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The effect of pulse methylprednisolone induction therapy in Chinese patients with dialysis-dependent MPO-ANCA associated vasculitis

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ABSTRACT

Background: Pulse methylprednisolone (MP) was routinely used before commencing standard immunosuppressive therapy for induction of remission in patients with dialysis-dependent anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in spite of the paucity of evidence of benefit. The aim of this study was thus to determine whether the addition of pulse MP to standard induction immunosuppressive therapy in severe myeloperoxidase (MPO) -AAV patients who were on dialysis at onset is associated with an improvement in kidney recovery and patient survival. Furthermore, we analyzed the factors associated with restoration of kidney function and mortality in a single Chinese cohort.

Methods: 69 MPO-AAV patients who were on dialysis at the time of diagnosis were included in this study. The MP group (n = 30) received pulse MP (5–10 mg/kg/day) for 3 days before the standard immunosuppressive therapy. The Non-MP group (n = 39) had no MP pulses. The outcomes and adverse events between the two groups were compared. In addition, the predictive value of the clinical and histological parameters for kidney and patient survival was assessed using univariate and multivariate logistic regression analysis.

Result: There was no difference in patient survival, kidney recovery and the rates of adverse events between the two groups. A higher Birmingham Vasculitis Activity Score (BVAS) was shown to be a negative prognostic factor for kidney function restoration (p = 0.046, OR 0.811, 95% CI 0.660–0.997). BVAS was also demonstrated to be an independent predictor for both all-cause death (p = 0.007, OR 1.324, 95% CI 1.079–1.624) and therapy-related death (p = 0.003, OR 1.574, 95% CI 1.171–2.115). Patients' eGFR at the presentation of the disease was shown to be an independent predictor for therapy-related death (p = 0.027, OR 2.535, 95% CI 1.112–5.779).

Conclusions: This retrospective study of MPO-AAV patients who required dialysis at presentation in a single Chinese center suggests that the addition of pulse MP to standard immunosuppressive induction therapy for remission appears to confer no benefit in terms of improving patient outcomes. Further research is required to determine the role of pulse MP in severe MPO-AAV.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a common autoimmune disease which frequently causes kidney injury [1]. Microscopic polyangiitis (MPA) was the dominant form of AAV in China [2]. Although population-based data from China are rare, several reports suggested that the majority of patients in China are myeloperoxidase (MPO)-ANCA positive [3]. It has been demonstrated that even in patients with granulomatosis with polyangiitis (GPA), the proportion of MPO-ANCA was higher than proteinase 3 (PR3)-ANCA [4]. It has been recognized that there are significant differences between PR3-AAV patients and MPO-AAV patients and evidence is accumulating that PR3-AAV and MPO-AAV are two distinct diseases [5].

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The prognosis of AAV has improved significantly since the inauguration of effective immunosuppressive treatment [6,7]. The kidney is one of the most commonly involved organs in MPO-AAV [8]. The severity of kidney injury is consistently associated with poor survival [9]. There is a cumulative increase in mortality with an increased creatinine level at onset, and patients requiring kidney replacement therapy showed higher mortality compared to those not requiring dialysis [10].

It has been recommended that using steroids and either cyclophosphamide (CTX) or rituximab as induction therapy for patients with severe AAV requiring dialysis by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [11,12] and the 2016 European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) recommendations [13]. However, many physicians also frequently use pulse methylprednisolone (MP) prior to starting high dose oral steroids in addition to CTX or rituximab with or without plasmapheresis. A fundamental reason for pulse methylprednisolone may be related to its rapid and strong anti-inflammatory effect. In addition, high-dose MP may also result in a rapid decrease of ANCA-producing plasma cells [11]. The use of pulse MP must be balanced with their extensive side effects and the potentially lethal adverse effects of these drugs, such as infections. However, there have been no randomized controlled trials in severe AAV patients who were on dialysis at onset exploring whether the use of pulse MP confers a benefit or whether it is associated with harm for these patients hitherto.

Given the paucity of information with regards to benefit or harm for pulse methylprednisolone in the AAV literature, we attempted to determine whether the addition of pulse MP to standard immunosuppressive therapy for induction of remission in severe MPO-AAV patients who were on dialysis at onset is associated with an improvement in kidney recovery, survival within the first year after diagnosis. Moreover, since the mortality rate is especially high in severe AAV patients who were on dialysis at presentation [9,14,15], it is also of clinical relevance to evaluate factors associated with death. For this purpose, we retrospectively studied patients with severe MPO-AAV who were dialysis-dependent at onset from 2010 to 2017 in a single Chinese cohort.

2. Methods

2.1. Study population

This retrospective observational study included all patients with MPO-AAV, who were on dialysis at the time of diagnosis, diagnosed from January 2010 to December 2017 in the department of Nephrology, Xiangya Hospital, totally 69 patients. All patients fulfilled the 2012 Chapel Hill Consensus Conferences Nomenclature of vasculitis and were then reclassified in accordance with the algorithm suggested by the European Medicines Agency in 2007 [16,17]. Patients with eosinophilic granulomatosis with polyangiitis (EGPA) or secondary vasculitis were excluded from this study. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Xiangya Hospital (IRB approval number 201212001).

Disease activity was determined by the Birmingham Vasculitis Activity Score (BVAS) [18]. Baseline demographic data, laboratory and ultrasonography parameters were reviewed from the electronic medical record system in the hospital. The estimated glomerular filtration rate (eGFR) was determined as described previously [19].

2.2. Detection of ANCA

Both indirect immunofluorescence (IIF) assay and antigen-specific enzyme-linked immunosorbent assay (ELISA) for MPO-ANCA and PR3-ANCA in all patients were performed to detect the serum ANCA level. Standard IIF assay (Euroimmun, Lübeck, Germany) and ELISA (Inova Diagnostics, San Diego, USA) were performed in accordance with the manufacturer's instructions.

2.3. Kidney histopathology

27 out of the 69 (39.1%) patients received a kidney biopsy at the time of diagnosis and before the commencement of immunosuppressive therapy. Biopsies were independently scored by two pathologists using direct immune fluorescence, light microscopy. The biopsy specimens were assigned to 4 categories according to the definition of the 2010 histological classification [20] and a previously standardized protocol for scoring renal biopsies of patients with AAV [4]. Interstitial and tubular lesions were scored as described previously [15]. Arteriosclerosis was scored as presence or absence.

2.4. Treatment

As described previously, all the patients received the standard induction therapy including oral prednisone combined with CTX [4]. Prednisone was prescribed at a commencing dosage of 1 mg/kg/day for 4–6 weeks, with a gradual reducing to 12.5–15 mg by 3 months. CTX was administered by intravenous 0.5 g/m^2 every month. Twenty-five percent dose reduction of CTX was made for those over 65 years old. CTX was conditionally withdrawn for patients who developed leukocytopenia. Intravenous CTX every 3 months or daily oral azathioprine (AZA) or mycophenolate mofetil (MMF) was given for maintenance therapy for at least 2 years. Patients who have taken azathioprine for maintenance therapy were given 2 mg/kg/d of azathioprine (maximum 200 mg) after remission is achieved. The dose was reduced to 1.5 mg/kg/d after 12 months.

The MP group received intravenous pulse MP (5–10 mg/kg/day) for 3 days before the standard induction therapy. The Non-MP group had no intravenous pulse MP. All the patients had no plasmapheresis.

2.5. Outcomes

In this study, the clinical outcome variables were dialysis dependence, dialysis independence, and death at 12 months. We also collected data over the first 12 months post AAV diagnosis and commencement of therapy as follows: infections, leukopenic episodes (white cell count $< 4 \times 10^9$/L), thrombocytopenia episodes (platelet count $< 100 \times 10^9$/L) and diagnosis of new-onset diabetes mellitus. As described previously [21], severe infections were defined as those requiring hospitalization or treatment with intravenous and/or prolonged antibiotics. In addition, herpes zoster recurrences were also considered to be severe infections as they reflected consistent treatment- induced immunosuppression [21]. All the severe infections were classified according to the site of infection and pathogenic microorganisms.

2.6. Statistical analysis

All continuous variables are presented as mean ± standard deviation or median with interquartile range. Categorical variables are presented as frequencies. Analyses were performed using SPSS statistical software (version 23.0). To compare the difference between two groups when the continuous data fitted a normal distribution, an unpaired Student's *t*-test was used. To compare the differences for nonparametric data between the groups, the Mann–Whitney *U* test was used. Differences between qualitative results were compared by means of the chi-square test. Kaplan-Meier survival analysis was used to assess kidney and patient survival. If the p-value was < 0.05 (2-sided), the difference was considered to be significant. Univariate and multivariate logistic regression analysis was utilized to assess kidney survival as well as patient survival. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI).

Table 1
Baseline clinical and serologic characteristics of the patients in MP group and non-MP group.

	Total (n = 69)	MP group (n = 30)	Non-MP group (n = 39)	p value[a]
Male/female	42/27	21/9	21/18	0.173
Age, year (mean, SD)	57.12 ± 17.08	59.6 ± 15.11	55.20 ± 18.41	0.293
Duration of disease, d	65.65 ± 50.26	61.70 ± 49.56	68.69 ± 51.21	0.571
White blood cells (10^9/L)	9.5 ± 4.99	8.844 ± 3.378	10.01 ± 5.939	0.339
Hemoglobin, g/L	72.57 ± 15.31	73 ± 16.19	72.23 ± 14.80	0.838
Platelet (10^9/L)	213.8 ± 89.95	217.87 ± 96.70	210.67 ± 85.55	0.744
Serum albumin (g/L)	41.03 ± 16.83	39.15 ± 16.57	42.46 ± 17.09	0.421
Serum globulin (g/L)	29.86 ± 6.32	29.49 ± 6.557	30.14 ± 6.205	0.676
Proteinuria, g/d	1.52 ± 0.81	1.65 ± 0.812	1.428 ± 0.812	0.265
Scr, μmol/L	736.1 ± 200.59	744.28 ± 240.1	729.89 ± 166.9	0.769
eGFR (mL/min/1.73 m^2)	6.22 ± 1.82	6.228 ± 1.693	6.205 ± 1.931	0.959
ESR (mm/h)	58.42 ± 36.34	65.6 ± 39.13	52.89 ± 33.50	0.151
CRP (mg/L)	52.75 ± 59.26	57.11 ± 56.72	49.39 ± 61.66	0.595
C3, mg/L	675.38 ± 207.37	648.84 ± 220.03	696.77 ± 197.60	0.395
C4, mg/L	226.12 ± 109.61	246.32 ± 109.72	209.83 ± 108.53	0.219
IgA, mg/L	2226.59 ± 847.65	2265.16 ± 859.32	2195.48 ± 851.04	0.763
IgG, g/L	13.39 ± 4.88	13.15 ± 5.43	13.58 ± 4.47	0.748
IgM, mg/L	885.29 ± 422.07	933.04 ± 404.44	846.78 ± 438.53	0.452
Left kidney length (cm)	10.25 ± 1.08	10.72 ± 1.21	9.882 ± 0.806	0.002
Right kidney length (cm)	10.13 ± 1.08	10.56 ± 1.10	9.802 ± 0.948	0.003
BVAS	15.3 ± 3.47	15.53 ± 3.43	15.12 ± 3.53	0.634
Pulmonary hemorrhage, n (%)	20(28.99%)	9(30%)	11(28.21%)	0.871
Total cyclophosphamide dose (12 months), g (median, IQR)	4.8(4.8,4.8)	4.8(4.8,4.8)	4.8(4.8,4.8)	0.580
Comorbidities				
Hypertensive diseases, n (%)	44(63.77%)	18(60%)	26(66.67%)	0.619
Ischemic heart diseases, n (%)	10(14.49%)	4(13.33%)	6(15.39%)	> 0.999
Diabetes mellitus, n (%)	5(7.25%)	2(6.67%)	3(7.69%)	> 0.999
Osteoporosis, n (%)	13(18.84%)	3(10%)	10(25.64%)	0.128

[a] Comparison between MP group and Non-MP group.

3. Results

3.1. Subject characteristics

Altogether 69 MPO-AAV patients were included in this study. There were 30 patients in the MP group and 39 patients in the Non-MP group. 60/69 (87.0%) patients were classified as MPA, 6/69 (8.7%) patients were classified as GPA and 3/69 (4.3%) as renal limited vasculitis (RLV).

The baseline clinical characteristics of this study population are described in Table 1. There were no significant differences in demographic and laboratory results at baseline between MP group and Non-MP group, with the exception of that the ultrasonic kidney length was significantly less in the Non-MP group than that in the MP group. No significant difference with regard to the total CTX dose over the first 12 months following diagnosis was found between two groups. With regard to common comorbidities, no statistically significant differences were found for hypertensive diseases, ischemic heart disease and diabetes mellitus between MP group and Non-MP group. Compared with MP group, patients in Non-MP group had an increase in the rate of osteoporosis, though this finding was not statistically significant.

Only 27 patients in this study had kidney biopsy (13 biopsies in the MP group and 14 biopsies in the Non-MP group). The renal histopathology was compared between the MP group and the Non-MP group in Table 2. Compared with the Non-MP group, patients in the MP group had a higher percentage of cellular crescents ($p < 0.05$). Moreover, patients in the MP group had less severity of tubular atrophy ($p < 0.05$). No significant differences in proportions of normal glomeruli, fibrous crescents, glomerular global sclerosis, interstitial fibrosis or arteriosclerosis were found between two groups. Patient biopsies in both groups divided by EUVAS classification were comparable [20].

3.2. Outcomes and adverse events

No difference with regard to the kidney recovery was found between two groups, with 23.3% of patients in the MP group and 20.51% of patients in the Non-MP group having achieved renal recovery by 12 months ($p = 0.778$) (Table 3). Similarly, no difference in overall survival between patients was found in both groups (Fig. 1 and Table 3). By the end of observation, 8 patients in the MP group and 9 patients in the Non-MP group died ($p = 0.737$); Severe infection was the leading cause of death, followed by cardiovascular diseases. 15 patients (50%) in MP group and 22 patients (56.41%) in Non-MP group were on maintaining dialysis ($p = 0.597$).

As shown in Table 4, infection was the most common form of adverse events in both groups. There was no significant difference for infections overall as well as severe infections between MP group and the Non-MP group by the end of 12 months. As shown in Supplemental Table 1, all the severe infections were classified according to the site of infection and pathogenic microorganisms. Pulmonary infection was the most common site of infection in both groups. Additionally, the rates of thrombocytopenia and leukopenia were similar between both groups. Although there was a trend toward higher rate of new onset diabetes in MP group compared with the Non-MP group, this did not reach statistical significance. There was no difference with regard to the rates of adverse events in the first 3 months following diagnosis (Supplemental Fig. S1) and commencement of therapy or during 3 and 12 months.

3.3. Predictors of dialysis independence

In order to assess histological predictors for dialysis independence, only those who received renal biopsy (n = 27) were included for analysis. In order to determine clinical predictors for dialysis independence, all patients (n = 69) were included.

We then reclassified 69 patients into two groups according to the outcomes. 15 patients with the outcome of dialysis independence were classified in one group while 54 patients with the outcome of death or maintaining dialysis were classified in the other group. The characteristics of both groups were compared in Table 5. The duration of the disease in dialysis independent group was significantly shorter than that in the group of death or maintaining dialysis (50.60 ± 20.56 vs

Table 2
The pathological characteristics of patients in MP group and Non-MP group.

	MP group (n = 13)	Non-MP group (n = 14)	p value
Normal glomeruli % (median, IQR)	9.09 (2.6/11.8)	10.42(0/20.36)	0.787
Glomerulosclerosis % (median, IQR)	18.18 (8.9/30.8)	40.40 (16.1/61.7)	0.058
Cellular crescent % (median, IQR)	33.33 (19.6/46.1)	14.58 (0/22.3)	0.009
Fibrous crescents % (median, IQR)	19.05 (12.8/32.3)	22.65 (18.6/35.4)	0.225
Interstitial infiltrates (−/+/++/+++) (case)	0/5/7/1	0/4/8/2	0.513
Interstitial fibrosis (−/+/++) (case)	0/12/1	0/11/3	0.325
Tubular atrophy (−/+/++) (case)	0/13/0	0/10/4	0.040
Arteriosclerosis (−/+) (case)	12/1	9/5	0.165
EUVAS classification (focal/mixed/crescentic/sclerotic)	0/2/10/1	0/3/5/6	0.091

Table 3
The patient outcomes in MP group and Non-MP group.

	MP group (n = 30)	Non-MP group (n = 39)	P value
Dialysis independent	7,23.33%	8,20.51%	0.778
On dialysis	15,50%	22,56.41%	0.597
Dead	8,26.67%	9,23.08%	0.737
Severe infections	5,62.5%	7,77.78%	
Pneumonia infection	4,50%	5,55.56%	
Sepsis	1,12.5%	2,22.22%	
Cardiovascular diseases	2,25.0%	1,11.11%	
Unknown	1,12.5%	1,11.11%	

Table 4
Adverse events in MP group and Non-MP group.

Adverse events	MP group (n = 30)	Non-MP group (n = 39)	p value
Infection	15(50%)	17(43.59%)	0.597
Severe infection	10(33.33%)	12(30.77%)	0.821
Mild infection	5(16.67%)	5(12.82%)	0.719
Thrombocytopenia	6(20%)	7(17.95%)	0.829
Leukopenia	8(26.67%)	8(20.51%)	0.548
Diabetes	5(16.67%)	3(7.69%)	0.281

69.83 ± 55.20, $p < 0.05$). As shown in Table 6, multivariable analysis showed that BVAS was shown to be associated with kidney function restoration independently (p = 0.046, OR 0.811, 95% CI 0.660–0.997). No histological parameter was found to be independently associated with renal function restoration.

3.4. Factors associated with mortality

By using multivariate analysis, BVAS was also demonstrated to be an independent predictor for both all-cause death (p = 0.007, OR 1.324, 95% CI 1.079–1.624) and therapy-related death (p = 0.003, OR 1.574, 95% CI 1.171–2.115), which were due to secondary infection caused by immunosuppressive therapy, as described in the EUVAS study [14]. Patients' eGFR at onset of the disease was also manifested to be an independent predictor for therapy-related death (p = 0.027, OR 2.535, 95% CI 1.112–5.779).

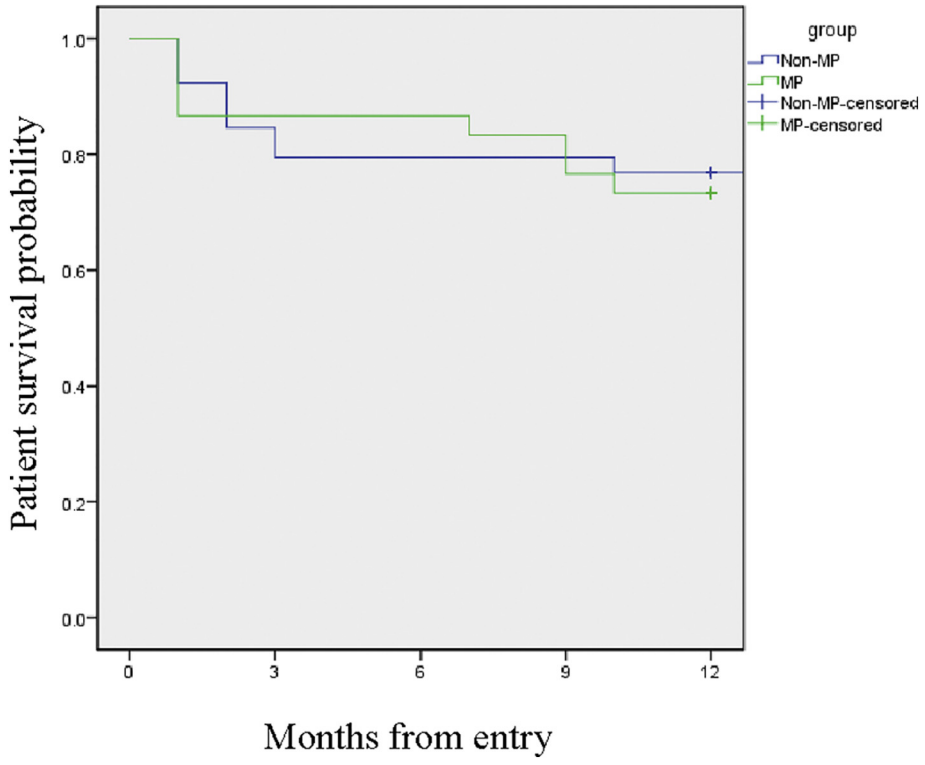

Fig. 1. Patient survival (Kaplan-Meier) in intravenous pulse methylprednisolone group (MP) versus Non-MP group (p = 0.757).

Table 5
General data of patients with different outcomes.

	Dialysis independent (n = 15)	On dialysis/died (n = 54)	p value
MP/non-MP	7/8	23/31	0.778
Male/female	8/7	34/20	0.499
Age, year (mean, SD)	60.07 ± 9.11	56.30 ± 18.69	0.282
Duration of disease, d	50.60 ± 20.56	69.83 ± 55.20	0.041
White blood cells (10^9/L)	11.72 ± 7.83	8.89 ± 3.74	0.193
Hemoglobin, g/L	72.00 ± 11.66	72.72 ± 16.27	0.873
Platelet (10^9/L)	237.53 ± 78.56	207.20 ± 92.45	0.251
Serum albumin (g/L)	42.41 ± 17.56	40.64 ± 16.77	0.723
Serum globulin (g/L)	30.85 ± 6.57	29.58 ± 6.28	0.495
Proteinuria, g/d	1.55 ± 0.86	1.52 ± 0.81	0.879
Scr, μmol/L	729.50 ± 300.97	737.93 ± 166.37	0.887
eGFR (mL/min/1.73 m^2)	6.30 ± 2.03	6.19 ± 1.78	0.845
ESR (mm/h)	57.73 ± 37.12	58.61 ± 36.47	0.935
CRP (mg/L)	48.98 ± 65.56	53.80 ± 58.02	0.783
C3, mg/L	692.54 ± 250.10	670.19 ± 195.75	0.737
C4, mg/L	241.44 ± 141.90	221.49 ± 99.42	0.57
IgA, mg/L	2154.23 ± 837.65	2248.47 ± 859.25	0.729
IgG, g/L	14.49 ± 4.64	13.05 ± 4.96	0.619
IgM, mg/L	991.77 ± 412.80	853.10 ± 424.29	0.304
Left kidney length (cm)	10.14 ± 0.71	10.28 ± 1.17	0.665
Right kidney length (cm)	10.10 ± 0.79	10.14 ± 1.15	0.898
BVAS	14.07 ± 2.55	15.65 ± 3.63	0.119
Pulmonary hemorrhage, n (%)	3,20%	17,31.48%	0.585
Normal glomeruli % (median, IQR)	8.68(1.3, 24.6)	9.09(0, 12.5)	0.747
Glomerulosclerosis % (median, IQR)	26.90(9.2, 35.6)	20(12.5, 60)	0.71
Cellular crescent % (median, IQR)	21.59(9.8, 39.9)	21.4(5.9, 44.44)	0.873
Fibrous crescents % (median, IQR)	25.15(12.4, 42.4)	22.2(16.7,33.3)	0.79
Interstitial infiltrates (−/+/++/+++) (case)	0/3/5/0	0/6/10/3	0.699
Interstitial fibrosis (−/+/++) (case)	0/8/0	0/15/4	0.285
Tubular atrophy (−/+/++) (case)	0/6/2	0/17/2	0.558
Arteriosclerosis (−/+) (case)	7/1	14/5	0.633
EUVAS classification (Focal/Mixed/ Crescentic/sclerotic)	0/2/5/1	0/3/10/6	0.621

Table 6
Predictors for dialysis independence.

Predictor	Odds ratio (95% CI)	p value
Age	1.019(0.975–1.066)	0.406
Duration of disease	0.990(0.972–1.008)	0.257
White blood cells	1.115(0.972–1.278)	0.119
Platelet	1.001(0.994–1.009)	0.716
BVAS	0.811(0.660–0.997)	0.046

4. Discussion

In this retrospective study, we found no difference in overall patient survival or kidney recovery by 12 months between patients that received pulse MP in addition to standard induction therapy and those that did not receive pulse MP, despite that the ultrasonic kidney length was significantly less in Non-MP group than that in the MP group and patients in the MP group had a higher percentage of cellular crescents and less extent of tubular atrophy. These results are in line with a recently published retrospective analysis of a large cohort of patients who presented with severe AAV in five large vasculitis centers in Europe and the United States [22]. However, in contrast to our findings, a recently published study by Ma et al. from China suggested that the use of MP might improve the long-term outcomes in Chinese patients presenting with severe renal involvement [23]. The fact for this difference could be due to several reasons. The most plausible explanation for this difference may be due to the unbalanced distribution of biopsies between the MP group and the Non-MP group in the Ma et al. study. Patients in the Non-MP group might have a higher burden of chronic and fibrotic changes, potentially accounting for the inferior kidney recovery outcomes in Non-MP treated patients in that study. Alternatively, there was a trend toward increased serum creatinine and urine protein in Non-MP treated patients in the study of Ma et al., although the differences observed did not reach statistical significance. Since the severity of renal dysfunction and urine protein are associated with poor outcomes of AAV patients [7], it is reasonable to postulate all these factors together result in inferior kidney recovery outcomes in Non-MP treated patients in the Ma et al. study.

Furthermore, there was no difference in adverse events between groups in this study. This data is consistent with that obtained by Ma et al. [23] but is somewhat inconsistent with that obtained by Chanouzas et al. [22]. The reason for this difference is unclear. We suspect that one plausible explanation for this difference is the dissimilarity of genetic background for the patients recruited in different studies. Although the difference did not reach statistical significance, there was a trend toward higher rate of new onset diabetes in MP group compared with the Non-MP group. Therefore, we speculated that there might be a significant difference of new onset diabetes between two groups if we enroll in more patients in the future study.

In our cohort, a high BVAS at presentation was the main significant negative prognostic factor for patient survival and renal function restoration. Importantly, patients' eGFR at onset of the disease was also shown to be an independent predictor for therapy-related death. Our data are in accordance with that obtained by other investigators [10,25,26]. Somewhat unexpectedly in this study, no histological parameter was found to be independently associated with renal function restoration and mortality. The most plausible explanation may be that only about 40% of the patients received kidney biopsy in this study, which might lead to some bias and reduce the power to demonstrate associations between renal biopsy findings and outcomes. The main reason for this low rate of the renal biopsy was that some patients had contraindications for renal biopsy, for example, poor kidney structure implied by the kidney ultrasonic examination. Another important reason was that some patients were reluctant to receive an invasive examination. In addition, lack of medical insurance was also a reason for some patients refused to take kidney biopsy.

Since our study was a retrospective study from a single Chinese center, it has several limitations. First, none of the patients in this study received plasmapheresis, which could be due to several reasons. On one hand, limited by economic factors and the shortage of plasma, plasmapheresis might not be performed sufficiently in those who receive plasmapheresis in our center. On the other hand, 2012 KDIGO guidelines strongly recommended the addition of plasmapheresis for patients who were on dialysis at presentation [11]. The recommendation was mainly based on the results of a large, multicenter controlled trial-the MEPEX trial [14]. Short-term results of the trial suggested plasmapheresis improved kidney recovery [14]. Nevertheless, after a median of almost 4 years follow-up, there was no evidence of a net difference between plasmapheresis and MP in clinical outcomes [24]. More recently, the primary results of the Plasma Exchange and Glucocorticoids for Treatment of Antineutrophil Cytoplasm Antibody–Associated Vasculitis (PEXIVAS) trial (NCT00987389) revealed that plasmapheresis does not reduce the risk of end-stage renal disease or death in patients with AAV [27]. Second, as mentioned above, only about 40% of the patients received renal biopsy, which might lead to some bias and reduce the power to demonstrate associations between renal biopsy findings and outcomes. Third, with the retrospective nature of data collection, the maintaining immunosuppressive regimen in two groups was not unified. Fourth, the numbers of patients on both groups are

relatively small in this study. In addition, due to inclusion of only a small number of patients in the present study, there may have been a selection bias. Therefore, a well-designed, randomized, controlled study with larger sample size is needed to further confirm the results.

In conclusion, this retrospective study of MPO-AAV patients who required dialysis at presentation in a single Chinese center suggests that the addition of intravenous pulse MP to standard induction of remission therapy with CTX and high-dose oral steroids may not confer any benefit in terms of improving patient outcomes. Among patients with severe MPO-AAV who were dialysis-dependent at presentation, the main causes of death within the first year were infection and cardiovascular disease. Those with higher BVAS have less chance of restoration of renal function. Increased risk for all-cause death and therapy-related death appears to be higher BVAS. Patients' eGFR at the presentation of the disease was also shown to be an independent predictor for therapy-related death. Given the poor outcomes of patients with severe AAV, more targeted and improved treatments are urgently needed.

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Declaration of competing interest

The authors declare no competing interests.

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