


## RESEARCH ARTICLE

# Clinical efficacy of plasma exchange in patients with autoimmune encephalitis

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## Introduction

Autoimmune encephalitis (AE), with an estimated incidence of 1.4–1.5 per million population per year,<sup>1</sup> is a potentially reversible disorder with a good clinical outcome if diagnosed and treated promptly. However, fulminant cases remain a challenge, and fatal cases are still seen. As an example, 75% of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis patients may require care in the intensive care unit (ICU).<sup>2</sup> Severe AE patients are in critical condition and may have status epilepticus, serious autonomic nervous dysfunction, central hypoventilation leading to respiratory failure, and consciousness disorders. The relatively high rate of ICU admissions highlights the importance of increasing knowledge about potentially critical conditions and preventing detrimental courses in patients with AE.<sup>3</sup>

## Abstract

**Objective:** To determine the clinical and antibody response after therapeutic plasma exchange (TPE) in patients with severe refractory antibody-associated autoimmune encephalitis (AE). **Methods:** This single-center prospective cohort included all patients consecutively admitted to our hospital because of severe refractory AE over the period from July 2014 to June 2019. All patients received immunotherapy (steroids, intravenous immunoglobulin (IVIG), and/or TPE). The primary outcome was evaluated at 1- and 2-month postenrollment, and the long-term outcome was followed up at 6 and 12 months. AE antibody titers in the cerebrospinal fluid and plasma were evaluated before and after TPE/IVIG. **Results:** This study enrolled 57 patients with severe refractory AE, including anti-NMDA receptor encephalitis ( $n = 51$ ), anti-GABA<sub>B</sub> receptor encephalitis ( $n = 3$ ), anti-LGI 1 encephalitis ( $n = 2$ ), and anti-AMPA receptor encephalitis ( $n = 1$ ). Of all 57 patients, 33 patients received TPE for a total of 193 procedures, and 24 patients with contraindications or refusal of TPE were in the non-TPE group. Compared with the non-TPE group, the TPE group exhibited greater clinical improvement: 21 (37%) versus 8 (14%) after 1 month ( $P = 0.03$ ) and 31 (54%) versus 16 (28%) after 2 months ( $P = 0.01$ ), respectively. Complications and adverse events associated with TPE occurred in 91 procedures (47%) without serious adverse events associated with the use of TPE. **Interpretation:** TPE might be an effective rescue therapy associated with rapid functional improvement in patients with severe steroid/IVIG refractory antibody-associated AE from this nonrandomized control trial.

Therapeutic plasma exchange (TPE) is one of the recommended treatments for AE because of its immune-mediated pathogenesis.<sup>4–7</sup> The aim of TPE is to remove putative disease mediators from the body, such as toxic macromolecules and pathogenic autoantibodies.<sup>8</sup> However, the use of TPE in the treatment of AE is still limited for various reasons, including plasma accessibility, cost, and other considerations, such as the lack of sufficient scientific evidence revealing the therapeutic mechanism of TPE. These are real-world challenges that neurologists face despite mounting evidence of the benefits of TPE.<sup>9</sup> Whether TPE can rapidly relieve or control severe steroid/intravenous immunoglobulin (IVIG)-refractory antibody-associated AE is not clear. In addition, whether TPE is effective for AE involving intrathecal autoantibody synthesis in cerebrospinal fluid (CSF) antibody-positive but serum antibody-negative patients remains unclear.

Therefore, this single-center, prospective cohort study aimed to explore the clinical efficacy of TPE and its effects on antibody titers in patients with severe refractory antibody-associated AE.

## Materials and Methods

### Patients

Patients with severe refractory antibody-associated AE who were consecutively admitted to the neurological ICU at the Xuanwu Hospital of Capital Medical University between 1 July 2014, and 30 June 2019, were enrolled. The inclusion criteria were as follows: (1) 14–65 years old; (2) met all three of the following AE diagnostic criteria<sup>10</sup>: (i) subacute onset (rapid progression of <3 months) of working memory deficits, altered mental status, or psychiatric symptoms; (ii) at least one of the following: new focal central nervous system (CNS) findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis (white blood cell count of more than five cells per mm<sup>3</sup>), magnetic resonance imaging (MRI) features suggestive of encephalitis, and (iii) reasonable exclusion of alternative causes; (3) the presence of antibody in serum or CSF indicating a positive diagnosis of AE; (4) critically ill with a modified Rankin scale (mRS) score<sup>11</sup> of 3–5, respiratory failure requiring mechanical ventilation, disturbances of consciousness, or status epilepticus; (5) no improvement after steroid and/or IVIG treatment for at least 10 days from the end of initial immunotherapy; and (6) informed consent obtained from family members. This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, adhered to the tenets of the Declaration of Helsinki and was registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-14004931).

### Treatment protocol

All patients received tumor screening, symptomatic supportive treatment, and immunotherapy after enrollment in this study. All patients with tumors underwent tumor resection. First-line immunotherapy included intravenous glucocorticoid therapy (1000 or 500 mg of methylprednisolone for 3 or 5 days, followed by a gradual dose reduction), IVIG (0.4 g/kg per day for each course for 5 days), and/or TPE (3–5 procedures in each course). The relevant contraindications of TPE included severe active hemorrhage, disseminated intravascular coagulation, severe hypotension or shock, unstable cardiac failure, cerebral hernia, bloodstream infection, severe abnormal mental behaviors, and other dangerous conditions. Patients without TPE contraindications whose families signed an informed consent form were treated with

TPE. According to the TPE treatment status, patients were divided into a TPE group and a non-TPE group. In the TPE group, the patients simultaneously accepted steroids and TPE, as well as IVIG after TPE. In the non-TPE group, the patients simultaneously accepted steroids and IVIG. The patients accepted one more course of TPE in the TPE group or one more course of IVIG in the non-TPE group if they did not have any clinical response to the first course of TPE/IVIG after 3 weeks.

Patients without contraindications and whose families signed an informed consent received second-line immunotherapy with immunosuppressants (rituximab, cyclophosphamide, mycophenolate mofetil, or azathioprine) after the first course of TPE/IVIG 4 weeks later.

### TPE treatment

TPE treatments were performed using a MultiFiltrate apheresis device (Fresenius, Bad Homburg, Germany). Treatments were administered every other day, with breaks allowed on weekends for most patients. Plasma removed during TPE was replaced with a substitute fluid: 5% albumin with 0.9% saline and plasma. The volume exchanged was 1 plasma volume for each procedure. The plasma volume was estimated according to the following formula: plasma volume (in liters) =  $0.07 \times \text{weight (kg)} \times (1 - \text{hematocrit})$ . Heparin was added to the exchange circuit to prevent blood clotting within the equipment. The rates of removal and replacement were monitored, recorded, and balanced to prevent cardiovascular instability; blood pressure and other vital signs were closely monitored at 15-min intervals throughout the exchange, and urine output was measured.

The complications and adverse events associated with TPE were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines<sup>11</sup>: Grade 1 was defined as mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 was defined as moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Grade 3 was defined as severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living. Grade 4 was defined as life-threatening consequences; urgent intervention indicated. Grade 5 was defined as death related to adverse event.

### Data collected and outcomes evaluated

The data collected included demographics (age, sex), time of onset, clinical manifestations, presence of tumors, AE

antibody titers in the CSF and plasma, mRS score upon study enrollment, disease duration prior to immunotherapy (steroids, IVIG, TPE), number of TPE sessions, and clinical outcomes. All serum and CSF antibodies were measured using indirect immunofluorescence test (IIFT) kits that were purchased from EUROIMMUN AG (Lübeck, Germany) and used according to the manufacturer's instructions. Samples were classified as strong positive (titer of 1:100 and above), positive (1:32), weak positive (1:10), and negative according to the antibody titer levels in plasma and CSF.

The primary outcome was evaluated at 1- and 2-month postenrollment in this study. The presence of clinical improvement (fulfilling one of the following criteria) included (1) an mRS<sup>12</sup> score decrease in at least 1, (2) a status change from disturbed consciousness to conscious, (3) an improvement from ventilator-assisted treatment to removal of the ventilator, and (4) an improvement from epilepsy to no seizures.

The long-term outcome was evaluated at 6 and 12 months after enrollment. The mRS<sup>12</sup> was used for outcome evaluations. After discharge, outcome evaluations were performed during a clinical visit to an experienced neurologist who was blinded to the clinical manifestations and treatments or performed by telephone follow-up. The evaluation standards were as follows: an mRS<sup>12</sup> score of 0–2 indicated a favorable outcome, and an mRS score of 3–6 indicated an unfavorable outcome.

### Assessments of antibody titers after TPE/IVIG

In the TPE group, the CSF and plasma samples were collected to check AE antibody titers before initiating the first TPE procedure and within 3 days after the final TPE procedure of the first course. In the non-TPE group, AE antibody titers in the CSF and plasma were evaluated before initiating the first IVIG and after the first course of IVIG 1 week later.

### Statistical analysis

Statistical analyses were performed with the statistical software SPSS 22.0 (IBM Corporation, Armonk, NY). The Kolmogorov–Smirnov test was used to check the normality of continuous data. Normally distributed data were expressed as the mean  $\pm$  standard deviation, whereas nonnormally distributed data were expressed as the median (interquartile range, IQR). Student's *t*, Mann–Whitney *U* or chi-square tests were used for intergroup comparisons, when appropriate. Binary data were analyzed using Fisher's exact test to examine the differences in each observed indicator between the TPE and non-TPE

groups. All analyses were two-tailed, and  $P < 0.05$  was considered statistically significant.

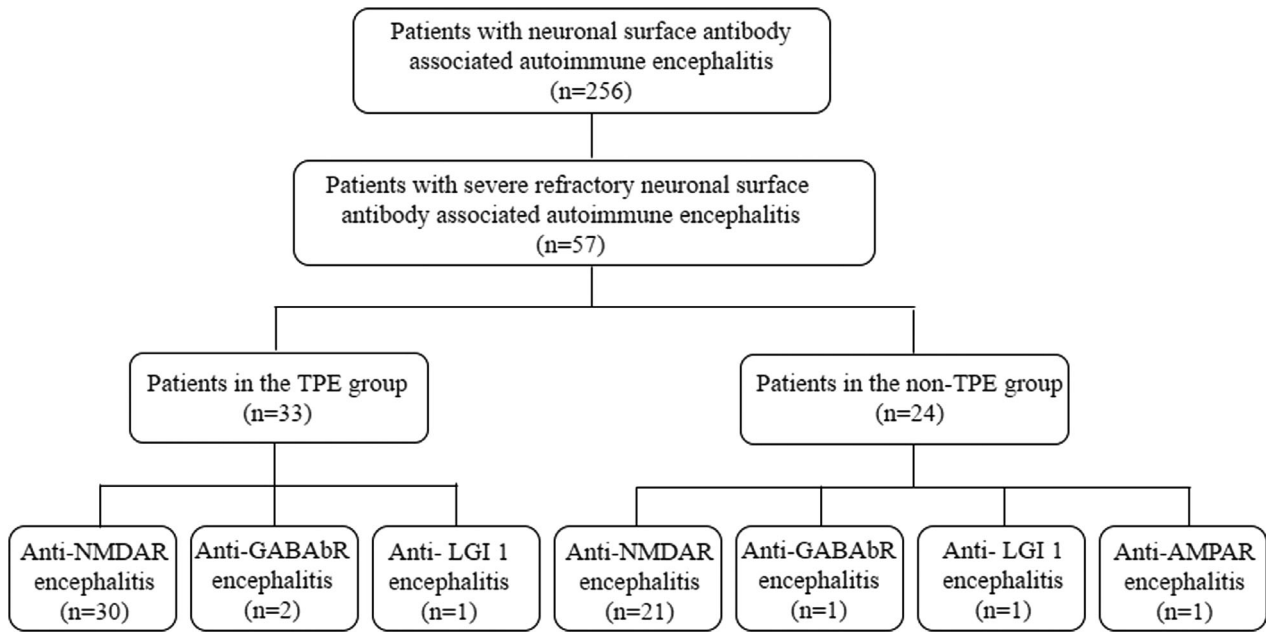
## Results

### Patient characteristics

This study enrolled 57 patients (Fig. 1) with severe refractory antibody-associated AE, including 30 males (53%) and 27 females (47%) (Table 1). The median age of the patients was 26 years (IQR 21, 40). Diagnoses included anti-NMDAR encephalitis ( $n = 51$ ), anti-gamma-aminobutyric acid receptor type b (GABA<sub>B</sub>R) encephalitis ( $n = 3$ ), anti-leucine-rich glioma inactivated 1 (LGI 1) encephalitis ( $n = 2$ ), and anti- $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) encephalitis ( $n = 1$ ). All 57 patients, except 10 patients with contra-indications (4 cause severe hypotension, 3 cause bloodstream infection, and 3 cause severe abnormal mental behaviors), were offered TPE. Fourteen patients' families refused consent for TPE. The other 33 patients (17 male, 16 female) were treated by TPE (TPE group). The 24 patients with contraindications or refusal of TPE were combined with the non-TPE group.

Of all the patients, 58% had prodromal symptoms of fever, headache, or upper respiratory tract infection. The three most common clinical manifestations of severe AE patients were disturbance of consciousness (93%), mental behavior disorder (86%), and epileptic seizures (81%). The number of patients with epileptic seizures or autonomic nervous dysfunction in the TPE group was greater than that in the non-TPE group ( $P < 0.05$ ). Fifty-three patients (93%) had electroencephalogram abnormalities. Thirty-two patients (56%) had brain MRI abnormalities (Table 1).

The median duration between onset of the most recent event and TPE initiation was 43 days (range 13–300). All patients ( $n = 33$ ) initially received medical immunotherapy, including high-dose steroids or IVIG, prior to TPE, with a median treatment duration of 21 days (range 10–150). Thirty-one patients initially received high-dose steroids prior to TPE, with a median treatment duration of 18 days (range 10–150). Because three female patients' weights were less than 50 kilograms, they received intravenous 500 mg methylprednisolone pulse therapy; two of the patients were in the TPE group, and one was in the non-TPE group. The other 28 patients received intravenous 1000 mg methylprednisolone pulse therapy. Twenty-five patients initially received IVIG prior to TPE, with a median treatment duration of 25 days (range 14–140). Twenty-three patients initially received both high-dose steroids and IVIG before TPE. There were no significant differences in the days between onset and



**Figure 1.** Flowchart for patient selection.

steroids/IVIG in the non-TPE group and the TPE group (Table 2).

All 33 patients received TPE for a total of 193 procedures. Twenty-six patients received one TPE course, and seven received two TPE courses. The majority of patients received an average of five TPE procedures (range, 3–10 procedures).

### Clinical response to TPE

Clinical response and outcomes are shown in Table 2. A comparison of improvements in clinical manifestations between the TPE group and the non-TPE group revealed significant differences at 1- and 2-month post enrollment. Compared with the non-TPE group, the TPE group exhibited greater clinical improvement: 21 (37%) versus 8 (14%) after 1 month ( $P = 0.03$ ) and 31 (54%) versus 16 (28%) after 2 months ( $P = 0.01$ ), respectively. Compared with the non-TPE group, the TPE group exhibited greater mRS improvement: 12 (36%) versus 4 (17%) after 1 month ( $P = 0.03$ ) (Fig. 2) and 18 (55%) versus 10 (42%) after 2 months ( $P = 0.01$ ) (Fig. 3), respectively. However, there were no significant differences in outcomes between the TPE group and the non-TPE group after 6 and 12 months.

### Adverse events associated with TPE

Complications and adverse events associated with TPE occurred in 91 procedures (47%) (Table 3). Only once

did hypotension, and twice did clots in the TPE tubes lead to interruptions in TPE procedures. No serious adverse events or treatment-related deaths were detected. Hypotension occurred during 56 (29%) procedures, including transient hypotensive episodes that responded to either a fluid bolus or vasopressor treatment during 55 procedures and more serious hypotension (65/40 mmHg) that required discontinuation of TPE during 1 procedure. During the 193 TPE procedures, the occurrence of involuntary movements increased during 45 (32%) procedures in patients who already had involuntary movements prior to the TPE procedures; during 44 of these 45 procedures, the patients needed sedatives or increased doses of the original sedatives to continue TPE. Clots in the TPE tube occurred during 2 (1.0%) procedures, and TPE had to be discontinued. The patient's body temperature increased during 1 (0.5%) procedure, and it returned to normal 4-h post-TPE. One patient experienced an anaphylactic reaction that manifested as bilateral conjunctival edema during 1 (0.5%) procedure; the patient was treated with antiallergic therapy, and the symptoms disappeared after 1 day.

### Antibody titers after immunotherapy

The antibody titers of CSF decreased after immunotherapy in 21 patients (21/57, 37%) (Table 2). The proportion of patients with decreasing CSF antibody titers in the TPE group was higher than that in the non-TPE group (17 [30%] versus 4 [7%],  $P = 0.01$ ). In the TPE group,

**Table 1.** Demographics and clinical manifestations of patients with severe refractory AE.

	Total (n = 57)	Non-TPE (n = 24)	TPE (n = 33)	P value
Male, n (%)	30 (53)	13 (54)	17 (52)	1.00
Age, y, median (IQR; range)	26 (21, 40)	30 (22, 60)	25 (21, 32)	0.14
Prodromal symptoms, n (%)	33 (58)	15 (63)	18 (55)	0.60
First onset, n (%)	54 (95)	23 (96)	31 (94)	1.00
Clinical manifestations, n (%)				
Disturbance of consciousness	53 (93)	22 (92)	31 (94)	1.00
Mental behavior disorder	49 (86)	19 (79)	30 (91)	0.26
Epileptic seizures	46 (81)	15 (63)	31 (94)	0.01
Status epilepticus	9 (16)	4 (17)	5 (15)	1.00
Involuntary movements	44 (77)	17 (71)	27 (82)	0.36
Central hypoventilation	38 (67)	16 (67)	22 (67)	1.00
Autonomic nervous dysfunction	25 (44)	6 (25)	19 (58)	0.02
Antibodies, n (%)				
NMDAR	51 (90)	21 (88)	30 (91)	0.69
GABA <sub>B</sub> R	3 (5)	1 (4)	2 (6)	1.00
LGI 1	2 (4)	1 (4)	1 (3)	1.00
AMPA <sub>R</sub>	1 (2)	1 (4)	0 (0)	0.42
CSF antibody titer, n (%)				
Negative	0 (0)	0 (0)	0 (0)	1.00
Weakly positive	6 (11)	3 (13)	3 (9)	0.69
Positive	28 (49)	15 (63)	13 (39)	0.11
Strongly positive	23 (40)	6 (25)	17 (52)	0.06
Plasma antibody titer, n (%)				
Negative	24 (42)	11 (46)	13 (39)	0.79
Weakly positive	14 (25)	7 (29)	7 (21)	0.54
Positive	17 (30)	6 (25)	11 (33)	0.57
Strongly positive	2 (4)	0 (0)	2 (6)	0.50
Pressure of lumbar puncture, mmH <sub>2</sub> O, mean ± SD	197 ± 8	188 ± 61	203 ± 62	0.37
CSF				
Pleocytosis, n (%)	39 (68)	15 (63)	24 (73)	0.57
Cell count, ×10 <sup>6</sup> /L, median (IQR; range)	23 (8, 44)	21 (5, 46)	27 (9, 41)	0.33
Proteins increased, n (%)	12 (21)	6 (25)	6 (18)	0.74
Protein level, mg/dL, median (IQR; range)	30 (19, 43)	31 (17, 45)	29 (21, 41)	0.47
Brain MRI abnormalities, n (%)	32 (56)	13 (54)	19 (58)	1.00
EEG abnormalities, n (%)	53 (93)	24 (100)	29 (88)	0.13

AE, autoimmune encephalitis; TPE, therapeutic plasma exchange; IQR, interquartile range; NMDAR, N-methyl-D-aspartate receptor; GABA<sub>B</sub>R, gamma-aminobutyric acid receptor type b; LGI1, leucine-rich glioma inactivated1; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CSF, cerebrospinal fluid; SD, standard deviation; MRI, magnetic resonance imaging; EEG, electroencephalogram.

antibody titers in the CSF decreased after the TPE procedure in 17 patients (17/33, 52%); among 13 severe AE patients with negative blood antibody but positive CSF antibody, 7 patients had decreased CSF antibody titers after TPE treatment. In the non-TPE group, antibody titers in the CSF decreased after the IVIG procedure in four patients (4/24, 17%).

The antibody titers in the plasma decreased in 14 patients (14/57, 25%) after immunotherapy (Table 2). The proportion of patients with decreasing plasma antibody titers in the TPE group was higher than that in the non-TPE group (11 [19%] versus 3 [5%],  $P = 0.12$ ). In the TPE group, antibody titers in the plasma decreased after the TPE procedure in 11 patients (11/33, 33%). In

the non-TPE group, antibody titers in the plasma decreased after the IVIG procedure in 3 patients (3/24, 13%).

## Discussion

This study demonstrates that the antibody-associated AE patients who received TPE exhibited some degree of rapid clinical improvement (1–2 months) after an absent response to first-line pharmacotherapy. In addition, although TPE is an invasive treatment and severe AE patients probably have unstable vital signs, no serious adverse events or treatment-related deaths were detected in this study.

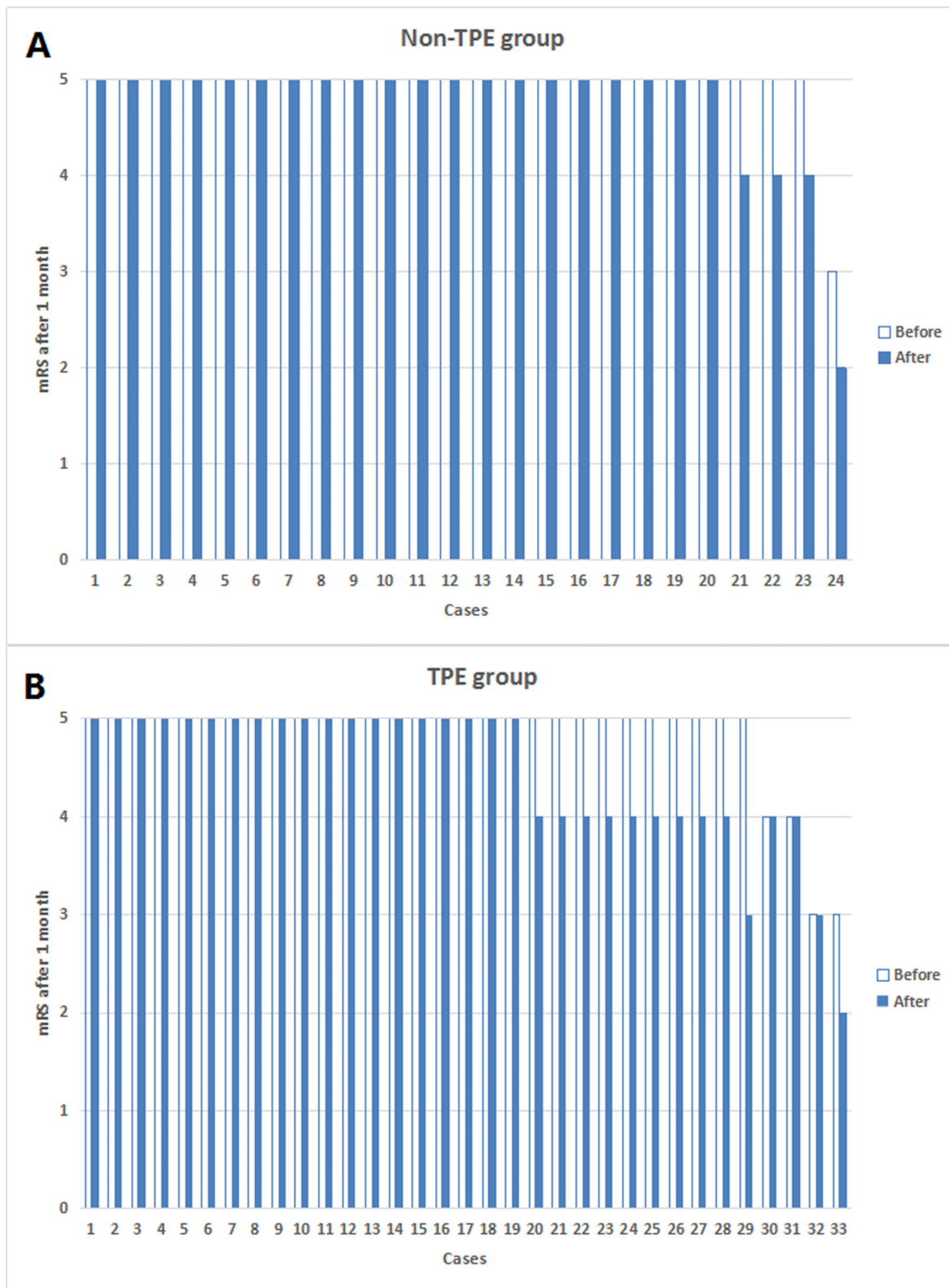
**Table 2.** Details of immunotherapy and outcomes of patients with severe refractory AE.

Item	Total (n = 57)	Non-TPE (n = 24)	TPE (n = 33)	P value
Days between onset and immunotherapy, median (IQR; range)	20 (13, 37)	25 (18, 50)	18 (11, 31)	0.12
Tumor comorbidity, n (%)	10 (18)	3 (13)	7 (21)	0.49
Steroids, n (%)	55 (97)	22 (92)	33 (100)	0.17
Days between onset and steroids, median (IQR; range)	22 (12, 42)	25 (17, 50)	22 (11, 40)	0.29
IVIg, n (%)	57 (100)	24 (100)	33 (100)	1.00
Days between onset and IVIg, median (IQR; range)	26 (18,40)	28 (19, 48)	25 (16, 37)	0.37
Days between onset and TPE, median (IQR; range)	43 (23, 58)	–	43 (23, 58)	–
Immunosuppressants, n (%)				
RTX	6 (11)	1 (4)	5 (15)	0.38
CYC	4 (7)	1 (4)	3 (9)	0.63
MMF	19 (33)	4 (17)	15 (46)	0.03
AZA	3 (5)	1 (4)	2 (6)	1.00
CSF antibody titer after TPE/IVIg, n (%)				
Negative	0 (0)	0 (0)	0 (0)	–
Weakly positive	15 (25)	5 (21)	10 (30)	0.55
Positive	33 (58)	15 (63)	18 (55)	0.60
Strongly positive	9 (16)	4 (17)	5 (15)	1.00
Decreased CSF antibody titer after TPE/IVIg, n (%)	21 (37)	4 (17)	17 (52)	0.01
Plasma antibody titer after TPE/IVIg, n (%)				
Negative	30 (53)	12 (50)	18 (55)	0.79
Weakly positive	19 (33)	8 (33)	11 (33)	1.00
Positive	8 (14)	4 (17)	4 (12)	0.71
Strongly positive	0 (0)	0 (0)	0 (0)	–
Decreased plasma antibody titer after TPE/IVIg, n (%)	14 (25)	3 (13)	11 (33)	0.12
mRS score before enrollment, n (%)				
3	3 (5)	1 (4)	2 (6)	0.39
4	2 (4)	0 (0)	2 (6)	
5	52 (91)	23 (96)	28 (85)	
Clinical improvement after 1 month, n (%)	29 (51)	8 (33)	21 (64)	0.03
Clinical improvement after 2 months, n (%)	47 (83)	16 (67)	31 (94)	0.01
mRS score after 6 months, n (%)				
0–2	38 (67)	15 (64)	23 (70)	0.77
3–6	17 (30)	8 (33)	9 (27)	
Loss to follow-up	2 (4)	1 (4)	1 (3)	
mRS score after 12 months, n (%)				
0–2	39 (68)	14 (58)	25 (76)	0.33
3–6	13 (23)	7 (29)	6 (18)	
Loss to follow-up	5 (9)	3 (13)	2 (6)	

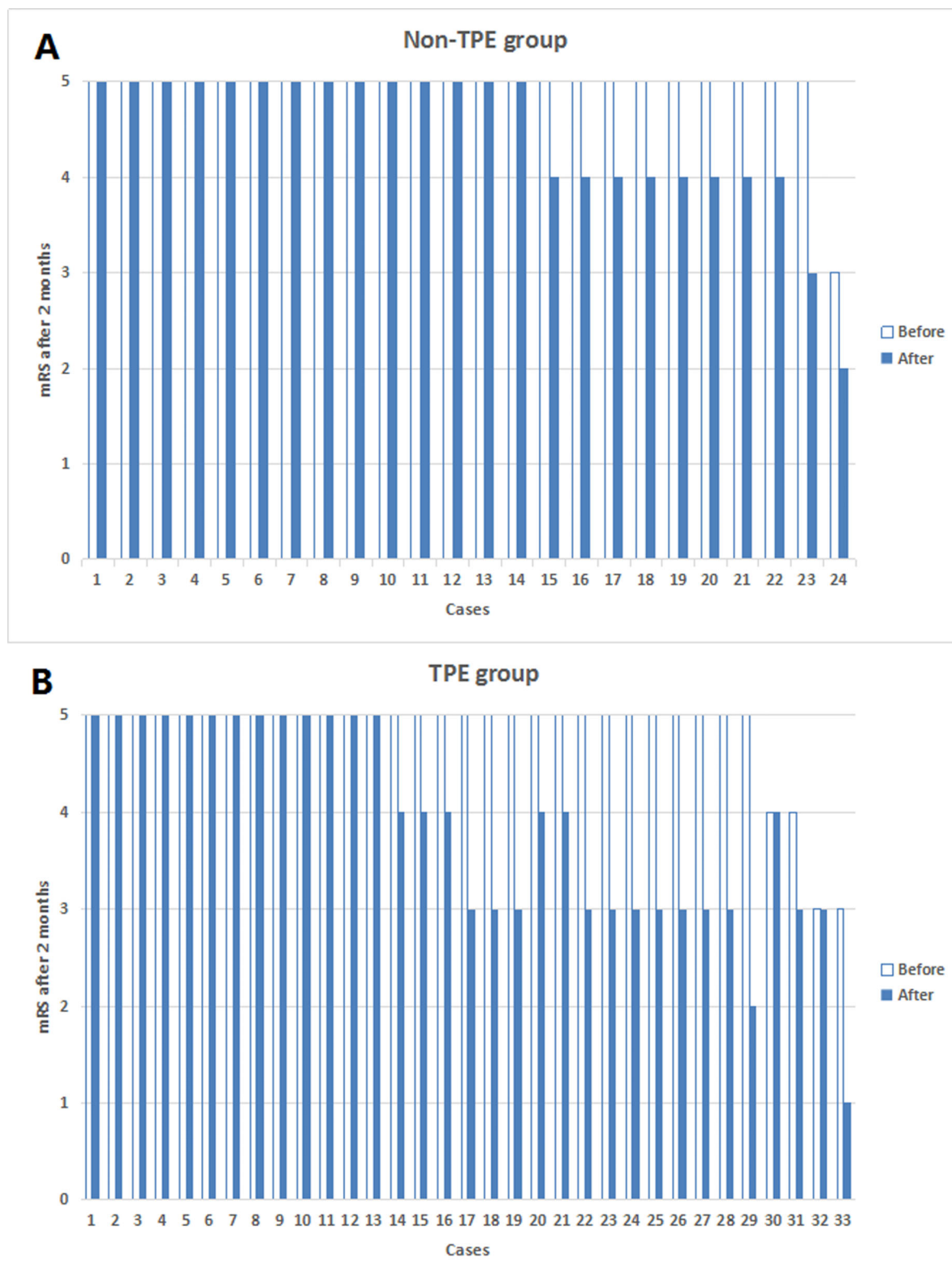
AE, autoimmune encephalitis; TPE, therapeutic plasma exchange; IQR, interquartile range; IVIg, intravenous immunoglobulin; mRS, modified Rankin scale; RTX, rituximab; CYC, cyclophosphamide; MMF, mycophenolate mofetil; AZA, azathioprine; CSF, cerebrospinal fluid.

These results support recently renewed interest in TPE as an effective treatment to rapidly reduce the concentration of circulating autoantibodies in patients with devastating rapidly progressive AE secondary to antibodies against LGI1, contactin-associated protein-2 (CASPR2), and NMDAR.<sup>13</sup> Severe AE poses significant clinical challenges to neurologists due to its rapid progression and the risk of permanent neurological disability if not treated early and aggressively. Although there is little evidence from randomized clinical trials, experience from published case series suggests that TPE is important to improve the patient's clinical condition. In a pediatric

case series from the United Kingdom,<sup>14</sup> 89% (8/9) of patients who received TPE during their initial treatment made a full eventual recovery, compared with 47% of patients receiving IVIg and steroids. Similarly, compelling preliminary data from another retrospective review comparing intravenous methylprednisolone and TPE suggested that corticosteroids may not be as effective as steroids followed by TPE.<sup>15</sup> According to the recent guidelines published by the American Society for Apheresis, the use of TPE is recommended in patients with anti-NMDAR encephalitis (Category I, grade 1C), voltage-gated potassium channel-complex antibody-associated



**Figure 2.** The mRS between the TPE group and the non-TPE group at 1-month postenrollment. Compared with the non-TPE group (A), the TPE group (B) exhibited greater mRS improvement: 12 (36%) versus 4 (17%) ( $P = 0.03$ ). mRS, modified Rankin scale; TPE, therapeutic plasma exchange.



**Figure 3.** The mRS between the TPE group and the non-TPE group at 2-month postenrollment. Compared with the non-TPE group (A), the TPE group (B) exhibited greater mRS improvement: 18 (55%) versus 10 (42%) ( $P = 0.01$ ). mRS, modified Rankin scale; TPE, therapeutic plasma exchange.



**Table 3.** Severity of complications and adverse events associated with TPE.

Grading	Complications and adverse events	Number of events	Percentage of total TPE procedures
Grade I	Fever	1	1.0%
	Involuntary movements	1	1.0%
Grade II	Hypotension	55	52.4%
	Anaphylactic reaction	1	1.0%
	Involuntary movements	44	41.9%
Grade III	Hypotension	1	1.0%
	Clot in the tube	2	1.9%

TPE, therapeutic plasma exchange.

diseases (Category II, grade 1B), and paraneoplastic neurological syndromes (Category III, grade 2C).<sup>7</sup>

Our results showed that even if plasma antibody tests were negative before TPE treatment, the antibody titers in the CSF also decreased in some patients, and the patients could still benefit from TPE. Disruption to the blood–brain barrier has been observed in many acute disorders of the CNS (e.g., acute disseminated encephalomyelitis), which manifests as gadolinium enhancement on neuroimaging.<sup>8</sup> In this state of compromised barrier integrity, TPE may be able to equilibrate antibodies between the plasma and CSF, likely followed by an antibody shift from the CSF toward the systemic circulation.<sup>16</sup>

In this study, although some patients showed rapid clinical improvement within 2 months, the titers of plasma or CSF antibodies remained unchanged. The mechanism of action of TPE appears to be more complex than simply removing circulating pathogenic antibodies from the circulation. Some published papers indicated that other mechanisms include the removal of circulating immune complexes, complement components, cytokines, and adhesion molecules; the replacement of missing plasma components; alteration of the numbers of immune cells and the function of regulatory T cells (Treg) and natural killer cells; and sensitization of antibody-producing cells to immunosuppressant agents.<sup>16–18</sup> Prior studies have evaluated the role of cytokines/chemokines in AE. Anti-NMDAR encephalitis patients showed distinct CSF interleukin-17 (IL-17)/IL-6 axis activation, which might promote intrathecal antibody synthesis, resulting in delayed responses after immunotherapy.<sup>19</sup> Serum IL-17 and IL-23 titers were found to be increased in patients with cell surface antibody-associated AE compared to patients with other CNS inflammatory diseases or healthy controls, and the cytokine titers correlated with antibody titers.<sup>20</sup> Furthermore, a study reported that the titers of CXCL13 were

increased in the CSF of anti-NMDAR encephalitis patients and that the chemokine titers correlated with intrathecal antibody titers, treatment response, and relapse.<sup>21</sup> These studies suggest that cytokines/chemokines play a vital role in AE, although subtype-related alterations have not been evaluated.<sup>19</sup>

Considering that TPE immediately after IVIG could negate the benefits of IVIG or reduce its efficacy, we performed TPE at least 14 days after the end of IVIG. Patients who receive TPE might exhibit rapid clinical improvement, and a previous study showed that early initiation of TPE seems to be beneficial: patients who received IVIG after TPE fared better than those who received IVIG before TPE.<sup>22</sup> After the rapid clearance of pathogenic antibodies and inflammatory mediators by TPE, the neutralization of reduced autoantibodies by IVIG<sup>23</sup> might help to further improve the outcomes of the disease. In this study, there were no serious adverse events associated with the use of TPE or treatment-related deaths. There is overlap (20 patients) between our prior cohort<sup>6</sup> and the cohort in the current trial, and the constituent ratio of various types of adverse events was basically consistent.

Our study has some limitations. First, this study is not a randomized controlled trial (RCT). One of the important reasons for not performing an RCT is that the patients' families were worried about the risk of invasive TPE and did not choose TPE. In addition, some critically unwell patients who had severe hypotension, bloodstream infection, or severe abnormal mental behaviors might not be able to tolerate TPE or cooperate during the process. We must admit that the reasons for the exclusion of TPE may have led to a more prolonged recovery and might partly explain the initial worse outcome but later similar outcome. Second, we cannot exclude overlapping effects of the immunosuppressants on long-term prognosis. Patients who had no improvement after first-line immunotherapy received immunosuppressants (rituximab, cyclophosphamide, mycophenolate mofetil, or azathioprine) after the first course of TPE/IVIG 4 weeks later. The primary outcome was evaluated at 1- and 2-month post enrollment. Although rituximab and cyclophosphamide may be fast-acting, the clinical effects within 1 month could not be attributed to them. Mycophenolate mofetil and azathioprine work too slowly to affect the primary outcome. However, these immunosuppressants could affect the long-term prognosis. Third, we did not evaluate the level of cytokines/chemokines or the number of T cells and natural killer cells before and after TPE to explore the changes in immunologic factors and cells. Fourth, most of the patients in the cohort had a diagnosis of anti-NMDAR encephalitis, thereby biasing the results; thus, any assertions about other antibodies or AE, in general, might be limited by the composition of the sample.

In conclusion, tumor removal and pharmacotherapy currently remain the first-line treatment in the majority of AE cases, but TPE might be a reasonable option to consider in patients with severe antibody-associated AE with absent or limited improvement after pulse steroids or IVIG after weighing the potential benefits and risks on an individualized basis. To confirm the rapid effectiveness of TPE, more prospective and standardized studies of severe AE are needed to evaluate the early implementation of this potentially life-saving therapy.

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## Conflict of Interest

The authors declare no conflicts of interest.

## Ethics Approval

This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, adhered to the tenets of the Declaration of Helsinki, and was registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-14004931).

## Authors' Contributions

Yan Zhang involved in study concept and design, analysis and interpretation of the data, and drafting and revising the manuscript. Hui-jin Huang, Wei-bi Chen, and Gang Liu involved in collection of clinical data, clinical management, and revising the manuscript. Fang Liu involved in technical and material support. Ying-ying Su carried out clinical management, analysis, and interpretation of the data.

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