

# Anti-N-methyl-D-aspartate receptor encephalitis: a prospective study focused on thyroid hormones and functional outcome

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## Research Article

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## Abstract

We aimed to investigate the association between thyroid hormones and functional outcome in patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. 137 consecutive inpatients (2016-2019) were registered prospectively and followed up for 12 months. 96 eligible patients were included in the study. The modified Rankin scale (mRS) score of 3-6 was defined as poor functional outcome. Logistic regression analysis was performed. The patients were classified into 3 subgroups based on their free triiodothyronine (fT3) levels, and the subgroup differences were analyzed by parametric or nonparametric tests as appropriate. We found that the fT3 value upon admission was correlated with functional outcome ( $P=0.004$ ), and this effect remained significant after adjustment for age, gender, tumor presence and consciousness declination. Patients in the low-fT3 subgroup had a higher disease severity during the acute phase, represented by greater maximum mRS scores during hospitalization ( $P=0.011$ ) and higher percentages of intense care unit admission ( $p<0.001$ ). In Conclusion, the relatively low fT3 value is associated with a poor functional outcome. Besides, patients with relatively low fT3 tend to have a higher disease severity during the acute phase. Our preliminary data suggest that the fT3 value might serve as a potential predictor of functional outcome in patients with anti-NMDAR encephalitis.

## Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a newly identified autoimmune encephalitis (AE) associated with antibodies against functional NMDA receptors that predominantly affects young females and exhibits a well-defined set of clinical features<sup>1</sup>. To tackle the challenges of early diagnosis and risk stratification, several clinical prognostic factors have been developed. Altered consciousness, intensive care unit (ICU) admission and no use of immunotherapy seem to be variables associated with poor prognosis in anti-NMDAR encephalitis, whereas other factors, including age, gender, abnormalities of cerebrospinal fluid (CSF) and changes of magnetic resonance imaging (MRI), remain controversial<sup>2,3</sup>. Since the prognostic accuracy of these clinical factors still demonstrates a level of uncertainty, there is interest for novel prognostic biomarkers, each mirroring different pathophysiological mechanisms.

Abnormal serum levels of thyroid hormones have been reported in patients with a variety of non-thyroidal illnesses. The free triiodothyronine (fT3), an indicator of thyroid function, has been proven to be associated with a worse cardiovascular risk factor profile and could lead to progression of atherosclerosis<sup>4</sup>. Besides that, emerging evidence suggests that fT3 may also serve as a prognostic factor in several critical diseases (e.g., sepsis, respiratory failure, and stroke) and some autoimmune diseases (e.g., systemic lupus erythematosus and neuromyelitis optica spectrum disorders)<sup>5-10</sup>. Thyroid hormones play a critical role in the proliferation and differentiation of neuronal and glial progenitors during normal brain development and in regulation of adult hippocampal neurogenesis<sup>11,12</sup>. This constitutes the bases for evaluation of the potential association between thyroid hormones and the prognosis of anti-NMDAR encephalitis. To date, there are only a few data on this issue<sup>13,14</sup>, and its

predictive value of functional outcome remains to be determined. Herein, we aimed to investigate the association between the thyroid hormones and functional outcome in patients with anti-NMDAR encephalitis.

## Results

### Descriptive characteristics of the study population

In total, 137 consecutive patients were screened, and 96 patients met the inclusion criteria (median 30 [21-40.5] years; 44.79% females). **Figure 1** summarizes the cohort selection process, and the baseline clinical features of the study population is shown in **Table 1**. The most common main symptoms included psychiatric behaviors (79.17%), seizures (65.63%) and cognitive dysfunction (58.33%). More than half of the patients had abnormal MRI (57.29%) and pneumonia (56.25%), but only a few of them (5.21%) were detected with tumors, including 2 pulmonary cancers and 3 immature ovarian teratomas. A quarter of the patients had thyroid dysfunction, including 11 patients with subclinical hyperthyroidism (11.46%), 1 patient with clinical hyperthyroidism (1.04%), 2 patients with subclinical hypothyroidism (2.08%), 6 patients with low T3 syndrome (6.25%), 4 patients with other conditions (4.17%). A majority of the patients (94.79%) received first-line immunotherapies, but only a minority of them (12.5%) were treated with second-line immunotherapies additionally. All patients were followed for 12 months, and most of them (76.04%) achieved a favorable functional outcome. A small number of the patients (6.25%) died within 12 months due to serious complications, including 3 patients with severe infections and 3 patients with intractable status epileptics.

### Association between the fT3 value and functional outcome

In the univariable logistic regression analysis (**Table 2**), serum fT3 value was significantly correlated with functional outcome (OR, 0.385; 95% CI, 0.202-0.732; P=0.004). However, other thyroid hormones, including fT4 (OR, 0.937; 95% CI, 0.789-1.112, P=0.457) and TSH (OR, 0.764; 95% CI, 0.471-1.236; P=0.272), were not related with functional outcome. Other related factors included age (P=0.038), gender (P=0.008), tumor presence (P=0.018), consciousness declination (P=0.047), central hypoventilation (P=0.002), ICU admission (P=0.003), and blood neutrophil proportion (P=0.02).

To further explore the potential underline factors correlated with the relationship between the fT3 value and functional outcome, we divided the patients into three subgroups based on their serum fT3 concentrations (**Figure 1**). As expected, compared with those in the middle-fT3 and high-fT3 subgroup, patients in the low-fT3 group had the lowest chance of achieving a favorable functional outcome (53.13% vs 84.38%, P=0.029; 53.13% vs 90.63%, P=0.007) (**Table 1**). Intriguingly, compared with those in the high-fT3 subgroup, patients in the low-fT3 subgroup had a higher disease severity during the acute phase, measured by a greater maximum mRS score during hospitalization (5 [4-5] vs 3 [3-3.5], P<0.001) and a higher percentage of ICU admission (87.5% vs 31.25%, P<0.001). Besides, their infectious status tended to be more common, represented by a higher rate of pneumonia (71.88% vs 34.48%, P=0.01), a

higher level of WBC (9.15 [7.45-12.8] vs 6.99 [6.2-8.9]  $\times 10^9/L$ , P=0.049), CRP (5.87 [2.21-11.11] vs 1 [0.17-2.2] mg/L, p<0.001), and blood neutrophil proportion (78.31 [1.72] vs 67.44 [1.89] %, p<0.001). In addition, they also had an older age at onset (34 [23.5-48.5] vs 26 [17-33] years old, P=0.003), a higher rate of consciousness declination (65.63% vs 28.13%, P=0.01) and central hypoventilation (34.38% vs 6.25%, P=0.036), and a lower level of TSH (0.76 [0.49-1.18] vs 1.48 [0.71-2.13]  $\mu$ U/ml, P=0.001). The differences remained significant between the low-fT3 subgroup and the middle-fT3 subgroup for frequencies of consciousness declination (65.63% vs 34.38%, P=0.042) and ICU admission (87.5% vs 43.75%, P=0.002), levels of blood neutrophil proportion (78.31 [1.72] % vs 71.72 [1.83] %, P=0.034) and CRP (5.87 [2.21-11.11] vs 1.69 [0.74-3.02] mg/L, P=0.025), and the maximum mRS score during hospitalization (5 [4-5] vs 3 [3-5], p<0.001).

To check if the fT3 value was an independent factor associated with functional outcome, we performed the multivariable logistic regression. After adjustment for age, gender, tumor presence and consciousness declination, the serum fT3 value remained to be a significant prognostic factor related to functional outcome (OR, 0.472; 95% CI, 0.226-0.986; P=0.046) (**Table 3**). However, this difference was non-significant after additional adjustment for ICU admission and other related factors.

## Discussion

This study has demonstrated two major findings. First, the fT3 value was associated with the functional outcome in patients with anti-NMDAR encephalitis, and this effect remained significant after adjusting for age, gender, tumor presence and consciousness declination. Second, patients with relatively low fT3 state had a higher disease severity during the acute phase, represented by greater maximum mRS scores during hospitalization and higher chances of ICU admission. This might be related to their higher rates of consciousness declination, central hypoventilation and pneumonia.

It has been reported that a low serum fT3 level independently predicts a poor functional outcome in gravely ill patients<sup>5,15,16</sup>. Thyroid hormones are able to cross the blood–brain barrier and affect neurogenesis, cell differentiation, and myelination<sup>12,17</sup>. A growing body of literature shows that thyroid hormones are also closely involved in regulating neurosphere biology and immune system function (e.g., cell-mediated immunity)<sup>18,19</sup>. Anti-NMADR encephalitis is the most common AE mediated by antibodies to neuronal surface antigens, with 25% suffer significant morbidity or mortality<sup>20,21</sup>. It is plausible that the fT3 might also play a detrimental effect on outcome in patients with anti-NMDAR encephalitis, however, few studies have addressed this issue. Lin et al. evaluated 42 patients with anti-NMDAR encephalitis and discovered that those with positive anti-thyroid antibodies had a higher mRS score at discharge<sup>13</sup>. Ma et al. examined 43 patients with anti-NMDAR encephalitis and found that those with low T3 syndrome had a significantly longer hospital stay and higher mRS scores at discharge. Nevertheless, they failed to establish a reasonable correlation between the fT3 value and functional outcome, possibly due to a small sample size and short follow-up period (3 months)<sup>14</sup>. Thus, this research sought to clarify the ambiguous findings of previous studies. Indeed, we observed that the fT3, but not fT4 or TSH, was

significantly associated with poor functional outcome, and this effect remained significant after adjusting for age, gender, tumor presence and consciousness declination. Contrary to one former study (25.6%)<sup>14</sup>, our data didn't support the low T3 syndrome as a common finding in patients with anti-NMDAR encephalitis (6.25%), however, the relatively low fT3 value, although within the reference range, was associated with a poor functional outcome and might serve as a potential predictor of prognosis.

To further explore the underline relevant factors, we compared the clinical features between patients of different fT3 levels. Intriguingly, our data showed that the fT3 could also be considered as a measurement of disease severity during the acute phase, as patients in the low-fT3 subgroup were more prone to be admitted to the ICU and had greater maximum mRS scores during hospitalization. The underline reasons could be related to their higher rates of consciousness declination, central hypoventilation and pneumonia, since patients with higher mRS scores and decreased consciousness might simultaneously present with other serious complications, which could result in a poor prognosis<sup>1,3</sup>. Similar to previous studies<sup>1,3,21</sup>, our study confirmed the ICU admission and central hypoventilation as possible prognostic markers. Given these findings, we speculate that the above factors might be correlated with the association of fT3 and outcome. The multivariable logistic regression bolstered our hypothesis, as the prognostic value of fT3 attenuated after adjusted for ICU admission, central hypoventilation and other related factors. In this regard, the relatively low fT3 state might as well be at first interpreted as just a biological risk factor, but not as a direct causal factor contributing to the poor prognosis of patients with anti-NMDAR encephalitis.

Two possible mechanisms might play a role in the association between low fT3 value and poor prognosis in patients with anti-NMDAR encephalitis. First, acute illnesses can result in reduced enzyme activity of 5' monodeiodinase responsible for converting T4 into T3 in peripheral tissues, in the absence of a primary thyroid disorder<sup>6</sup>. Some in vitro studies have reported that fT3 exerts a protective effect against glutamate toxicity in neurons and glial cells through both transcriptional and non-transcriptional mechanisms<sup>22,23</sup>. Accordingly, patients with low fT3 might experience decreased neuroprotection and increased secondary brain damage after anti-NMDAR encephalitis, leading to poor outcomes. Second, increasing evidence suggests that thyroid hormones are closely related to brain acetylcholine activity, cholinergic function, and the secretion of various neurotrophic factors such as nerve growth factor<sup>24</sup>. Specially, fT3 is crucial for the generation and maturation of new neurons and axonal myelination<sup>25</sup>. Thus, patients with low fT3 might exhibit a suppression of endogenous brain repair systems and it is plausible to take into account whether thyroid hormones play important roles in the pathogenesis and evolution of anti-NMDAR encephalitis. However, the exact effects of thyroid hormones still require further studies and discussions.

Several limitations merit consideration in the interpretation of this study. First, it is observational in nature and based on data from a single hospital, which might have led to unintentional bias. Second, the number of patients in this analysis is of only moderate size limiting the statistical power. Third, we only evaluated serum thyroid hormones at a single time point. The level of fT3 in critical illness changes over

time, which is a dynamic process<sup>26,27</sup>. Future studies evaluating multiple time points are required for validating the predictive role of fT3 in anti-NMDAR encephalitis.

In conclusion, our analysis suggests that the serum fT3 on admission might be a useful index of functional outcome following anti-NMDAR encephalitis. Still, it remains obscure whether the low fT3 value is just an epiphomenon of disease process or modifies disease disability. Further investigations in larger cohort of patients are definitely needed to confirm the prognostic value of fT3.

## Methods

### Subjects and evaluation

In this prospective study, we evaluated consecutive inpatients with anti-NMDAR encephalitis admitted in the Zhengzhou University First Affiliated Hospital between January 1, 2016 and December 31, 2019. Depending on the clinical status, informed consent was obtained from the patients or their relatives. Prior approval of the study protocol was obtained from the ethical committee. All patient records and information were anonymized and de-identified prior to analysis. The inclusion criteria were (1) met the diagnostic criteria of definite anti-NMDAR encephalitis, i.e. in the presence of one or more of the six major groups of symptoms and positive IgG anti-GluN1 antibodies in the CSF, after reasonable exclusion of other disorders<sup>1</sup>; (2) thyroid hormones obtained within 24h of admission, including serum fT3, free thyroxine (fT4) and thyroid stimulating hormone (TSH).

Follow-up started from the day of diagnosis, i.e. the day of obtaining positive IgG anti-GluN1 antibodies in the CSF. Each patient underwent a follow-up evaluation by telephone or outpatient interview for 12 months. Disease severity during the acute phase and the functional outcome were assessed using the maximum modified Rankin Scale (mRS) during hospitalization and the mRS at the time of 12-month follow-up, respectively. A favorable functional outcome was defined as a mRS score of 0–2 and a poor outcome was defined as a score of 3–5 or death (mRS score of 6).

### Clinical information and thyroid function measurements

Clinical data and physical examination were obtained in all patients upon admission. Blood samples were collected within 24h of admission and, in addition to standard blood tests, serum levels of fT3, fT4 and TSH were determined using a direct chemiluminescence assay (ADVIA, Bayer Health Care LLC Tarrytown, NY, USA). The reference intervals of our laboratory were as follows: 3.28-6.47 pmol/L for fT3, 7.9-18.4 pmol/L for fT4, and 0.34-5.6 µIU/ml for TSH. A small number of patients also received tests of thyroid autoantibodies, including anti-thyroglobulin antibodies (TGAb), anti-thyroid peroxidase antibodies (TPOAb), and anti-thyroid receptor antibodies (TRAb)<sup>13,14</sup>. “Clinical hyperthyroidism” was defined as suppressed TSH and elevated fT4 levels with relevant clinical symptoms, and “subclinical hyperthyroidism” was defined as a suppressed TSH level, fT3 and fT4 levels within the normal ranges, and the absence of symptoms. In contrast, “clinical hypothyroidism” was defined as elevated TSH and suppressed fT4 levels with relevant symptoms, and “subclinical hypothyroidism” was defined as an

elevated TSH level, a normal fT4 level, and the absence of symptoms. "Low T3 syndrome" was defined as a low serum fT3, normal–low fT4, and normal–low TSH levels<sup>28</sup>. "Other conditions" included slightly elevated fT3 or fT4 levels, normal TSH and the absence of symptoms.

During hospitalization, all patients underwent the lumbar puncture, and the IgG anti-GluN1 antibodies in the CSF were detected by cell-based assays (CBA), using Euroimmun IIFT kits: Autoimmune Encephalitis Mosaic 1 (FA 1121-1005-1), and/or NMDAR kits (FA112d-1005-51), according to the manufacturer's instructions<sup>1</sup>. All measurements were performed by laboratory staff who were blinded to patients' clinical information. All patients received the following examinations to screen tumors, including the brain MRI, computerized tomography (CT) scan of the thorax, ultrasound of the abdomen, pelvic and reproductive regions. None of the patients were given methylprednisolone or any other immunotherapies before admission, and the immunotherapies were not started until the GluN1 antibodies in the CSF were confirmed. The "pneumonia" was diagnosed by respiratory physicians according to the relevant criteria. The "tumor presence" was defined as having ovarian teratoma or any other malignant tumors. The "abnormal MRI" was defined as having relevant brain lesions confirmed by radiologists. The "immunotherapy delay" was defined as the interval between the onset of symptoms and the initiation of immunotherapy. "First-line immunotherapy" included steroids, intravenous immunoglobulins or plasma exchange alone or combined. "Second-line immunotherapy" comprised rituximab, azathioprine or cyclophosphamide treatment alone or combined<sup>21</sup>.

## Statistical analysis

The categorical variables were expressed as counts (%), whereas the continuous variables were expressed as the mean (standard deviation, SD) or median (interquartile range [IQR]) values as appropriate. The age, immunotherapy delay, white blood counts (WBC) and the concentrations of c-reactive protein (CRP) were log-transformed to approximate a normal distribution. The univariate logistic regression was used to identify factors significantly associated with an increased risk of poor outcome; for each variable, the odds ratio (OR), and 95% confidence interval (CI) were given. Relevant variables with P<0.10 in the invariable analysis were entered into multivariable logistic regression models to identify whether variables were independently associated with poor outcome.

Patients were equally divided into three subgroups based on their serum fT3 levels. Baseline demographic and clinical features were compared across the three subgroups using the one-way analysis of variance (ANOVA), the equality-of-medians test or the Fisher's exact test as appropriate. For differences within subgroups, the pair wise comparison with Bonferroni correction was used. All analyses were performed using Stata for Windows, Version 14.0 (StataCorp LLC., USA). A P value <0.05 was considered to be statistically significant.

## Declarations

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## Author contributions

The corresponding author was LYJ, who dominated this article. JT and HZ completed the collection of clinical data and the writing. WCZ and ZQM guided the completion of this paper. LYJ had provided lots of help in literature retrieval and article revision. All authors read and approved the final manuscript.

## Additional information

**Disclosure of conflicts of interest:** The authors declare no conflict of interest.

**Data Availability Statement:** Data that support the findings of this study are available upon reasonable request.

**Ethical approval:** The Ethics Committee of the Zhengzhou University First Affiliated Hospital approved this study. This study was performed in accordance with the 1964 Declaration of Helsinki and later amendments.

**Consent to participate and publication:** Written informed consents were obtained from all patients or their guardians prior to their inclusion for sample collection and publication of this paper.

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## Tables

**Table 1 Clinical features and subgroup comparisons of the study population**

	Total	Low-fT3 subgroup	Middle-fT3 subgroup	High-fT3 subgroup	P
<b>Basic characteristics</b>					
Cases, n	96	32	32	32	
Females, n (%)	43 (44.79)	18 (56.25)	11 (34.38)	14 (43.75)	0.235
Age at onset, median (IQR), years	30 (21-40.5)	34 (23.5-48.5)	29.5 (23-39.5)	26 (17-33)	0.004*
Pneumonia, n (%)	54 (56.25)	23 (71.88)	20 (62.50)	11 (34.38)	0.008*
Tumor presence, n (%)	5 (5.21)	2 (6.25)	2 (6.25)	2 (6.25)	1
Abnormal MRI, n (%)	55 (57.29)	18 (56.25)	22 (68.75)	15 (46.88)	0.263
<b>Symptoms</b>					
Prodromal symptoms, n (%)	61 (63.54)	22 (68.75)	20 (62.50)	19 (59.38)	0.804
Psychiatric behavior, n (%)	76 (79.17)	28 (87.5)	24 (75)	24 (75)	0.398
Cognitive dysfunction, n (%)	56 (58.33)	16 (50)	22 (68.75)	18 (56.25)	0.15
Speech dysfunction, n (%)	41 (42.71)	12 (37.5)	14 (43.75)	15 (46.88)	0.813
Seizures, n (%)	63 (65.63)	20 (62.5)	20 (62.5)	23 (71.88)	0.692
Movement disorder, n (%)	35 (36.46)	12 (37.5)	13 (40.63)	10 (31.26)	0.804
Consciousness declination, n (%)	41 (42.71)	21 (65.63)	11 (34.38)	9 (28.13)	0.006*
Autonomic dysfunction, n (%)	33 (34.38)	15 (46.88)	11 (34.38)	7 (21.88)	0.123
Central hypoventilation, n (%)	16 (16.67)	11 (34.38)	3 (9.38)	2 (6.25)	0.007*
<b>Blood tests</b>					
WBC, median (IQR), n x 10 <sup>9</sup> /L	8.5 (6.6-11.05)	9.15 (7.45-12.8)	8.75 (7.11-10.8)	6.99 (6.2-8.9)	0.047*
Neutrophil proportion, mean (SD), %	72.54 (1.13)	78.31 (1.72)	71.72 (1.83)	67.44 (1.89)	<0.001*
CRP, median (IQR), mg/L	2.1 (0.98-7.21)	6.87 (2.21-11.11)	1.69 (0.74-3.02)	1 (0.17-2.2)	<0.001*
<b>CSF tests</b>					
CSF with pleocytosis, n (%)	68 (70.83)	27 (84.38)	20 (62.5)	21 (65.63)	0.135
CSF with oligoclonal bands, n (%)	22 (22.92)	6 (18.75)	11 (34.38)	5 (15.63)	0.291
<b>Thyroid status</b>					

fT3, median (IQR), pmol/L	4.45 (3.88-5.01)	-	-	-	-
fT4, median (IQR), pmol/L	11.97 (10.63-13.52)	12.37 (9.89-13.33)	11.78 (10.84-13.21)	12.03 (10.82-14.69)	0.966
TSH, median (IQR), uIU/ml	1.07 (0.59-1.93)	0.76 (0.49-1.18)	1.14 (0.83-2.06)	1.48 (0.71-2.13)	0.005*
Positive TPOAb, n (%)	10 (10.42)	5 (15.63)	2 (6.25)	3 (9.38)	0.764
Positive TRAb, n (%)	2 (2.08)	1 (3.13)	0	1 (3.13)	0.524
Positive TGAb, n (%)	13 (13.54)	7 (21.88)	3 (9.38)	3 (9.38)	0.483
Immunotherapy					
First-line immunotherapy, n (%)	91 (94.79)	30 (93.75)	31 (96.88)	30 (93.75)	1
Second-line immunotherapy, n (%)	12 (12.5)	3 (9.38)	4 (12.5)	5 (15.63)	0.926
Immunotherapy delay, median (IQR), days	18 (13-31)	18 (14-29)	18 (12-32)	18.5 (13-30)	0.884
Prognosis					
ICU admission, n (%)	52 (54.17)	28 (87.5)	14 (43.75)	10 (31.25)	<0.001*
Maximum mRS during hospitalization, median (IQR)	4 (3-5)	5 (4-5)	3 (3-5)	3 (3-3.5)	0.011*
Favorable functional outcome (mRS 0-2), n (%)	73 (76.04)	17 (53.13)	27 (84.38)	29 (90.63)	0.002*

IQR, interquartile range; SD, standard deviation; MRI, magnetic resonance imaging; WBC, white blood counts; CRP, c-reactive protein; CSF, cerebrospinal fluid; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; TGAb, anti-thyroglobulin antibodies; TPOAb, anti-thyroid peroxidase antibodies; TRAb, anti-thyroid receptor antibodies; ICU, intense care unit; mRS, modified Rankin scale.  
 \*P<0.05

**Table 2 Univariable logistic regression analysis of predictors for functional outcome**

Variables	OR	95% CI	P
fT3 value	0.385	0.202-0.732	0.004
Age	1.036	1.002-1.07	0.038
Male	0.257	0.094-0.703	0.008
Tumor presence	15.158	1.599-143.649	0.018
ICU admission	5.758	1.782-18.599	0.003
Consciousness declination	2.65	1.012-6.941	0.047
Central hypoventilation	6.061	1.931-19.024	0.002
Blood Neutrophil proportion	1.058	1.009-1.109	0.02

OR, odds ratio; CI, confidence interval; fT3, free triiodothyronine; ICU, intense care unit.

Variables identified as predictors of a poor functional outcome in the univariate model ( $P < 0.05$ ) are included in this table.

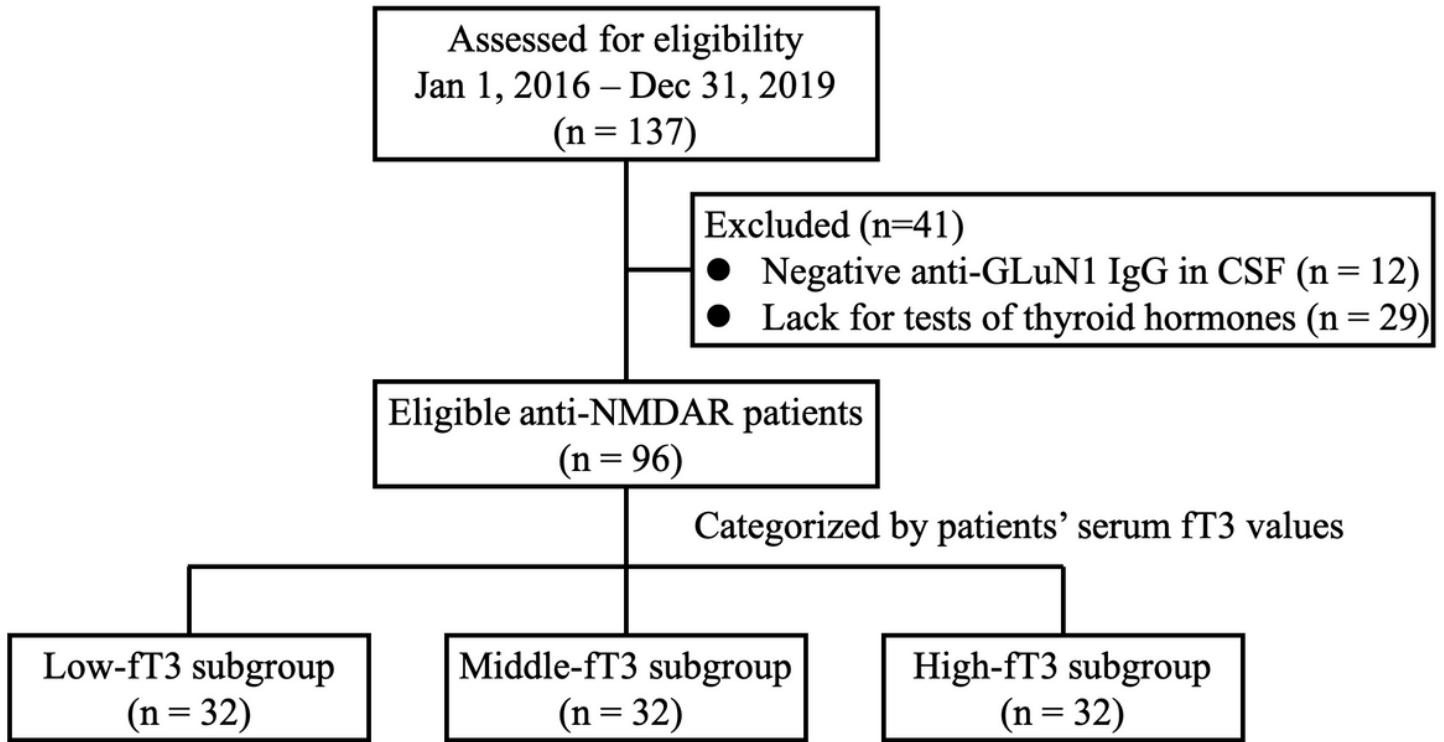
**Table 3 Multiple logistic regression analysis of fT3 as a predictor for functional outcome**

	OR	95% CI	P
Model 1	0.411	0.218-0.777	0.006
Model 2	0.476	0.245-0.925	0.029
Model 3	0.427	0.212-0.862	0.018
Model 4	0.472	0.226-0.986	0.046
Model 5	0.579	0.267-1.252	0.165

OR, odds ratio; CI, confidence interval; fT3, free triiodothyronine

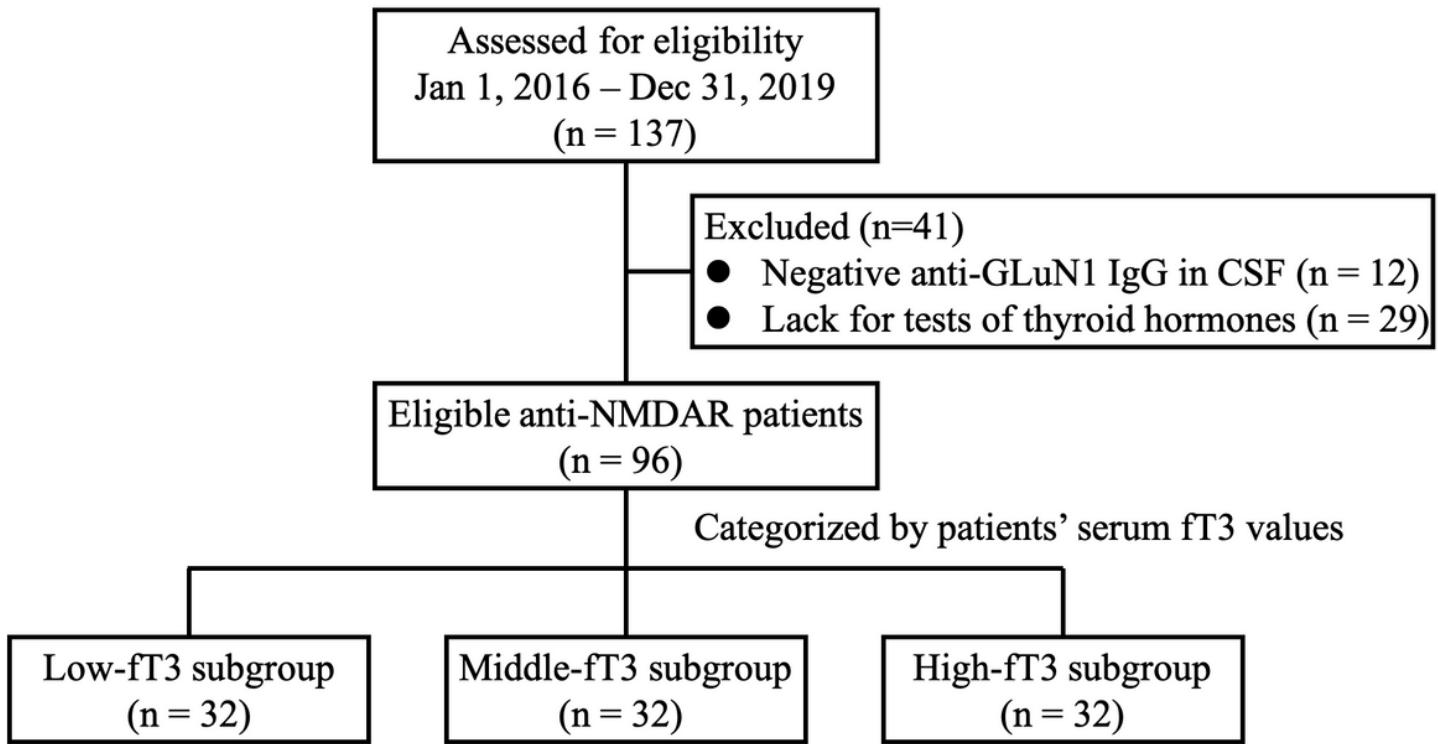
Model 1, adjusted by gender; Model 2, adjusted by gender and age; Model 3, adjusted by gender, age and tumor presence; Model 4, adjusted by gender, age, tumor presences, and consciousness declination; Model 5, adjusted by gender, age, tumor presences, consciousness declination, intense care unit admission, central hypoventilation and Blood Neutrophil proportion.

## Figures



**Figure 1**

Cohort selection process of the study population Of 137 admissions for anti-NMDAR encephalitis reviewed, 12 patients were excluded because their IgG anti-GluN1 antibodies were only positive in serum but negative in CSF, which couldn't meet the diagnostic criteria of definite anti-NMDAR encephalitis. Another 29 patients were excluded for the lack of results of thyroid hormones within 24h of admission. Ultimately, a total of 96 patients were included in this study. Based on the levels of serum fT3, the patients were equally divided into three subgroups, i.e. the low-fT3, middle-fT3 and high-fT3 subgroup.



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