Supplemental Methods

Exclusion Criteria and recruitment of healthy control

Patients with malignancy, infection, drug-induced vasculitis, secondary vasculitis, vasculitis mimics, and sarcoidosis were excluded from this study [1]. Patients with microscopic polyangiitis (MPA) who were treated with glucocorticoids at the time of admission were also excluded. For healthy controls, subjects (n = 10) who self-identified themselves to be in good health, with no history of autoimmune or cardiovascular diseases, were recruited based on their responses to a questionnaire.

Measurement of laboratory parameters

Patient demographic characteristics (age, sex), the period from appearance of respiratory symptoms to start of treatments, and the contents of treatments were evaluated. White blood cell counts, albumin, creatinine, C-reactive protein, Krebs von den Lungen-6 (KL-6), Surfactant protein D (SP-D), myeloperoxidase (MPO)- anti-neutrophil cytoplasmic antibody (ANCA), and proteinase 3 (PR3)-ANCA were measured. The serum level of KL-6 was measured using an electrochemiluminescence immune assay, whereas serum SP-D was measured using enzyme immunoassays. The serum MPO-ANCA and PR3-ANCA titers were measured using ELISA. These assays

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were commercially conducted by SRL (Tokyo, Japan).

Pulmonary function testing

Pulmonary function testing (PFT) was conducted by spirometry (SYSTEM21; Minato Medical Science, Osaka, Japan) on admission. Forced vital capacity was determined by the N2 washout method, and diffusion capacity of the lung for carbon monoxide was determined by the single-breath method [2, 3, 4]. All PFT results are expressed as percentages of the predicted value.

Evaluation of high-resolution computed tomography scoring

Interstitial lung disease was assessed by chest high-resolution computed tomography (HRCT) scans that were assessed by pulmonary radiologists. Prior to treatment, all patients underwent chest HRCT with a 64-detector row CT Aquilon multiscanner (Toshiba Medical System Corporation, Tokyo, Japan). HRCT was obtained using 1.0- or 1.5-mm-thick sections at 10-mm intervals throughout the entire lung. Ground-glass opacity (GGO) and fibrosis were evaluated independently as scores on HRCT images by three observers (T.Su., T. Ko. and T.Sh.) blinded to patient clinical information, as previously described [5]. The average of the scores was summed as the total HRCT

score.

Evaluation of disease severity and outcome

Disease severity was determined according to the European Vasculitis Study Group categorization system [6], and organ involvement was evaluated according to the Birmingham Vasculitis Activity Score version 3 [7]. The 2009 five-factor score, which is used to evaluate prognosis of MPA, was evaluated for each patient [8]. The primary outcome was the occurrence of severe infection. Cases which required intravenous administration of antibacterial, antifungal, or antiviral agents, were defined as severe infections according to the Common Terminology Criteria for Adverse Events (v.4.0) [9].

The detection limits of serum biomarkers

The concentrations and detection limits of serum biomarkers were determined using standard curves generated from standards in each kit with the MasterPlex QT 2010 Software weighted 5 parameter logistic curve fitting procedure. Extrapolation was used when concentrations were below the lowest interval of the standard. The detection limits for all potential biomarkers (in pg/mL) were as follows: IL-1β (1.54), IL-2 (0.34),

IL-4 (10.71), IL-6 (1.23), IL-8 (0.52), IL-10 (0.71), IL-13 (145.58), IL-17A (0.04), IL-23 (12.19), CCL2 (24.74), M-CSF (5.79), CXCL13 (13.35), TNF-α (1.48), IFN-γ (5.78), G-CSF (10.44), GM-CSF (0.25), TIMP-1 (0.08), PDGF (15.0) , VEGF, (10.0), TGF-β (4.6), and LRG (170.0). We defined the cytokine levels as undetectable when the proportion of samples under detection limit accounted for over 50% of the total samples.

PCA of serum biomarkers in MPA-ILD patients

Following the Kaiser-Guttman rule and using the scree plot method, we selected three eigenvectors with the highest eigenvalues as PC1 (eigenvalue 5.2), PC2 (eigenvalue 4.1), and PC3 (eigenvalue 1.5) based on their individual contribution rate (Supplementary Figure 1). The values for PC1, PC2, and PC3 were also calculated for each patient with MPA-ILD. After the PCA, we performed the varimax rotation with Kaiser normalization, and only absolute variables with a loading of > 0.40 were retained [10].

Cluster analyses of MPA-ILD patients

The cluster algorithm started with each patient as a single cluster. The closest clusters

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were repeatedly merged to form new clusters until the entire data were contained in one cluster. We defined the number of clusters based on a scree plot, as described previously (Supplementary Figure 2) [11]. The point of natural break, where the distance increased suddenly, was considered the cut-off point. We defined the proper number of clusters as 2.

Immunohistochemical analysis

The specimens were fixed in 10% formalin, embedded in paraffin, and cut into 4-mm thick sections. Tissue staining was performed using a Bond-MAX autoimmunostainer (Leica Biosystems, Wetzlar, Germany), as well as hematoxylin and eosin staining. Deparaffinized and rehydrated sections were subjected to endogenous peroxidase blocking, and after heating in antigen-unmasking solution, slides were incubated with the following antibodies:CCR4 (1:50, NBP1-86584; Novus Biologicals, Littleton, CO, USA), IL-4 (1:800; ab239508; Abcam, Cambridge, MA), CXCL13 (1:50; ab246518; Abcam, Cambridge, MA), CD20 (1:50; clone L26; Dako, Santa Clara, CA). Color development was performed using 3,3'-diaminobenzidine tetrahydrochloride, and slides were counterstained with hematoxylin. CCR4 stained Th2 cells and CXCL13 stained B cells in each sample were counted in five different fields (×400) on a BZ-X710

microscope (Keyence, Osaka, Japan).

Supplementary Figures

Supplementary Figure 1. Scree plot for principal components analysis

X-axis shows the number of principal components. Y-axis shows the eigenvalues.

Supplementary Figure 2. Scree plot for cluster analysis

The scree plot shows a point for each cluster joint.

Supplementary Figure 3. Kaplan-Meier curves for severe infection-free survival rate of the CFD group and CID group. The 4-year severe infection-free survival rate was significantly lower in the CFD group (15.8%) than in the CID group (82.1%) (log-rank test, p=0.02).

Supplementary Figure 4. Immunohistochemical staining of CCR4 and IL-4 in lung biopsy sections from patients with MPA-ILD

Representative images of sections stained with anti-CCR4 antibody and anti-IL-4 antibody in the lung biopsy samples in patients with MPA-ILD. CCR4 positive cells (white arrow) were located in the interstitium of MPA-ILD lungs. Strong IL-4

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immunostaining (black arrow) was confined to these CCR4 positive cells.

A, B: Magnification (200×), scale bar 100 μm. C, D: Magnification (400×), scale bar 100 μm. MPA-ILD: MPA-ILD: microscopic polyangiitis with interstitial lung disease; CCR: CC chemokine receptor; IL: interleukin.

Reference

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Supplementary Table 1. The range of standard curves in each cytokine, and number of samples whose serum cytokine levels are over detection limits in MPA and HC measured by the Luminex Screening Assay.

	limit of quantification		Number of positive samples		Number of positive samples	
Cytokines	**Lower**	**Upper**	**MPA (N=49)**	**%**	**HC(N=10)**	**%**
Th1 related cytokine						
GM-CSF, pg/mL	**14.01**	**2869.90**	**29**	**59**	**5**	**50**
IL-2, pg/mL	**38.21**	**8980.025**	**46**	**94**	**5**	**50**
IFN-γ, pg/mL	**45.84**	**10691.17**	**39**	**80**	**2**	**20**
Th2 related cytokine						
IL-4, pg/mL	**24.43**	**3660.135**	**49**	**100**	**10**	**100**
IL-13, pg/mL	**416.07**	**95213.48**	**40**	**82**	**4**	**40**
Th17 related cytokine						
IL-17A, pg/mL	**13.52**	**3140.225**	**19**	**39**	**2**	**20**
IL-23, pg/mL	**62.54**	**29023.81**	**12**	**24**	**0**	**0**
M1 Macrophage related cytokine						
IL-1β, pg/mL	**21.01**	**4260.27**	**39**	**80**	**1**	**10**
TNF-α, pg/mL	**9.66**	**1929.98**	**49**	**100**	**10**	**100**
M2 Macrophage related cytokine						
CCL-2, pg/mL	**27.78**	**7370.50**	**49**	**100**	**10**	**100**
IL-10, pg/mL	**5.28**	**1010.27**	**32**	**65**	**4**	**40**

M-CSF, pg/mL	**124.09**	**23731.52**	**40**	**82**	**3**	**30**
B cell related cytokine						
IL-6, pg/mL	**5.74**	**1150.01**	**49**	**100**	**10**	**100**
CXCL13, pg/mL	**31.59**	**4941.00**	**49**	**100**	**10**	**100**
Neutrophil related cytokine						
IL-8, pg/mL	**4.77**	**890.035**	**49**	**100**	**10**	**100**
G-CSF, pg/mL	**28.00**	**5730.13**	**44**	**90**	**4**	**40**

Samples whose serum cytokine levels are over detection limits were defined as positive. MPA: microscopic polyangiitis, HC: healthy controls.

Supplementary Table 2. Comparison of clinical characteristics, disease severity classification between MPA patients with and without ILD

Characteristics	MPA with ILD (n=32)	MPA without ILD (n= 17)	*P* value
Age, years	76(71-82)	71(68-77)	0.047*
Female, n (%)	15(46.9)	9(52.9)	0.77
Laboratory findings			
WBC, /mm^3	11975(7113-14873)	12900(8835-15070)	0.48
Alb, g/dl	2.5 (2.0-3.3)	2.2 (1.8-2.6)	0.06
Cr, mg/dl	0.94 (0.68-1.7)	1.6 (1.2-4.6)	0.01*
CRP, mg/dl	8.8 (2.5-11.9)	12.5(3.2-15.3)	0.07
Positive, anti-MPO-ANCA, n (%)	32(100)	16(94)	0.35
Positive, anti-PR3-ANCA, n (%)	2 (6.3)	1 (5.9)	1.00
MPO-ANCA titer, U/mL	95.1 (61.8-244.3)	174 (63.9-282)	0.43
KL-6, U/ml	372(238-624)	154(113-242)	<0.0001***
BVAS at onset	14 (8-21)	18 (13.5-25.5)	0.18
Five factor score 2009			
≦1	7 (21.9)	5 (29.4)	0.73
2	20 (62.5)	7 (41.2)	0.23
≧3	5 (15.6)	5 (29.4)	0.29
EUVAS-defined disease activity			
Localized	2 (6.3)	1 (5.9)	1.00
Early systemic	6 (18.8)	3 (17.7)	1.00

Systemic	20 (62.5)	10 (58.8)	1.00
Severe	4 (12.5)	3 (17.7)	0.68

The laboratory markers are presented as the median (interquartile range). The P-values were estimated using Fisher's exact test or Wilcoxon rank sum test. *P < 0.05, **P < 0.01, ***P < 0.001. MPA: microscopic polyangiitis; ILD: interstitial lung disease; WBC: white blood cell; Alb: albumin; Cr: creatinine; CRP: C-reactive protein; MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic autoantibody; PR3-ANCA: proteinase 3-anti-neutrophil cytoplasmic antibody; KL-6: Krebs von den Lungen-6; BVAS: Birmingham Vasculitis Activity Score; EUVAS: European Vasculitis Study Group.

Supplementary Table 3. Comparison of the cytokine levels between MPA and healthy control

Cytokines	**MPA (N=49)**	**Normal (N=10)**	***P***
Th1 related cytokine			
GM-CSF, pg/mL	1.5 (0.3-5.2)	0.4 (0.3-4.0)	0.44
IL-2, pg/mL	5.7 (4.6-7.8)	1.4 (0.3-3.5)	0.0005***
IFN-γ, pg/mL	19.1 (11.2-43.5)	undetectable	
Th2 related cytokine			
IL-4, pg/mL	93.3 (84.8-99.9)	70.1(63.1-78.9)	0.0006***
IL-13, pg/mL	444.1 (265.9-519.9)	undetectable	
Th17 related cytokine			
IL-17A, pg/mL	undetectable	undetectable	
IL-23, pg/mL	undetectable	undetectable	
M1 Macrophage related cytokine			
IL-1β, pg/mL	5.0 (3.4-8.9)	undetectable	
TNF-α, pg/mL	12.4 (10.1-15.1)	7.2 (6.0-8.5)	<0.0001***
M2 Macrophage related cytokine			
CCL-2, pg/mL	317.6 (248.3-417.3)	230.6 (185.6-284.9)	0.01*
IL-10, pg/mL	1.4 (0.17-2.5)	undetectable	
M-CSF, pg/mL	126.5 (38.1-412.3)	undetectable	
B cell related cytokine			
IL-6, pg/mL	28.7 (10.3-71.2)	3.9 (3.5-4.6)	<0.0001***
CXCL13, pg/mL	201.9 (138.9-332.7)	69.2 (59.9-101.3)	<0.0001***
Neutrophil related cytokine			
IL-8, pg/mL	25.2 (15.4-47.6)	6.5 (4.9-7.6)	<0.0001***

G-CSF, pg/mL	39.2 (29.4-54.2)	undetectable	
Pro-fibrotic biomarkers			
TIMP-1, pg/mL	331.1 (229.9-444.7)	132.6 (102.3-148.1)	<0.0001***
TGF-β, ng/mL	35.4 (25.4-50.5)	28.4 (24.9-35.6)	0.09
LRG, ng/mL	170.83 (103.6-270.0)	22.6 (16.6-26.0)	<0.0001***
VA related biomarkers			
VEGF, pg/mL	517.8 (317.5-924.1)	77.7 (35.0-174.4)	<0.0001***
PDGF, ng/mL	8.0 (5.0-11.6)	7.0 (5.7-12.1)	1.00

The laboratory markers are presented as the median (interquartile range). The P-values were estimated using Wilcoxon rank sum test. *P <0.05, **P < 0.01, ***P < 0.001. MPA: microscopic polyangiitis; VA: vascular angiogenesis.

Supplementary Table 4. Comparison of the cytokine levels between MPA-ILD and MPA without ILD

Cytokines	**MPA with ILD(N=32)**	**MPA without ILD (N=17)**	***P***
Th1 related cytokine			
GM-CSF, pg/mL	0.5 (0.3-2.5)	5.0 (0.3-12.0)	0.02*
IL-2, pg/mL	5.1 (3.5-6.7)	6.7 (5.1-11.0)	0.04*
IFN-γ, pg/mL	17.8 (5.8-36.4)	19.1 (11.2-59.9)	0.34
Th2 related cytokine			
IL-4, pg/mL	91.6 (83-96.6)	96.6 (89.9-104.7)	0.15
IL-13, pg/mL	382.3 (175.7-500.9)	444.1 (360.9-555.1)	0.12
M1 Macrophage related cytokine			
IL-1β, pg/mL	5.0 (2.0-7.8)	6.6 (5.0-11.8)	0.09
TNF-α, pg/mL	11.5 (9.5-14.6)	13.6 (11.5-15.7)	0.17
M2 Macrophage related cytokine			
CCL-2, pg/mL	327.6 (296.8-461.6)	249.1(188.5-319.5)	0.002**
IL-10, pg/mL	1.8 (0.2-2.6)	0.17 (0.17-2.8)	0.27
M-CSF, pg/mL	112.5 (8.1-341.8)	145.2 (98.6-520.4)	0.10
B cell related cytokine			
IL-6, pg/mL	24.0 (10.1-61.4)	35.2 (10.1-123.1)	0.17
CXCL13, pg/mL	202.2 (136.7-361.0)	186.6 (136.9-274.3)	0.93
Neutrophil related cytokine			
IL-8, pg/mL	21.6 (15.0-43.2)	31.7 (13.5-107.4)	0.38
G-CSF, pg/mL	39.2 (29.4-52.2)	39.2 (26.6-71.2)	0.71

Pro-fibrotic biomarkers			
TIMP-1, pg/mL	318.2 (215.6-432.8)	387.1 (285.9-475.1)	0.17
TGF-β, ng/mL	36.2 (25.3-48.2)	33.5 (25.8-52.7)	0.84
LRG, ng/mL	150.6 (92.9-218.6)	205.2 (116.1-285.9)	0.11
VA related biomarkers			
VEGF, pg/mL	517.8 (287.6-986.3)	449.4 (327.4-724.3)	0.85
PDGF, ng/mL	8.0 (5.2-11.6)	6.5 (4.9-14.0)	0.90

The laboratory markers are presented as the median (interquartile range). The P-values were estimated using Wilcoxon rank sum test. *P <0.05, **P < 0.01, ***P < 0.001. MPA: microscopic polyangiitis; VA: vascular angiogenesis.

Supplementary Table 5. PCA coordinates for the first 3 varimax rotated principal components

Cytokines	Component1	Component2	Component3
GM-CSF, pg/mL	-0.02	**0.76**	0.19
IL-2, pg/mL	0.11	**0.86**	0.10
IFN-γ, pg/mL	0.33	-0.10	**-0.61**
IL-4, pg/mL	-0.14	**0.81**	0.12
IL-13, pg/mL	-0.07	**0.75**	-0.01
IL-1β, pg/mL	0.18	**0.86**	0.05
TNF-α, pg/mL	0.24	**0.55**	0.37
CCL-2, pg/mL	0.17	-0.40	**0.51**
IL-10, pg/mL	0.16	0.25	**0.57**
M-CSF, pg/mL	0.09	0.27	**0.57**
IL-6, pg/mL	**0.73**	-0.22	0.30
CXCL13, pg/mL	**0.57**	0.13	-0.07
IL-8, pg/mL	**0.45**	0.05	0.16
G-CSF, pg/mL	**0.60**	0.30	-0.06
TIMP-1, pg/mL	**0.86**	-0.09	0.18
TGF-β, ng/mL	**0.87**	0.06	-0.14
LRG, ng/mL	**0.79**	-0.04	-0.07
VEGF, pg/mL	**0.73**	-0.05	0.08
PDGF, ng/mL	**0.82**	0.02	0.08
Variance explained (%)	27	22	8
Cumulative variance explained (%)	27	49	57

Absolute Variables with coordinates of less than 0.40 were omitted from the component. Components

indicate primary components. The proportion of total variance in the data set, as explained by each component, is shown. The cumulative proportion of total variance explained by the sum of each of the components and the preceding components has been shown. Components indicate primary components.

Supplementary Table 6. Correlation between serum biomarker levels and disease activity indicators of MPA-ILD

	WBC	Alb	CRP	KL-6	SP-D	MPO-ANCA	%FVC	%DIco	BVAS	Total GGO	Total fibrosis score
PCA defined group 1											
IL-6, pg/mL	0.72***	-0.87***	0.85***	-0.46**	-0.52*	-0.13	0.04	-0.17	0.10	0.007	0.03
CXCL13, pg/mL	0.29	-0.56***	0.41*	0.06	-0.04	-0.27	-0.26	-0.03	-0.10	0.53**	0.38*
IL-8, pg/mL	0.23	-0.31	0.19	0.009	-0.37	0.015	-0.18	-0.32	0.31	0.18	0.17
G-CSF, pg/mL	0.34	-0.51**	0.46**	-0.05	-0.05	-0.13	-0.32	-0.15	0.08	0.17	0.15
PDGF, ng/mL	0.63***	-0.62***	0.73***	-0.24	-0.46*	0.02	0.18	0.11	-0.06	-0.01	-0.11
VEGF, pg/mL	0.60***	-0.63***	0.7***	-0.18	-0.37	-0.08	0.27	0.19	-0.004	0.04	0.01
TGF-β, ng/mL	0.74***	-0.60***	0.81***	-0.39*	-0.38	-0.10	0.19	0.18	-0.08	-0.05	-0.09
LRG, ng/mL	0.62***	-0.58***	0.62***	-0.52***	-0.52*	0.04	0.20	-0.08	0.22	-0.19	-0.23
TIMP-1, pg/mL	0.78***	-0.77***	0.85***	-0.51**	-0.61**	0.15	-0.04	-0.09	0.37*	-0.10	-0.11
PCA defined group 2											
GM-CSF, pg/mL	-0.19	0.14	-0.03	0.13	-0.04	-0.17	-0.09	0.16	0.05	-0.02	0.02
IL-2, pg/mL	-0.21	0.20	-0.10	0.24	0.12	-0.32	-0.14	-0.02	0.11	0.20	0.32
IL-1β, pg/mL	-0.09	0.05	0.08	0.19	0.21	-0.2	-0.18	0.19	0.02	0.12	0.09
TNF-α, pg/mL	0.10	-0.20	0.15	-0.14	-0.44*	0.02	-0.26	-0.04	0.44*	0.07	0.07
IL-4, pg/mL	-0.26	0.25	-0.27	0.15	0.22	-0.09	-0.29	0.14	0.21	0.14	0.11
IL-13, pg/mL	-0.11	0.17	-0.07	0.08	0.35	-0.28	-0.32	0.10	0.10	0.24	0.35*
PCA defined group 3											
IL-10, pg/mL	0.17	-0.17	0.10	-0.14	-0.32	-0.39*	-0.04	0.18	0.12	0.05	0.08
M-CSF, pg/mL	0.18	-0.23	0.09	-0.10	-0.29	0.13	-0.36	-0.09	0.30	0.08	0.17
CCL-2, pg/mL	0.25	-0.27	0.26	-0.13	-0.31	-0.03	0.02	-0.14	0.19	-0.15	-0.19
IFN-γ, pg/mL	0.21	-0.15	0.30	-0.27	-0.03	-0.11	0.09	0.10	0.17	-0.09	-0.15

Statistical analyses were performed using Spearman's rank correlation coefficient. *P < 0.05, **P < 0.01, ***P < 0.001. MPA: microscopic polyangiitis; ILD: interstitial lung disease; WBC: White blood cell; Alb: albumin; CRP: C-reactive protein; KL-6: Krebs von den Lungen-6; SP-D: Surfactant Protein-D; MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide; GGO: ground-glass opacity; CXCL: C-X-C motif chemokine ligand; CCL: C-C motif chemokine ligand.

Supplementary Table 7. Comparison of the cytokine levels between Cluster1 and Cluster 2 in MPA-ILD

Cytokines	Cluster1 (N=17)	Cluster 2 (N=15)	*P* value
PCA defined group 1			
IL-6, pg/mL	10.9 (8.0-17.9)	47.5 (28.7-75.4)	<0.0001***
CXCL13, pg/mL	168.5 (112.6-239.3)	236.0 (201.9-442.0)	0.01*
IL-8, pg/mL	18.6 (15.1-27.1)	35.1 (14.5-98.5)	0.036*
G-CSF, pg/mL	29.4 (17.8-48.0)	43.7 (34.4-62.1)	0.039 *
PDGF, ng/mL	5.4 (3.1-7.8)	11.6 (8.2-12.6)	<0.0001***
VEGF, pg/mL	307.6 (131.8-560.5)	990.6 (517.8-1335.1)	<0.0001***
TGF-β, ng/mL	25.7 (20.9-31.3)	49.9 (40.6-52.4)	<0.0001***
LRG, ng/mL	101.2 (69.9-139.4)	206.8 (170.8-285.9)	<0.0001***
TIMP-1, pg/mL	228.7 (158.9-321.1)	437.0 (323.2-512.9)	0.0002***
PCA defined group 2			
GM-CSF, pg/mL	1.5 (0.25-4.0)	0.25 (0.25-1.5)	0.16
IL-2, pg/mL	5.7 (4.6-6.7)	4.6 (2.5-7.8)	0.23
IL-1β, pg/mL	5.0 (2.5-9.6)	3.37 (1.5-6.6)	0.42
TNF-α, pg/mL	11.8 (10.4-14.5)	10.6 (8.3-14.8)	0.47
IL-4, pg/mL	96.6 (86.5-104.7)	86.5 (72.0-93.3)	0.012*
IL-13, pg/mL	403.6 (265.9-607.3)	360.9 (145.6-444.1)	0.20
PCA defined group 3			
IL-10, pg/mL	0.99 (0.17-2.7)	2.0 (0.38-2.7)	0.61
M-CSF, pg/mL	107.9 (5.8-431.0)	117.2 (15.0-238.7)	0.86
CCL-2, pg/mL	312.3 (279.1-445.6)	334.3 (319.5-467.6)	0.20
IFN-γ, pg/mL	16.5 (7.2-34.0)	26.6 (5.8-91.8)	0.30

The laboratory markers are presented as the median (interquartile range). The P-values were estimated using Wilcoxon rank sum test. *P <0.05, **P <0.01, ***P <0.001. MPA: microscopic polyangiitis; ILD: interstitial lung disease; CXCL: C-X-C motif chemokine ligand; CCL: C-C motif chemokine ligand.

Supplementary Table 8. Comparison of systemic symptoms between Cluster 1 and Cluster 2 in MPA-ILD

Characteristics	Cluster 1 (n= 17)	Cluster 2 (n=15)	*P* value
Systemic Symptoms			
General, n (%)	9 (52.9)	13 (86.7)	0.06
Cutaneous, n (%)	0 (0)	0 (0)	NS
Mucous membrane, n (%)	1 (5.9)	2 (13.3)	0.59
Ear, nose, throat, n (%)	4 (23.5)	6 (40.0)	0.45
Chest, n (%)	2 (11.8)	2 (13.3)	1.00
Alveolar hemorrhage, n (%)	1 (5.9)	1 (6.7)	1.000
Cardiovascular, n (%)	0 (0)	1 (6.7)	0.47
Abdominal, n (%)	0 (0)	0 (0)	NS
Renal, n (%)	13 (76.5)	8 (53.3)	0.27
Nervous system, n (%)	8 (47.1)	9 (60.0)	0.50

The laboratory markers are presented as the median (interquartile range). The P-values were estimated using Fisher's exact test or Wilcoxon rank sum test. *P < 0.05. MPA: microscopic polyangiitis; ILD: interstitial lung disease; NS: not significance.

Supplementary Table 9. Factors associated with severe respiratory infections in MPA-ILD

Variables	Univariate analysis		Multivariate analysis	
	HR [95% CI]	p-Value	HR [95% CI]	p-Value
Age, per 1 year	1.05（0.96-1.15）	0.34		
Female (vs male)	0.39（0.08-1.9）	0.24		
WBC, per 1 cell/mm^3	0.999（0.999-1.000）	0.12		
Alb, per 1 g/dl	1.43（0.58-3.2）	0.42		
CRP, per 1 mg/dl	0.93 (0.81-1.04)	0.21		
KL-6, per 1 U/ml	1.003 (1.001-1.007)	0.01	1.006 (1.002-1.01)	0.001
Sp-D, per 1 ng/mL	1.004 (0.997-1.011)	0.25		
%FVC, per 1%	0.95 (0.892-0.997)	0.04	0.96 (0.90-1.01)	0.11
BVAS at onset, per 1point	1.09 (0.98-1.23)	0.12		
Initial PDN dose, per 1 mg	1.03 (0.99-1.06)	0.16		
Total IVCY dose, per 1g	1.90 (0.62-4.90)	0.23		

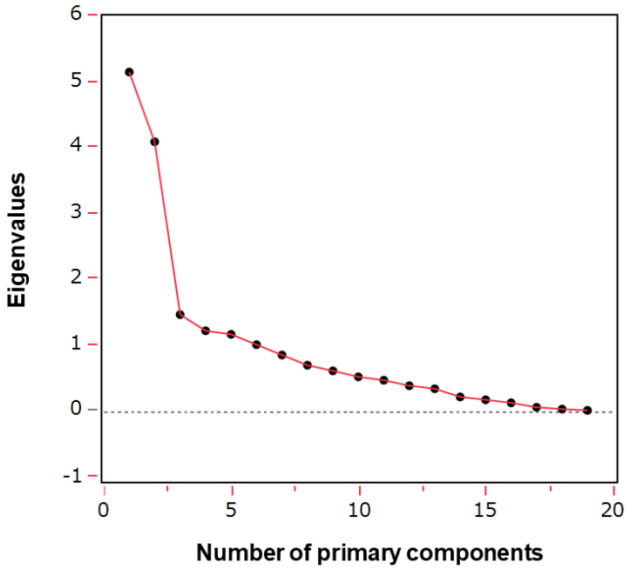
Each variable with a univariate $p<0.05$ was included in the multivariate analysis. HR: hazard ratio; CI: confidence interval; WBC: white blood cell; Alb: albumin; CRP: C-reactive protein; KL-6: Krebs von den Lungen-6; Sp-D: Surfactant protein D; FVC: forced vital capacity; BVAS: Birmingham Vasculitis Activity Score; PDN: prednisolone; IVCY: intravenous cyclophosphamide.

Supplementary Table 10. Comparison of clinical characteristics of three patients in MPA-ILD who underwent lung biopsy.

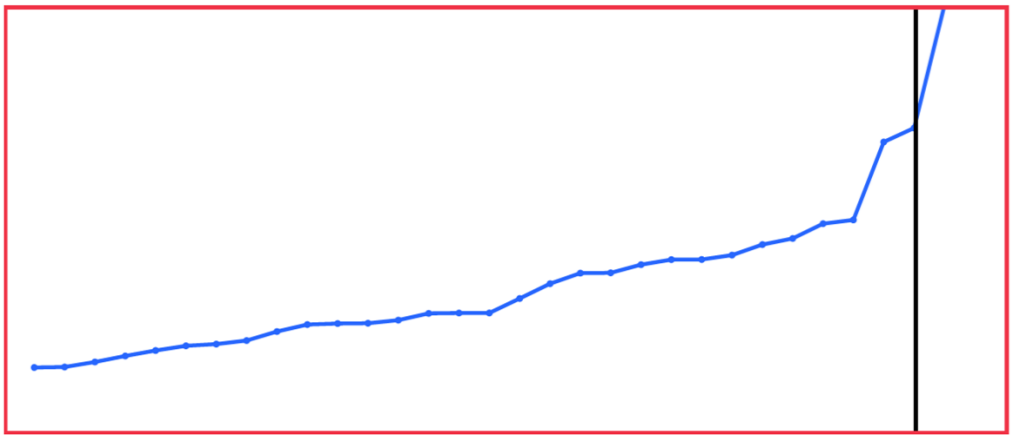
Characteristics	Case 1	Case 2
Age, years	77	63
Disease duration of ILD (months)	72	84
Total Fibrosis score	9.9	8.7
Serum CXCL13 levels, pg/mL	253.71	363.06
The number of CXCL13 positive B cells (HPF) (400×)	26	46
The number of CCR4 positive Th2 cells (HPF) (400×)	81	54
Serum IL-4 levels, pg/mL	91.64	83.0
Serum IL-13 levels, pg/mL	360.91	360.91

MPA: microscopic polyangiitis; ILD: interstitial lung disease; Disease duration of ILD: the period from appearance of respiratory symptoms to start of treatment; HPF: high power field; Th2: T helper 2.

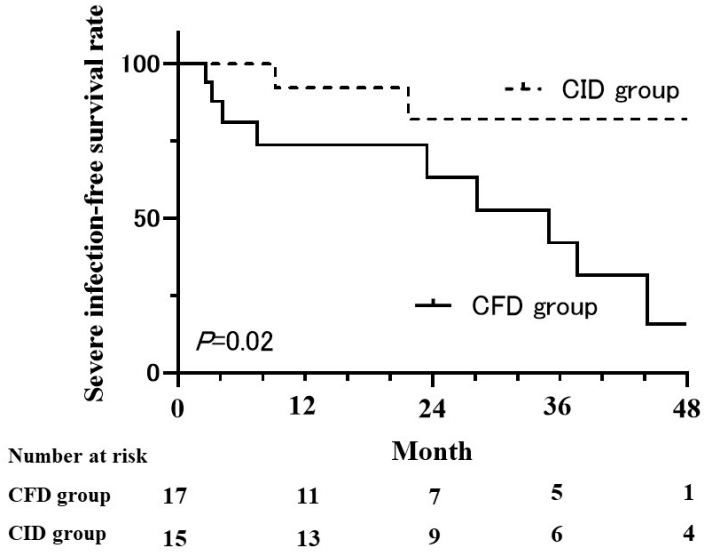
Supplementary Figure 1. Scree plot for principal components analysis



Supplementary Figure 2. Scree plot for cluster analysis



Supplementary Figure 3. Kaplan-Meier curves for severe infection-free survival rate of the CFD group and CID group



Supplementary Figure 4. Immunohistochemical staining of CCR4 and IL-4 in lung biopsy sections from patients with MPA-ILD