winter	39	3.75%	1000	96.25%	1039	0.305	0.424
	Spring-Summer	24	2.80%	833	97.20%	857		
PL-7	Fall-Winter	43	4.14%	996	95.86%	1039	0.841	0.574
	Spring-Summer	33	3.85%	824	96.15%	857		
PL-12	Fall-Winter	22	2.12%	1017	97.88%	1039	0.823	0.927
	Spring-Summer	16	1.87%	841	98.13%	857		
EJ	Fall-Winter	10	0.96%	1029	99.04%	1039	1	0.850
	Spring-Summer	8	0.93%	849	99.07%	857		
OJ	Fall-Winter	13	1.25%	1026	98.75%	1039	0.613	0.078
	Spring-Summer	14	1.63%	843	98.37%	857		
Ro-52	Fall-Winter	171	16.46%	868	83.54%	1039	0.204	0.222
	Spring-Summer	122	14.24%	735	85.76%	857		
CN-1A	Fall-Winter	39	8.23%	435	91.77%	474	1	0.813
	Spring-Summer	33	8.05%	377	91.95%	410		
HMGCR	Fall-Winter	21	4.43%	453	95.57%	474	0.066	0.179
	Spring-Summer	30	7.32%	380	92.68%	410		

tibodies in the fall and winter seasons, as found in the analysis of overall positivity. Our findings are further supported by a study in an Italian cohort (17), which found that anti-PM-Scl75 autoantibody occurs more frequently during the fall-winter seasons as well.

Regarding MSAs, anti-TIF-1γ autoantibodies were borderline significantly clustered in the fall-winter seasons based on absolute numbers analysis, indicating a potential seasonality, which was not confirmed when analysing frequencies. In line with our findings, the Italian study found that anti-TIF-1γ antibodies were significantly clustered in the fall-winter season, based on the analysis of absolute numbers of autoantibodies (17). Concerning anti-OJ autoantibodies, our findings reported a circular mean in March, which may be in agreement with those reported by Sarkar *et al*. (15), who observed a seasonal pattern in myositis onset in patients with antisynthetase autoantibody positivity in the US. Specifically, they reported that in non-black males with

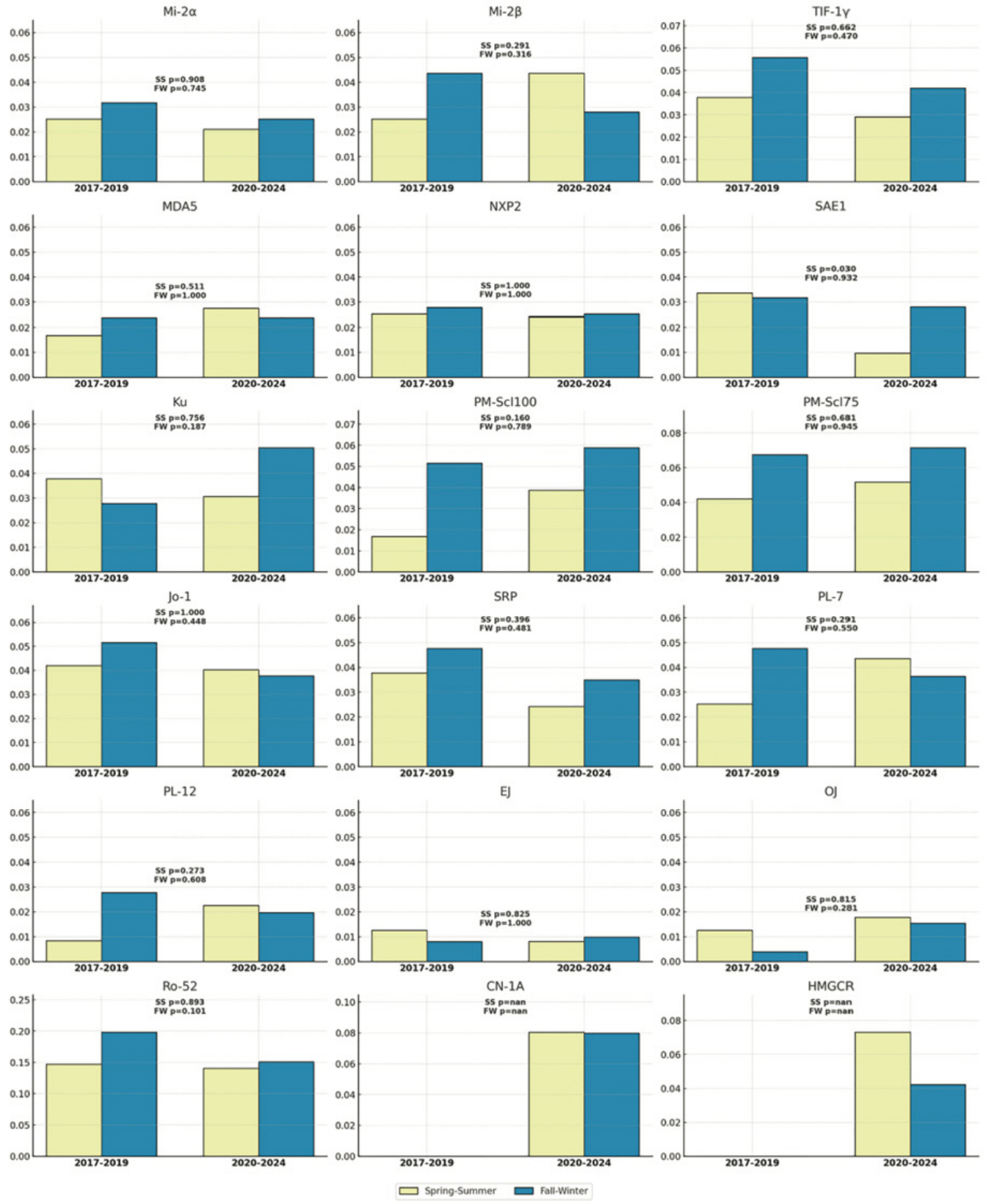

Fig. 3. Bar plots illustrating a comparative analysis of myositis autoantibodies' rates identified in spring-summer and fall-winter seasons before COVID-19 (2017-2019) and during COVID-19 (2020-2024). Statistical analysis was performed separately for both the spring-summer and fall-winter seasons, comparing autoantibody rates between the 2017-2019 and 2020-2024 periods using the χ^2 test.
SS: Spring-Summer; FW: Fall-Winter.

positive antisynthetase autoantibodies, myositis onset peaked in March-April (15). We also found that anti-HMGCR autoantibody showed a trend of being detected more frequently in the spring and summer seasons when analysing overall positivity. Based on the analysis of medium-positive autoantibodies, the frequency of anti-HMGCR autoantibody in spring-summer seasons increased significantly. The seasonal prevalence of anti-HMGCR has not been addressed in the literature so far. Furthermore, while we did not identify a pattern of seasonality in MDA5 prevalence, other studies have variably reported so. Palterer *et al*. found that anti-MDA5 autoantibodies were detected more frequently during fall-winter seasons (17). Additionally, a multicentre study in Japan revealed that ILD anti-MDA5 positivity cases occurred predominantly between October and March (22). So *et al*. also observed seasonal patterns in patients with rapidly progressive RP-ILD anti-MDA5 related DM with similar ethnogeographic background of Chinese origin. Importantly, they noted fewer anti-MDA5 cases between July and September and observed RP-ILD anti-MDA5 peaks in October–December, suggesting that environmental factors such as infections may be the causation (16). Supplementary Table S2 summarises the findings of our study and other related studies.

As mentioned, our findings on the seasonal prevalence of MAAs/MSAs are partially consistent with the findings of the Italian study, which may be supported by the fact that Greece and Italy both have a Mediterranean climate. The influence of the Mediterranean climate on seasonal temperature variations may have a similar effect on the seasonal occurrence of viral infections in the two countries (23). The occurrence of anti-PM-Scl75 and anti-TIF-1γ autoantibodies in the fall-winter seasons in Greece and Italy could be associated with the presence of specific pathogens during these seasons, which may trigger an autoimmune reaction with IIM symptomatology (24, 25). Moreover, discrepancies in the findings between Italian study and ours could be attributed to colder and wetter climate in different regions of Italy (26). These regional variations could contribute to longer and more intense seasonal outbreaks, which may impact the occurrence of autoantibodies such as anti-MDA5, correlated with different viral infections (3).

Another observation could be that fall-winter seasons are associated with reduced sunlight, in the Northern hemisphere, which in turn may affect vitamin D (VitD) levels during these months (27). Various immune cells, including T cells, B cells, dendritic cells (DCs), monocytes, macrophages, and natural killer (NK) cells, express both VitD receptor (VDR) and 1α-hydroxylase enzyme (CYP27B1). This enzyme activates VitD precursors (25(OH)VitD) to calcitriol. VitD (calcitriol) directly and indirectly influences the immune system by affecting immune cells' activation and proliferation (28). Importantly, observation studies have shown that serum VitD deficiency or insufficiency is prevalent in patients with IIMs as well as other autoimmune diseases. Decreased VitD levels were further associated with adverse muscle health parameters in IIMs patients, while its deficiency also correlated with the presence of anti-Jo-1 and anti-Mi-2 antibodies. These findings may further highlight the immunomodulatory role of VitD (29).

Viral infections may contribute to the development of autoimmune responses against the PM/Scl-100 and PM/Scl-75, components of the PM/Scl complex (Human or RNA exosome), potentially through mechanisms of molecular mimicry and epitope spreading (30). The human exosome is a multiprotein complex with a crucial role in host and viral RNA processing and degradation (30-32). Specifically, the human exosome and antiviral cofactors (ZAP and DDX60) function together to degrade viral RNA (31, 33). Additionally, the human exosome is involved in the regulation of immune processes, including cytokine production and negative regulation of nucleic acid recognition, preventing autoimmunity (33). In a healthy cell, the human exosome targets the cytokine mRNAs through ARE-binding proteins (AUBPs) and rapidly decays them (33). On the contrary, in cases of stress or infection, immune-related signalling pathways such as the Erk and p38 MAPK reduce the cytoplasmic proteins called AUBPs, preventing the cytokine mRNAs from being destroyed by the human exosome and finally leading to rapid production of proinflammatory cytokines (33). To date, the exact mechanism that triggers the initial immune response against autoantigens and specifically against the human exosome components remains largely unknown.

Of note, the pathogenicity of autoantibodies and autoantigens may be a consequence of environmental, viral and other triggers, that may invariably result in their production, with some of them favouring possibly the fall-winter seasons (18). Moreover, this expression of autoantigens and autoantibodies may result in distinct pathogenetic mechanisms that hold the potential to drive distinct clinical phenotypes (34). When considered together, the data presented here can be utilised in research to better understand the cascade of immune responses that may lead to autoimmunity in IIM.

This study, in addition to its primary aims, provided a unique opportunity to leverage our data before and during the COVID-19 pandemic. Given that infections have been long considered to trigger autoimmune responses (20, 21, 35), we wished to explore how the COVID-19 pandemic may have affected the distribution of these autoantibodies, comparing the prevalence of these antibodies in two distinct periods before COVID-19 (2017-2019) and during COVID-19 (2020-2024). In these analyses, the frequency of positive autoantibodies before and during COVID-19 did not show statistically significant differences. There is a possibility that the statistical significance was also affected by limited accessibility to testing facilities due to positive COVID-19 cases and quarantine. A single-centre study showed that during the COVID-19 pandemic, despite the increased incidence and severity of IIM, no significant differences in the frequency of MAAs and MSAs were

observed compared to the frequency of autoantibodies before the COVID-19 pandemic (36).

Overall, our findings provide valuable insights into the seasonality of MAAs and MSAs. The fact that our centre accepts samples from around Greece contributes significantly to ensuring wider geographic representation and increases the statistical power, enhancing the generalizability of the findings in the Greek population. However, certain limitations of the present study should be considered, including the unavailable information regarding the time of onset of symptoms in relation to the test date and the confirmed final diagnoses for all participants. In addition, information about the COVID-19 infection or vaccination status of patients was also unavailable.

Taking everything into account, we highlighted here that specific MAAs and MSAs particularly anti-PM-Scl100 and anti-PM-Scl75 displayed seasonal prevalence, suggesting that various environmental factors may contribute to the occurrence of autoantibodies and clinical manifestations of IIMs.

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