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Risk factors for mortality in patients with anti-NMDA receptor encephalitis

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Objective: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune disorder with a mortality of 5%-7%, but few studies have focused on the predictors of death in this disease. In this study, we aim to investigate predictors and causes of death in patients with anti-NMDAR encephalitis.

Methods: In this cohort study, patients with anti-NMDAR encephalitis were enrolled at the West China Hospital of Sichuan University between June 2011 and October 2015. The outcomes of patients were evaluated by long-term follow-up. Cox regression analysis was used to assess the association between potential predictors and death.

Results: Altogether 96 patients were included in this study, and 11 died after median 24.5 (7-57) months of follow-up. The mortality of anti-NMDAR encephalitis was 11.46%. Multivariate analysis results showed that Glasgow Coma Scale (GCS) score ≤8 at admission (HR=15.917, 95% CI=1.729-146.562; *P*=.015), the number of complications (HR=7.772, 95% CI=1.944-31.072; *P*=.004), and admission to an intensive care unit (HR=70.158, 95% CI=2.395-2055.459; *P*=.014) were significantly associated with increased risk of mortality. Twelve patients received second-line immunotherapy, and the cohort was relatively under-treated compared with other studies. The main causes of death were severe pneumonia, multiple organ dysfunction syndrome, and refractory status epilepticus.

Conclusion: GCS score ≤8 at admission, number of complications, and admission to an intensive care unit are predictors of death. Management of complications may improve the prognosis of anti-NMDAR encephalitis.

KEYWORDS
anti-NMDA receptor encephalitis, death causes, mortality, predictors

1 | INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder in the central nervous system, associated with antibodies that are directly against the NR1 subunit of the NMDA receptor.[1–3] Until now, different research groups have gradually revealed the clinical characteristics of different kinds of autoimmune encephalitis. Anti-NMDAR encephalitis is more common in young women, presenting with severe neuropsychiatric symptoms, seizure, memory loss, and decreased consciousness, often accompanied with ovarian teratoma.[4,5] Despite that anti-NMDAR encephalitis is treatment responsive by immunotherapy and tumor removal, the mortality rate of anti-NMDAR encephalitis is still around 5%-7%.[6–9] However, very few studies have focused on the analysis of death of anti-NMDAR encephalitis, and the predictors of death of patients with anti-NMDAR encephalitis are unknown. Therefore, we conducted this cohort study to further analyze the outcome of patients with anti-NMDAR encephalitis and explore the predictors of death of patients with anti-NMDAR encephalitis.

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2 | MATERIAL AND METHODS

2.1 | Study design

Patients with a definitive diagnosis of anti-NMDAR encephalitis were enrolled at the West China Hospital of Sichuan University between June 2011 and October 2015. The diagnosis and treatment of patients with anti-NMDAR encephalitis were decided by the same team of neurologists. The serum and/or cerebrospinal fluid (CSF) samples of all patients were sent to two institutions (Oumeng Biotechnology Corporation, or Peking Union Medical College Hospital, Beijing, China) to detect antibodies against NMDAR. Samples were classified as positive or negative by indirect immunofluorescence using EU 90 cells according to the previous study.[10]

Consent forms were signed by immediate relatives or patients, and this study was approved by the institutional review board of Sichuan University.

2.2 | Inclusion and exclusion criteria

Patients who met the definition of anti-NMDAR encephalitis with positive serum and/or CSF result were included, or otherwise excluded. In addition, patients diagnosed with infectious encephalitis or unknown cause encephalitis were excluded according to the clinical data and ancillary examination. Patients with less than 4 months of follow-up or missing data were also excluded.

2.3 | Definition

Status epilepticus (SE) was defined according to the new definition of SE reported by the International League Against Epilepsy.[11] Refractory status epilepticus (RSE) was defined as continuous SE despite appropriate anticonvulsant treatment for up to 2h.[12] The failure of two or more vital organ systems was defined as multiple organ dysfunction syndrome (MODS).[13]

2.4 | Data extraction

Demographic characteristics and clinical information of included patients were reviewed by two authors (Xiaosa Chi and Wei Wang). The levels of consciousness of patients at admission were graded by Glasgow Coma Scale (GCS) score. In addition, the highest body temperature during disease, complications, and the interval between the disease onset and admission (days) were obtained. The intracranial pressure was measured in the lumbar puncture. The results of laboratory tests (serum potassium, serum sodium, CSF examination, complete blood count, and serum biochemical indicators), electroencephalography (EEG), and brain magnetic resonance imaging (MRI) were also assessed in this study. The EEG results were considered as abnormal when showing electrographic seizures, slow and disorganized activity, excessive beta activity, or delta brush.[14] All patients were screened for systemic tumors by ultrasound scan, contrast-enhanced computed tomography, and tumor markers. The immunotherapies including intravenous methylprednisolone (MTP), intravenous immunoglobulin (IVIG), plasma exchange, and second-line immunotherapy (rituximab or cyclophosphamide) were recorded. Hospitalization data were obtained for the following: admission to intensive care unit (ICU), length of ICU stay, and length of hospital stay.

2.5 | Follow-up

All patients were followed up in person or on telephone and evaluated by modified Rankin Scale (mRS) at 1 month and every 3 months after the initiation of immunotherapy. The Zung Depression Scale (ZDS) and the Zung Anxiety Scale (ZAS) were used to assess the psychological status of patients. Patients were considered as non-depressed when ZDS <50, and non-anxious when ZAS<45. The end point of observation was the death of patients.

2.6 | Outcome

Patients who died during the disease course were included in the death group, and patients with improvement and stable vital symptoms for at least 2 months were included in the survival group. The cause of death and main complications were evaluated.

2.7 | Statistical analysis

Statistical analysis was conducted using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). Parameters with skewed distribution including highest temperature, interval between onset and admission, number of complications, interval to immunotherapy, interval to diagnosis, and length of hospital stay were described by the median variable and analyzed by the *t* test or Mann–Whitney *U* test. The Fisher exact test, Fisher–Freeman–Halton test, and chi-squared test were used for categorical variables, such as gender, seizure, psychiatric symptom, consciousness, tumor, laboratory tests, and immunotherapy. Predictors of death were estimated using a Cox regression model. Hazard ratios (HRs) in the cox model and corresponding 95% confidence interval (CI) were conducted to evaluate the strength of association. P <.05 (two-sided) was considered as significant.

3 | RESULTS

Altogether, 101 patients met the diagnosis of anti-NMDAR encephalitis at our hospital between June 2011 and October 2015, and four (4/101, 3.96%) patients were lost during follow-up. One patient committed suicide after full recovery for 14 months with ZDS score of 48 and ZAS score of 39 and took neither treatment nor examination. As it is hard to decide if the patient died of autoimmune encephalitis, we excluded this patient from this study (details are shown in Table 1). Therefore, we included 96 patients with anti-NMDAR encephalitis in this study The demographic characteristics, clinical information, and univariable analysis are shown in Table 2.

TABLE 1 Clinical information of patients who died of anti-NMDAR encephalitis

No.	Sex, age (year)	Chief complaint	SE	Immunotherapy	Tumor	Main complication	Interval from onset to death	Cause of death
1	F, 39	Psychiatric symptoms for 15 days	No	MTP, IVIG	No	MODS, septic shock, pneumonia, Acute severe pancreatitis, respiratory failure	1.5 months	MODS
2	F, 24	Psychiatric symptoms for 5 days	RSE	MTP	Bladder cancer	Severe pneumonia, respiratory failure	2 months	Severe pneumonia
3	M, 28	Headache for 7 days, GCS twice	RSE	MTP	No	MODS, pneumonia, drug eruption	2.5 months	MODS
5	M, 15	Headache for 9 days, repeated GCS for 6 days	RSE	IVIG	No	Severe pneumonia, respiratory failure, urinary tract infection	2 months	Severe pneumonia
6	M, 25	Psychiatric symptoms for 31 days, repeated GCS for 20 days	RSE	IVIG	Malignant mediastinal germ cell tumor	MODS, severe pneumonia, Acute pancreatitis, urinary tract infection, respiratory failure, heart failure	5 months	MODS
7	M, 33	Psychiatric symptoms and repeated GCS for 10 days	SE	IVIG	No	Severe pneumonia	2.5 months	Severe pneumonia
8	F, 26	Psychiatric symptoms for 20 days	No	MTP, IVIG	No	Severe pneumonia, gastrointestinal hemorrhage	1.5 months	Severe pneumonia
9	F, 25	Psychiatric symptoms for 10 days and repeated GCS for 7 days	RSE	IVIG, MTP	No	Severe pneumonia, Respiratory failure	1.5 months	RSE
10	M, 57	Psychiatric symptoms for 10 days	RSE	IVIG, MTP	No	Pneumonia, thrombocytopenia	1.5 months	RSE
11	M, 63	Move disorder and psychiatric symptom for 3 months	no	IVIG, MTP, CTX	Non-Hodgkin lymphoma	pneumonia, hypovolemic shock, respiratory failure	4.5 months	Hypovolemic shock
12	F, 27	Psychiatric symptoms for 30 days, repeated GCS for 7 days	SE	MTP, IVIG	no	Pneumonia, respiratory failure	17 months	Suicide

MTP, methylprednisolone; IVIG, intravenous immunoglobulin; CTX, cyclophosphamide; SE, status epilepticus; RSE, refractory status epilepticus; MODS, multiple organ dysfunction syndrome.

The median age was 24.5 (9-71) years, with 36 (37.50%) men and 60(62.50%) women. Altogether, 13 (13.54) patients were detected with tumor.

It took median 27 (11-128) days before the patients were diagnosed with anti-NMDAR encephalitis, and median 25 (10-130) days to receive immunotherapy. In this study, 48 (50.00) patients received MTP (1 g/d for 5 days), 80 (83.33) patients were treated with IVIG (0.4 g/kg/d for 5 days), and 12 (12.50) patients received second-line immunotherapy, while four (4.17%) patients refused to receive immunotherapy. In the course of disease, 22.92%(22/96) of the patients need intubation, and 13.54% (13/96) of the patients were transferred to ICU with median 39 (6-112) days in ICU. The median length of hospital stay was 28 (4-141) days.

3.1 | Findings in fatal cases

After median follow-up duration of 24.5 (7-57) months, 11 patients died of anti-NMDAR encephalitis and one patient committed suicide (data shown in Table 1). The median age of patients who died was 26 years, ranging from 15 to 63 years, with seven men and four women. During the disease course, eight patients suffered from SE including seven patients with RSE. Three patients were diagnosed with tumor, which included bladder cancer, malignant mediastinal germ cell tumor, and non-Hodgkin lymphoma. The median interval length between symptom onsets to death was 2.25 (1.5-5) months in patients who died of anti-NMDAR encephalitis. Four patients died of severe pneumonia, four died of MODS, two died of RSE, and one died of hypovolemic shock.

TABLE 2 The demographic characteristics, clinical information, and univariable analysis of patients with anti-NMDAR encephalitis

Variables	Total (n=96,%)	Death (n=11,%)	Survival (n=85,%)	Statistical value	*P* value
Demographic data					
Sex (male)	36 (37.50)	7 (63.63)	29 (34.12)	1.756	.185[a]
Age (years)	24.5 (9-71)	26 (15-63)	24 (9-71)		
<18	26 (27.08)	2 (18.18)	24 (28.24)	0.119	.730[a]
>18	70 (72.92)	9 (81.82)	61 (71.76)		
Clinical information					
Highest temperature	37.62 ± 4.05	38.64 ± 1.31	37.49 ± 4.26	0.890	.376[b]
Seizure	77 (80.21)	8 (72.73)	69 (81.18)	0.067	.795[a]
Psychiatric symptom	87 (90.63)	10 (90.91)	77 (90.59)	0.000	1.000[a]
Internal between onset and admission (days)	14 (2-120)	10 (5-90)	15 (2-120)	−1.104	0.275[a]
GCS score ≤8	15 (15.63)	6 (54.55)	9 (10.59)	11.135	.001[a]
High intracranial pressure	33 (34.38)	5 (45.45)	28 (32.94)	0.235	.628[a]
SE	29 (30.21)	8 (72.73)	21 (24.71)	8.497	.004[a]
RSE	13 (13.54)	6 (54.55)	7 (8.54)	14.105	<.001[a]
Tumor	13 (13.54)	3 (27.27)	13 (15.29)	0.895	.344[a]
Number of complications (mean, range)	1.16 (0-5)	2.55 (1-5)	0.98 (0-3)	−4.009	<.001[b]
MODS	5 (5.21)	5 (45.45)	0 (0.00)	24.126	<.001[a]
Ancillary examination					
Abnormal EEG	61/82 (73.63)	6/9 (66.67)	55/73 (74.07)	0.025	.875[a]
Abnormal MRI	48/107 (44.86)	8/11 (72.73)	20/96 (41.67)	2.696	.101[a]
Hypokalemia	41 (42.71)	7 (63.63)	34 (40.00)	1.363	.243[a]
Hyponatremia	17 (17.71)	5 (45.45)	12 (14.12)	4.589	.032[a]
Pleocytosis	55 (57.29)	6 (54.55)	49 (57.65)	0.000	1.000[a]
Leukocytosis	43 (44.79)	7 (63.63)	36 (42.35)	1.027	.311[a]
Hypo-albuminemia	38 (39.58)	8 (72.73)	30 (35.29)	4.249	.039[a]
Treatment					
Intubation	13 (13.54)	6 (54.55)	7 (8.24)	14.105	<.001[a]
Internal to immunotherapy (days, n=92)	25 (10-130)	28 (15-120)	25 (10-130)	−0.294	.774[b]
Internal to diagnosis (days)	27 (11-128)	29 (15-120)	27 (11-128)	−0.081	.939[b]
Immunotherapy					
MTP	48 (50.00)	8 (72.73)	40 (47.06)	2.567	.199[a]
IVIG	80 (83.33)	8 (72.73)	72 (84.71)	0.329	.567[a]
Second-line immunotherapy	12 (12.50)	1 (9.09)	11 (12.94)	0.000	1.000[a]
Without immunotherapy	4 (4.17)	0 (0.00)	4 (4.71)	0.996	.673[a]
Hospitalization data					
Admission to ICU	13 (13.54)	6 (54.55)	7 (8.24)	14.105	<.001[a]
Length of hospital stay (days)	28 (4-141)	35 (11-112)	27 (4-141)	−1.162	.250[b]
Complications					
Pneumonia	63 (65.63)	11 (100)	52 (61.18)	4.900	.027[a]
Respiratory failure	14 (14.58)	7 (63.64)	7 (8.23)	19.757	<.001[a]
Urinary tract infection	17 (17.71)	3 (27.27)	14 (16.47)	0.215	.643[a]
Circulatory system	6 (6.25)	4 (36.36)	2 (2.35)	11.517	.001[a]
Digestive System	11 (11.46)	3 (27.27)	8 (9.41)	1.555	.212[a]

GCS score, Glasgow Coma Scale score; SE, status epilepticus; RSE, refractory status epilepticus; MODS, multiple organ dysfunction syndrome; EEG, electroencephalography; MRI, magnetic resonance imaging; MTP, methylprednisolone; IVIG, intravenous immunoglobulin; ICU, intensive care unit.

[a]The Fisher exact test, Fisher–Freeman–Halton, or chi-squared test was used for numerical variables.

[b]*T* test or Mann–Whitney *U* test was used for categorical variables.

3.2 | Univariable analysis of predictors of death

3.2.1 | Demographic characteristics and clinical information

Seven patients in the death group were male (63.63%), and 29 patients in the survival group were male (34.12%, *P*=.185). No significant difference was detected in age (*P*=.730).

The rate of low GCS score (≤8) in the death group was 54.55% (6/11), which was significantly higher compared with the survival group (10.59%, *P*=.001). During the course of disease, 72.73% (8/11) patients in the death group experienced SE, which was significantly higher than that in the survival group (24.71%, *P*=.004). Besides, 54.55% (6/11) patients experienced RSE in the death group, whereas only 8.54% (7/85) patients in the survival group experienced RSE (*P*<.001). Patients in the death group developed almost three (Range: 1-5) kinds of complications, which was significantly higher than that of the survival group (0.98, range: 0-3, *P*<.001). The details of the complications are presented in Table 2. In the death group, the rate of pneumonia was 100% (11/11), which was significantly higher than that of the survival group (52/85, 61.18%, *P*=.027). Besides, the rates of respiratory failure and circulatory system disorders in the death group were also significantly higher than those in the survival group (*P*<.05). However, no significant difference was detected in urinary tract infection and digestive system disorders between the two groups (*P*>.05). Five (45.45%) patients in the death group developed MODS, whereas no patient was diagnosed with MODS in the survival group (*P*<.001). No significant difference was detected in the highest temperature, high intracranial pressure, or tumor between the two groups (*P*>.05).

3.2.2 | Ancillary examination

Abnormal MRI results were T2 or FLAIR signal hyperintensity in cortex, multifocal white matter changes, and cortical atrophy. Besides, 45.45% (5/11) of the dead patients had hyponatremia, but only 14.12% (12/85) of the survival patients was diagnosed (*P*=.032) with it. The rate of hypo-albuminemia (8/11, 72.73%) in the death group was significantly higher than that in the survival group (30/85, 35.29%; *P*=.039). The rates of abnormal EEG, MRI, hypokalemia, pleocytosis, or leukocytosis were not significantly different between the two groups (*P*>.05).

3.2.3 | Treatment

The rate of intubation (63.63%, 7/11) in the death group was significantly higher than that in the survival group (17.65%, 15/85; *P*=.002). In the death group, it took an average of 28 (15-120) days before immunotherapy was prescribed, longer than that in the survival group (25, 10-130), but no significant difference was detected (*P*=.774). The common immunotherapy in the death group was IVIG (8/11, 72.73%) and MTP (8/11, 72.73%), with only one (9.09%) patient receiving second-line immunotherapy. In the survival group, the most common therapy was IVIG (72/85, 84.71%), with 11 (12.94%) patients not taking second-line immunotherapy. However, immunotherapy strategies between the two groups were not significantly different (*P*<.05).

Altogether, 12.50% (12/96) patients received second-line immunotherapy. The mortality of patients with second-line immunotherapy was 8.33% (1/12), with 11.90% (10/84) of those who did not, but no significant difference was detected (*P*=1.000).

3.2.4 | Hospitalization data

The transfer rate of ICU in the death group (5/11, 45.45%) was significantly higher than that of the survival group (8/85, 9.41%). The median length of hospital stay in the death group (35, 11-112 days) was longer, but not significantly different from the survival group (*P*=.250).

3.3 | Multivariable analysis of predictors of death

The multivariable analysis results showed that GCS score ≤8 was significantly associated with death (HR=15.917, 95% CI=1.729-146.562; *P*=.015). The results are presented in Table 3. In addition, the number of complications during the disease course was significantly associated with increased risk of death (HR=7.772, 95% CI=1.944-31.072; *P*=.004). Admission to an intensive care unit was also related with the risk of death (HR=70.158, 95% CI=2.395-2055.459; *P*=.014). No significant association with other predictors of death like CSE, RSE, MODS hyponatremia, hypo-albuminemia, and intubation was found (*P*>.05).

4 | DISCUSSION

In this study, we reported 11 patients who died of anti-NMDA receptor encephalitis and assessed the predictors of death in Chinese anti-NMDA receptor encephalitis for the first time. The mortality of

TABLE 3 Multivariate analysis of factors associated with death in patients with anti-NMDAR encephalitis

Variables	Hazard Ratios	95% CI	*P* value
GCS score ≤8	15.917	1.729-146.562	.015
SE	9.908	0.545-180.193	.121
RSE	0.450	0.026-7.942	.586
Number of complications	7.772	1.944-31.072	.004
MODS	1.366	0.166-11.261	.772
Hyponatremia	0.147	0.013-1.718	.126
Hypo-albuminemia	3.718	0.380-36.399	.259
Intubation	0.090	0.006-1.453	.090
Admission to ICU	70.158	2.395-2055.459	.014

CI, confidence interval; GCS score, Glasgow Coma Scale score; SE, status epilepticus; RSE, refractory status epilepticus; MODS, multiple organ dysfunction syndrome; ICU, intensive care unit.

anti-NMDAR encephalitis in this research was 11.45% (11/96), which was much higher compared with 7% in Japan[7] and 5.2% in USA and Spain,[6] indicating a treatment gap compared with developed country. Thus, we evaluated the predictors based on demographic data, clinical data, and treatment to improve the outcome of anti-NMDAR encephalitis.

The multivariate analysis results showed that patients with GCS score ≤8 at admission were found to have an increased risk of death. According to our clinical data, patients with GCS score ≤8 usually deteriorated rapidly and fell into a coma within a few days from the onset of the disease. Moreover, no significant difference was detected in the interval between onset and admission between two groups. Thus, the result indicated that rapidly progressing anti-NMDA receptor encephalitis may have a bad outcome in spite of timely immunotherapy. In a retrospective analysis of acute encephalitis, GCS score ≤8 at admission and coma were associated with poor outcome.[15,16] Besides, coma increased the risk of complications such as pneumonia, severe infection, respiratory infection, and MODS,[17] which may threaten life.

In addition, we found that the number of complications was a predictive factor of mortality in anti-NMDAR encephalitis. Complications such as MODS, severe pneumonia, and RSE were the main causes of death for anti-NMDA receptor encephalitis patients. Previous reports also showed that sepsis, RSE, and organ failure were frequent causes of death in patients with anti-NMDAR encephalitis.[18,19] Thus, management of complications may be an important and practical way to improve the survival rate. The antibody-mediated inflammation may induce neuronal loss and dysfunction of synaptic plasticity, contributing to consciousness disorder, hypoventilation, and seizure.[3,20,21] In addition, long-term bedridden and intubation may also increase the risk of sepsis especially pneumonia for patients with autoimmune encephalitis.

Moreover, the present study also showed that patients admitted to ICU had increased risk of death. This result also indicated that the severity of anti-NMDAR encephalitis may affect the prognosis of the disease. Compared with developed countries, patients in China had a much lower rate of stay in ICU (14% vs 75%),[6] and shortened length of hospital stay,[7,22] but a higher mortality. High hospitalization costs in ICU may be the leading cause of giving up treatment for patients in serious condition. Therefore, the rate of admission to ICU may be underestimated in this study.

The results indicated that intervals between onset to immunotherapy and immunotherapy were not the predictors of death in this study. Interestingly, the median time to treat with immunotherapy was shorter than the diagnosis of anti-NMDAR encephalitis. Given that a few days were needed to detect the anti-NMDAR antibody, the immunotherapies were used when suspected anti-NMDAR encephalitis diagnosis according to the clinical data and ancillary examination results. Besides, immunotherapy and neoplasm search are also recommended for probable anti-NMDAR encephalitis based on neurological assessment and conventional test before the anti-antibody test is finished.[23] In addition, only 12 (12.50%) patients with anti-NMDAR encephalitis received second-line immunotherapy, compared with 57% of patients receiving second-line therapy in developed countries.[6] Previous reports indicated that second-line immunotherapy was usually effective when first-line therapy failed, and improved outcomes.[6,24] Therefore, rituximab and cyclophosphamide should be taken into consideration when there is no sustained improvement from first-line therapy. The low rate of second-line immunotherapy may be a factor to the relatively higher mortality in this study. Interestingly, four patients in this study did not take any immunotherapy but recovered fully or recovered with mild deficit. Nevertheless, the symptoms were less severe with these four patients and without any complication.

Notably, one patient committed suicide 17 months after the onset of disease, with depressed emotional state 1 month before death. This patient's psychiatric symptom was the main symptom of autoimmune encephalitis, and prolonged depression caused by anti-NMDAR encephalitis was also reported in other study,[25] so it was hard to decide if the patient had relapsed without a CSF or serum test. Personality changes, depression, and anxiety are common in viral encephalitis sequela, but few reports have focused on mood disorder after autoimmune encephalitis. Therefore, long-term monitoring of emotional disorders or psychiatric symptoms after autoimmune encephalitis should be taken into consideration and distinguished from relapse.

5 | CONCLUSION

In conclusion, this study indicated that multiple organ dysfunction syndrome, refractory status epilepticus, and severe pneumonia are main causes of death in anti-NMDAR encephalitis. Moreover, GCS score ≤8 at admission, number of complications, and admission to ICU are independent risk factors for death. More prospective studies with larger cohorts are needed to validate these findings.

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CONFLICT OF INTEREST

Authors in this study declared no conflict of interest.

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