Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Prevalence, Risk Factors, and Mortality of Invasive Pulmonary Aspergillosis in Patients with Anti-MDA5 + Dermatomyositis: A Retrospective Study in China

Xixia Chen[1], Sang Lin[2], Qiwen Jin[1], Lu Zhang[3], Wei Jiang[3], Xin Lu[3], Guochun Wang[1,3], Yongpeng Ge[3]

[1]Peking University China-Japan Friendship School of Clinical Medicine, Beijing, People's Republic of China; [2]Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, People's Republic of China; [3]Department of Rheumatology, Key Myositis Laboratories, China-Japan Friendship Hospital, Beijing, People's Republic of China

Correspondence: Yongpeng Ge, Department of Rheumatology, China-Japan Friendship Hospital, Yinghua East Road, Chaoyang District, Beijing, 100029, People's Republic of China, Tel +86 13716106183, Email gyp2016@163.com

Objective: To investigate the prevalence, risk factors and prognosis of invasive pulmonary aspergillosis (IPA) in patients with anti-melanoma differentiation-associated gene 5 positive dermatomyositis (anti-MDA5+ DM).

Methods: A retrospective analysis was conducted in anti-MDA5+ DM patients diagnosed between January 2016 and March 2023. Patients with lower respiratory tract specimens were categorized into IPA+ and IPA- groups based on the presence of IPA and their clinical characteristics and prognoses then compared.

Results: Of the 415 patients diagnosed with anti-MDA5+ DM, 28 cases had IPA (prevalence rate of 6.7%) with *Aspergillus fumigatus* being the most common species. The patients were categorized into IPA+ (n=28) and IPA- (n=98) groups, with no significant age or gender-related differences ($P>0.05$). The IPA+ group had a lower lymphocyte count, particularly the CD4+ T-cell count, and reduced serum albumin and higher serum ferritin levels (P all<0.05). An elevated bronchoalveolar lavage fluid (BALF) galactomannan level was found to be the sole independent risk factor for the occurrence of IPA (adjusted OR=2.191, $P=0.029$) with a cut-off value of 0.585 and area under the curve of 0.779. The mortality rate in the IPA+ group was 25%. Compared to survivors, non-survivors in this group exhibited a higher incidence of rapidly progressive interstitial lung disease, lower lymphocyte counts, and increased co-infection with *Pneumocystis jirovecii* (P all<0.05).

Conclusion: IPA was not rare in patients with anti-MDA5+ DM, with elevated BALF galactomannan levels being an independent risk factor for IPA occurrence. Clinicians must exercise vigilance to identify patients exhibiting the aforementioned risk factors.

Keywords: invasive pulmonary aspergillosis, opportunistic infection, anti-MDA5+ dermatomyositis, prevalence, risk factors, prognosis

Introduction

Aspergillus species are ubiquitous fungi that cause a broad spectrum of diseases in humans. One of the most severe forms is invasive aspergillosis, which primarily affects the lungs and is known as invasive pulmonary aspergillosis (IPA).[1] IPA is encountered frequently in individuals with compromised immune systems, particularly those with severe or prolonged neutropenia, deficiencies in cell-mediated immunity, hematologic malignancies, recipients of hematopoietic stem cell or solid organ transplants, and patients undergoing chemotherapy.[2,3] Globally, the number of reported cases of invasive aspergillus is greater than 300,000 annually,[4] with a high mortality rate ranging from 30 to 80%.[5–8] This trend is expected to continue due to the widespread use of immunosuppressants and biologics, which increase the risk of fungal infections.

Anti-melanoma differentiation-associated gene 5 positive dermatomyositis (anti-MDA5+ DM) is a distinct subtype of idiopathic inflammatory myopathy (IIM), with a particularly high prevalence in East Asia. It is characterized by a hallmark rash of dermatomyositis, absent or minimal muscle involvement, and prominent interstitial lung disease

Received: 21 January 2024
Accepted: 8 May 2024
Published: 20 May 2024

(ILD).[9] Recently, the occurrence of opportunistic infections, particularly fungal infections, has been reported to be prevalent in patients with anti-MDA5+ DM, and represents an additional risk factor for mortality in addition to rapidly progressive ILD (RPILD).[10,11] However, the occurrence of IPA in anti-MDA5+ DM remains poorly understood, with only a small number of published studies available on this subject. Baray et al[12] reported a case of an anti-MDA5+ DM patient who developed IPA and experienced rapid progression to respiratory failure, ultimately resulting in death. The absence of large-scale clinical studies has limited the understanding of the diagnosis and treatment of IPA in patients with anti-MDA5+ DM. Therefore, the aim of the current study was to investigate the prevalence, risk factors, and prognosis of IPA in anti-MDA5+ DM patients treated at our center, with the objectives of achieving early identification of high-risk individuals, timely intervention, and enhancement of patient outcomes.

Methods

Study Population

A retrospective analysis was carried out on patients diagnosed with anti-MDA5+ DM between January 2016 and March 2023 at the Rheumatology Department of the China Japan Friendship Hospital. The diagnosis of IIM was based on the Bohan and Peter criteria[13] and subsequently re-validated retrospectively by two experienced rheumatologists, in accordance with either the 2017 EULAR/ACR IIM classification criteria[14] or the 2018 ENMC DM criteria.[15] The myositis-specific antibody (MSA) profile featuring the anti-MDA5 antibody was detected via immunoblotting, according to the manufacturer's instructions (Euroimmun, Lübeck, Germany). Patients with a concurrent presence of positive anti-MDA5 antibodies and other MSA were excluded from the study. Additionally, individuals diagnosed with other connective tissue diseases or those with concurrent malignant tumors were also excluded. The research protocol was granted approval by the Ethics Committee of the China Japan Friendship Hospital (reference number 2022-KY-156), and the study was conducted in accordance with the Declaration of Helsinki, 2000. Considering the retrospective nature of this investigation, patient consent was waived because their privacy was preserved and medical care was not impacted.

Patients who had previously undergone lower respiratory tract specimen examinations, such as deep sputum, bronchoalveolar lavage fluid (BALF), or lung tissue analyses, to diagnose pulmonary fungal infection were selected for subsequent investigation. These patients were classified according to the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria, which included either proven, probable, or possible IPA.[16] "Proven" cases required histopathological or cytopathological confirmation, while "probable" cases required the presence of a host factor usually immune suppression, clinical features such as fever unresponsive to antibacterial treatment, and mycologic detection. Patients who met the criteria for a host factor and had clinical characteristics without mycological evidence were classified as "possible" cases. The diagnostic criteria for aspergillus colonization were based on the proposals of Soontrapa et al[17] that included the following aspects: 1. Pathological study compatible with other causes; 2. No evidence of positive galactomannan (GM) and no compatible imaging; and 3. The patient survived for at least 30 days without antifungal treatment. The IPA-positive (IPA+) group only included cases diagnosed with proven or probable IPA, whereas other cases were categorized as the IPA-negative (IPA-) group.

Clinical Data

All patient-related demographic information, laboratory test results, and details of treatment were documented comprehensively. Laboratory data were acquired concomitantly with the examination of lower respiratory tract specimens, encompassing assessments of neutrophil, lymphocyte, CD4+ T-cell, and CD8+ T-cell counts, as well as the erythrocyte sedimentation rate (ESR) and serum levels of albumin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin. Additional tests were conducted to screen for possible fungal infections, which included serum (1,3)-beta -D-glucan (BDG) level (reference range: < 10 pg/mL), serum GM level (reference range: < 0.5), BALF GM level, tracheoscopy involving the detection of leukoplakia or ulcers on the wall of the airway, and chest imaging that involved the evaluation of ground-glass opacity (GGO), consolidations, cavities, nodules, halo signs, pleural effusion and bronchiectasis.[18] The presence of ILD was assessed by means of chest computed tomography (CT), while RPILD was defined using previously published established criteria.[19]

Comprehensive documentation of the patient's treatment history within the three-month period preceding etiological testing was conducted, which included information on the dose of glucocorticoid (GC) administered on a daily basis (expressed as prednisone equivalents), pulse methylprednisolone therapy (PMT), immunosuppressive agents, and intravenous immunoglobulin (IVIG).

Follow-Up Study

The duration of the follow-up period was determined by measuring the time elapsed from the onset of symptoms to the patient's death or last investigation/visit. All follow-up evaluations were concluded by March 2023, with the date of the last follow-up or death being documented meticulously for each patient. A 12-month interval was chosen as the reference point for survival analysis, with patients whose follow-up duration fell short of 12 months being categorized as censoring values.

Statistical Analysis

The statistical analysis was carried out using IBM SPSS software (version 23.0, Armonk, NY, USA). The data were expressed as mean ± SD, median (interquartile range), or number (percentage) where appropriate. Comparisons between groups were conducted using independent-sample *t*-tests or Mann–Whitney *U*-tests for continuous variables and Chi-square tests or Fisher's exact tests for categorical variables. Logistic regression was performed in the univariate and multivariate analyses to identify risk factors for the occurrence of IPA and to calculate the odds ratios (OR). The optimal cut-off value was determined by receiver operating characteristic (ROC) analysis, with the Kaplan-Meier method with Log rank testing used to evaluate survival differences. For all the analyses, a two-sided p-value < 0.05 was regarded as statistically significant.

Results

Microbiology

Of the 415 patients diagnosed with anti-MDA5+ DM, 28 (2 proven cases and 26 probable cases) were found to have IPA, representing a prevalence rate of 6.7% (Table 1). The distribution of aspergillus species isolated from the respiratory specimens of patients with IPA is shown in Figure S1. The most prevalent aspergillus species identified was *A. fumigatus*,

Table 1 Aspergillus Species Identified from Respiratory Specimens in Patients with Anti-MDA5+ Dermatomyositis

Case No	Sex	Age (Years)	Specimens	Diagnostic Procedure	Aspergillus spp.	Classification
1	M	40	Lung tissue	Histology	*A.flavus*	Proven
2	M	52	Lung tissue	Histology	*A.fumigatus*	Proven
3	M	65	Sputum	Fungal cultures	*A.fumigatus*	Probable
4	F	64	Sputum	Fungal cultures	*A.flavus*	Probable
5	M	45	Sputum	Fungal cultures	*A.terreus*	Probable
6	F	33	BALF	GM	Unrecognized	Probable
7	M	43	BALF	Fungal cultures	*A.flavus*	Probable
8	F	60	BALF	mNGS	*A.fumigatus*	Probable
9	F	37	BALF	mNGS	*A.fumigatus*	Probable
10	M	56	BALF	mNGS	*A.retardis*	Probable
11	M	64	BALF	mNGS	*A.Fischeri*	Probable
12	M	34	BALF	mNGS	*A.nidulans*	Probable
13	M	34	BALF	mNGS	*A.fumigatus*	Probable
14	F	61	BALF	mNGS	*A.flavus*	Probable
15	F	29	BALF	mNGS	*A.fumigatus*	Probable

(*Continued*)

Table 1 (Continued).

Case No	Sex	Age (Years)	Specimens	Diagnostic Procedure	Aspergillus spp.	Classification
16	F	43	BALF	mNGS	*A.tubingensis*	Probable
17	F	43	BALF	mNGS	*A.tubingensis*	Probable
18	M	46	BALF	mNGS	*A.flavus; A.terreus*	Probable
19	M	60	BALF	mNGS	*A.niger*	Probable
20	F	60	BALF	mNGS	*A.flavus*	Probable
21	F	61	BALF	mNGS	*A.versicolor*	Probable
22	F	73	BALF	mNGS	*A.fumigatus*	Probable
23	M	55	BALF	mNGS	*A.terreus*	Probable
24	M	51	BALF	mNGS	*A.fumigatus*	Probable
25	F	60	BALF	mNGS	*A.niger*	Probable
26	F	31	BALF	mNGS	*A.fumigatus*	Probable
27	F	69	BALF	mNGS	*A.fumigatus*	Probable
28	M	46	BALF	mNGS	*A.fumigatus; A.oryzae*	Probable

Abbreviations: BALF, bronchoalveolar lavage fluid; F, female; GM, galactomannan test; M, male; mNGS, metagenomic next-generation sequencing.

accounting for 37.9% of cases, followed by *A. flavus* 20.7%, *A. terreus* 10.3%, and *A. tubinggensis* and *A. niger* at 6.9% each. In addition, *A. versicolor, A. retardis, A. Fischeri, A. nidulans*, and *A. oryzae* were each isolated in only a single patient (3.4%).

Patient Characteristics

Of the 415 patients diagnosed with anti-MDA5+ DM, 126 had a lower respiratory tract specimen examined at our center and were included for further analysis. In the study cohort, 28 patients were classified as the IPA+ group, while the remaining 98 patients did not demonstrate any clinical evidence of IPA and were categorized as the IPA- group. A comprehensive analysis comparing the clinical characteristics of these two groups is summarized in Table 2.

This analysis showed that there were no significant differences in demographic characteristics, comorbidities, clinical symptoms, and treatment regimens between the IPA+ and the IPA- groups. The mean age and gender distribution in the IPA+ group were similar to those of the IPA- group (50.5 ± 12.6 vs 48.1 ± 11.4 years, $P = 0.337$; 50% vs 59.2%, $P = 0.386$, respectively). However, compared to the IPA- group, the IPA+ group had a significant decrease in lymphocyte count,

Table 2 Baseline and Clinical Characteristics of Anti-MDA5+ DM Patients with and without IPA

Variables	IPA+ Group (n = 28)	IPA- Group (n = 98)	P value
Age, mean ± SD, yrs	50.5 ± 12.6	48.1 ± 11.4	0.337
Female, n (%)	14 (50.0)	58 (59.2)	0.386
Smoking history, n (%)	6 (21.4)	17 (17.3)	0.622
Disease course, median (IQR), mth	3.0 (1.3, 6.5)	3.0 (2.0, 6.0)	0.967
Comorbidity, n (%)			
Hypertension	8 (28.6)	17 (17.3)	0.189
Diabetes mellitus	5 (17.9)	7 (7.1)	0.137
Malignancy	0 (0.0)	3 (3.1)	1.000
RPILD	16 (57.1)	60 (61.2)	0.796
Clinical symptoms, n (%)			
Specific rash[a]	27 (96.4)	96 (98.0)	0.533
Cough	17 (60.7)	68 (69.4)	0.388
Dyspnea	14 (50.0)	63 (63.3)	0.206
Chest pain	1 (3.6)	3 (3.1)	1.000
Fever	18 (64.3)	58 (59.2)	0.626

(*Continued*)

Table 2 (Continued).

Variables	IPA+ Group (n = 28)	IPA- Group (n = 98)	P value
Initial laboratory indicators			
Neutrophil count, $\times 10^9$/L	4.7 (3.0, 6.2)	4.1 (2.6, 5.8)	0.259
Lymphocyte count, $\times 10^6$/L	700.0 (417.5, 1002.5)	710.0 (470.0, 960.0)	0.363
CD3+ T-cell count, $\times 10^6$/L	476.0 (211.0, 591.0)[c]	540.0 (376.0, 736.0)[f]	0.044
CD4+ T-cell count, $\times 10^6$/L	249.0 (124.0, 429.0)[c]	339.0 (244.0, 511.0)[f]	0.020
CD8+ T-cell count, $\times 10^6$/L	98.0 (60.0, 214.0)[c]	166.0 (105.0, 229.0)[f]	0.057
Albumin, median (IQR), g/L	32.3 (27.3, 36.3)[d]	35.2 (32.7, 37.3)[g]	0.021
LDH, median (IQR), IU/L	352.0 (257.3, 524.5)	308.5 (264.8, 402.5)	0.252
CRP, median (IQR), mg/dl	0.61 (0.25, 1.92)[e]	0.46 (0.22, 1.13)[h]	0.405
ESR, median (IQR), mm/hr	18.5 (11.5, 37.3)[d]	24.5 (13.8, 37.0)	0.382
FET, median (IQR), ng/mL	1432.3 (688.0, 2752.3)	673.5 (367.2, 1371.4)[i]	0.009
Treatment, 3 months prior to pathogen detection			
Steroid used, n (%)	24 (85.7)	74 (75.5)	0.252
GCs dosage, median (IQR), mg/d	41.3 (7.5, 77.0)	42.3 (3.5, 65.3)	0.662
PMT, n (%)	4 (14.3)	12 (12.2)	0.753
Cumulative time at risk (Prednisone use ≥ 20 mg/d or equivalent GCs), median (IQR), day	16.5 (0.0, 37.5)	16.5 (0.0, 55.8)	0.933
Immunosuppressant used, n (%)	18 (64.3)	60 (61.2)	0.769
CYC	5 (17.9)	17 (17.3)	1.000
CNI	12 (42.9)	36 (36.7)	0.556
MMF	1 (3.6)	4 (4.1)	1.000
JAKi	4 (14.3)	10 (10.2)	0.511
Others[b]	2 (7.1)	8 (8.2)	1.000
Total number of immunosuppressant ≥2, n (%)	7 (25.0)	16 (16.3)	0.295
IVIG, n (%)	18 (64.3)	49 (50.0)	0.182

Notes: [a]Specific rash included Heliotrope rash, Gottron's sign, mechanic's hand and digital tip ulceration. [b]Others refer to hydroxychloroquine, tripterygium wilfordii or tocilizumab. [c]Data available for 27 patients. [d]Data available for 26 patients. [e]Data available for 25 patients. [f]Data available for 95 patients. [g]Data available for 91 patients. [h]Data available for 96 patients. [i]Data available for 97 patients.

Abbreviations: CNI, calcineurin inhibitors; CYC, cyclophosphamide; GCs, glucocorticoids; IVIG, intravenous immunoglobulin; JAKi, Janus kinase inhibitors; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; PMT, pulse methylprednisolone therapy.

particularly the CD4+ T-cell count (249.0 × 10^6/L vs 339.0 × 10^6/L, $P = 0.020$), as well as reduced levels of serum albumin (32.3 vs 35.2 g/L, $P = 0.021$), and an increase serum ferritin levels (1432.3 vs 673.5 ng/mL, $P = 0.009$).

Different Detection methods for IPA Infection

A comparative analysis of the serum levels of BDG and GM, and tracheoscopy findings in patients diagnosed with anti-MDA5 + DM showed no significant variations between the IPA+ and IPA- groups (Table S1). In the IPA+ group, the positive rates of serum BDG and GM levels and the incidence of leukoplakia and ulcers observed by tracheoscopy were very low, with values of 14.3%, 7.1%, 18.2%, and 4.5%, respectively. In contrast, the levels of GM in BALF were significantly higher in the IPA+ group than that measured in the IPA- group (0.75 vs 0.16, $P < 0.001$). In addition, the results of the radiological examinations showed that GGO, consolidation, halo sign, cavity, pleural effusion, and other manifestations were similar between the IPA+ and IPA- groups, with the exception of pulmonary nodules being more frequently observed in the IPA+ group (22.2% vs 6.2%, $P = 0.022$). Representative radiological images are shown in Figure 1.

Risk Factors for IPA Occurrence in Anti-MDA5+ DM

We employed a binary logistic model regression to determine the risk factors associated with the occurrence of IPA (Table S2). Univariate analysis showed that increased levels of serum LDH (OR = 1.003, $P = 0.044$), serum ferritin (OR = 1.000, $P = 0.037$), BALF GM (OR = 2.490, $P = 0.004$), and the presence of pulmonary nodules (OR = 4.333, $P = 0.019$) were significant risk factors for the occurrence of IPA. On the other hand, an increased CD4+ T-cell count (OR = 0.997, $P = 0.034$) and higher serum albumin

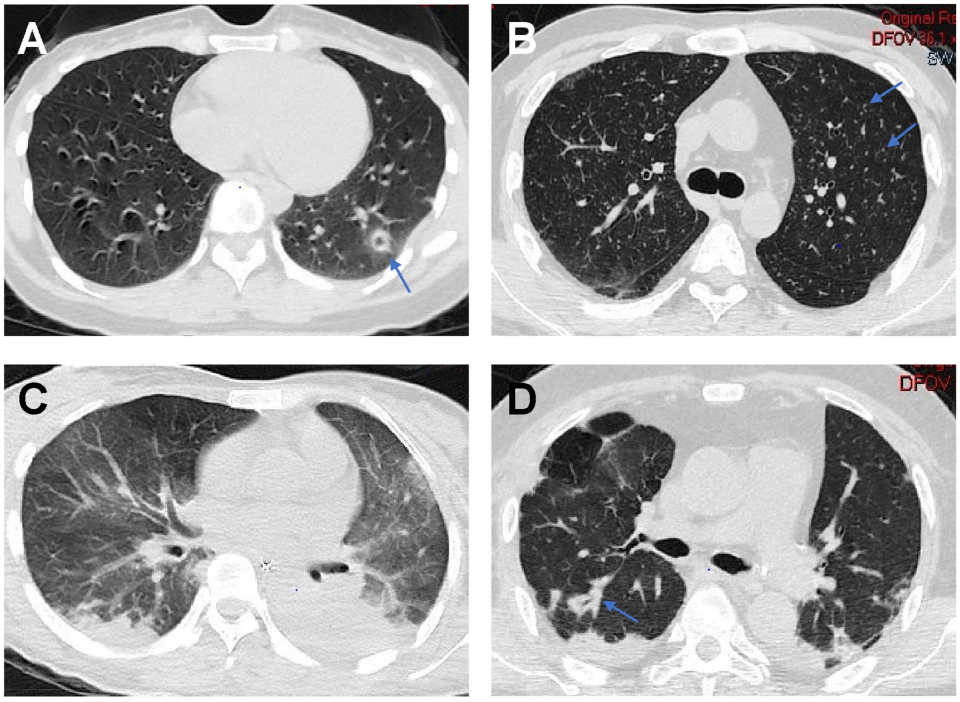

Figure 1 Representative radiological images of anti-MDA5+ DM patients with IPA. (**A**) Axial CT image showing a cavitary lesion in a patient with IPA (arrow). (**B**) Axial CT image of a patient with IPA demonstrating the presence of diffuse micronodules throughout both lungs (arrows). (**C**) A patient diagnosed with IPA with bilateral pulmonary consolidation and diffuse ground-glass opacities. (**D**) A patient diagnosed with IPA with bilateral subpleural and bronchial vascular bundle consolidation (arrow).

level (OR = 0.889, P = 0.018) were shown to be important protective factors. However, multivariate analysis showed that increased BALF GM levels were the sole independent risk factor after adjusting for confounding variables (adjusted OR = 2.191, $P = 0.029$). We then performed a ROC analysis to identify the optimal BALF GM level for detecting IPA and demonstrated the cut-off value was 0.585, with the area under the curve (AUC) being 0.779 (Figure S2). As a consequence, a BALF GM value exceeding 0.585 was considered positive, with a sensitivity and specificity of 60.0% and 87.5%, respectively.

Antifungal Treatments and Outcomes

None of the patients in our study had received prophylactic antifungal therapy prior to their diagnosis of IPA. Instead, voriconazole-based antifungal therapy was initiated immediately upon diagnosis in all the patients. Two patients received caspofungin in combination with voriconazole, while one patient received concurrent administration of amphotericin B and voriconazole.

Regarding prognosis, our study showed a 12-month mortality rate of 25.0% (7/28) in the IPA+ group, which was higher than the 15.3% (15/98) observed in the IPA- group. However, this difference between the two groups was not statistically significant. Further analysis of the clinical characteristics of survivors and non-survivors in the IPA+ group showed that non-survivors had a longer interval between disease onset and IPA diagnosis (4.0 vs 1.0 month, $P = 0.008$), higher incidence of RPILD (100.0% vs 42.9%, $P = 0.010$), lower lymphocyte count (450 $\times 10^6$/L vs 840 $\times 10^6$/L, $P = 0.020$), more co-infections with *Pneumocystis jirovecii* (57.1% vs 14.3%, $P = 0.043$), and a greater number of disease-related complications such as respiratory failure (85.7% vs 33.3%, $P = 0.029$), ICU admissions (57.1% vs 4.8%, $P = 0.008$), and mechanical ventilation (57.1% vs 9.5%, $P = 0.021$) compared to that observed in the survivors (Table 3). The survival curves are shown in Figure 2, with further Supplementary Information available in Table S3.

Discussion

Although the occurrence of IPA in rheumatic diseases has not been studied extensively, its high fatality rate highlights the need for heightened awareness.[20] Our investigations showed that the prevalence of IPA in anti-MDA5+ DM was 6.7%,

Table 3 Comparison of Clinical Characteristics Between Surviving and Non-Surviving Patients with Anti-MDA5+ DM and IPA

Variables	Survivors (n = 21)	Non-Survivors (n = 7)	P value
Age, mean ± SD, yrs	49.1 ± 12.5	54.9 ± 12.8	0.272
Female, n (%)	10 (47.6)	4 (57.1)	1.000
Disease onset to IPA diagnosis, median (IQR), mth	1.0 (1.0, 2.0)	4.0 (2.0, 9.0)	0.008
RPILD, n (%)	9 (42.9)	7 (100.0)	0.010
Initial laboratory indicators			
Lymphocyte count, $\times 10^6$/L	840 (450, 1020)	450 (140, 470)	0.020
CD3+ T-cell count, $\times 10^6$/L	524.0 (348.3, 714.3)[a]	211.0 (112.0, 266.0)	0.009
CD4+ T-cell count, $\times 10^6$/L	315.5 (194.0, 432.0)[a]	124.0 (50.0, 225.0)	0.016
CD8+ T-cell count, $\times 10^6$/L	159.5 (77.0, 277.0)[a]	56.0 (30.0, 78.0)	0.019
LDH, median (IQR), IU/L	323 (238, 395)	527 (386, 847)	0.007
Coinfections, n (%)			
Bacteria	9 (42.9)	3 (42.9)	1.000
PJ	3 (14.3)	4 (57.1)	0.043
CMV	5 (23.8)	0 (0.0)	0.290
Complications, n (%)			
Respiratory failure	7 (33.3)	6 (85.7)	0.029
Mediastinal emphysema	4 (19.0)	1 (14.3)	1.000
ICU admission	1 (4.8)	4 (57.1)	0.008
Mechanical ventilation	2 (9.5)	4 (57.1)	0.021

Note: [a]Data available for 20 patients.
Abbreviations: CMV, *cytomegalovirus*; LDH, lactate dehydrogenase; PJ, *Pneumocystis jirovecii*; RPILD, rapid progressive interstitial lung disease.

with *A. fumigatus* being the predominant aspergillus species. While there were no pathognomonic clinical features observed following IPA infection in anti-MDA5+ DM patients, identifying BALF GM in this subgroup has some potential significance as an independent predictor of IPA. Notably, patients with an established IPA diagnosis and co-occurrence of RPILD, decreased lymphocyte count, or a *Pneumocystis jirovecii* co-infection tended to have worse outcomes. Therefore, early recognition of patients at a higher risk of developing IPA, prompt diagnosis, and timely initiation of antifungal therapy are vital to improve prognosis and ultimately enhance the care of patients with anti-MDA5+ DM.

Individuals with rheumatic diseases exhibit a unique susceptibility to infectious complications, attributable, in part, to inherent immune dysfunction associated with the disease and partially to the administration of immunosuppressive therapies. In our previous investigation, we reported that patients with IIM had an infection frequency of 27.6% and an opportunistic infection rate of 10.4%.[10] Notably, patients with anti-MDA5+ DM, a subtype of IIM, have been shown to be particularly susceptible to diverse infections.[11] However, there are only limited reports on the prevalence of IPA in anti-MDA5+ DM. Our study determined that the prevalence of IPA in patients with anti-MDA5+ DM was 6.7%, roughly equivalent to the incidence observed in patients with hematologic malignancies.[21] Consistent with several published studies,[17,22] we identified *A. fumigatus* as the predominant aspergillus species in anti-MDA5+ DM patients. However, this finding was different from reports in African nations, where *A. flavus* and *A. niger* are the most prevalent aspergillus species.[23] This discrepancy may stem from variations in environmental conditions, geography, climate, and other factors across different regions.

As a consequence of its nonspecific clinical manifestations, IPA presents considerable clinical challenges for early diagnosis in patients with anti-MDA5+ DM. Identification of the risk factors for the occurrence of IPA is therefore crucial. Host factors listed in the EORTC/MSG criteria traditionally serve as classic risk factors for IPA.[16] Emerging research has also identified additional non-classical risk factors such as critical illness, chronic lung disease, biologics, small molecule kinase inhibitors, and viral pneumonia.[3,24] Importantly, patients with anti-MDA5+ DM often exhibit dysregulated immunity in the initial stages of the disease. Our study demonstrated specifically that the IPA+ group had a more substantial reduction in lymphocyte count than the IPA- group, particularly for CD4+ T-cells. Cramer et al confirmed the involvement of CD4+ T-cells

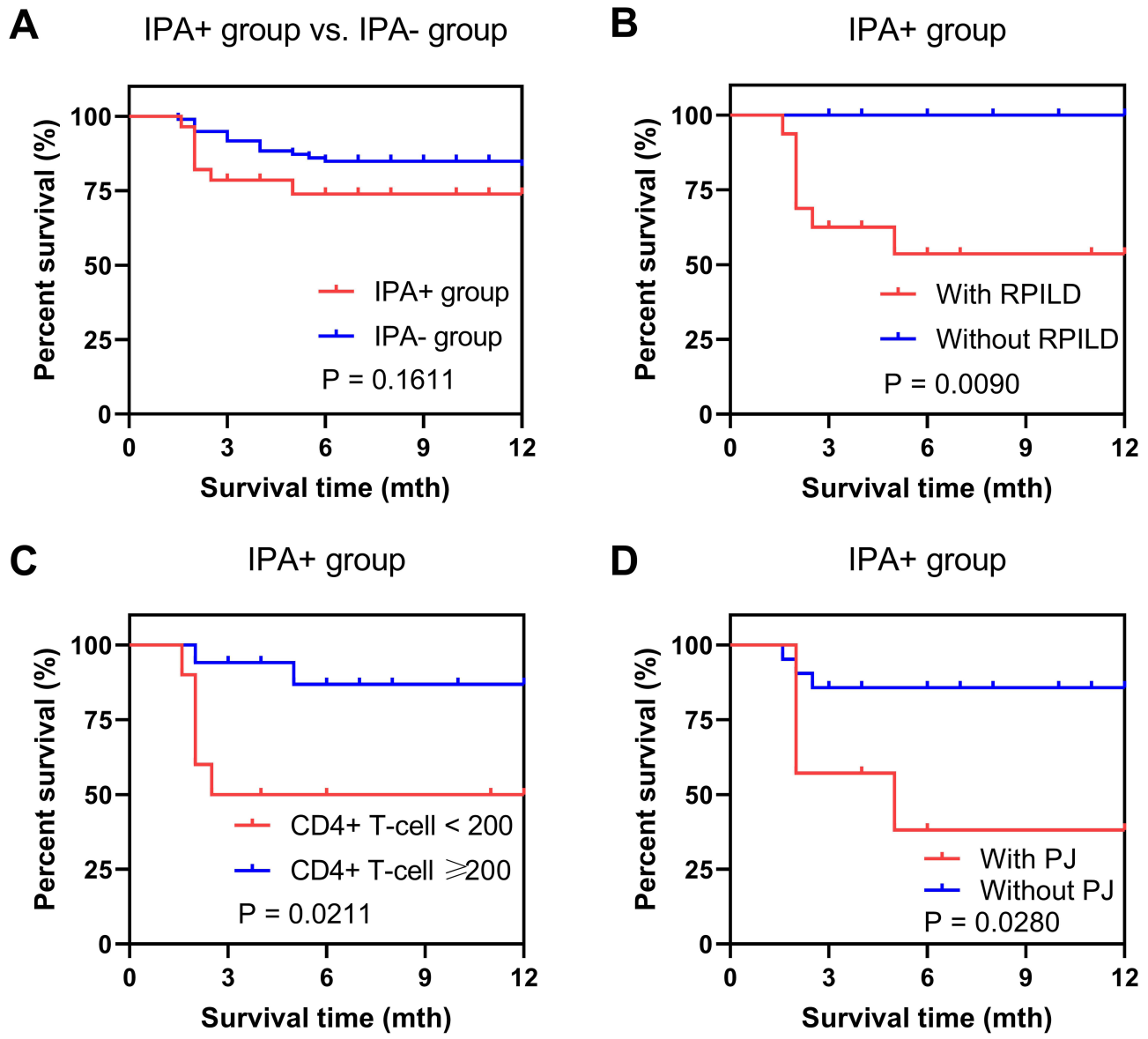

Figure 2 Kaplan-Meier curves of anti-MDA5+ DM patients with and without IPA. (**A**) Patients with IPA had a lower survival rate than those without IPA, although this difference was not statistically significant ($P = 0.1611$). (**B**) Patients with RPILD in the IPA+ group had a significantly lower survival rate than those in the IPA- group ($P = 0.0090$). (**C**) Patients with a CD4+ T-cell count < 200×10^6/L had lower survival rates compared to those with a CD4+ T-cell count ≥ 200×10^6/L ($P = 0.0211$). (**D**) Patients coinfected with *Pneumocystis jirovecii* had lower survival rates compared to those without this infection ($P = 0.0280$).
Abbreviations: RPILD, rapidly progressive interstitial lung disease; PJ, *Pneumocystis jirovecii*.

in the pathogenesis of IPA by demonstrating that fungus-specific CD4+ T-cells had a significant protective effect against IPA.[25] Moreover, Camargo et al proposed that impaired T cell responsiveness and depletion of naive CD4+ T-cells in patients with hematologic malignancies following chemotherapy or hematopoietic stem cell transplantation may be crucial risk factors for the development of IPA.[26] However, the precise pathophysiological mechanisms underlying the role of CD4+ T-cells in defending against IPA remain to be fully elucidated.

The timely identification of patients with suspected IPA is therefore imperative, with reliable non-invasive detection methods playing a pivotal role in achieving this goal. Nevertheless, presently available clinical detection methods have certain limitations. Although serum and BALF GM level are recommended as markers for the diagnosis of IPA,[27] prior investigations have indicated that serum GM levels have a sensitivity range of 41% to 78%, while BALF GM has a higher sensitivity range of 60%-100%.[28] However, our study showed that serum GM level had a low sensitivity in patients with anti-MDA5+ DM, making it unsuitable for IPA screening. Only an increased GM level in BALF qualified

as an independent risk factor for the occurrence of IPA. In addition, tracheoscopy and radiological findings do not have sufficient specificity to identify anti-MDA+ DM patients with IPA. The detection of more pulmonary nodules on chest CT scans we observed in the IPA+ group compared to that in the IPA- group was limited by a low sensitivity, precluding their use in IPA screening, but warranting their use for disease surveillance during follow-up. Therefore, we consider that the development of more accurate, effective, and non-invasive IPA screening methods is imperative.

The predominant therapeutic approach for IPA advocates voriconazole monotherapy as the primary treatment modality, with isavuconazole and posaconazole recommended as alternative options in cases where voriconazole is contraindicated. Liposomal amphotericin is proposed as an alternative regimen for patients receiving mold-active azole therapy or experiencing intolerance to voriconazole. Furthermore, echinocandins are acknowledged as promising choices for second-line or salvage therapy.[29] Despite adherence to standard treatment protocols, our patients continue to exhibit high mortality rates within the IPA+ cohort.[5–8] In the current study, the IPA+ group had a higher 12-month mortality rate (25%) compared to that of the IPA- group (15.3%), although this difference was statistically insignificant. We speculate that this lack of significance may be attributable to the small sample size in our study. Non-survivors in the IPA+ group had a longer interval between disease onset and IPA diagnosis, suggesting the possibility of delayed diagnosis and treatment. Furthermore, non-survivors in this group had a higher prevalence of RPILD, with severe lymphocyte depletion and co-infection with *Pneumocystis jirovecii*. As a consequence, clinicians should exercise utmost caution and closely monitor anti-MDA5+ DM patients who present with these unfavorable prognostic factors, and promptly initiate antifungal therapy and other supportive measures.

This study had several limitations that should be acknowledged. Firstly, the study was a single-center retrospective design, and therefore intrinsic bias could not be avoided completely. Secondly, only patients suspected of having fungal infections underwent fungus-related assessments, potentially leading to an underestimation of the prevalence of IPA in anti-MDA5+ DM patients. Also, the challenge of breaking down fungal cell walls may have exacerbated this underestimation by decreasing the detection rate. Thirdly, as lung tissue biopsy is invasive and challenging to implement widely in anti-MDA5+ DM patients, most patients with IPA were classified as probable rather than proven cases. Finally, although the use of antibiotics may correlate with IPA incidence, we did not analyze this association because of the complex nature of their use in anti-MDA5+ DM patients.

Conclusions

While IPA is not rare in patients with anti-MDA5+ DM, early diagnosis remains a challenge due to the limited clinical specificity of symptoms. For patients suspected of having IPA, detecting GM in BALF is valuable for making a timely diagnosis, as this increase is an independent risk factor for IPA occurrence. Furthermore, co-occurrence of RPILD, decreased lymphocyte counts, and co-infection with *Pneumocystis jirovecii* may serve as potential adverse prognostic factors, with early antifungal therapy in patients with these risk factors possibly improving their prognosis.

Data Sharing Statement

The original contribution presented in the study are included in the article/Supplementary Files, further inquiries can be directed to the corresponding author.

Ethics Approval and Informed Consent

The research protocol was granted approval by the Ethics Committee of the China Japan Friendship Hospital (reference number 2022-KY-156). Considering the retrospective nature of this investigation, patient consent was waived because their privacy was preserved and medical care was not impacted.

Funding

This work was supported by the National High Level Hospital Clinical Research Funding (2022-NHLHCRF-YS-02), and Elite Medical Professionals Project of China-Japan Friendship Hospital (NO. ZRJY2023-GG02).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Godoy MCB, Ferreira Dalla Pria HR, Truong MT, Shroff GS, Marom EM. Invasive fungal pneumonia in immunocompromised patients. *Radiol Clin North Am*. 2022;60(3):497–506. doi:10.1016/j.rcl.2022.01.006
2. Mudrakola HV, Tandon YK, DeMartino E, Tosh PK, Yi ES, Ryu JH. Autopsy study of fatal invasive pulmonary aspergillosis: often undiagnosed premortem. *Respir Med*. 2022;199:106882. doi:10.1016/j.rmed.2022.106882
3. Cadena J, Thompson GR 3rd, Patterson TF. Aspergillosis: epidemiology, diagnosis, and treatment. *Infect Dis Clin North Am*. 2021;35(2):415–434. doi:10.1016/j.idc.2021.03.008
4. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. *J Fungi*. 2017;3 (4):57. doi:10.3390/jof3040057
5. Chen M, Xu Y, Hong N, et al. Epidemiology of fungal infections in China. *Front Med*. 2018;12(1):58–75. doi:10.1007/s11684-017-0601-0
6. Pagano L, Girmenia C, Mele L, et al. Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA Infection Program. *Haematologica*. 2001;86(8):862–870.
7. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine*. 2000;79(4):250–260. doi:10.1097/00005792-200007000-00006
8. Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis*. 2010;50 (12):1559–1567. doi:10.1086/652768
9. Wu W, Guo L, Fu Y, et al. Interstitial lung disease in anti-MDA5 positive dermatomyositis. *Clin Rev Allergy Immunol*. 2021;60(2):293–304. doi:10.1007/s12016-020-08822-5
10. Ge YP, Shu XM, He LR, Wang GC, Lu X. Infection is not rare in patients with idiopathic inflammatory myopathies. *Clin Exp Rheumatol*. 2022;40 (2):254–259. doi:10.55563/clinexprheumatol/yps7ai
11. Chen X, Shu X, He L, et al. High prevalence and mortality of Pneumocystis jirovecii pneumonia in anti-MDA5 antibody-positive dermatomyositis. *Rheumatology*. 2023;62(10):3302–3309. doi:10.1093/rheumatology/kead063
12. Baray M, Wopperer S, Varipapa R, Lazarous D. A case of fatal invasive pulmonary aspergillosis in a patient with anti-MDA5 dermatomyositis. *Chest*. 2021;160(4):340A–340A. doi:10.1016/j.chest.2021.07.342
13. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292(7):344–347. doi:10.1056/nejm197502132920706
14. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017;76(12):1955–1964. doi:10.1136/annrheumdis-2017-211468
15. Mammen AL, Allenbach Y, Stenzel W, Benveniste O. 239th ENMC International Workshop: classification of dermatomyositis, Amsterdam, the Netherlands, 14–16 December 2018. *Neuromuscul Disord*. 2020;30(1):70–92. doi:10.1016/j.nmd.2019.10.005
16. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46(12):1813–1821. doi:10.1086/588660
17. Soontrapa P, Chongtrakool P, Chayakulkeeree M. Characteristics and outcomes of patients with invasive pulmonary aspergillosis and respiratory tract aspergillus colonization from a Tertiary University Hospital in Thailand. *J Fungi*. 2022;8(4):344. doi:10.3390/jof8040344
18. Marom EM, Kontoyiannis DP. Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients. *Curr Opin Infect Dis*. 2011;24(4):309–314. doi:10.1097/QCO.0b013e328348b2e1
19. Won Huh J, Soon Kim D, Keun Lee C, et al. Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. *Respir Med*. 2007;101(8):1761–1769. doi:10.1016/j.rmed.2007.02.017
20. Di Franco M, Lucchino B, Spaziante M, Iannuccelli C, Valesini G, Iaiani G. Lung infections in systemic rheumatic disease: focus on opportunistic infections. *Int J Mol Sci*. 2017;18(2):293. doi:10.3390/ijms18020293
21. Lestrade PP, van der Velden W, Bouwman F, et al. Epidemiology of invasive aspergillosis and triazole-resistant Aspergillus fumigatus in patients with haematological malignancies: a single-centre retrospective cohort study. *J Antimicrob Chemother*. 2018;73(5):1389–1394. doi:10.1093/jac/dkx527
22. Apostolopoulou A, Esquer Garrigos Z, Vijayvargiya P, Lerner AH, Farmakiotis D. Invasive pulmonary aspergillosis in patients with SARS-CoV-2 infection: a systematic review of the literature. *Diagnostics*. 2020;10(10):807. doi:10.3390/diagnostics10100807
23. Yerbanga IW, Nakanabo Diallo S, Rouamba T, et al. A systematic review of epidemiology, risk factors, diagnosis, antifungal resistance, and management of invasive aspergillosis in Africa. *J Mycol Med*. 2022;33(1):101328. doi:10.1016/j.mycmed.2022.101328
24. Moldoveanu B, Gearhart AM, Jalil BA, Saad M, Guardiola JJ. Pulmonary aspergillosis: spectrum of disease. *Am J Med Sci*. 2021;361(4):411–419. doi:10.1016/j.amjms.2020.12.009
25. Cramer RA, Rivera A, Hohl TM. Immune responses against Aspergillus fumigatus: what have we learned? *Curr Opin Infect Dis*. 2011;24 (4):315–322. doi:10.1097/QCO.0b013e328348b159
26. Camargo JF, Bhimji A, Kumar D, et al. Impaired T cell responsiveness to interleukin-6 in hematological patients with invasive aspergillosis. *PLoS One*. 2015;10(4):e0123171. doi:10.1371/journal.pone.0123171
27. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018;24(Suppl 1):e1–e38. doi:10.1016/j.cmi.2018.01.002
28. Zhou W, Li H, Zhang Y, et al. Diagnostic value of galactomannan antigen test in serum and bronchoalveolar lavage fluid samples from patients with nonneutropenic invasive pulmonary aspergillosis. *J Clin Microbiol*. 2017;55(7):2153–2161. doi:10.1128/jcm.00345-17
29. Douglas AP, Smibert OC, Bajel A, et al. Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021. *Intern Med J*. 2021;51(Suppl 7):143–176. doi:10.1111/imj.15591