High Incidence and Mortality of Pneumocystis Jiroveci Infection in Anti-MDA5-Antibody Positive Dermatomyositis: Experience From a Single Center

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Research article

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Abstract

Background

Idiopathic inflammatory myopathies (IIM) was associated with a significantly higher risk of opportunistic infections that including Pneumocystis jiroveci pneumonia (PJP), a potentially fatal opportunistic infection. However, no prior studies have evaluated the PJP infection in subtypes of IIM.

Objectives

To investigate the incidence rate and mortality rate of PJP infection in subgroups of Idiopathic inflammatory myopathies (IIM) patients according to myopathy specific antibodies.

Methods

In the first part, 463 consecutive patients with IIM were prospectively followed up for a period of at least one year to analyze incidence of PJP. In the next part, we enrolled 30 consecutive PJP patients with any rheumatic disease were to identify the mortality rate and risk factors by Cox regression. Kaplan-Meier curve with log-rank test was used to access differences in survival.

Results

We found that the incidence rate of PJP in IIM patients is 3.0/100 person-year, while in MDA5^{+}DM patients is 7.5/100 person-year and in MDA5^{-}IIM patients is 0.7/100 person-year. ($P < 0.05$). PJP typically happened in the first two months for MDA5 + DM patients who have a significant decrease in the CD4^{+} T cell counts and Lymphocyte counts ($P < 0.05$). In PJP + patients, the mortality was lethally higher in MDA5^{+}DM patients than those with other rheumatic diseases (83.3% VS. 38.9%, $P < 0.05$). Unlike patients with other rheumatic diseases, MDA5 + patients seemed not to benefit from prompt anti-PJP treatment. For patients with other rheumatic diseases, anti-PJP treatment within 6 days was confirmed to crucially increased the survival ($P < 0.05$).

Conclusion

PJP has alarming high incidence and mortality in MDA5^{+}DM patients. Timely treatment for PJP does not improve the prognosis of this particular subtype. Therefore, the necessity of further study of PJP prophylaxis treatment in MDA5^{+}DM patients is verified.

Key Messages

1. The incidence of PJP in IIM patients has significant MDA5$^+$subtype preference.
2. The mortality of PJP with MDA5$^+$DM is lethally higher than that with other rheumatic diseases.
3. Timely-anti-PJP-treatment can significantly improve the prognosis of PJP in other rheumatic disease yet has no benefit on the prognosis of MDA5$^+$DM patients.
4. Our data suggest the necessity of further study of PJP prophylaxis treatment in MDA5$^+$DM patients, especially in the first three months treatment or in the situation of patients' CD4$^+$ T cell count < 200 cells.

Introduction

Patients with rheumatic diseases receiving intensive immunosuppression therapy, who are immunocompromised individuals, are often associated with opportunistic infections.[1] The risk of opportunistic infection was highest for dermatomyositis/polymyositis, followed by Systemic Lupus Erythematosus, systemic sclerosis, rheumatoid arthritis, and primary Sjogren's Syndrome[2]Pneumocystis jirovecii pneumonia(PJP) is a rare but potentially life-threatening opportunistic infection with a 30–60% mortality rate among immunocompromised (non-HIV) patients[3][4] In patients with rheumatic immune diseases, most PJP occurs in the first 3 months after the use of immunosuppressants.[2][5].

Idiopathic inflammatory myopathy (IIM) is a group of autoimmune diseases characterized by myasthenia and typical skin rash, among which polymyositis (PM) and dermatomyositis (DM) are the most common. Myositis-specific antibodies have long been identified and their value for stratifying patients with different outcomes has been recognized. There are few reports on PJP in IIM subtypes. A recent study identified anti-melanoma differentiation associated gene 5 antibody (anti-MDA5) as the only myositis-specific antibody that associated with PJP in a multicenter juvenile DM cohort. [6]

Unfortunately, MDA5$^+$DM is one of the subtypes with poor prognosis, which is mainly characterized by progressive interstitial lung disease, with or without muscle damage [7]. For adult MDA5 + patients, there is only a report on two PJP + cases who are dead. [8] The mortality of PJP in these patients are still unknown. Therefore, in this study, we first investigated the incidence of PJP in IIM patients with or without anti-MDA5, then we analyzed the outcomes of anti-PJP treatment and mortality risk factors of PJP infection in rheumatic diseases.

Patients And Methods

Patients

In first part, we evaluated PJP incidence in an IIM cohort. All adult IIM patients clinically diagnosed fulfilling the 1997 classification criteria[9] were prospectively observed from May 2017 to January 2020 at department of Rheumatology, Renji Hospital, China. Patients were screened for myositis myositis-specific antibodies and myositis associated antibodies using a commercial immunoblot assay with 16

autoantigens. Baseline characteristics of patients in hospital, including demographic, clinical and laboratory data, were acquired from the Electronic Medical Record. Follow-up data were collected until January 2021.The occurrence of PJP was evaluated in these patients.

In the second part, anti-PJP treatment outcomes were evaluated in all PJP patients with rheumatic diseases. 30 adult PJP patients with rheumatic diseases were recruited in a consecutive cohort study from May 2017 to January 2020 at department of Rheumatology, Renji Hospital, China, once the diagnosis of PJP was confirmed. Baseline characteristics of patients including demographic, clinical and laboratory data, were acquired at patients first admission in hospital. Follow-up data were collected a period of at least 3 months. The cumulative survival rates at 3-month were evaluated. Written informed consent was obtained from each study participant. The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Renji Hospital, Shanghai, China. (ID: 2013-126)

The diagnosis of PJP

The diagnosis of PJP was based on comprehensive evaluation by clinical manifestations such as fever or acute dyspnea, characteristic radiographic findings, and etiology evidence data. A confirmed case needed to have positive microbiological tests such as next generation of sequencing and Grocott-Gomori methenamine-silver staining of bronchoalveolar lavage fluid. A probable case who had typical manifestations but failed to get etiology evidence needed confirmation by two infection specialists.However, a positive sequencing of PJP result while in the absence of clinical manifestations was not considered as PJP case.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 software package (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0(GraphPad Software). We used chi-square test or Fisher's exact test to compare the categorical variables and Student’s t test or the Mann-Whitney U test was applied to compare continuous variables. Cox proportional hazards regression was performed as multivariable analysis to identify independent risk factors for death and calculate their hazard ratios. The optimal cut-off value was determined by using receiver operating characteristic (ROC) analysis and Kaplan-Meier curve with log rank test was employed to access difference in survival. For all analysis, the two-tailed p-values less than 0.05 was considered statistically significant.

Results

PJP incidence analysis in IIM cohort

14 PJP patients was found in IIM cohort (n=463) after one-year follow-up. All IIM patients was divided by PJP+ group and PJP- group to compare the risk factors of PJP infection. (table 1) We found that anti-MDA5+ is a risk factors for PJP infection in IIM (85.7% VS. 33.0%, P<0.0001), We calculated the incidence rate of PJP in IIM cohort is 3.0/100 person-year, while in $MDA5^{+}$DM patients is 7.5/100 person-year and in

MDA5$^-$IIM patients is 0.7/100 person-year. (Figure 1 7.5% VS. 0.7%, P<0.00001) Besides that, factors like shorter median course (2 months VS. 6 months); interstitial lung (92.9% VS. 70.4%); complicated with diabetes (42.9% VS. 13.6%); higher prednisone exposure (50mg VS. 30mg), and laboratory examination differences such as higher erythrocyte sedimentation rate and ferritin, lower serum albumin, CD4$^+$T lymphocytes counts, and lymphocytes (P < 0.05) may also contribute to PJP occurrence as well. In consideration that some of the factors mentioned above are characteristics of MDA5$^+$DM, we further divided MDA5$^+$DM patients into PJP+ group and PJP- group to confirm PJP infection factors. The Supplementary table S1(online) shows that PJP occurred in a median time of 2 months and with obvious decrease of CD4$^+$ T cell counts and lymphocytes, which suggests that we may need to be on guard against the occurrence of PJP for MDA5$^+$DM patients in the first 2 months of the disease or in the time when lymphocytopenia occur or CD4$^+$ T cell counts decreases.

PJP+ cohort with rheumatic diseases

To evaluate the impact of anti-MDA5 (+) phenotype on mortality of PJP, we further analyzed all PJP+ patients (n=30) admitted into our medical center during the same period of the IIM cohort. The clinical features between MDA5$^+$DM and other rheumatic disease were compared in Supplementary table S2(online), more details of 30 PJP+ patients in Supplementary table S3(online).

As shown in Figure 2A, The MDA5$^+$DM (12, 39.60%) constituted the largest part of PJP+ patients, followed by Systemic Lupus Erythematosus (7, 22.70%), MDA5$^-$IIM (2, 6.93%), ANCA associated vasculitis (AAV; 2, 6.93%), and Adult-Onset Still's disease (AOSD; 2, 6.93%), primary Sjogren's Syndrome (pSS; 2, 6.93%), Undifferentiated connective tissue disease (UCTD; 2, 6.93%) and rheumatoid arthritis (RA; 1, 2.97%). The heatmap Figure 2B shows the rheumatic disease duration when PJP infection occurred. For IIM, AAV, AOSD patients, PJP infection most happened within 6 months of disease duration; while a little unexpectedly for SLE patients, PJP seemed to occur at any stage of disease in this cohort.

PJP mortality analysis in PJP cohort

The mortality of anti-MDA5-ab-positive was lethally higher than that of other rheumatic diseases (83.3% versus 38.9% P=0.016) as shown in Figure 2C and D. For 3-month-mortality risk factors, we identified age, CD4$^+$ T cell counts and MDA5$^+$DM with p values less than 0.10 in univariate analysis and then put the three factors in the cox regression model. It turned out that MDA5$^+$DM and CD4$^+$ T cell counts were identified as independent risk factors for death by multivariate analysis. Notably in these two, though as traditional PJP mortality factor [10], CD4$^+$ T cell counts only had hazard ratio of 0.994 (95% CI 0.989-1.000) while MDA5$^+$DM had HR of 3.254 (95% CI 1.209-8.756). (Table 2)

Besides baseline risk factors, prompt anti-PJP treatment is critical for patient survival. It has been long noticed that early diagnosis and early treatment can improve the prognosis of PJP patients [11][12]. We try to find the period-limitation for PJP-treatment by ROC curve analysis, but the cut-off valve of was not statistically significant (Supplementary figureS1A, P=0.0983, cut-off valve=7days). When we further

stratified all the patients by anti-MDA5, a similar ROC curve as previous reports showed in patients with rheumatic diseases other than MDA5$^+$DM. The time-to-PJP-treatment cut-off point of 6 days showed 85.7% sensitivity and 63.6% specificity, and with the Area Under Curve (AUC) 81.2% base on ROC curve. The time of six-day was the optimal cut-off point for timely treatment for PJP (Supplementary figureS1B, P=0.0297). However, in MDA5$^+$DM patients, the ROC curve did not show at all (Figure S1C). We then analyzed patient survival to confirm the cut-off value. Consistent with previous reports, patient with other rheumatic disease tended to have better survival if they received anti-PJP treatment within 6 days after initial symptoms (Figure 3A, 1-year survival rate: 87.5% VS. 40%, P=0.057); while in MDA5$^+$DM patients this phenomenon did not appear at all (Figure 3B, P=0.327). Timely-anti-PJP-treatment did not benefit the survival of MDA5$^+$DM patients in our center.

Discussion

Though early in 1996, a previous research reported that the prevalence of PJP in Systemic Lupus Erythematosus patients is 1.7%, while in DM patients is 37.5%, based on a small cohort. (n = 75)[13]. Our study is the first time to report the incidence of PJP in MDA5$^+$DM patients in an independent and the largest cohort study so far. Among rheumatic diseases, IIM has been noticed to have the highest PJP infection risk. Our data for the first time describe the different incidence of PJP between anti-MDA5 positive and negative IIM patients. The incidence rate of MDA5$^+$DM patients is up to 7.5/100 person-year in our cohort. Cockland review recommends prophylactic treatment should be taken when the risk of PJP infection in non-HIV Immunocompromised people is greater than 6.2/100 person-year. [14]

The reason why MDA5$^+$DM is easy to be infected by Pneumocystis carshi is still unknown. According to previous reports, high risk factors for rheumatic disease complicated with PJP included granulomatosis with polyangiitis, microscopic polyangiitis, autoimmune interstitial pneumonia, high-dose glucocorticoid, cyclophosphamide [15] high-dose methotrexate, elderly, diabetes, nutritional deficiency, severe lymphocytopenia or low CD4 T cell count patients [16][17]. Our study shows that CD4$^+$ T cell counts at admission, Lymphocyte counts at admission, the lowest lymphocyte count during hospitalization and rheumatic disease duration is significantly lower in 160 cases of MDA5$^+$DM than 303 cases of MDA5- IIM (Supplementary tableS4). These findings indicate us to pay more attention to PJP in MDA5 + DM patients, especially in the first three months of disease duration, or in the situation of patients' CD4 T cell count < 200 cells.

Further, our study first reported the 3-month mortality rate of MDA5$^+$DM patients was as high as 83.3% (all patients die in single hospitalization). MDA5$^+$DM and CD4$^+$ T cell counts were identified as independent risk factors for death by multivariate analysis in our study. Since baseline lung involvement has been noticed as a possible factor leading to the progression of fatal interstitial pneumonia in RA patients when infected by pneumocystis jiroi [18], we speculate that the extremely high prevalence of ILD in MDA5$^+$DM patients may contribute the high mortality after pneumocystis jiroi infection. For CD4$^+$ T

cytopenia, a recent report by Freiwald et al supported that CD4 $^{+}$ T cell lymphopenia can predict mortality in kidney transplant patients with PJP. [19]

Our study first found that timely PJP treatment could not improve the prognosis as other rheumatic diseases complicated with PJP. The risk of death is increased significantly once MDA5^{+}DM patient with PJP infection. It is very important to take measures to deal with such a dangerous disease, in which prophylaxis against PJP may be a good method. [20] It is proved that prophylaxis against PJP for rheumatic patients can significantly reduce the incidence of PJP without severe adverse event. [21] The prophylaxis rate was only 4%(n = 19) patients at admission in our IIM cohort, and merely 43(9.3%) patients had taken continuous anti-PJP prophylaxis since the treatment for IIM in our hospital. There is no recommendation for PJP management in MDA5^{+}DM patients. The data suggest the necessity of further study of PJP prophylaxis treatment in MDA5^{+}DM patients who may need a routine prophylaxis.

The limitations of this study include were shown as following. First, the study of evaluating PJP occurrence in IIM was an observation study, a limitation inherent to observational studies; Second, the number of PCP cases in this study was rather small so we could not perform independent PJP occurrence factors in IIM or MDA5^{+}DM. Third, the number of patients who take a PJP prophylactic treatment is too small for us to assess the prophylactic effect of trimethoprim-sulfamethoxazole in MDA5^{+}DM patients. there may need a randomized controlled study to compare the prophylactic effect and the prevalence of adverse events.

Conclusions

In conclusion, we show here that MDA5^{+}DM patient is easy to be infected by pneumocystis jiroi which is hard to be cured than other background rheumatic disease. The reason related to the higher incidence and mortality may be associated with MDA5^{+}DM which characterized by lower CD4 T cell counts and progressive interstitial lung disease. The data suggests the necessity of further study of PJP prophylaxis treatment in MDA5^{+}DM patients.

List Of Abbreviations

Abbreviation	Full name
MDA5+ DM	anti-melanoma differentiation associated gene 5 antibodies positive dermatomyositis
MDA5-IIM	anti-melanoma differentiation associated gene 5 antibodies negative Idiopathic inflammatory myopathy
PJP	pneumocystis jiroveci pneumonia
IIM	Idiopathic inflammatory myopathy
PM	polymyositis
TMP-SMX	trimethoprim/sulfamethoxazole

Declarations

Ethics approval and consent to participate

The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Renji Hospital, Shanghai, China.(2013-216).

Consent for publication

No individual person's data were presented in any form in this study, and therefore, no consent to publish is required.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files]

Competing interests: The authors declare that they have no competing interests

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Authors' contributions

All authors discussed the results and contributed to the final manuscript. The authors read and approved the final manuscript.

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Tables

Table 1 Comparison of risk factors in PJP and non-PJP cases for IIM patients

	PJP (n=14)	Non-PJP (n=449)	P value
MDA5^{+}DM, n(%)	12(85.7%)	148(33.0%)	0.000
Non-MDA5 IIM, n(%)	2(14.3%)	301(67.0%)	
male gender, n(%)	6(42.9%)	135(30.1%)	0.376
assess age, mean ± SD	54±10	53±12	0.635
Disease duration, year, median	2	6	0.001
ILD(%)	13(92.9%)	316(70.4%)	0.077
Medications three month before PCP infection, n (%)			
Corticosteroid (≥20mg pred≥1month)	10(71.4%)	226(50.4%)	0.12
Corticosteroid, mg, median	50	30	0.001
Cyclophosphamide	1(7.1%)	39(87.1%)	1.000
Methotrexate	0(0%)	43(9.6%)	0.630
Azathioprine	0(0%)	35(7.8%)	0.614
Cyclosporine	5(35.7%)	73(16.3%)	0.069
Tacrolimus	4(28.6%)	55(12.2%)	0.089
Mycophenolate Mofetil	1(7.1%)	28(6.2%)	0.601
hydroxychloroquine	5(35.7%)	104(23.2%)	0.334
Biologics	1(7.1%)	16(3.6%)	0.412
Others	1(7.1%)	83(18.5%)	0.482
Diabetes, n (%)	6(42.9%)	61(13.6%)	0.009
ESR, mm/h, median	34.5	21	0.085
CK, U/L, median	26.5	67.5	0.02
LDH, U/L, median	464.5	321	0.028
Ferritin, ug/ml,median	1122	341	0.001
Pre-albumin, g/L,median	208.5	214	0.832
Albumin, mg/L,median	29.4	32.5	0.005
CD4^{+} T cell counts at admission x10^9/L,median	113.4	350.4	0.000
Lymphocyte counts at admission x10^9/L,median	0.695	0.9	0.004

The lowest lymphocyte count x10^9/L,median during hospitalization	0.39	0.81	0.000

Table 2 Risk factors for 3-month mortality of PJP with rheumatic disease

	Univariable		Multivariable	
Clinical factors	HR(95%CI)	P value	HR(95%CI)	P value
Assessed age	0.981(0.951-1.012)	0.225	0.975(0.940-1.010)	0.158
Gender	0.437(0.207-0.923)	0.798	*	*
$MDA5^{+}DM$	2.830(1.067-7.505)	0.037	3.254(1.209-8.756)	0.02
AAV	0.674(0.089,5.099)	0.702	*	*
SLE	1.062(0.346,3.265)	0.916	*	*
$CD4^{+}$ T cell counts	0.995(0.989-1.001)	0.083	0.994(0.989-1.000)	0.04
lymphocyte counts	0.142(0.025-0.808)	0.028	*	*
Interstitial lung disease	1.537(0.540-4.375)	0.421	*	*
Steroid dose	0.291(0.063,1.350)	0.115	*	*
Cyclophosphamide	1.807(0.586,5.568)	0.303	*	*
Rituximab	0.854(0.113,6.450)	0.878	*	*
Time to anti-PJP treatment	1.577(0.607-4.099)	0.35	*	*

CI, confidence interval;

*Not included in the multivariable model due to lack of significant association in the univariable analysis;

Figures

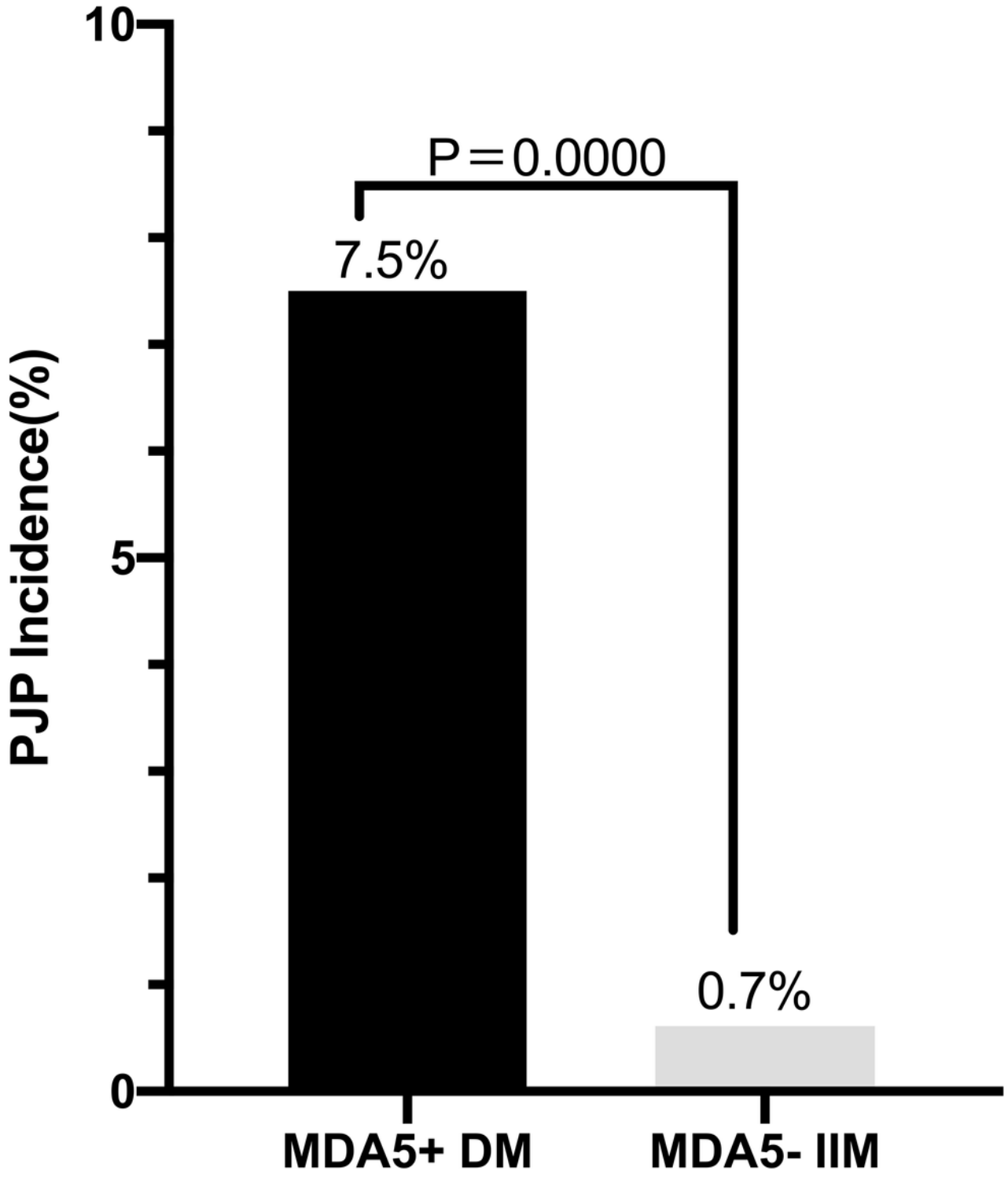

Figure 1

1-year PJP incidence rate

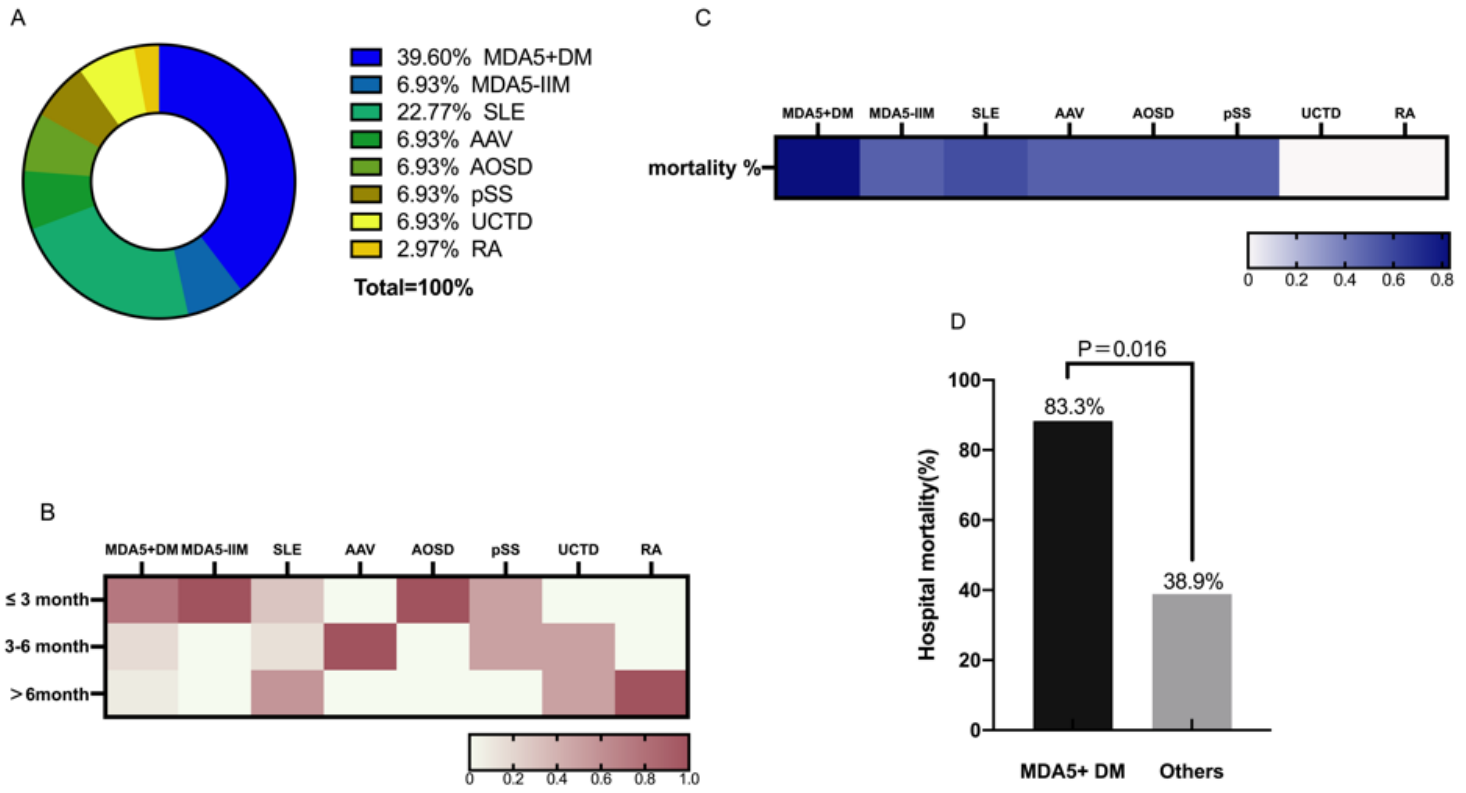

Figure 2

The risk of PJP infection and mortality in PJP cohort consists of all PJP patients with Rheumatic disease

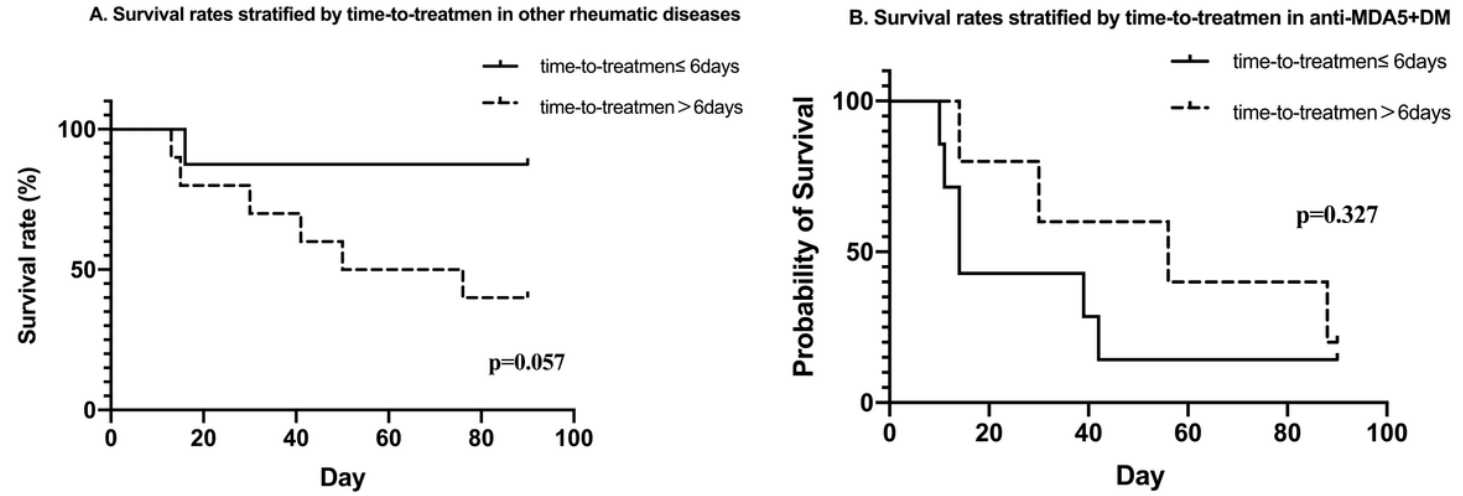

Figure 3

Survival rates stratified by time-to-anti-PJP-treatment in PJP patients

Supplementary Files

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