The Journal of Rheumatology 2021;48:410–16
doi:10.3899/jrheum.191042
First Release January 15 2021

The Journal of Rheumatology

Clinical Characteristics and Prognostic Analysis of Microscopic Polyangiitis With Diffuse Alveolar Hemorrhage

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ABSTRACT. ***Objective.*** To analyze the clinical features and prognostic factors of microscopic polyangiitis (MPA) with diffuse alveolar hemorrhage (DAH).

Methods. We conducted a retrospective study of 92 patients diagnosed with MPA with DAH at the First Affiliated Hospital of Chongqing Medical University between March 1, 2012, and March 12, 2018. The cumulative survival rate was analyzed by the Kaplan-Meier method, and survival curves were drawn. A Cox hazard model was used to determine the prognostic factors for survival by univariate and multivariate analysis.

Results. The mean age at the onset of MPA with DAH was 66.32 years. Among the 92 MPA with DAH patients with follow-up visits, 41 (44.57%) were critically ill and 79 (85.87%) had pulmonary and renal involvement. The cumulative survival rates of the 92 patients at 1, 3, and 5 years were 63.7%, 51.2%, and 47.3%, respectively, and the median survival time was 46 months. In the multivariate analysis, age > 65 years (HR 4.30, 95% CI 1.94–9.55), sCr > 500 μmol/L (HR 2.04, 95% CI 1.05–3.97), PaO_2/FiO_2 < 300 mmHg (HR 4.10, 95% CI 1.97–8.53), and lung involvement area ≥ 50% (HR 2.93, 95% CI 1.40–6.13) were independent prognostic factors ($P < 0.05$).

Conclusion. The incidence and mortality of DAH are high in MPA patients. Age > 65 years, sCr > 500 μmol/L, PaO_2/FiO_2 < 300 mmHg, and lung involvement area ≥ 50% are independent prognostic factors for MPA with DAH.

Key Indexing Terms: antineutrophil cytoplasmic antibody-associated vasculitis, microscopic polyangiitis, prognosis, pulmonary hemorrhage

Microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA) are collectively referred to as antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV). A recent epidemiological study from Olmsted County, Minnesota, showed that the annual incidence of MPA is 3.3 per 100,000 adults, which is similar to that of GPA[1]. There has been an increase in the overall incidence of MPA, as well as an increase in incidence rates in the Asia-Pacific region[1]. MPA is a pauci-immune, systemic, necrotizing vasculitis that mainly involves the small vessels of the lungs and kidneys[2]. The main manifestations of MPA with pulmonary involvement are pulmonary interstitial fibrosis and diffuse alveolar hemorrhage (DAH). DAH is a critical illness and a significant survival factor for patients with MPA; however, there have been few clinical and prognostic studies on MPA with DAH. In this study, we retrospectively examined the survival curve and prognostic factors in 92 patients who had MPA with DAH, to facilitate the early diagnosis and treatment.

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Accepted for publication June 8, 2020.

MATERIALS AND METHODS

From March 1, 2012, to March 31, 2018, there were 297 MPA patients who were hospitalized, treated, and followed up at the First Affiliated Hospital of Chongqing Medical University. Among them, 275 (92.59%) had pulmonary involvement, including nonspecific interstitial pneumonia, usual interstitial pneumonia, and DAH. One hundred patients (33.67%) had MPA with DAH, 8 of whom were lost to follow-up and were excluded; the remaining 92 patients were included in this study. All data were extracted retrospectively from the clinical files. Patients met the 2012 Chapel Hill revised criteria[3]. Patients who met at least 3 of the following 4 criteria were diagnosed with DAH[4,5,6]: (1) pulmonary symptoms including hemoptysis, dyspnea, hypoxemia; (2) acute diffuse lung infiltrates on thoracic computed tomography (CT) scans; (3) hemoglobin that decreased by > 1.5 mg/dL within 24–48 hours for unknown reasons and did not match the hemoptysis volume; and (4) bloody bronchoalveolar lavage fluid (BALF) and/or 20% hemosiderin-laden macrophages in the BALF cell differential count. In addition, patients were excluded if the DAH could be explained by another medical condition, such as acute pulmonary edema, pulmonary embolism, idiopathic pulmonary hemosiderosis, severe coagulopathy, or other diseases.

Pulmonary involvement[7] was defined as the presence of clear MPA with the exclusion of pneumonia caused by pathogenic infection and the suggestion of pulmonary lesions (including but not limited to interstitial pneumonia or alveolar hemorrhage) on chest CT/high-resolution CT (HRCT) with or without respiratory manifestations such as cough, hemoptysis, and dyspnea. Respiratory failure was defined as an arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) ratio (PaO_2/FiO_2)

< 300 mmHg or a resting PaO_2 < 60 mmHg at sea level while breathing room air. Type I was defined as PaO_2 < 60 mmHg and partial pressure of carbon dioxide (PCO_2) ≤ 50 mmHg. Type II was defined as PaO_2 < 60 mmHg and PCO_2 > 50 mmHg.

Renal involvement[6] was defined as the presence of hematuria, proteinuria on urinalysis, the need for renal replacement therapy, new biopsy-proven pauci-immune necrotizing glomerulonephritis, an increase in the level of serum creatinine > 30%, or a decrease in the estimated glomerular filtration rate (eGFR) > 25% attributable to active vasculitis.

Three levels of severity were defined according to the 2007 British College of Rheumatology (BSR) and the Rheumatology Professional Association (BHPR) as follows: localized/early systemic disease, generalized/threatened organ involvement, and severe/life-threatening disease[8]. The disease activity of MPA with DAH was assessed by the Birmingham Vasculitis Activity Score version 3 (BVAS v.3)[9].

Semiquantitative CT analysis[10] was used to evaluate the lung involvement area. With the level of the carina and pulmonary vein as the boundary, the lungs were divided into 6 zones (upper, middle, and lower zones of the right and left lung). The percentage accounted for by lesions (including patches, speckles, ground-glass opacities, grids, and honeycombs) at each level in the lung parenchyma was independently visually analyzed by a chest radiologist and a respiratory physician, and final conclusions on the findings were reached by means of consensus. The lung involvement area was divided into 4 grades: (1) < 25%, (2) 25–50%, (3) 50–75%, and (4) > 75% of the image. When the lesions involved multiple layers, the percentage of each layer was accumulated and then averaged to obtain the involvement area of the region.

Ninety-two patients diagnosed with MPA plus DAH in our hospital were followed up by outpatient and telephone visits until March 1, 2019, or death. The follow-up time or survival time was calculated from the beginning of the diagnosis of MPA with DAH to March 1, 2019, or death. Of the 100 patients with MPA and DAH, 8 patients who were lost to follow-up were excluded, and only 92 patients had complete follow-up data. The primary outcome was the all-cause mortality of MPA with DAH.

Statistical analyses. Data were reported as number (percentage), mean ± SD, or median (range). The Cox regression hazard model was used to estimate the HR of each variable with regard to mortality. The effect was estimated as the HR with the 95% CI. All statistical analyses were performed with SPSS 22.0 (IBM Corp.) statistical software. All tests were bilateral, and the level of statistical significance was set at 0.05.

Ethical approval. The study received approval from the First Affiliated Hospital of Chongqing Medical University's Ethics Committee (2019-187). Due to the retrospective nature of the study, informed consent was not required. This study was conducted in accordance with the ethics standards of the Helsinki Declaration.

RESULTS

Demographic and clinical data at disease onset. Among the 92 patients, 43 were male and 49 were female, and the male: female sex ratio was 1:1.19. The mean age at onset was 66.32 ± 11.72 years (range 24–86 yrs), and 51 patients (55.43%) were older than 65 years. The duration of follow-up ranged from 10 days to 80 months.

Table 1 shows the characteristics at diagnosis, treatment details, and outcomes of 92 patients with MPA and DAH. Pulmonary and renal involvement were very common. Cough, dyspnea, and hemoptysis were the most common respiratory symptoms. Renal involvement included hematuria, proteinuria, and edema. Gastrointestinal (GI), EENT, and neurological system, involvement, as well as systemic symptoms are also shown in Table 1. Fifty-one patients had generalized/threatened organ involvement, and the other 41 had severe/life-threatening

Table 1. The main clinical characteristics of 92 patients.

	N = 92
Age at disease onset, yrs, mean ± SD	66.32 ± 11.72
M/F, n	43/49
Deaths	41 (44.57)
Organ involvement	
Pulmonary	92 (100.00)
Cough	77 (83.70)
Hemoptysis	43 (46.74)
Dyspnea	62 (67.39)
Respiratory failure[a]	41 (44.57)
Type I	34 (36.96)
Type II	7 (7.61)
Renal	79 (85.87)
Hematuria	76 (82.61)
Proteinuria[b]	68 (73.91)
Edema	52 (56.52)
Pulmonary and renal	79 (85.87)
Pulmonary, renal, and other	50 (54.35)
GI bleeding	29 (31.52)
EENT	18 (19.57)
Neurological system	10 (10.87)
PNS	6 (6.52)
CNS	4 (4.35)
Systemic symptoms	
Fever	48 (52.17)
Fatigue	48 (52.17)
Arthralgia/myalgia	43 (46.74)
Skin involvement	10 (10.87)
Weight loss	10 (10.87)
Duration, median (range), months[c]	3.5 (0.1–720)
Severity	
Localized/early systemic disease	0 (0.00)
Generalized/threatened organ involvement	51 (55.43)
Severe/life-threatening disease	41 (44.57)
Treatment	
GC and IST	78 (84.78)
GC	78 (84.78)
IST	78 (84.78)
CYC	78 (84.78)
Tacrolimus	1 (1.09)
CSA	1 (1.09)
MMF	1 (1.09)
Plasmapheresis	1 (1.09)
Ig	17 (18.48)

Values are n (%) unless otherwise specified. [a] Respiratory failure: PaO_2/FiO_2 < 300 mmHg or arterial partial pressure of oxygen < 60 mmHg, at sea level and at rest while breathing room air; Type I: PaO_2 < 60 mmHg and PCO_2 ≤ 50 mmHg; Type II: PaO_2 < 60 mmHg and PCO_2 > 50 mmHg. [b] Proteinuria: quantitative proteinuria > 150 mg daily or qualitatively positive for urine protein. [c] Duration: time from onset to diagnosis of DAH. CNS: central nervous system; CSA: cyclosporine A; CYC: cyclophosphamide; DAH: diffuse alveolar hemorrhage; EENT: eye, ear, nose, and throat; GC: glucocorticoids; GI: gastrointestinal; IST: immunosuppressant therapy; MMF: mycophenolate mofetil; PaO_2/FiO_2: arterial oxygen partial pressure/fractional inspired oxygen; PCO_2: partial pressure of carbon dioxide; PNS: peripheral nervous system.

Table 2. Univariate and multivariate analysis of prognosis.

	Values	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	*P*	HR	95% CI	*P*
Age > 65, yrs	51 (55.43)	2.41	1.22–4.8	0.01	4.30	1.94–9.55	< 0.001
Sex, female	49 (53.26)	0.94	0.50–1.77	0.86			
Cough	77 (83.70)	1.25	0.47–3.21	0.64			
Hemoptysis	43 (46.74)	1.44	0.77–2.70	0.26			
Dyspnea	62 (67.39)	2.45	1.13–5.32	0.02			
Renal involvement[a]	79 (85.87)	1.45	0.52–4.08	0.48			
Neurologic involvement	10 (10.87)	1.23	0.54–2.80	0.62			
EENT involvement	18 (19.57)	0.57	0.22–1.45	0.24			
GH	29 (31.52)	1.68	0.89–3.17	0.11			
Systemic symptoms	85 (92.39)	0.89	0.27–2.88	0.84			
WBC > 10, cells/μL	62 (67.39)	1.17	0.59–2.31	0.65			
Hb < 9, g/dL	56 (60.87)	1.64	0.84–3.23	0.15			
Plt > 300, cells/μL	46 (50)	0.79	0.42–1.47	0.45			
CRP > 8, mg/L[b]	79 (92.94)	3.40	0.47–24.79	0.23			
ESR > 43, mm/h[b]	52 (82.54)	0.90	0.34–2.38	0.83			
Alb < 3, g/dL[b]	47 (51.65)	1.51	0.80–2.84	0.20			
LDH > 500, IU/L[b]	32 (57.14)	3.27	1.71–6.28	< 0.001			
sCr > 500, μmol/L	41 (44.57)	2.61	1.37–4.95	0.003	2.04	1.05–3.97	0.035
eGFR < 90, mL/min/ 1.73 m^2	61 (66.30)	1.46	0.73–2.92	0.29			
sC3 < 0.79, g/L	30 (32.61)	2.21	1.18–4.13	0.01			
sC4 < 0.16, g/L	12 (13.04)	1.07	0.42–2.73	0.89			
MPO-ANCA– positive	88 (95.65)	2.04	0.28–14.84	0.48			
PR3-ANCA–positive	10 (10.87)	0.63	0.19–2.04	0.44			
ANA titer ≥ 1:320	16 (17.39)	0.90	0.38–2.14	0.81			
RF > 20, IU/mL	17 (54.84)	0.44	0.14–1.40	0.17			
PaO_2/FiO_2 < 300, mmHg	41 (44.57)	4.31	2.18–8.52	< 0.001	4.10	1.97–8.53	< 0.001
LIA ≥ 50%	42 (45.65)	3.14	1.62–6.11	0.001	2.93	1.40–6.13	0.004
Duration, months, median (range)[c]	3.5 (0.1–720)	1.00	1.000–1.004	0.06			
BVASv.3, mean ± SD	23.076 ± 8.541	1.06	1.02–1.10	0.001			

Values are n (%) unless otherwise specified. [a] Renal involvement: hematuria, proteinuria, edema; systemic symptoms: fever, rash, arthralgias, myalgias, and weight loss. [b] Data missing. [c] Duration: time from onset to diagnosis of MPA with DAH. Alb: albumin; ANA: antinuclear antibody; ANCA: antineutrophil cytoplasmic autoantibody; BVASv.3: the Birmingham Vasculitis Activity Score version 3; CRP: C-reactive protein; EENT: Eye-ears-nose-throat involvement; eGFR: estimated glomerular filtration rate determined by the CKD-EPI method; DAH: diffuse alveolar hemorrhage; ESR: erythrocyte sedimentation rate; GH: gastrointestinal hemorrhage; Hb: hemoglobin; LDH: lactate dehydrogenase; LIA: lung involvement area; PaO_2/FiO_2: arterial pO_2/fraction of inspired oxygen; Plt: platelet; sCr: serum creatinine; sC3/sC4: serum level of C3/C4; MPA: microscopic polyangiitis; MPO: myeloperoxidase-ANCA; PR3: proteinase 3; RF: rheumatoid factor; WBC: white blood cells.

disease. Eighty-two cases of DAH were associated with MPA at the time of diagnosis, and the other 10 cases were associated with MPA during relapse. The mean BVASv.3 was 23.076 ± 8.541 (Table 2).

Laboratory results. The sCr level was > 500 μmol/L in 41 patients. Hb < 9 g/dl was present in 56 patients. The eGFR was < 90 mL/min/1.73 m^2) in 61 patients. The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were elevated in 79 and 52 patients, respectively. All patients were positive for antineutrophil cytoplasmic antibodies (ANCA): 88 were positive for MPO-ANCA, 10 were positive for PR3-ANCA, and 7 were positive for both. MPO-ANCA– and PR3-ANCA–positive patients did not use drugs to treat hyperthyroidism. All patients tested negative for antiglomerular basement membrane antibodies. The antinuclear antibody (ANA) spectrum included ANA and antiextractable nuclear antigen antibodies. ANA were positive in 37 (43.02%) patients according to indirect immunofluorescence. Sixteen patients had ANA titers ≥ 1:320. The remaining laboratory results are shown in Table 2.

Imaging findings and lung involvement area. Fifty-eight patients underwent chest HRCT, and the remaining 34 underwent chest CT. Lung involvement was shown as patches, speckles, ground-glass opacities, grids, and honeycombs on imaging. Semiquantitative analysis of thoracic CT showed that 42 (45.65%) patients had lung involvement areas ≥ 50%. The main CT findings of MPA with DAH were ground-glass opacities and/or consolidation. Lesions were mainly concentrated in the inner and middle zones rather than the subpleural zone. Figures 1A–D show all manifestations of DAH, from small lobular exudation to almost all alveoli.

Treatment. Eighty-eight patients received treatment with glucocorticoids (GC), immunosuppressants, dialysis, plasmapheresis, Ig pulse therapy, and mechanical ventilation. Seventy-eight patients received daily oral prednisone with or

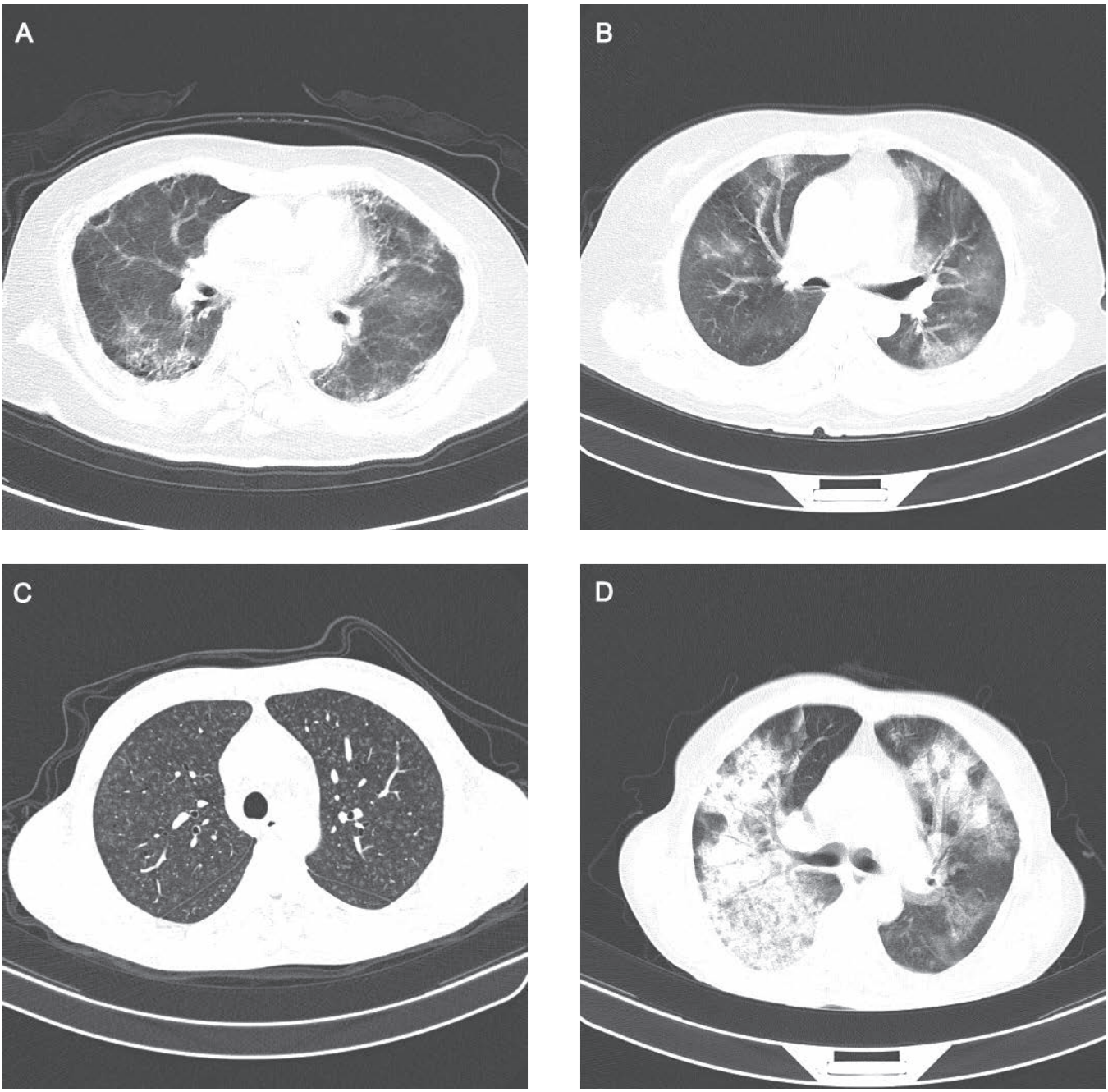

Figure 1. Thoracic HRCT findings of MPA with DAH. (Panels A–D) The performance of MPA with DAH on chest HRCT. HRCT: high-resolution computed tomography; MPA: microscopic polyangiitis; DAH: diffuse alveolar hemorrhage.

without 500–1000 mg daily intravenous (IV) methylprednisolone (MP) pulse therapy for 3 consecutive days and an immunosuppressant [i.e., cyclophosphamide (CYC) in 78 patients], which was switched to tacrolimus in 1 patient, azathioprine in 1 patient, mycophenolate mofetil in 1 patient, and cyclosporine A in 1 patient. Fourteen patients were not treated with GC or immunosuppressants. Four patients rejected GC and immunosuppressants because of side effects (3 died, 1 survived). Three patients older than 80 years may have experienced a poor therapeutic effect because of endstage renal disease (ESRD; 1 died, 2 survived). Two patients died because it was too late to use GC and immunosuppressants, and 5 patients did not use them due to severe infections (2 died, 3 survived). None of our patients used rituximab (RTX).

Most of the 51 patients with systemic/organic function impairment received oral prednisone (1 mg/kg/d) with oral CYC (2 mg/kg/d) or IV pulse CYC, 10–15 mg/kg, every 2–3 weeks. For patients with acute kidney injury and rapidly progressive kidney injury caused by aggravation of primary vasculitis, the recommended dose of cyclophosphamide was used. After induction remission therapy, there were still some patients whose renal function could not be restored to normal. For these patients

with long-term renal insufficiency, the minimum of the recommended dose was usually used, and patients over 65 years can appropriately reduce the dose by 20–30%[11]. Forty-one patients with severe/life-threatening conditions received high-dose GC combined with CYC therapy, 16 of whom received 500–1000 mg IV MP pulse therapy daily for 3 days combined, with IV CYC pulse therapy for DAH with respiratory failure and/or acute renal failure. Seventeen patients received high-dose IV Ig (0.1–0.3 g/kg/d, 3–5 days), 17 patients with ESRD needed hemodialysis, and 1 patient received plasmapheresis, which consisted of 7 exchanges over 14 days of 60 mL/kg per session, using 3% albumin as a replacement solution. Among the 41 patients with respiratory failure, 15 received noninvasive mechanical ventilation, and 6 received invasive mechanical ventilation; the remaining patients were treated with a mask or nasal catheter oxygen therapy, after which respiratory failure was corrected. Relapse was observed in 21 patients (22.83%).

Prognostic factors and survival analysis. Kaplan-Meier analysis showed that the cumulative survival rates of all patients at 1, 3, and 5 years were 63.7%, 51.2%, and 47.3%, respectively, and the median survival time was 46 months (Figure 2). During the follow-up period, 41 patients (44.57%) died for the following reasons: infection, aggravated vasculitis, multiple organ failure, cerebral infarction, cerebral hemorrhage, malignant arrhythmia, GI hemorrhage, and unknown causes in 11, 9, 9, 3, 1, 1, 1, and 6 patients, respectively (Table 3). Among the patients who died of infection, lung infections were the most common, followed by sepsis, systemic infections, and intestinal infections. Fifteen patients died during the first hospitalization, mainly due to infections and multiple organ failure. Ten patients died within 3 months after the diagnosis of DAH, mainly due to infection and vasculitis. Sixteen patients died after 3 months, mainly due to aggravated vasculitis.

Twenty-nine variables were considered clinically meaningful after reviewing the literature, including clinical manifestations, laboratory tests, imaging characteristics, and BVASv.3. The relationship between mortality and each variable was evaluated by Cox univariate analysis, which identified age > 65 years old, dyspnea, PaO_2/FiO_2 < 300 mmHg, lung involvement area ≥ 50%, sCr > 500 μmol/L, LDH > 500 IU/L, sC3 < 0.79 g/L, and BVASv.3 as the factors affecting the survival rate ($P < 0.05$), as shown in Table 2. The 8 factors that were significantly associated with increased mortality according to the univariate analysis were gradually submitted to forward regression by the Cox hazard model; the level of introduction was 0.05, and the rejection level was 0.10. Multivariate analysis showed that age > 65 years (HR 4.30, 95% CI 1.94–9.55, $P < 0.001$), sCr > 500 μmol/L (HR 2.04, 95% CI 1.05–3.97, $P = 0.04$), PaO_2/FiO_2 < 300 mmHg (HR 4.10, 95% CI 1.97–8.53, $P < 0.001$), and lung involvement area ≥ 50% (HR 2.93, 95% CI 1.40–6.13, $P = 0.04$) were independent risk factors for death in patients with MPA and DAH.

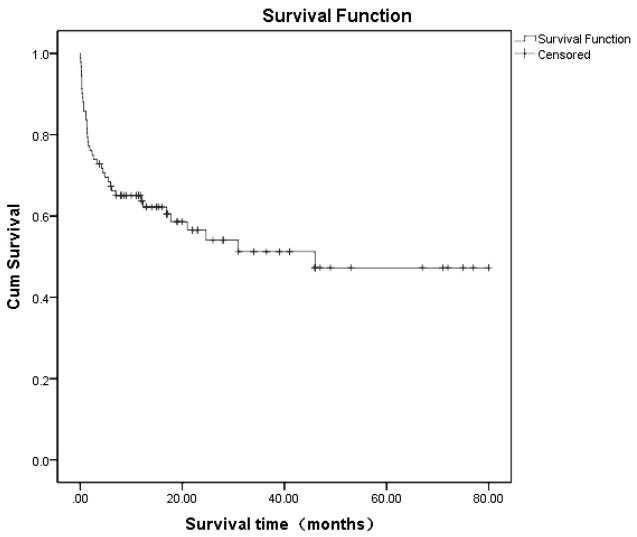

Figure 2. The cumulative survival rates of 92 patients with MPA with DAH. Cum: cumulative; DAH: diffuse alveolar hemorrhage; MPA: microscopic polyangiitis.

Table 3. Causes of death in 41 patients.

	N1 = 15	N2 = 10	N3 = 16	n (%)
Infection	6	3	2	11 (26.83)
Lung	5	3	2	10 (24.39)
Intestinal	1	0	1	2 (4.88)
Systemic	1	1	2	4 (9.76)
Septic shock	6	0	1	7 (17.07)
Aggravated vasculitis	2	3	4	9 (21.95)
Others	7	4	10	21 (51.22)
Multiple organ failure	4	3	2	9 (21.95)
Cerebral infarction	1	1	1	3 (7.32)
Cerebral hemorrhage	1	0	0	1 (2.44)
Malignant arrhythmia	1	0	0	1 (2.44)
GI hemorrhage	0	0	1	1 (2.44)
Unknown[a]	0	0	6	6 (14.63)

N1: Patients who died during the first hospitalization. N2: Patients who died within 3 months excluding N1 group. N3: Patients who died after 3 months. [a] Unknown: Patients who died during follow-up in other hospitals after diagnosis in our hospital. GI: gastrointestinal.

DISCUSSION

DAH is the main manifestation of severe vasculitis and is an important prognostic factor. In this study, 33.67% of MPA patients were complicated with DAH, which is similar to the percentages reported in other studies, which range from 10–40.9%[2,4,12]. The most common manifestations of DAH are cough, dyspnea, and hemoptysis[13]. In our current study, only 46.74% of patients had hemoptysis, and more than half had concealed alveolar hemorrhage, which only manifested as dyspnea and decreased hemoglobin. Therefore, thoracic HRCT or bronchoalveolar lavage should be performed in a timely manner if unexplained dyspnea or decreased hemoglobin occurs.

The 1- and 5-year survival rates of MPA patients after treatment are 80–100% and 65–95%, respectively[14,15]. In our current study, the 1- and 5-year cumulative survival rates of MPA patients with DAH were 63.7% and 47.3%, respectively, which were lower than those of the general population of MPA

patients. Thus, DAH is an important factor leading to death. In this study, the first 3 months after diagnosis were the period of high mortality because some patients already had severe lung involvement at first diagnosis. In addition, some patients died for various other reasons during the follow-up period. Therefore, the early diagnosis, treatment, full management, and regular follow-up of MPA with DAH are essential to improve survival.

In the multivariate analysis, the mortality risk of patients over 65 years was 4.30-times higher than that of patients under 65 years, suggesting that old age was a poor prognostic factor for MPA patients with DAH, which is similar to the findings of other studies[14,15,16]. Elderly patients have a poor compensatory ability, and the risk of death increases significantly when multiple organs are involved at the same time.

The mortality risk of patients with PaO_2/FiO_2 < 300 mmHg was 4.10-times higher than that of patients with PaO_2/FiO_2 ≥ 300 mmHg. The PaO_2/FiO_2 reflects the degree of lung injury from the aspect of respiratory function. Casian, *et al*[4] found that the mortality of AAV patients with DAH was as high as 50% for cases among those with respiratory failure requiring ventilator support.

In our current study, a semiquantitative CT analysis was used to evaluate the degree of lung involvement from the morphological perspective. It was found that a lung involvement area ≥ 50% was an independent predictor of survival. The degree of lung involvement varied from small lobular exudation to almost all alveoli. More research is needed to evaluate whether the lung involvement area could be used as an index to assess the severity of the disease.

Multivariate analysis showed that the risk of death in patients with sCr > 500 μmol/L was 2.04-times higher than that in patients with sCr ≤ 500 μmol/L. sCr > 500 μmol/L indicates severe vasculitis in the BSR/BHPR guidelines[8]. Most studies suggest that renal failure increases the risk of death in MPA patients with DAH[15,17]. GC and CYC pulses should be used in a timely manner to reduce mortality[12].

In our present study, LDH was a predictor of poor prognosis in the univariate analysis. In patients with H1N1 pneumonia, some researchers found that LDH content was correlated with the severity of the disease and was even an independent risk factor for death[18,19]. The elevation of the level of LDH may be related to the release of LDH into the blood caused by diffuse alveolar injury. DAH may also lead to diffuse alveolar injury, leading to the elevation of the LDH level.

In this study, BVASv.3 was associated with the risk of mortality with an HR of 1.06 in the univariate analysis; however, BVASv.3 was not identified as a predictive factor in the multivariate analysis, which is similar to the findings of other studies[17,20]. Therefore, more studies are needed to clarify whether BVASv.3 can be used as a predictive factor.

In critical cases, GC combined with CYC pulse therapy are needed[4,12,21]. Our patients have a high infection rate, which may be related to GC pulse therapy (especially when using 500–1000 mg IV MP daily for 3 days) combined with CYC and the absence of prophylactic antibiotics. The 2009 European League Against Rheumatism/European Vasculitis Study Group guidelines recommend prophylactic antibiotics in all patients being treated with CYC[22]. The CYCLOPS trial indicated pulse CYC regimen-induced remission of AAV as well as the daily oral regimen at a reduced cumulative CYC dose and caused fewer cases of leukopenia[23]. Therefore, we also preferred to choose CYC pulse therapy.

According to the 2007 BSR/BHPR guidelines[8], plasma exchange should also be considered in patients with pulmonary hemorrhage. However, among patients with severe AAV, plasma exchange did not reduce the incidence of death[24]. RTX therapy was not inferior to daily CYC treatment for the induction of remission in patients with severe AAV and may be superior in relapsing disease[25]. More studies are needed to confirm the efficacy of plasma exchange or RTX in patients with AAV.

Our study had the limitations inherent to all retrospective studies, including recall bias, limited data, and some missing data from laboratory tests. Our study was a single-center small sample study. The proportion of patients with MPA with DAH is high, and nearly half of the patients were critically ill. Even after treatment, the 5-year survival rate was low. It is particularly important to improve the understanding of the disease and to achieve early diagnosis and treatment. For patients with acute onset and rapid progression, it is necessary to identify the prognostic factors to formulate reasonable and effective treatment measures in time.

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