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Original Article

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Real-world application of the international myositis assessment and clinical studies group guidelines on cancer risk stratification

Maria Rosa Pellico[1,2,‡,⋆], Cristina Bochicchio[1,2], Claudia Iannone[1,2,‡], Silvia Cavalli[1,2], Ilaria Magi[1,2], Veronica Batani[3,4,5], Antonio Tonutti[6,7], Silvia Grazzini[8], Silvia Della Pina[9], Alessia Gatti[9], Manuel Sette[1,2], Antonina Minniti[1,2], Maria De Santis[6,7], Angela Ceribelli[6,7], Edoardo Conticini[8], Ilaria Cavazzana[9], Corrado Campochiaro[3,4], Giacomo De Luca[3,4], Roberto Caporali[1,2], Nicoletta Del Papa[1,2]

[1]Department of Rheumatology and Medical Sciences, ASST Gaetano Pini-CTO Institute, Milan, Italy
[2]Department of Clinical Sciences and Community Health, Research Centre for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy
[3]Unit of Immunology, Rheumatology, Allergy and Rare Disease, IRCCS San Raffaele Hospital, Milan, Italy
[4]Faculty of Medicine, Vita Salute San Raffaele University, Milan, Italy
[5]Rheumatology Unit – Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy
[6]Department of Biomedical Sciences, Humanitas University, Milan, Italy
[7]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[8]Rheumatology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
[9]Rheumatology and Clinical Immunology, ASST Spedali Civili di Brescia, Department of Clinical and Experimental Sciences, University of Brescia, ERN ReCONNET, Brescia, Italy
⋆Correspondence to: Maria Rosa Pellico, Università degli Studi di Milano, Milan, Italy; Reumatologia Clinica, ASST-PINI-CTO; Piazza Cardinal Ferrari 1, 20122, Milan, Italy. E-mail: mariarosa.pellico@unimi.it
‡Maria Rosa Pellico and Claudia Iannone contributed equally.

Abstract

Objectives: **The 2023 International Myositis Assessment and Clinical Studies Group (IMACS) guidelines introduced a standardized risk-stratification model for cancer screening in idiopathic inflammatory myopathies (IIM). However, real-world data on their application remain limited. This study aimed to evaluate the effectiveness of IMACS-based risk stratification in predicting malignancy and assess adherence to cancer screening recommendations in a multicentric Italian IIM cohort.**

Methods: **We conducted a multicentre retrospective study including 411 IIM patients from five Italian rheumatology centres, classified into IMACS-defined standard, intermediate and high-risk groups. Cancer occurrence within three years of IIM diagnosis was assessed. Screening practices prior to the implementation of IMACS guidelines were compared with their recommendations. Logistic regression analysis was used to evaluate the predictive value of IMACS stratification.**

Results: **Among 411 patients, 180 (43.8%) were classified as high-risk, 156 (37.7%) as intermediate-risk and 75 (18.2%) as standard-risk. Cancer was diagnosed in 9.2% of patients within three years of IIM onset, with high-risk patients significantly more likely to develop malignancy (OR = 4.05, $P = 0.026$). Anti-TIF1γ (OR = 12.3, $P < 0.001$) and anti-SAE1 (OR = 11.9, $P = 0.012$) were independent predictors of cancer. Screening adherence varied, with underutilization of enhanced screening in intermediate-risk patients and a decline in screening over time.**

Conclusion: **The IMACS stratification model effectively predicts cancer risk in IIM. However, real-world screening practices show inconsistencies, particularly in intermediate-risk patients. These findings support the need for optimized, risk-adapted malignancy surveillance in IIM and refinement of current guidelines based on real-world data.**

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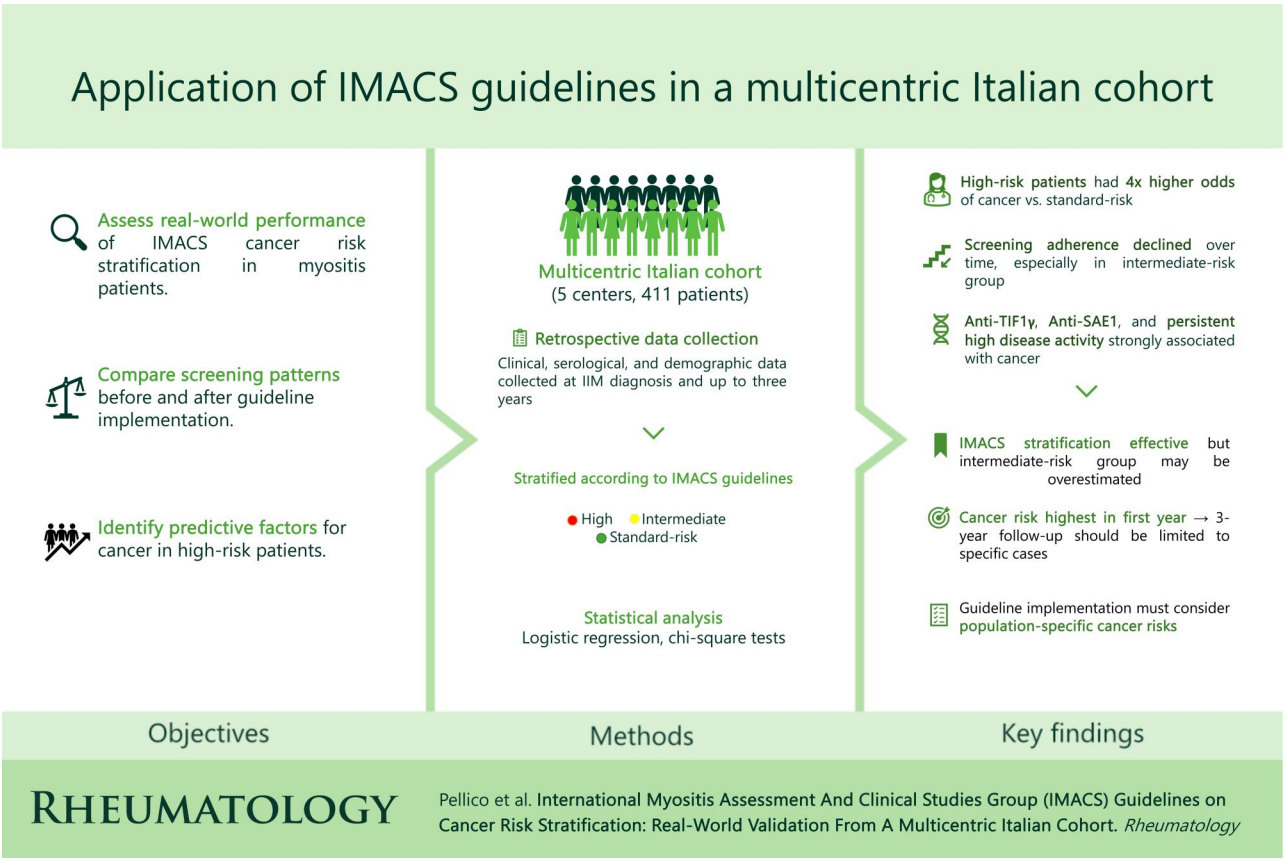
Graphical abstract



Keywords idiopathic inflammatory myopathies, cancer screening, IMACS guidelines, risk stratification, dermatomyositis, autoantibodies, malignancy, real-world data, predictive model, rheumatology

Rheumatology key messages

- International Myositis Assessment and Clinical Studies (IMACS) guidelines effectively predict cancer risk in idiopathic inflammatory myopathies.
- Real-world cancer screening practices show inconsistencies, particularly in intermediate-risk patients.
- Anti-TIF1γ and anti-SAE1 are strong independent predictors of malignancy in idiopathic inflammatory myopathies (IIM).

Introduction

Idiopathic inflammatory myopathies (IIM) are complex and heterogeneous clinical entities that share an autoimmune aetiology. They primarily affect skeletal muscles but may also present with a wide array of systemic manifestations, ranging from skin rashes and interstitial lung disease to cardiac and gastrointestinal involvement.

IIM are further categorized into different subgroups according to their clinical presentation and the presence of specific autoantibodies: dermatomyositis (DM), polymyositis (PM), clinically amyopathic dermatomyositis (CADM), immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ARS), connective tissue disease related myositis (CTD-IIM) and inclusion body myositis (IBM).

Notably, adults with recent-onset IIM have a higher cancer risk compared with the general population, especially in the three years before and after their diagnosis [1]. In IIM, cancer is a leading cause of death and its prevalence varies significantly across different study populations, affecting up to 13% of patients [1–4].

In 2023, the International Myositis Assessment and Clinical Studies Group (IMACS) published the first consensus guidelines for IIM-associated cancer screening, suggesting that patients should be stratified into high, intermediate and standard risk groups based on their demographic, clinical and serological characteristics [5].

Basic screening is recommended at the time of diagnosis for all patients, while additional screening methods should be applied to intermediate and high-risk groups [5]. The IBM subset

has not shown an association with malignancy, therefore cancer screening is not recommended for this IIM subtype [5].

To the best of our knowledge, these guidelines, due to their recent publication, have not yet been extensively applied. Therefore, the aim of our study is to retrospectively compare the cancer screening approaches utilized prior to the implementation of current guidelines with the classification and risk stratification methods proposed by these guidelines. Additionally, we aim to evaluate the effectiveness of current guidelines in identifying cancer risk and assess the screening practices previously employed in their absence.

Methods

Study population and data collection

This multicentre retrospective study included patients with IIM followed up between January 2014 and April 2024 in the Myositis Clinics of all participating centres: ASST Gaetano Pini-CTO in Milan, Spedali Civili di Brescia, Santa Maria alle Scotte Hospital in Siena, Humanitas Research Hospital in Rozzano and San Raffaele Hospital in Milan.

Patients over 18 years of age at IIM diagnosis and meeting at least one of the following criteria were included: (i) 2017 EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Myopathies and their Major Subgroups [6]; (ii) Bohan and Peter Criteria for DM and PM [7, 8]; (iii) Classification criteria of CADM described by Sontheimer *et al.* [9]; (iv) ARS Classification Criteria described by Connors *et al.* or Solomon *et al.* [10, 11]; and (v) 224th ENMC Clinico-sero-pathological classification of IMNM [12].

Patients who had missing mandatory data (see Supplementary Table S1 for details) or with <3 years of follow-up were excluded to align with IMACS recommendations for intensified cancer surveillance during the first three years after IIM onset and to minimize misclassification due to incomplete screening trajectories.

Demographic, clinical and risk factor data, as well as cancer screening methodologies, were collected at different time points: at IIM diagnosis (T0) and at one (T1), two (T2) and three (T3) years of follow-up, and the last available observation (T4).

Myositis-specific autoantibodies (MSA) were tested in each centre using line-blot immunoassays (Autoimmune Inflammatory Myopathy profile, EUROIMMUN, Germany). Autoantibody results were confirmed by at least two separate determinations in the original clinical records. The strength of autoantibody positivity was considered only in cases with multiple antibodies to help assign a primary specificity. Anti-HMGCR antibodies were assessed using ELISA methodology, as they are not included in the standard line-blot immunoassay panel. Anti-cN1A antibodies were tested when available using the recently introduced line-blot assay but were not mandatory for study inclusion as they are not part of the IMACS-relevant autoantibodies panel required for risk stratification.

Patients were then stratified into standard, intermediate and high-risk groups for cancer according to IMACS guidelines as detailed below [5].

Subsequently, cancer development within each risk group was assessed to evaluate the performance of IMACS stratification.

Moreover, screening methods employed for the same risk group were compared with the standards recommended by the new guidelines for the same group at baseline (T0), one year (T1) and subsequent follow-up visits.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (Comitato Etico Lombardia 3, ID 4646, study number 1351). All patients were enrolled in the respective centre's registry, and written informed consent was obtained at time of enrolment. According to national legislation and institutional policies, no additional consent was required for retrospective data analysis.

IMACS classification criteria

Patients were stratified into standard, intermediate and high-risk groups for cancer according to the 2023 IIMACS guidelines [5]. The IMACS risk stratification model assigns patients to risk categories based on the presence of specific risk factors:

High-risk factors include: DM, anti-TIF1γ positivity, anti-NXP2 positivity, age >40 years at IIM onset, persistent high disease activity despite immunosuppressive therapy, moderate to severe dysphagia and cutaneous necrosis/ulceration.

Intermediate-risk factors include: CADM, PM, IMNM, anti-SAE1 positivity, anti-HMGCR positivity, anti-Mi2 positivity, anti-MDA5 positivity and male sex.

Standard-risk factors include: ARS, CTD-IIM, anti-SRP positivity, anti-Jo1 positivity, non-Jo1 ARS antibody positivity, myositis-associated antibody positivity (MAA) (PM-Scl, Ku, anti-RNP, Ro/La), Raynaud's phenomenon, inflammatory arthropathy and interstitial lung disease.

Risk categories were assigned as follows: high-risk ($\geq$2 high-risk factors), moderate-risk (one high-risk factor OR $\geq$2 intermediate-risk factors) and standard-risk (patients not meeting high or moderate risk criteria). These risk categories represent cancer risk relative to the overall IIM population, not the general population.

Statistical analysis

Descriptive statistics were used to show the characteristics of the study population. Continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), as appropriate.

A multivariate logistic regression model was used to identify independent predictors of cancer occurrence within three years of IIM diagnosis. All clinical and serological variables included in the IMACS guidelines (IIM subsets, positivity for anti-TIF1y, anti-NXP2, anti-SAE1, anti-HMGCR, anti-Mi2, anti-MDA5, anti-SRP, anti-Jo1, non-Jo1 ARS antibodies, MAA, age >40 years at IIM onset, high disease activity despite therapy, dysphagia, cutaneous necrosis, male sex, presence of Raynaud phenomenon, inflammatory arthropathy, interstitial lung disease) were initially considered as candidate predictors. The dependent variable was the presence or absence of cancer within three years from diagnosis (binary: 1 = cancer, 0 = no cancer).

As an initial screening step, candidate variables were evaluated in univariate analyses comparing patients who developed cancer within three years and those who did not. Continuous variables were compared using Student's *t* test or non-parametric equivalents, as appropriate, and categorical

variables using χ^2 or Fisher's exact tests. A significance threshold of $\alpha = 0.05$ was adopted.

Multicollinearity among predictors was assessed using variance inflation factors (VIF), and variables with a VIF >5 were excluded to ensure model stability. Due to strong collinearity with autoantibody status, IIM clinical subtypes were excluded from the multivariate model.

Multivariate model building was guided by a combination of statistical results and clinical judgment. Variables with no evidence of association in multivariate analysis were progressively removed; however, variables considered clinically relevant or biologically plausible were retained regardless of statistical significance to avoid the exclusion of established risk factors. Details of the variable selection process are provided in Supplementary Fig. S1.

A separate logistic regression model was built to evaluate the association between predefined cancer risk classes (high, intermediate and standard) and the outcome. The categorical variable 'risk class' was recoded using dummy variables, with the standard risk class as the reference category (coded as 3).

This model allowed estimation of the odds of cancer at 3 years for the high-risk and intermediate-risk groups relative to the standard group. To enable direct comparison between all three groups (high, intermediate and standard), the model was re-estimated using alternative reference categories.

Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and associated *P*-values. Model fit was assessed using Nagelkerke's R^2, and model accuracy was expressed as the percentage of correctly classified cases.

Statistical analyses were performed by IBM Statistics Package for Social Sciences (SPSS) v29.

Results

A total of 497 patients were enrolled. Among them, 51 patients were excluded for missing data on autoantibody profile, date of diagnosis, characteristics at baseline or follow-up data, 10 as they were lost to follow-up three years after diagnosis, 14 for non-univocal IIM classification and 11 patients because clinical records were unavailable at designed timepoints.

Out of 411 patients included in the analysis, 294 (71.5%) were female with a median age at IIM diagnosis of 55 (IQR 23.5) years. Most were of Caucasian ethnicity (368, 89.5%). The most common clinical subtype was DM, affecting 141 patients (34.3%), including 19 patients with CADM (13.5% of DM); 126 patients (30.7%) were diagnosed with ARS, followed by 79 cases (19.2%) of PM, 32 (7.8%) of CTD-IIM, 11 (2.7%) of IMNM and three cases (0.7%) of IBM. Other demographics and clinical features are summarized in Table 1.

Cancer detection and performance of IMACS guidelines in risk stratification

Application of the IMACS guidelines to baseline characteristics resulted in 180 (43.8%) patients being classified in the high-risk group, 156 (37.7%) in the intermediate-risk group and 75 (18.2%) in the standard-risk group. Synchronous cancers were globally found in 47 cases, with 38 patients (9.2%) developing cancer in the 3 years after IIM diagnosis and nine patients (2.2%) three years prior to their IIM diagnosis.

Overall, cancer prevalence within the 3 years after IIM diagnosis was higher in patients in the high-risk group (see Table 2). Patients with cancer were more likely to be older than 40 years at diagnosis (97.9% *vs* 88.2%), belong to the DM subset (57.4% *vs* 31.6%) and be positive for anti-TIF1y (29.8% *vs* 4.7%) or anti-SAE1 (6.4% *vs* 1.6%), compared with patients without cancer. They also presented more frequently with moderate to severe dysphagia (38.3% *vs* 21.7%) and with high disease activity despite initial therapy (38.3% *vs* 20.1%).

Conversely, a lower prevalence of cancer was detected in patients in the ARS or CTD-IIM subtype and in patients with Raynaud's phenomenon or ILD as clinical features (see Table 2).

Among the 38 patients who developed cancer within three years after IIM diagnosis, 25 (65.8%) belonged to the high-risk group, 10 (26.3%) to the intermediate-risk group and three patients (7.9%) to the standard-risk one. The median time of cancer diagnosis was 2.34 months (IQR 0.24–9.69 months) after IIM diagnosis and most of them (81.6%) were detected within the first year (Fig. 1). The most common types of malignancies detected were breast, urothelial and ovarian cancers, found in 10 females (26.3%), four males (10.5%) and four females (10.5%), respectively. Single cases (2.6%) of adrenal, nasopharyngeal and oropharyngeal cancer were observed. Notably, five patients (13.2%) were diagnosed with more than one type of cancer. A summary of the malignancies is listed in Fig. 2.

The nine patients who received a cancer diagnosis within 3 years prior to their IIM diagnosis were all females; seven were classified as high-risk and two as intermediate risk, according to IMACS. Within the high-risk group, we registered three cases of breast cancer, followed by two cases of ovarian cancer, one of thyroid cancer and one of acute myeloid leukaemia.

During the entire follow-up period (median 4.59 years, IQR 3.0–9.4), a total of 82 cancers (20%) were diagnosed in the cohort. Sixty-three patients (15.3%) were lost to follow-up after three years from IIM diagnosis, which may have led to an underestimation of the true cancer incidence after the first three years from diagnosis.

Nineteen patients (4.6%) died during follow-up. Among these, nine (47.4%) deaths were attributed to cancer-related complications, three (15.8%) due to rapidly progressive or acute exacerbations of ILD and seven (36.8%) due to severe infections. Among patients who died, the median survival time was 1.55 years and it differed between groups: patients with cancer had a median survival of 0.63 years compared with 2.11 years for patients without cancer.

Logistic regression analysis demonstrated that the high-risk group was significantly more likely to develop cancer than both the standard-risk group [OR=4.054; 95% CI (1.185, 13.873); $P = 0.026$] and the intermediate-risk group [OR = 2.181; 95% CI [(1.035; 4.596); $P < 0.001$]. The likelihood of developing cancer was not significantly different between the intermediate- and the standard-risk group [OR = 1.859; 95%CI (0.503, 6.875), $P = 0.353$].

Multivariable logistic regression revealed male sex [OR = 9.95; 95%CI (1.92; 51.57); $P = 0.006$], anti-TIF1y [OR = 12.296; 95%CI (2.943; 51.374); $P < 0.001$], anti-SAE1 [OR = 11.983; 95%CI (1.713; 83.839); $P < 0.012$], anti-SRP [OR = 9.014; 95%CI (1.077; 75.420); $P < 0.012$] and high disease activity despite therapy [OR = 3.401;

Table 1 Demographic, clinical and serological characteristics of IIM patients in different risk groups per IMACS guidelines.

	All (*n* = 411)	High risk (*n* = 180)	Intermediate risk (*n* = 156)	Standard risk (*n* = 75)
Follow-up period, median (IQR)	4.59 (3.0–9.4)	3.49 (3.0–7.4)	5.67 (3.01–10.2)	5.52 (3.0–10.9)
Male, *n* (%)	117 (28.5)	48 (26.7)	55 (35.2)	14 (18.7)
Age, median (IQR)	60.2 (22.6)	61.0 (21.0)	62.5 (21.1)	48.9 (24.9)
Age at diagnosis, median (IQR)	55.0 (23.5)	56.9 (22.3)	55.9 (19.9)	43.8 (25.5)
Age >40, *n* (%)	368 (89.5)	172 (95.6)	141 (90.4)	55 (73.3)
Current smoker, *n* (%)	49 (11.9)	18 (10.0)	23 (14.8)	8 (10.7)
Past smoker, *n* (%)	64 (15.6)	24 (13.3)	30 (19.2)	10 (13.3)
Ever smoker, *n* (%)	113 (27.5)	42 (23.3)	53 (33.9)	18 (24.0)
Ethnicity[a]				
Caucasian, *n* (%)	370 (90.0)	169 (93.8)	139 (89.1)	62 (82.7)
Hispanic, *n* (%)	7 (1.7)	3 (1.7)	3 (1.9)	1 (1.3)
Black Americans, *n* (%)	13 (3.2)	1 (0.6)	3 (1.9)	9 (12.0)
Arab, *n* (%)	2 (0.5)	1 (0.6)	1 (0.6)	0
Asian, *n* (%)	4 (1.0)	3 (1.7)	0	1 (1.3)
IIM subtype				
DM, *n* (%)	141 (34.3)	122 (67.8)	16 (10.3)	3 (4.0)
CADM, *n* (%)	19 (4.6)	14 (7.8)	3 (1.9)	2 (2.7)
ARS, *n* (%)	126 (30.7)	8 (4.4)	64 (41.3)	54 (72.0)
PM, *n* (%)	79 (19.2)	24 (13.3)	48 (31.0)	7 (9.3)
IIM-CTD, *n* (%)	32 (7.8)	8 (4.4)	16 (10.3)	8 (10.7)
IBM, *n* (%)	3 (0.5)	0	2 (1.2)	1 (1.3)
IMNM, *n* (%)	11 (2.7)	4 (2.2)	7 (4.5)	0
Cancer within 3 years (after), *n* (%)	38 (9.2)	25 (13.9)	10 (6.5)	3 (4.0)
Cancer ever, *n* (%)	82 (20.0)	47 (26.1)	26 (16.8)	9 (12.0)
Clinical manifestations, *n* (%)				
Raynaud, *n* (%)	103 (25.1)	34 (18.9)	43 (27.7)	26 (34.7)
ILD, *n* (%)	166 (40.4)	45 (25.0)	74 (47.7)	47 (62.7)
Dysphagia, *n* (%)	97 (23.6)	64 (35.6)	25 (16.1)	8 (10.7)
Skin necrosis, *n* (%)	51 (12.4)	27 (15.0)	21 (13.5)	3 (4.0)
Inflammatory arthropathy, *n* (%)	172 (41.8)	50 (27.8)	76 (49.0)	46 (61.3)
Unintentional weight loss, *n* (%)	69 (16.8)	40 (22.2)	18 (11.6)	11 (14.7)
Family history of cancer, *n* (%)	28 (6.8)	14 (7.7)	10 (6.5)	4 (5.3)
Night sweats, *n* (%)	8 (1.9)	6 (3.3)	1 (0.6)	1 (1.3)
Unexplained fever, *n* (%)	53 (12.9)	15 (8.3)	19 (12.3)	19 (25.3)
ANA, *n* (%)	250 (60.8)	113 (75.3)	94 (60.6)	43 (57.3)
Anti-TIF1g, *n* (%)	31 (7.5)	31 (17.2)	0	0
Anti-NXP2, *n* (%)	14 (3.4)	12 (6.7)	2 (1.3)	0
Anti-MDA5, *n* (%)	17 (4.1)	12 (6.7)	3 (1.9)	2 (1.3)
Anti-SAE, *n* (%)	9 (2.2)	6 (3.3)	2 (1.3)	1 (1.3)
Anti-HMGCR, *n* (%)	8 (1.9)	5 (2.8)	3 (1.9)	0
Anti-Mi2, *n* (%)	26 (6.3)	19 (10.6)	6 (3.9)	1 (1.3)
Anti-SRP, *n* (%)	8 (1.9)	3 (1.7)	5 (3.2)	0
Anti-Jo1, *n* (%)	80 (19.5)	3 (1.7)	45 (29.0)	32 (42.7)
Non-Jo1 ARS, *n* (%)	46 (11.1)	5 (2.8)	19 (12.1)	22 (29.3)
PL-7	15 (3.6)	2 (1.1)	6 (3.9)	7 (9.3)
PL-12	14 (3.4)	2 (1.1)	6 (3.9)	6 (8.0)
EJ	9 (2.2)	0	5 (3.2)	4 (5.3)
OJ	1 (0.2)	0	0	1 (1.3)
KS	3 (0.7)	0	0	3 (4.0)
Zo	4 (1.0)	1 (0.5)	2 (1.2)	1 (1.3)

(continued)

Table 1 (continued)

	All ($n=411$)	High risk ($n=180$)	Intermediate risk ($n=156$)	Standard risk ($n=75$)
Anti-cn1A[a], *n* (%)	4 (1.0)	4 (2.2)	0	0
Multiple MSA positivity, *n* (%)[b]	13 (3.2)	7 (3.9)	3 (1.9)	3 (4.0)
Mi2/SAE1	5	5	0	0
Mi2/NXP2	5	2	3	0
Jo1/KS	1	0	0	1
Jo1/PL-7	2	0	0	2
MAA, *n* (%)	157 (38.2)	50 (27.8)	66 (42.6)	41 (54.7)
Anti-Ro, *n* (%)	117 (28.5)	33 (18.3)	50 (32.3)	34 (45.3)
Anti-Ro52, *n* (%)	65 (15.8)	23 (12.8)	33 (21.3)	9 (12.0)
Anti-Ro60, *n* (%)	1 (0.2)	0	1 (0.6)	0
Anti-Ku, *n* (%)	14 (3.4)	6 (3.3)	7 (4.5)	1 (1.3)
Anti-PM-Scl, *n* (%)	29 (7.1)	12 (6.7)	11 (7.1)	6 (8.0)
Anti-U1-RNP, *n* (%)	10 (2.4)	2 (1.1)	4 (2.6)	4 (5.3)
Persistent high disease activity despite therapy, *n* (%)	91 (22.1)	42 (23.3)	35 (22.6)	14 (18.7)

[a] Data not available for all patients.
[b] Autoantibody with the highest strength is reported as first.
ANA: anti-nuclear antibody; ARS: anti-tRNA-synthetase syndrome; CADM: clinically amyopathic dermatomyositis; DM: dermatomyositis; IBM: inclusion body myositis; IIM-CTD: overlap IIM-connective tissue disease-associated myositis; ILD: interstitial lung disease; IMNM: immune mediated necrotizing myopathy; MAA: myositis-associated antibody; MSA: myositis-specific antibody; PM: polymyositis.

95%CI (1.358; 8.515); $P=0.042$] as independent predictors of cancer (see Table 3).

Comparison of real-life cancer screening practices with IMACS guidelines recommendations

Historical cancer screening modalities from all participating centres were reviewed and compared against the expected screening practices outlined in the IMACS guidelines. Nine patients who developed cancer within the three years preceding their IIM diagnosis were excluded from this evaluation to avoid potential confounding. Significant variability in the screening modalities was observed across risk groups and time points. Basic screening modalities, according to IMACS guidelines [5], demonstrated high and consistent utilization across all risk categories and time points, with adherence rates exceeding 85% (see Supplementary Tables S2, S3 and S4). However, advanced screening methods recommended in the IMACS enhanced panel, such as CT scans, mammography, tumour marker tests (e.g. PSA and CA-125), faecal occult blood testing and ovarian ultrasound were underutilized, particularly in the intermediate-risk group and standard-risk group. For instance, baseline (T0) chest CT scans were performed in 78.5% (135/172) patients in the high-risk group compared with 62.3% (96/155) patients in the intermediate-risk group and 36.0% (27/75) in the standard-risk group. At baseline, mammography was performed more frequently in the high-risk group (50.6%) than in the intermediate-risk (26.6%) and standard-risk groups (4.0%). Similarly, ovarian ultrasound screening was performed in 50.0% (86/172) of high-risk patients at T0, compared with 37.4% (58/155) in the intermediate group and only 5.3% (4/75) in the standard-risk group. Longitudinal adherence to screening decreased over time. Namely, at 1 year (T1) the utilization of ovarian ultrasound declined to 31.8% in the high-risk group and to 18.5% in the intermediate group, while standard-risk patients had negligible screening rates beyond T0. Similarly, we observed a reduction in faecal occult blood testing from 19.8% at T0 to 5.9% at T1 in the high-risk group.

Discussion

To the best of our knowledge, this is the first European multicentric study to assess cancer risk stratification and detection in IIM patients according to the IMACS guidelines. This retrospective analysis also offers valuable insights into clinical practice of five Rheumatology referral centres before the release of recommendations. Applying the IMACS risk stratification model, 43.8% of our patients were classified as high-risk, 37.7% as intermediate-risk and 18.2% as standard-risk malignancy. This predominance of high-risk patients aligns with findings from a Slovenian cohort, where high-risk patients similarly represented the largest proportion, suggesting consistency of the IMACS model across diverse populations [13]. In contrast, the distribution of intermediate- and standard-risk groups differed between cohorts, which may be attributable to variations in the underlying distribution of IIM subtypes.

Real-world screening practices compared with IMACS guidelines

The IMACS guidelines recommend enhanced screening for intermediate-risk and high-risk groups at baseline. If applied to our cohort, enhanced screening would be required at baseline in 81.6% of patients. However, this is in contrast with our historical practice. For instance, in our cohort, baseline chest CT scan was performed in 78.5% of patients in the high-risk group but only in 62.3% of the intermediate-risk and in 36.0% of the standard-risk

Table 2 Differences in the cancer risk profiles between patients with and without cancer in our cohort.

	Cancer within 3 years before and after IIM diagnosis (*n* = 47)	Without cancer at 3 years (*n* = 364)
Death, *n* (%)	8 (17.0)	11 (3)
Median time from diagnosis to death, median (IQR)	0.63 (0.13–6.09)	2.11 (0.71–2.96)
Male, *n* (%)	14 (29.7)	103 (28.3)
Age >40, *n* (%)	46 (97.9)	321 (88.2)
DM, *n* (%)	27 (57.4)	115 (31.6)
PM, *n* (%)	8 (17.0)	71 (89.9)
CADM, *n* (%)	2 (4.2)	17 (4.6)
ARS, *n* (%)	8 (17.0)	118 (32.4)
IMNM, *n* (%)	2 (4.3)	9 (2.5)
IBM, *n* (%)	0 (0)	3 (0.8)
CTD-IIM, *n* (%)	0 (0)	31 (8.5)
Anti-TIF1y, *n* (%)	14 (29.8)	17 (4.7)
Anti-NXP2, *n* (%)	1 (2.1)	13 (3.6)
Anti-SAE1, *n* (%)	3 (6.4)	6 (1.6)
Anti-HMGCR, *n* (%)	1 (2.1)	7 (1.9)
Anti-Mi2, *n* (%)	4 (8.5)	22 (6.0)
Anti-MDA5, *n* (%)	2 (4.3)	15 (4.1)
Anti-SRP, *n* (%)	2 (4.3)	6 (1.6)
Anti-Jo1, *n* (%)	5 (10.6)	74 (20.3)
Non-Jo1 ARS, *n* (%)	1 (2.1)	33 (9.1)
MAA, *n* (%)	15 (53.6)	141 (55.3)
Dysphagia (moderate to severe), *n* (%)	18 (38.3)	79 (21.7)
Cutaneous necrosis, *n* (%)	8 (17.0)	51 (14.0)
High disease activity despite therapy, *n* (%)	18 (38.3)	73 (20.1)
Raynaud phenomenon, *n* (%)	6 (12.8)	97 (26.6)
Inflammatory arthropathy, *n* (%)	16 (34.0)	158 (43.4)
ILD, *n* (%)	11 (23.4)	155 (42.7)
High risk, *n* (%)	31 (66.0)	149 (40.9)
Intermediate risk, *n* (%)	13 (27.7)	143 (39.2)
Standard risk, *n* (%)	3 (6.4)	72 (19.7)

ANA: anti-nuclear antibody; ARS: anti-tRNA-synthetase syndrome; CADM: clinically amyopathic dermatomyositis; DM: dermatomyositis; IBM: inclusion body myositis; IIM-CTD: overlap IIM-connective tissue disease-associated myositis; ILD: interstitial lung disease; IMNM: immune mediated necrotizing myopathy; MAA: myositis-associated antibody; MSA: myositis-specific antibody; PM: polymyositis.

Table 3 Multivariate logistic regression for the prediction of cancer within 3 years of IIM diagnosis.

Variable	OR (Exp(B))	95% CI (Lower–Upper)	*P*-value
Age >40 years	0.666	0.023–19.56	0.814
Male sex (*vs* female)	9.95	1.92–51.57	**0.006**
High disease activity despite therapy	3.401	1.358–8.515	**0.042**
TIF1γ antibody positivity	12.296	2.943–51.374	**<0.001**
SRP antibody positivity	9.014	1.077–75.420	**<0.012**
SAE1 antibody positivity	11.983	1.713–83.839	**<0.012**
Dysphagia (yes *vs* no)	1.05	0.20–5.68	0.952
Constant (intercept)	0.317	0.011–8.995	0.501

CI: confidence interval; OR: odds ratio.
Statistically significant results are in bold.
Model performance: Nagelkerke R^2=0.503; classification accuracy = 81.2%; percentage correctly classified among cancer cases = 86.5%. Multivariate logistic regression model showing independent predictors of cancer within three years after IIM diagnosis. The analysis included demographic (age, sex), clinical (high disease activity, dysphagia) and serological (myositis-specific autoantibodies) variables. Odds ratios (ORs) are presented with 95% confidence intervals (CIs) and associated *P*-values.

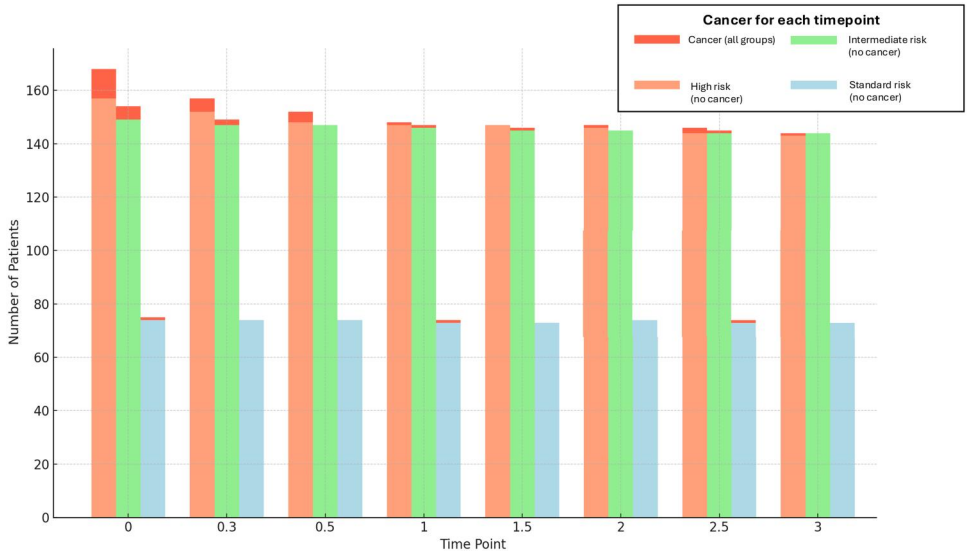


Figure 1 Malignancy risk stratification of patients with Ca-IIM at each time point in different risk groups

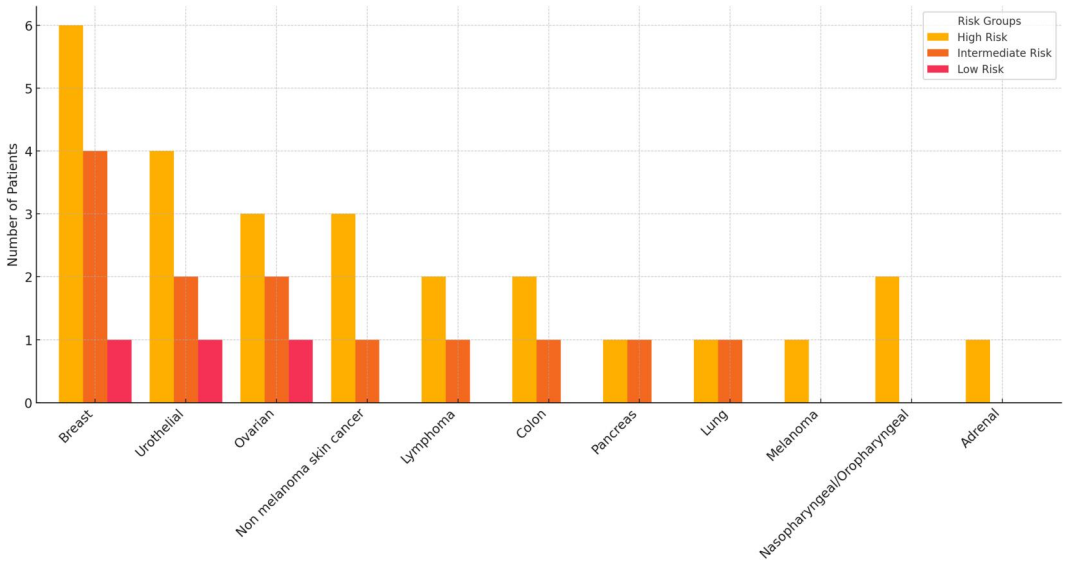


Figure 2 Types of cancer detected in IIM patients in different risk groups according to IMACS guidelines

group. Mammography was performed in 50.6% of high-risk patients at baseline, while it was used in 26.6% of patients at intermediate-risk and 4.0% of patients in the standard-risk group. Less than 20% of patients at high-risk and intermediate-risk received faecal occult blood testing at baseline.

According to the IMACS guidelines, patients in the high-risk group should receive the same basic screening yearly for three years after IIM diagnosis. However, in our cohort chest X-ray was performed in 33.1% of patients, but its use declined significantly over time, being registered in 19.2% at one-year, and in 6.1% at three-year follow-up.

Breast cancer was the most common malignancy in our cohort, supporting the IMACS recommendation for age- and sex-appropriate screening programs. In Italy, routine breast cancer screening targets women aged 50–69, with some regions extending the range to 45–74 years.

Cancer incidence and impact on survival

In our cohort, 38 (9.2%) patients were diagnosed with cancer within 3 years after their IIM diagnosis: most cancers (81.6%) occurred within the first year, as has been observed in previous studies [14]. This prevalence is slightly lower than a Chinese cohort reporting a 15.9% prevalence in 479 patients [15]. Such difference may reflect variations in population-specific cancer risk, healthcare systems or study methodologies, as our cohort primarily comprises patients from Northern Italy.

Patients classified as high-risk in our cohort exhibited a significantly greater likelihood of developing cancer compared with those in the intermediate-risk and standard-risk groups, whereas the risk was similar comparing the last two groups. These findings suggest that, at least in our population, the intermediate-risk category could overestimate cancer risk in some patients.

Another important consideration in interpreting our cancer prevalence data is the impact of mortality during follow-up. Nineteen patients (4.6%) died during the study period, with a median time from diagnosis to death of 1.55 years. Among these deaths, nine (47.4%) were attributed to cancer-related complications and 10 (52.6%) to non-cancer associated death. Notably, there was a marked difference in survival between patient groups: those with cancer had a substantially shorter median survival of 0.63 years compared with 2.11 years for patients without cancer. This difference reflects the impact of malignancy on overall prognosis in the IIM population.

Predictors of cancer development

While taking into account the descriptive and exploratory objective of the multivariate model, the present study confirms anti-TIF1γ positivity as a particularly strong predictor of cancer, emphasizing its role in targeted screening. Conversely, we observed no association with anti-NXP2 positivity, mirroring inconsistencies among the IMACS guidelines and previous results from other cohorts [15–17]. This raises questions about its inclusion as a high-risk factor.

Moreover, anti-SAE1 positivity was associated with a significantly increased risk of cancer; this finding aligns with what was found in validation of IMACS guidelines in the Chinese cohort and is consistent with results from small cohorts of different ethnicities [15, 18, 19]. Despite the scarce numerosity, data on anti-SAE1-positive patients underscores the need for further research.

Regarding anti-SRP positivity, our findings showed a significant association with cancer risk (OR = 9.014, $P = 0.042$), which appears to contradict most current literature suggesting anti-SRP is not typically associated with malignancy risk. However, this finding should be interpreted with caution given the small number of anti-SRP positive patients in our cohort ($n = 8$), which results in wide confidence intervals (95% CI: 1.077–75.420) and reduced statistical power. The apparent association may reflect chance findings due to limited sample size, or potentially unmeasured confounding factors. Further studies with larger numbers of anti-SRP positive patients are needed to clarify this relationship, as our current data are insufficient to establish a definitive association between anti-SRP and cancer risk.

Our study confirms that subgroups such as CTD-IIM or ARS are rarely associated with cancer. Notably, none of the CTD-IIM patients and just eight out of 126 (6.3%) ARS patients developed cancer within three years. These subgroups are characterized by a high prevalence of Raynaud's phenomenon and interstitial lung disease, two clinical features that are less commonly observed in patients with IIM developing cancer. These data are in contrast with studies from Japan reporting a higher malignancy risk in patients with ARS antibodies [20, 21].

Refining risk stratification beyond IMACS

Based on our and previous results, it is evident that to enhance effectiveness and cost-efficiency, prompt and intensive cancer screening at diagnosis and during the first year of follow-up should focus on patients with strong cancer predictors. It is worth noting that anti-SAE1 is classified as an intermediate risk factor in the IMACS guidelines, while in our cohort this autoantibody seems to be associated with high risk of cancer development. Doubts still exist on the role of anti-NXP2 antibody as a cancer predictor as observed in both our cohort and the Chinese cohort.

A 'weighted' stratification approach should be implemented, and the predictive accuracy of these risk factors should be further validated in larger and more diverse cohorts.

Limitations and implications for future research

It is important to acknowledge that, due to the retrospective nature of the study, it was not always possible to determine whether each investigation—particularly imaging studies such as chest CT scans or abdominal ultrasounds—was specifically ordered for cancer screening or for the evaluation of other disease-related manifestations such as interstitial lung disease or systemic involvement. Similarly, in cases where malignancy was identified, it was not consistently possible to ascertain whether the cancer was detected through systematic screening or incidentally during diagnostic work-up for unrelated concerns. This introduces a potential indication bias and may lead to an overestimation of adherence to IMACS guidelines. Nonetheless, our primary objective was not to measure the diagnostic yield of specific screening tools, but rather to descriptively compare historical real-world practices, different for each centre, with the screening patterns recommended by the IMACS stratification model.

Moreover, since the study cohort was predominantly Caucasian and from Northern Italy, this may limit the generalizability of our findings to other populations and ethnicities, with different demographics or environmental risk factors for cancer.

A few methodological considerations also warrant discussion. Even though IMACS guidelines do not mandate specific testing methodologies for antibody detection [5], our autoantibody testing relied primarily on line-blot immunoassays across participating centres, without immunoprecipitation confirmation. To enhance reliability, all autoantibody results were confirmed by at least two separate determinations in the original clinical records, which helps mitigate concerns regarding false-positive results. This consideration, while reflecting a real-world scenario, should be taken into account when interpreting our findings.

Thus, we suggest that IMACS guidelines be further adapted according to local cancer epidemiology, population-specific needs and cancer prevalence.

Nevertheless, the IMACS model represents a significant step forward with respect to the different local clinical practice for cancer screening in IIM patients. Future research should validate the cost-effectiveness and clinical impact of IMACS-recommended screenings in different clinical realities.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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