Anti-NMDA Receptor Encephalitis: Efficacy of Treatment for Male Patients and miRNA Biomarker

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Abstract

Treatments for the anti-NMDA receptor encephalitis usually include steroids, intravenous immunoglobulin, plasma exchange, plasmapheresis, rituximab, cyclophosphamide and tumor resection. We aimed to compare the efficacy of the treatments including intravenous immunoglobulin, plasma exchange, plasmapheresis, rituximab or cyclophosphamide for male anti-NMDA receptor encephalitis patients without tumor and to discuss potential biomarkers for this disease. The Fisher exact test and the contingency table analysis were used to analyze the treatment efficacy for both male and female these patients. A hierarchical tree method was adopted to analyze the difference of the treatment efficacy between male and female patients. The results revealed that the efficacy rate of plasmapheresis (or plasma exchange) is not inferior to those of intravenous immunoglobulin and rituximab (or cyclophosphamide) for male patients without tumor. In addition, B-cell attracting C-X-C motif chemokine 13 (CXCL13) and microRNA let-7b are potential to be treatment response biomarkers for anti-NMDA receptor encephalitis. But they may not be useful prognostic biomarkers for this encephalitis unless they are not biomarkers for other autoimmune encephalitides.

Keywords: anti-NMDA receptor encephalitis, immunotherapy, efficacy rate, treatment

Introduction

Anti-NMDA receptor encephalitis is a disease occurring when antibodies produced by the body's own immune system attack N-methyl-D-aspartate (NMDA) receptors in the brain. The NMDA receptors are blocked when the antibodies are produced. This disease was originally described in 2007 by Dalmau et al. (1). Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from initial psychiatric symptoms to memory disturbances, seizures, dyskinesia, and catatonia. In addition, tumors, especially ovarian tumors, have been detected in a proportion of female patients (2). The patients with detectable tumors had significant improvement after tumor resection. For those patients without detectable tumors, the cause is often unknown (3).

Full recovery of this disease can take from several months to several years after disease onset (4). The choice of treatments may be a potential factor that facilitates an early recovery from anti-NMDA receptor encephalitis. To compare treatments, Wang (2016) investigated the efficacies of different combinations of therapy in the four categories: (I) intravenous immunoglobulin administration, (II) plasmapheresis or plasma exchange, (III) treatment with rituximab or cyclophosphamide and (IV) tumor removal (5, 6).

In this study, we focus on investigating the difference in treatment efficacy between male patients and female patients and mainly focus on the efficacy of treatment for male patients. A meta-analysis was utilized to investigate the effects of

treatment for male patients. Statistical analyses showed that the efficacy rate of plasmapheresis (or plasma exchange) is not inferior to those of intravenous immunoglobulin and rituximab (or cyclophosphamide) for male patients without tumor. A result showed that the outcome concluded in Wang (2016)(5), the treatment combinations including at least two forms of therapy resulted in higher efficacy rates than treatment with a single form of therapy, might not hold on male patients.

In addition, microRNAs (miRNAs) might be used as diagnosis and prognosis biomarkers as other diseases. The levels of the B-cell–attracting C-X-C motif chemokine 13 (CXCL13) and microRNA let-7b are potential to be used as biomarkers for the anti-NMDA receptor encephalitis (5, 7-9). The feasibility of using the levels CXCL13 or let-7b as useful biomarkers for this disease was discussed in this study.

Methods

1. Contingency table analysis

Treatments for the anti-NMDA receptor encephalitis usually include steroids, intravenous immunoglobulin (IVIG) or plasmapheresis (or plasma exchange) either alone or in combination constitute the first-line immunotherapies for anti-NMDA receptor encephalitis; rituximab or cyclophosphamide is administered alone or in combination as a second-line immunotherapy. It is usually recommended that identified tumors are resected from these patients.

Although 79% of anti-NMDA receptor encephalitis patients completely recovered within 2 years (4), many cases achieved good recovery within approximately one year

of symptom onset. To compare the efficacies of different treatment combinations and to identify treatment combinations that may shorten the recovery time, Wang (2016) reviewed case reports of 94 anti-NMDA receptor encephalitis patients, including 18 male patients and 76 female patients, and evaluated the efficacies of different treatment combinations using one year as a threshold for the recovery time. The result in that study showed that combinations of treatments from at least two of these categories had higher efficacy rates than did treatment with a single form of therapy.

Compared with female patients, there are fewer male patient cases reported in the literature. In this study, we focus on the discussion of male patients without tumor. In addition to the 18 male patients discussed in Wang (2016), we reviewed case reports of male patients in the literature and excluded those without tumor and without enough details. We collected another 25 male patients. The total of 43 male patients' ages ranged between 8 months and 73 years. None of them received tumor resection. Therefore, in this study, we excluded the tumor resection, and only compared the other treatments based on the outcome of these male patients. The treatment regimens of these patients were classified into three categories: (I) IVIG administration, (II) plasma exchange or plasmapheresis and (III) treatment with rituximab or cyclophosphamide. This study was approved by the Research Ethics Committee for Human Subject at National Chiao Tung University, Taiwan.

The treatments received by each male patient are listed in Table 1. As in Wang (2016), to compare the efficacies of different treatment regiments, we set one year as a threshold for the time to recovery. Table 1 lists the genders, ages, references and

treatments administered for the 43 patients, and also indicates whether patients' recovery times were approximately one year or less. The efficacy rate of a treatment in Wang (2016) was defined as the ratio of the number of patients with a recovery time within approximately one year to the total number of patients who received this treatment. The evaluation of a treatment in this study was based on this efficacy rate. That is, a treatment was regarded to be not inferior to another treatment if this treatment had a significantly higher efficacy rate than the other treatment.

In one case in Table 1, the patient's treatment requires explanation. The patient described in (10) began rituximab therapy at 13 months after initial discharge. Because the efficacy rate was computed only for the recovery time of approximately one year, we considered only the IVIG treatment given to this patient, as well. Among these 43 patients, four of them had a good clinical outcome without receiving any one of the treatments in the three categories. One is a 73-year-old missionary priest, and the ages of the other three patients are 27, 34 and 50, respectively. It reveals that male patients can have a good clinical outcome even if this disease is late-onset.

In this study, we do not consider to compare the efficacies of treatment combination. Instead, we compare the efficacy of individual treatment in the three categories. Although the treatment efficacy may be confounded because each patient may receive more than one treatment, due to the randomness of the sample, this matter may be eliminated.

Since these treatments carry risks and side effects, studies on the efficacy of these

treatments can help select an effective treatment instead of randomly selecting treatments. To compare the treatments, we analyzed the data from three aspects. The first one is to test whether the efficacy rate of a treatment reaches 0.8, 0.7 or 0.6. The second one is to test whether the efficacy rate of patients receiving a treatment is equal to patients without receiving this treatment. The third one is to test whether the efficacy rate of male patients receiving a treatment is equal to female patients receiving this treatment.

The null hypothesis of the first aspect can be presented as

$$H_0^{first} : r_A \geq 0.8 \qquad (1)$$

where A denotes a treatment in one of the three categories and r_A denotes the efficacy rate of this treatment. In addition to considering the efficacy rate 0.8, we also test the cases of the efficacy rate 0.7 and 0.6, respectively. To test (1), for patients receiving Treatment A, it is reasonable to assume that the number of patients, who recover within or by approximately one year, follows a binomial distribution $B(n_A, r_A)$, where n_A is the number of patients receiving this treatment. Since the sample size is not large, we used an exact test to test the proportion value r_A of a binomial distribution. The p-values of testing (1) for different treatments are given in Table 3.

The null hypothesis of the second aspect can be presented as

$$H_0^{second} : r_A = r_{A'} \qquad (2)$$

where $r_{A'}$ denotes the efficacy rate of patients who did not receive Treatment A. To

test (2), we apply a contingency table analysis. To analyze the contingency table, since the sample size is not large, we used the Fisher exact test to test the independence of the efficacy rates of patients receiving Treatment A and that of patients not receiving Treatment A. The results are presented in Table 4.

The null hypothesis of the third aspect can be presented as

$$H_0^{third} : r_A^{male} = r_A^{female} \quad (3)$$

where r_A^{male} and r_A^{female} denote the efficacy rate of male patients and female patients receiving Treatment A, respectively. As testing (2), we also applied a contingency table analysis and used the Fisher exact test to test the independence of the efficacy rates of male patients receiving Treatment A and female patients receiving Treatment A. The results are presented in Table 5.

In summary, we compared the treatments in these three aspects:

(i) test whether the efficacy rate of a treatment was greater than 0.8, 0.7 or 0.6;

(ii) test whether the efficiency rate of patients receiving a treatment was equal to patients without receiving this treatment;

and

(iii) test whether the efficiency rate of a treatment for male patients was equal to that for female patients.

2. Clustering tree

In addition to the contingency table analysis, we applied a hierarchical tree method to explore the relationship between treatments and the recovery situation. To plot the tree, for male patients, we mainly consider the four items, full recovery within or by

approximately one year, IVIG administration, plasma exchange (or plasmapheresis) and rituximab (or cyclophosphamide) in Table 1. For the female patients, in addition to the above four categories, we also consider another item, tumor resection, in Table 2. The steps of constructing a hierarchical tree method are first to calculate the pairwise distances for each pair of these categories, and then to adopt a clustering approach to classifying these categories using the calculated pairwise distances. We adopt the Euclidean distance to calculate the pairwise distance between vectors. For the clustering approach used in the second step, we apply the unweighted pair-group method with arithmetic averages (UPGMA) to plot the tree. The hierarchical trees for male patients and female patients are plotted in Figures 1 and 2.

Results

1. Efficacy of Treatment

The comparison results of the treatments in the three categories are provided in this section. First, Table 3 gives the results of testing whether the efficacy rate is greater than 0.6, 0.7 or 0.8 for the treatments in the three categories. When testing the hypothesis of efficacy rate greater than 0.8, the p-values are 5.904×10^{-8}, 0.1611 and 4.979×10^{-5} for IVIG, plasmapheresis (or plasma exchange) and rituximab (or cyclophosphamide), respectively. The first p-value and the third p-value are less than 0.05, which means that the hypotheses for IVIG and rituximab (or cyclophosphamide) are rejected under a type I error 0.05. It concludes that the efficacy rates for IVIG and rituximab (or cyclophosphamide) are less than 0.8. Similar results are obtained when testing the hypotheses of efficacy rate greater than 0.6 and 0.7. These outcomes reveal that the efficacy rate of plasmapheresis (or plasma exchange) is not

inferior to those of the treatments in the other two categories.

Next, we tested whether the efficiency rate was the same when a patient receives a treatment or not. From Table 4, the p-values corresponding to IVIG and rituximab (or cyclophosphamide) are 0.9543 and 0.8169, respectively, which reveals that the insignificance of the early recovery of these two treatments. Compared with these two treatments, the p-value of plasmapheresis (or plasma exchange) is 0.0902, which is much smaller than the p-values for the other two treatments and reveals that the significance of the early recovery of the plasmapheresis (or plasma exchange).

Finally, we compared the efficacy rate of male patients with that of female patients for each treatment. The treatments of the 76 female patients discussed in Wang (2016) are listed in Table 2. The references of these female patients are referred to Wang (2016). The null hypothesis assumes that the efficacy rate of female patients is equal to that of the male patient. From Table 5, the p-values of testing the null hypotheses for IVIG and rituximab (or cyclophosphamide) are 0.001 and 0.058, respectively, which results in the rejection of the null hypotheses under type I error 0.05 or 0.1. However, the p-values of testing the null hypotheses for plasmapheresis (or plasma exchange) is 0.4201, which does not lead a result to reject the null hypothesis. It indicates that the two treatments, IVIG, and rituximab (or cyclophosphamide), have less improvement for male patients compared with female patients. The odd ratios of the three contingency tables are 4.550, 1.551 and 6.514 for IVIG, plasmapheresis (or plasma exchange) and rituximab (or cyclophosphamide), respectively. The odd ratios for IVIG and rituximab (or cyclophosphamide) are higher

than plasmapheresis (or plasma exchange).

The efficacy rates for female and male patients are 0.7368(=56/76) and 0.4186(=18/43) for the 76 female cases and 43 male cases. Although the efficacy rates of female patients may be higher than male patients, four cases show that male patients can have a good clinical outcome even if this disease is late-onset. In these 43 male patients, there are ten patients receiving plasmapheresis (or plasma exchange). Seven of them were full recovery within or by approximately one year; four of them were not. Observing the four cases without early recovery, we found that all of them received the treatment rituximab (or cyclophosphamide). This may indicate that these four cases were in a more serious condition because they received the second-line immunotherapy.

In addition to our result that plasmapheresis (or plasma exchange) is not inferior to the treatments in the other two categories, a previous study showed that patients, including a male patient, were assessed for clinical improvement during the course of plasma exchange and immediately after completion of the last plasma exchange (11). They concluded that although the number of cases was small and the difference was not statistically significant, the observation suggested that plasma exchange was a relatively safe treatment option in patients with anti-NMDA receptor encephalitis and early initiation of it could be beneficial.

Although the contingency table analysis only shows the significance of the plasmapheresis for male patients, by Figure 1, the early recovery also associates with

rituximab or cyclophosphamide. For female patients, the early recovery is related to IVIG administration. These results reveal that the efficacies of treatments may depend on gender, and the results are potential to develop the personalized treatment for this disease.

Discussion

To treat this disease more effectively, biomarkers of clinical disease activity are needed. The use of the levels of CXCL13 in serum samples and cerebrospinal fluid (CSF) samples of patients with anti-NMDA receptor encephalitis as biomarkers of treatment response and outcome has been investigated (7, 9). CXCL13 is a B-cell–attracting chemokine that is not only found elevated in anti-NMDA receptor encephalitis patients but has also been found mildly elevated in other autoimmune disorders such as multiple sclerosis and neuromyelitis optica (12, 13).

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The study of Leypoldt et al. (2015) showed that 70% of patients with early-stage anti-NMDAR encephalitis had increased CXCL13 in CSF. Although this result revealed that the level of CXCL13 in CSF was a potential biomarker for Anti-NMDA receptor encephalitis, it is likely that CXCL13 is elevated in other autoimmune encephalitis. As a result, although the level of CXCL13 may be potential to be used as biomarkers of treatment response and outcome of this disease, it may not be a useful prognostic biomarker unless it can be shown to be a unique biomarker for anti-NMDA receptor encephalitis, but not a biomarker for another autoimmune encephalitides.

In addition, microRNA (miRNA) let-7b may also be a potential biomarker

and an indicator that reflect the molecular mechanism of anti-NMDA receptor encephalitis (5, 8). miRNAs are single-stranded, non-coding RNAs consisting of 22–24 nucleotides that play important roles in genome expression, which may contribute to chronic inflammation in the brain (14) and can be used as biomarkers for many diseases (15). Significant down-regulation of let-7a, let-7b, let-7d, and let-7f was demonstrated in anti-NMDA receptor encephalitis patients (8). In addition to anti-NMDA receptor encephalitis, it has been revealed that let-7 is closely associated with human cancer and innate immune responses (16). As a result as CXCL13, let-7b is potential to be a treatment response biomarker for anti-NMDA receptor encephalitis. However, it may not be a useful prognostic biomarker for this encephalitis unless it can be shown to be a unique biomarker for it, but not for other autoimmune encephalitides.

Discussion

There are limitations of this study. The study is retrospective and the allocation of treatments is physician-based, but not protocol-based, which may lead to a biased comparison result. However, due to the cost of these treatments and the choice of patients, it may be hard to design a protocol-based experiment. Therefore, we believe that any significant results obtained by analyzing data from these case reports can provide useful information about the efficacy of therapies for anti-NMDA receptor encephalitis.

Additionally, treatment decisions are based on the disease progression over time. The patients who have a good response to the first-line treatment are not assigned to

receive the second-line immunotherapy. Therefore, the patients that receive rituximab or cyclophosphamide might have more serious conditions. This may lead to a biased result when comparing the first-line immunotherapy and the second-line immunotherapy. For this reason, the comparison result only for the treatments of the first line immunotherapies, plasmapheresis (or plasma exchange) and IVIG, is more sensible. Although the sample size used in this study may not be large enough to draw a very firm conclusion, this would be a useful direction for further evidence to confirm it.

It is worth noting that the effect of treatments may depend on other factors such as dosing of therapies, clinical severity or phases of the disease. Due to the limited number of male patients, it is hard to compare therapies by considering many different conditions. It would be our future study to investigate the effect of treatments subject to more factors.

Conclusions

Anti-NMDA receptor encephalitis is a rare autoimmune encephalitis that presents with psychiatric symptoms, together with other symptoms of encephalitis. It occurs more often in female patients than in male patients. In Wang (2016), when both female and male patients were considered, the effects for the three categories of treatment cannot be distinguished. However, when a smaller group of patients (male patients) is considered, the plasma exchange (plasmapheresis) may be potential to dominate the other two. It reveals that we may find the effective treatment strategy for a specific group of patients although this treatment strategy may not always be

effective for the patients that are not in this specific group. Most studies for the anti-NMDA receptor encephalitis provided an overview statistical result for this disease but did not focus on any patient-specific treatment discussion. This study can provide a patient-specific treatment strategy that the efficacy rate of plasmapheresis (or plasma exchange) is not inferior to those of intravenous immunoglobulin and rituximab (or cyclophosphamide) for male patients without tumor.

In this study, we also reveal that the effects of treatments for male patients may be different to those for female patients. The data in Wang (2016) show that the female patients have a higher efficacy rate than male patients. The effects of treatments for male patients seem not as significant as those for female patients. Nevertheless, four cases revealed that male patients can have a good clinical outcome even if this disease is late-onset. The result section showed that female patients receiving IVIG and rituximab (or cyclophosphamide) had a higher efficacy rate than male patients, and the efficacy rate of the plasmapheresis (or plasma exchange) is not inferior to those of intravenous immunoglobulin and rituximab (or cyclophosphamide) for male patients without tumor.

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Competing interests

The author declares no conflict of interest.

Author Contributions H. Wang conceived and designed the study and wrote the manuscript.

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Figure Legend:

Figure 1. A classification tree showing the relationship between the recovery situation and treatments for male patients

Figure 2. A classification tree showing the relationship between the recovery situation and treatments for female patients

Table 1. The treatments for 43 male anti-NMDA receptor encephalitis patients

(I) IVIG administration, (II) plasma exchange or plasmapheresis and

(II) rituximab or cyclophosphamide

(III) .

Gender	Age (year)	Full recovery within or by approximately one year	Treatment			references
			I	II	III	
M	45			v	v	(17)
M	16		v			(18)
M	20month		v		v	(19)
M	30	v	v	v		(20)
M	2		v			(10)
M	8month		v			(21)
M	50	v				(22)
M	8		v			(23)
M	35				v	(24)
M	73	v				(25)
M	66	v	v	v	v	(26)
M	8	v	v		v	(27)
M	6	v	v			(28)
M	17	v	v	v		(29)
M	13.5		v			(30)
M	68					(31)
M	18		v		v	(32)
M	38		v	v	v	(33)
M	9		v	v	v	(34)
M	25	v	v		v	(35)
M	28		v		v	(35)

M	21	v	v			(35)
M	32		v			(35)
M	24	v	v		v	(35)
M	20		v		v	(35)
M	43	v	v			(35)
M	22		v		v	(35)
M	18		v		v	(35)
M	34					(36)
M	27	v				(36)
M	25		v			(36)
M	16		v			(36)
M	25		v			(36)
M	13		v			(37)
M	50		v		v	(37)
M	4	v		v		(38)
M	9	v	v	v	v	(39)
M	7		v	v	v	(40)
M	7	v	v			(36)
M	10	v	v	v	v	(41)
M	46		v			(42)
M	34	v				(43)
M	42	v		v	v	(44)
Total		18	33	11	19	

Table 2. The treatments for 76 female anti-NMDA receptor encephalitis patients (IV) IVIG administration, (II) plasma exchange or plasmapheresis, (III) rituximab or cyclophosphamide and (IV) tumor resection

Gender	Age (years)	Full recovery within or by approximately one year	Treatment			
			I	II	III	IV
F	30		v	v	v	
F	19	v	v	v		v
F	23	v	v	v	v	v
F	25					
F	9					
F	11	v	v		v	
F	17	v	v			v
F	9	v	v		v	
F	17		v	v	v	
F	3	v	v		v	
F	35	v	v		v	v
F	26	v				v
F	23		v			
F	3	v	v			
F	18	v		v		v
F	16	v	v	v		v
F	20 months	v	v		v	
F	9	v	v	v	v	v
F	4	v	v			
F	16		v			
F	3 years 2 months		v	v	v	
F	9	v	v		v	
F	14	v	v			
F	7		v	v	v	
F	8		v			
F	65			v	v	
F	4	v	v			
F	14		v			
F	5	v	v			

F	21	v	v	v		v
F	14	v	v		v	v
F	25	v	v	v		
F	26	v	v			
F	15	v	v		v	
F	15	v	v		v	
F	17	v	v	v	v	
F	31	v		v	v	
F	4		v			
F	24	v	v	v		v
F	21	v	v			v
F	14	v	v	v	v	
F	29	v	v		v	v
F	34	v	v	v	v	v
F	42	v				
F	38	v				
F	29	v		v	v	
F	17	v		v		v
F	41	v				
F	70	v			v	
F	19		v			
F	33	v		v		v
F	27 months	v	v		v	
F	27 months	v	v	v	v	
F	27	v	v			v
F	11	v		v		v
F	20	v				v
F	21	v	v	v		v
F	42		v			v
F	15	v	v			v
F	21		v	v		v
F	84		v	v		
F	65					v
F	19	v		v	v	v
F	21	v	v			v
F	3 years 9	v	v			

	months					
F	21					
F	15	v	v			v
F	20	v	v			v
F	17		v			
F	33		v			
F	5	v				
F	25	v	v			v
F	26	v	v			v
F	17	v				v
F	28	v				
F	18	v		v		v

Table 3. P-values of testing whether the efficacy rate is greater than 0.6, 0.7 or 0.8 for the three treatments

Null Hypothesis: the efficacy rate $\geq$ 0.8			
Treatment	IVIG	plasmapheresis (or plasma exchange)	rituximab (or cyclophosphamide)
p-value	5.904×10^{-8}	0.1611	4.979×10^{-5}
Null Hypothesis: the efficacy rate $\geq$ 0.7			
Treatment	IVIG	plasmapheresis (or plasma exchange)	rituximab (or cyclophosphamide)
p-value	6.636×10^{-5}	0.4304	0.0028
Null Hypothesis: the efficacy rate $\geq$ 0.6			
Treatment	IVIG	plasmapheresis (or plasma exchange)	rituximab (or cyclophosphamide)
p-value	0.0052	0.7037	0.0352

Table 4. Testing the equality of efficacy rate for male patients receiving a treatment or not

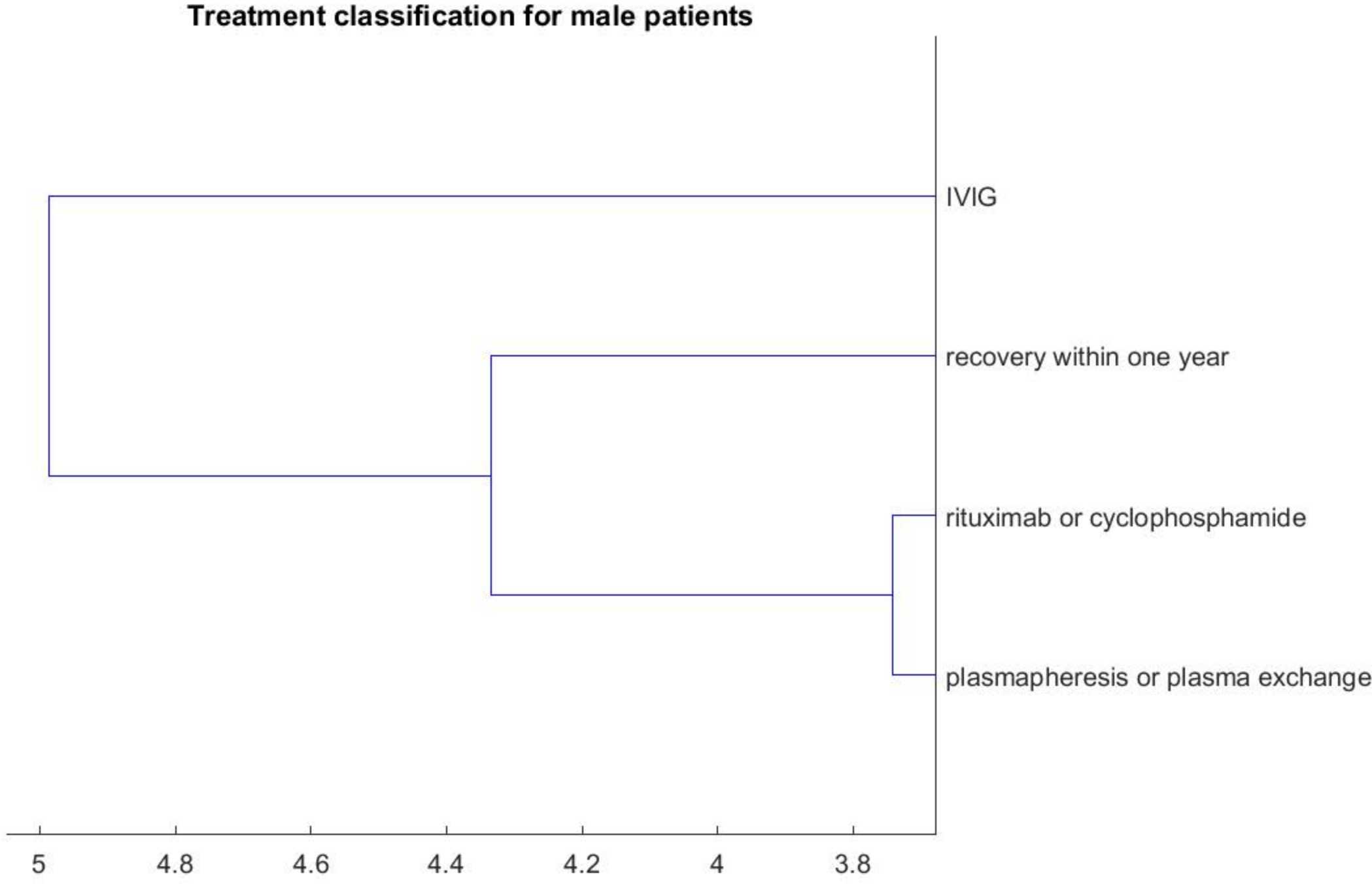
IVIG efficacy vs. No IVIG efficacy				
	IVIG	No IVIG	Total	Null Hypothesis H_0: the efficacy rate of receiving IVIG is equal to that of not receiving it p-value=0.9543 Do not reject the null hypothesis OddsRatio: 0.3810 90% Confidence Interval: [0.1128, 1.2868]
Full recovery within or by approximately one year	12	6	18	
No full recovery within or by approximately one year	21	4	25	
Total	33	10	43	
plasmapheresis (or plasma exchange) efficacy vs. No plasma exchange efficacy				
	plasma exchange or plasmapheresis	No plasma exchange and plasmapheresis	Total	Null Hypothesis H_0: the efficacy rate of receiving plasma exchange is equal to that of not receiving it p-value=0.0902 Do not reject the null hypothesis OddsRatio: 3.3409 90% Confidence Interval: [1.0072, 11.0815]
Full recovery within or by Approximately one year	7	11	18	
No full recovery within or by approximately one year	4	21	25	
Total	11	32	43	
rituximab (or cyclophosphamide) efficacy vs. No rituximab (or cyclophosphamide) efficacy				
	rituximab or cyclophosphamide	No rituximab or cyclophosphamide	Total	Null Hypothesis H_0: the efficacy rate of receiving rituximab (or cyclophosphamide) is equal to that of not receiving it
Full recovery within or by Approximatel	7	11	18	

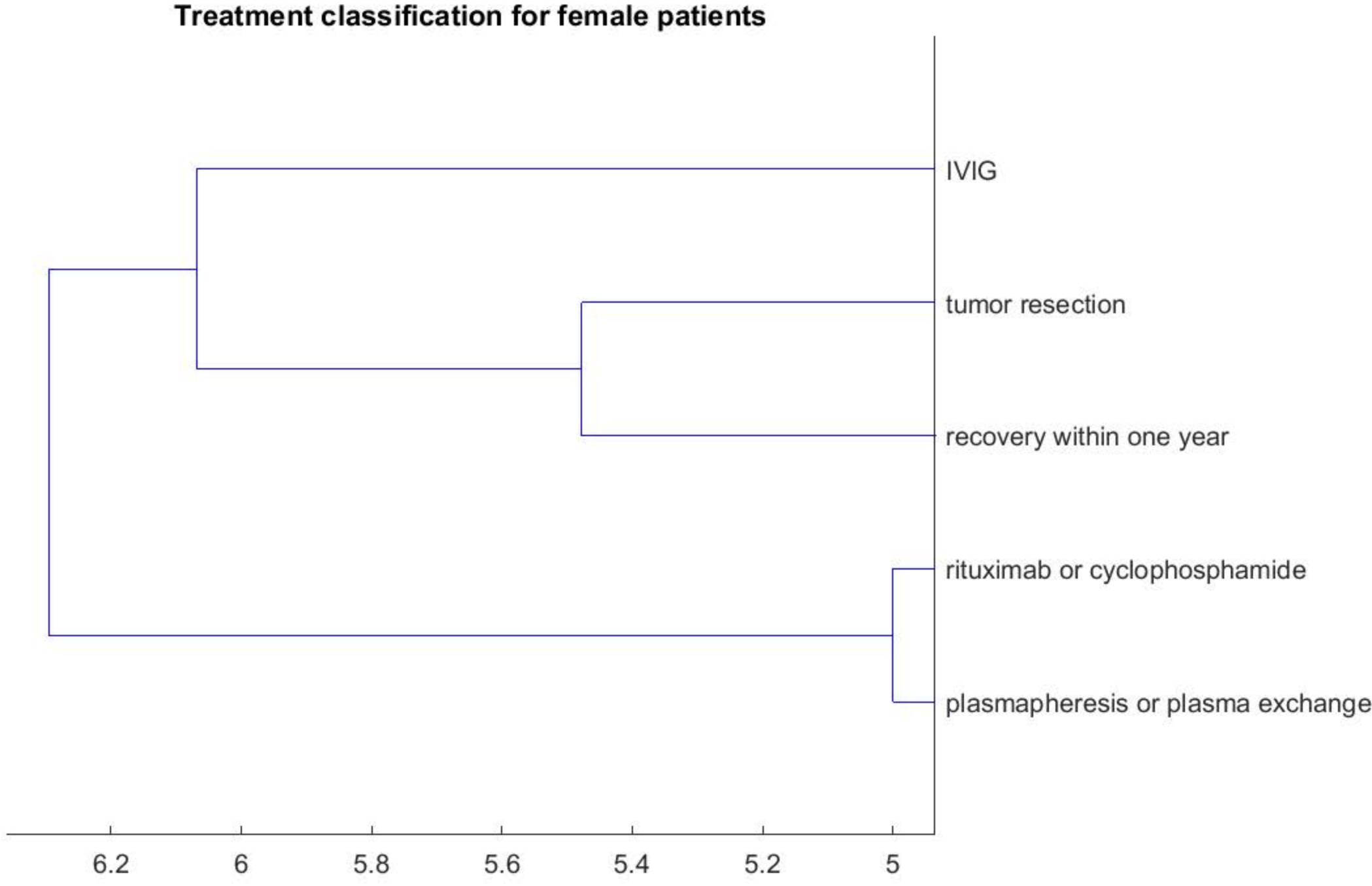
y one year				p-value=0.8169 Do not reject the null hypothesis OddsRatio: 0.6894 90% Confidence Interval: [0.2455, 1.9359]
No full recovery within or by approximately one year	12	13	25	
Total	19	24	43	

Table 5. Testing the equality of the efficacy rate for gender

IVIG efficacy with respect to gender				
	Female patient receiving IVIG	Male patient receiving IVIG	Total	Null Hypothesis H_0: the efficacy rate of female patients is equal to that of male patients p-value=0.001 Reject the null hypothesis OddsRatio: 4.550 90% Confidence Interval: [2.0916, 9.8979]
Full recovery within or by Approximately one year	39	12	51	
No full recovery within or by approximately one year	15	21	36	
Total	54	33	87	
plasmapheresis (or plasma exchange) efficacy with respect to gender				
	Female patient receiving plasma exchange or plasmapheresis	Male patient receiving plasma exchange or plasmapheresis	Total	Null Hypothesis H_0: the efficacy rate of female patients is equal to that of male patients p-value=0.4201 Do not reject the null hypothesis OddsRatio: 1.551 90% Confidence Interval: [0.4392, 5.4771]
Full recovery within or by Approximately one year	19	7	26	
No full recovery within or by approximately one year	7	4	11	
Total	26	11	37	
rituximab (or cyclophosphamide) efficacy with respect to gender				
	Female patient receiving rituximab or cyclophosphamide	Male patient receiving rituximab or cyclophosphamide	Total	Null Hypothesis H_0: the efficacy rate of female patients is equal to that of male patients p-value=0.058 Reject the null hypothesis
Full recovery within or by Approximately one year	19	7	26	
No full recovery within or by	5	12	17	

approximately one year				OddsRatio: 6.514 90% Confidence Interval: [2.0872, 20.3318]
Total	24	19	43	


Treatment classification for male patients
IVIG
recovery within one year
rituximab or cyclophosphamide
plasmapheresis or plasma exchange
5
4.8
4.6
4.4
4.2
4
3.8


Treatment classification for female patients
IVIG
tumor resection
recovery within one year
rituximab or cyclophosphamide
plasmapheresis or plasma exchange
6.2
6
5.8
5.6
5.4
5.2
5