The impact of COVID-19 epidemic on adult Myasthenia Gravis patients

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Abstract

Objects: To investigate the impact of COVID-19 epidemic on adult myasthenia gravis (MG) patients, in order to provide better medical advice for special patient population during the quarantine period.

Methods: Adult MG patients were randomly recruited to participate. The survey consisted of self-designed questionnaires and the revised 15-item Myasthenia Gravis Quality of Life Questionnaire (MGQOL15r). Participation was strictly voluntary and remained anonymous.

Results: A total of 214 adult MG patients (84 males and 130 females) gave valid replies. There were 49.53% patients reported they had the fear of COVID-19 outbreak at different levels. And female patients had a significant higher level of fear to COVID outbreak ($p=0.009$). It was found that the adult MG patients are more likely to be influenced by the COVID-19 epidemic compared to the general population. During the COVID-19 outbreak, 36.45% patients reported they got an improvement of MG disease severity. 57.01% patients reported they felt no change. 6.54% patients reported their condition got worse. The average of MGQOL15r score was 7.38 ± 6.22 . The higher level of the fear of COVID-19 outbreak, the higher score of MGQOL15r ($p=0.029$), the poorer quality of life. 96.73% patients hoped the specialist physicians could provide online consult. In addition, 64.95% patients would go to the tertiary hospital without hesitation if the Outpatients Department was opened even during the COVID-19 epidemic.

Conclusions: The COVID-19 epidemic has significant impact on the quality of life and psychological status in the adult MG patients. Compared to the general population, the adult MG patients are more likely to be influenced by the COVID-19 epidemic. Hence, it is important for health care organizations to provide professional therapeutic advice and psychosocial support in time.

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Background

In December 2019, an outbreak of a novel coronavirus disease (COVID-19) emerged in Wuhan, China, and subsequently spread to other provinces of China and other foreign countries^{1–3}. It has caused great panic and anxiety around the world because of its rapid transmission and atypical clinical symptoms. There were 80,844 cases of COVID-19 infection have been confirmed in China until March 14th 2020, while there are still no proven and specific antiviral therapeutics or vaccines.

It should be noted that this highly contagious disease not only has posed significant threats to international health and economy but also exerts considerable impacts on mental health⁴. In the face of extreme life-threatening tension and fear, people are trend to show some anxiety-related behaviors, including depression, anxiety disorders and increased use of alcohol and tobacco⁵. The previous work on the impact of severe acute respiratory syndrome (SARS) has indicated that this kind of grave public health emergencies bring great psychological stress to SARS survivors and related health care workers. Since the SARS outbreak in 2003, there has been a large number of surveys carried out to investigate the

psychological problems including depression, anxiety and posttraumatic symptoms(PTSD) in SARS survivors and related health care workers^{6,7}. However, it should be noted that these common mental health problems are not only restricted to infected patients and health care workers, as well as the general public and the population with special diseases. In this paper, we focused on a special population, the adult myasthenia gravis patients.

Myasthenia gravis (MG) is an autoimmune disease characterized by the presence of autoantibodies causing neuromuscular junction (NMJ) impairment⁸. The predominant manifestation is fatigable skeletal muscle weakness. Although the mechanisms leading to the production of pathogenic autoantibodies in MG remains unclear, it is strongly believed that environmental and psychological factors play crucial roles in the induction of MG. In order to maintain disease control, most MG patients are required to be treated with low-dose immunosuppressive drugs for a long time⁹. However, long-term immunosuppressive therapy may lead to a slightly increased risk of infections¹⁰. Since the outbreak of COVID-19, the Chinese government has taken a lot of powerful public health interventions to prevent the further disease transmission, such as early identification and isolation for suspected and confirmed patients, social distancing and community containment. Sensitivity analyses show these interventions could effectively lower the further transmission risk¹¹. But the social isolation would bring great challenges to MG patients. It might be difficult for them to go back to the hospital to complete regular follow-up visits in time. And they would suffer from extreme fear and uncertainty like the general population. Therefore, timely attention to the MG patients during the COVID-19 outbreak is urgently needed.

At the present, the research publications calling for the mental health care for the infected patients and health care workers have gradually increased. But there is little information about the MG patients' emotional response to the outbreak of COVID-19 pneumonia. This study was carried out to investigate the impact of COVID-19 epidemic on the quality of life and psychological status in adult MG patients.

Methods

Procedure and Participates

From February 10, 2020 to February 24, 2020, we randomly contacted a number of MG patients who were over the age of 18 and were diagnosed with "Myasthenia Gravis" in the XiangYa Hospital Central South University. There were 231 patients agreed to participate in this questionnaire survey. All participants were informed and agreed before completing the electronic questionnaire, and then started to complete the questionnaire further, and the content did not contain identifying/confidential patient information.

Questionnaire Measures

The questionnaire consisted of four parts. The first part was self-designed questions to collect demographic information including gender, age, educational level, occupation and marital status. The second part was a series of questions about the cognition of COVID-19, aiming to investigate the psychological status and emotional response during COVID-19 outbreak. The third part was self-designed questions to look into the current therapies of MG and the related behaviors response. The fourth part was the revised 15-item Myasthenia Gravis (MG) Quality of Life Questionnaire (MGQOL15r), to evaluate MG-associated dysfunction in different domains of life including physical, social, and psychological domains.

Statistical Analyses

Statistical analyses were performed by using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are reported as mean and percentage as appropriate. Comparison of mean values was performed by Independent Sample T test, one-way ANOVA test or Kruskal-Wallis test. *p* values less than 0.05 were considered statistically significant.

Results

3.1 Demographic characteristics of participants

There were 231 adult MG patients randomly recruited for this questionnaire survey study. Among them, 17 participants were excluded because of incomplete survey response or mismatch of age. Thus, the data of 214 adult MG patients was finally enrolled in the analysis, consisting of 84 (84/214, 39.25%) males and 130 (130/214, 60.75%) females and the male: female ratio was 1:1.5. The demographic information was shown in Table 1.

Table 1
Demographic characteristics of participants

Categories	Numbers
Gender	
Male	84 (39.25%)
Female	130 (60.75%)
Age	
18–35 years	99 (46.26%)
36–50 years	59 (27.57%)
>50 years	56 (26.17%)
Marital status	
Single	46 (21.50%)
Married	159 (74.30%)
Divorced	6 (2.80%)
Widowed	3 (1.40%)
Education level	
No HS diploma	72 (33.64%)
HS, no college	59 (27.57%)
Some college, no degree	38 (17.76%)
Bachelor degree or above	45 (21.03%)
HS, high school.	

3.2 Cognition Of Covid-19 Outbreak In Adult Mg Patients

The cognition of COVID-19 outbreak in adult MG patients was mainly evaluated by two questions. The first question was whether did them know about the route of infection. We set four degrees of self-reported familiarity with the knowledge of the ways for coronavirus transmission (very familiar, somewhat familiar, not very familiar, and not familiar at all). 112(112/214, 52.34%) participants reported they were very familiar with the knowledge of the ways for coronavirus transmission. 101(101/214, 47.20%) participants reported they were somewhat familiar with the knowledge of the ways for coronavirus transmission. Only 1(1/214, 0.46%) participant was not very familiar with the knowledge of the route of infection. No participant was not familiar with it at all. And the second question was how

concerned they were about the public news of COVID-19. We also set four levels of the attention for the public news of COVID-19 (very concerned, somewhat generally concerned, not very concerned, and not concerned at all). 167(167/214, 78.04%) participants reported they were very concerned about the public news of COVID-19. 44(44/214, 20.56%) participants reported they were somewhat concerned about the public news of COVID-19. 3(3/214, 1.40%) participants were not very concerned about the public news of COVID-19. Due to the popularity of network, there was no participant not concerned about the news of COVID-19.

3.3 The psychological impact of COVID-19 outbreak on adult MG patients

To examine the psychological impact of COVID-19 outbreak on adult MG patients, we ask the participants whether they were scared of it or not. There were 106(106/214, 49.53%) participants reported they had the fear of COVID-19 outbreak at different levels. 4 (4/214, 1.87%) participants reported they were very scared of COVID-19 outbreak. 29(29/214, 13.55%) participants were somewhat scared. 73(73/214, 34.11%) participants were not very scared. While, 108(108/214, 50.47%) participants reported that they were not scared at all. In order to investigate the factors affecting this kind of psychological status of the adult MG patients during the COVID-19 outbreak, the Kruskal-Wallis test was conducted. The results were shown in Table 2. Patients with different gender had a significant difference in the psychological status related to COVID-19 outbreak ($p = 0.009$). Female patients presented a higher level of the fear to the COVID-19 outbreak compared to the male patients. Other features like age, educational levels, married status and self-reported disease severity had no significant difference in the psychological status ($p > 0.05$).

Table 2
The psychological status related to COVID-19 outbreak in different subgroups

Subgroups	The degree of fear to COVID-19 outbreak				<i>P</i> value
	Very scared	Somewhat scared	Not very scared	Not scared at all	
Gender					
Male	0	10	22	52	0.009
Female	4	19	51	56	
Age					
18–35 years	1	18	29	51	0.662
36–50 years	1	6	20	32	
> 50 years	2	5	24	25	
Educational levels					
No HS diploma	2	9	24	37	0.851
HS, no college	1	7	24	27	
Some college, no degree	1	5	14	18	
Bachelor degree or above	0	8	11	26	
Married status					
Single	1	8	8	29	0.533
Married	3	20	62	74	
Divorced	0	1	3	5	
Widowed	0	0	1	2	
Self-reported disease severity					
Improved	1	10	27	40	0.792
Unchanged	3	16	41	62	
Worsen	0	3	5	6	
HS, high school.					

Table 3
MGQOL15r scores in different subgroups

Subgroups	Numbers	MG-QOL15r `x ± s	Test statistic	P value
Gender				
Male	84 (39.25%)	7.69 ± 6.22	0.589	0.557
Female	130 (60.75%)	7.18 ± 6.23		
Age				
18–35 years	99 (46.26%)	6.70 ± 6.40	1.115	0.330
36–50 years	59 (27.57%)	8.03 ± 6.03		
>50 years	56 (26.17%)	7.89 ± 6.08		
Educational levels				
No HS diploma	72 (33.64%)	7.31 ± 5.68	6.483	0.090
HS, no college	59 (27.57%)	9.12 ± 7.37		
Some college, no degree	38 (17.76%)	7.21 ± 6.67		
Bachelor degree or above	45 (21.03%)	5.36 ± 4.22		
Marital status				
Single	46 (21.50%)	5.59 ± 4.87	4.203	0.240
Married	159 (74.30%)	7.91 ± 6.47		
Divorced	6 (2.80%)	6.50 ± 3.62		
Widowed	3 (1.40%)	8.33 ± 11.93		
Psychological status				
Not scared at all	108 (50.47%)	6.26 ± 5.83	3.075	0.029
Not very scared	73 (34.11%)	9.05 ± 6.40		
Somewhat scared	29 (13.55%)	7.17 ± 6.47		
Very scared	4 (1.87%)	8.05 ± 6.61		
Self-reported disease severity				
Improved	78 (36.45%)	5.76 ± 5.48	12.684	0.002
HS, high school.				

Subgroups	Numbers	MG-QOL15r `x ± s	Test statistic	P value
Unchanged	122 (57.01%)	7.78 ± 5.91	2.406	0.068
Worsen	14 (6.54%)	12.93 ± 6.22		
The need for online consult				
Not need at all	7 (3.27%)	9.43 ± 4.79		
Not very need	14 (6.55%)	4.21 ± 5.70		
Somewhat need	98 (45.79%)	6.83 ± 5.78	2.406	0.068
Very need	95 (44.39%)	8.26 ± 6.65		
HS, high school.				

We further investigated the reasons why they were scared of COVID-19 outbreak among these 106 participants. 66(66/106, 62.26%) participants feared of COVID-19 because there are still no specific treatments. 75 (75/106, 70.75%) participants were scared due to the strong infectivity of COVID-19. 46(46/106, 43.40%) participants were afraid of COVID-19 because of the mortality of this novel coronavirus. 71(71/106, 66.98%) participants feared of COVID-19 because humans are widely susceptible to infection with COVID-19. Besides, the extensive media coverage also caused a certain degree of panic.

We also investigated the sleep quality of adult MG patients during the COVID-19 outbreak. 154(154/214, 71.96%) participants reported their sleep quality was not impacted. 42(42/214, 19.63%) participants reported their sleep quality was worse than before. 15(15/214, 7.01%) participants reported their sleep quality was much worse than before. 3(3/214, 1.40%) participants reported their sleep quality was ever better than before.

There were 192(192/214, 89.72%) participants reported their daily life was significantly affected by COVID-19 outbreak. 175(175/214, 81.87%) participants reported it was inconvenience for them to go out and their communication with others was restricted. 55(55/214, 25.70%) participants reported their income decreased. 77(77/214, 35.98%) participants reported they were stressed out and extremely afraid of infection with COVID-19.

3.4 The impact of COVID-19 outbreak on severity of MG

During the COVID-19 outbreak, 78(78/214, 36.45%) patients thought they got an improvement. 122(122/214, 57.01%) patients reported they felt no change. 14(14/214, 6.54%) patients reported their condition got worse. Among these 14 patients, 4 patients reduced the drug dose or stopped taking drugs. 3 patients reported they were overworked during these days. 4 patients reported they had a cold or

diarrhea. 5 patients thought their emotion response to the COVID-19 outbreak like anxiety, fear and depression posed a negative impact on the severity of MG. 1 patient reported a case of a miscarriage. And 4 patients did not find any obvious factors response for the deterioration.

The mean score of MGQOL15r was 7.38 ± 6.22 , including the average MGQOL15r score of 7.69 ± 6.22 for the 84 male patients, and the 130 female patients had an average MGQOL15r of 7.18 ± 6.23 . By Independent Sample T test, it suggested that there was no significant difference between MGQOL15r score and gender ($t = 0.589$, $p = 0.557$). By one-way ANOVA test, patients with different age had no significant difference in MGQOL15r score ($F = 1.115$, $p = 0.330$).

To examine whether there was any association between MGQOL15r score and other features like educational levels, married status and psychological states, one-way ANOVA test and Kruskal-Wallis test were conducted. The results suggested that patients with different educational levels had no significant difference in MGQOL15r score ($p = 0.090$). And there was no significant difference between MGQOL15r and married status ($p = 0.240$). Patients in different psychological status had a significant difference in MGQOL15r score ($F = 3.075$, $p = 0.029$). Those who were not scared of COVID-19 outbreak at all tended to have a lower MGQOL15r score. Patients with different self-reported disease severity had a significant difference in MGQOL15r score ($p = 0.002$). Those who thought their condition was worse tended to have a higher MGQOL15r score.

3.5 The Association Of Covid-19 Outbreak And Mg Therapy

There were 85(85/214, 39.72%) participants thought MG therapy was related to the outbreak of COVID-19. The relevant reasons were as follows: 1) 69(69/85, 81.18%) participants thought they could not go to the hospital as usual. 2) 28(28/85, 32.94%) participants thought their outdoor activities were limited and this might lower the immune system function. 3) 27(27/85, 31.76%) participants reported their emotion was significantly affected, it was easier for them to become anxious or depressed. 4) 26(26/85, 30.59%) participants thought they were likely to might get an infection such upper respiratory infection or diarrhea because of long-term immunosuppressive therapy. 5) 39(39/85, 45.88%) participants thought their condition related to MG would also get worse once they get upper respiratory infection. 6) 13(13/85, 15.29%) participants reported they had worse quality of diet and sleep since the outbreak of COVID-19 which might cause a negative impact on their disease severity of MG.

3.6 The impact of COVID-19 outbreak on MG therapy and the related behaviors

207(207/214, 96.73%) participants realized they should take immunosuppressive drugs every day even during the COVID-19 outbreak. And 189(189/214, 88.32%) participants reported they still had medicines at home.

To investigate the impact of COVID-19 epidemic on the MG therapy and the related behaviors, we supposed that the medicines at home were running out. 154(154/214, 71.96%) patients reported they would come to nearby pharmacy to buy drugs according to the former therapeutic plan. 23(23/214, 10.75%) patients would reduce the drug does in order to keep taking drugs every day. 22(22/214, 10.28%) patients would take drugs as usual and then stop immediately. 15(15/214, 7.01%) patients tended to choose other choices but not reported in detail.

We supposed that their body conditions were getting worse to investigate their behaviors in such condition. 18(18/214, 8.41%) patients would increase the drug does and keep staying at home. 79(79/214,36.92%) patients would take drugs according to the former therapeutic plan. 87(87/214, 40.65%) patients would come to the tertiary hospitals as much as possible. 25(25/214, 11.68%) patients would come to the nearby hospital or clinic which was much smaller than a tertiary hospital. 5(5/214, 2.34%) patients tended to choose other choices but not reported in detail.

If the Outpatient Department of the tertiary hospitals opened, there were 139(139/214,64.95%) patients would go to there looking for help for specialist physicians without hesitation. But 75(75/214, 35.05%) patients still would not go to the tertiary hospital. The factors affected their decisions included social isolation, fear of infection with COVID-19 and the constriction of public traffic during the COVID-19 epidemic.

3.7 The Factors Affecting The Need For Online Consult

With the development of internet, it is possible for adult MG patients to get online consult to specialist physicians. There were 207(207/214, 96.73%) patients hoped the specialist physicians to provide online consult. But only 179(179/214, 83.64%) patients would choose to contact specialist physicians on line. In order to distinguish those really in need and offer professional advice in time, we set four degree to evaluate the need for online consult (very need, somewhat need, not very need, not need at all), and then investigate the factors associated to it.

By one-way ANOVA test, it suggested that there was no significant difference between MGQOL15r score and the need for online consult ($F = 2.406$, $p = 0.068$). The results of Kruskal-Wallis tests were shown in Table 4. Patients with different age, gender, educational levels, married status, psychological status and self-reported disease severity presented no significant difference in the degree of need for online consult ($p > 0.05$).

Table 4
The need for online consult in different subgroups

Subgroups	The degree of need for online consult				P value
	Very need	Somewhat need	Not very need	Not need at all	
Gender					
Male	37	39	6	2	0.987
Female	38	59	8	5	
Age					
18–35 years	40	49	7	3	0.057
36–50 years	23	28	4	4	
> 50 years	32	21	3	0	
Educational levels					
No HS diploma	36	30	3	3	0.584
HS, no college	22	31	5	1	
Some college, no degree	17	15	4	2	
Bachelor degree or above	20	22	2	1	
Married status					
Single	16	25	3	2	0.446
Married	76	68	10	5	
Divorced	2	4	0	0	
Widowed	1	1	1	0	
Psychological status					
Not scared at all	42	56	7	3	0.084
Not very scared	39	29	4	1	
Somewhat scared	11	12	3	3	
Very scared	3	1	0	0	
Self-reported disease severity					
HS, high school.					

Subgroups	The degree of need for online consult				Pvalue
	Very need	Somewhat need	Not very need	Not need at all	
Improved	34	35	6	3	0.087
Unchanged	51	59	8	4	
Worsen	10	4	0	0	
HS, high school.					

Discussion

Since the COVID-19 outbreak, the Chinese government has taken several public healthy interventions like isolation, quarantine and social distancing to control further transmission. This study found that adult MG patients had different degrees of fear to this novel contagious disease under such conditions, which caused a negative impact on their life quality.

MG is rare chronic disorder, and is considered as a classic example of an anti-mediated autoimmune disease, with the characterizing symptom of localized or general muscle weakness¹². In most cases, MG still requires chronic immunotherapy with immunosuppressive drugs to maintain disease control¹³. In this study, we focused on the impact of COVID-19 outbreak on this kind of special population, the adult MG patients. Because they are suffering from the chronic autoimmune disease and also trouble with the outbreak of COVID-19 like the general population. Previous studies have found that grave public health emergencies have significant impact on people's quality of life and psychological status no matter in the short-term or in the long-term. Since the SARS outbreak in 2003, there are several researches carried out to investigate the impact of SARS on quality of life and mental health in SARS survivors and related health care workers, which suggested those people were emotionally affected and traumatized^{14,15}. At present, the public panic and mental health stress during the COVID-19 outbreak also have gotten great attention¹⁶. However, these studies primarily focus on the general public or the infected patients or the health care workers. There is very little information for those people with chronic autoimmune disease.

In this study, we found that 49.53% adult MG patients had the fear of COVID-19 outbreak. And female patients showed a significant higher level of fear compared to male patients. It is consistent with the results from previous studies which concluded that women tend to have an increased likelihood of stress, depression and PTSD¹⁷. However, there was no significant difference between other features like age, married status, educational levels and self-reported disease severity and the levels of fear to the COVID-19 outbreak. These findings appear to be not exactly same with the recent studies carried out on the general public. In a nationwide survey of psychological distress in Chinese people during the COVID-19 outbreak, it found that 35% of the general population experienced psychological distress, and the

psychological distress was not only associated with the gender, but also related with the age, education, occupation and region¹⁸. By comparing our findings with the general population, we can infer that the people with chronic autoimmune diseases are more likely to be influenced by the COVID-19 epidemic in the psychological aspect.

One strength of this study is that we investigate the impact of COVID-19 epidemic on both psychological status and the quality of life in adult MG patients. There were 36.45% patients reported they got an improvement of MG disease severity. 57.01% patients reported they felt no change. 6.54% patients reported their condition got worse. In addition to the self-reported disease severity, we investigate the quality of life by MGQOL15r, which is a revised version of the Questionnaire of Life Quality Specific for Myasthenia Gravis-15 items (MGQOL15). The total score of MGQOL15r ranges from 0 to 30, with higher scores indicating worse quality of life¹⁹. Studies have showed that patients with severe clinical manifestation and longer disease duration often manifest anxiety, depression, and have poorer quality of life²⁰. Our study found that patients who were more scared of COVID-19 outbreak and with worse self-reported disease condition had higher MGQOL-15r scores. These findings contribute to our knowledge of the psychological impact of COVID-19 on adult MG patients, which indicates that it is time for health care institutions to provide psychosocial support and intervention for MG patients.

Another strength of this study is that we attempt to investigate the change of therapy related behaviors in adult MG patients during the COVID-19 outbreak. It is difficult for these patients to complete a regular visit with specialist physicians under such a high level of quarantine rate. And most of outpatient departments are closed, which also brings great challenges to them. This study found that 64.95% patients would choose to go to the tertiary hospitals without hesitation if the Outpatient Department was opened even during the outbreak of COVID-19. Besides, there were 96.73% patients hoped the tertiary hospitals to provided online consult. However, the analysis results showed that patients with different age, gender, educational levels, married status, psychological status, self-reported disease severity and MGQOL15r scores presented no significant difference in the degree of need for online consult. This might because that online consult with specialist physicians was not widely available ever before. People are not familiar with online consult and they are afraid that it would not take effect because they could not communicate with the doctor face to face. It should be noted that in this digital and information era, it is convenient for the specialist physicians to give a professional suggestion through the official account on WeChat or a website. Our findings raise the awareness that specialist physicians should provide professional advice for those people with chronic autoimmune diseases who require long-term immunosuppressive therapy as soon as possible once grave public health emergencies happened. On the one hand, it would help these patients better maintain their disease control. On the other hand, it would assist them with the management of emotional distress and improve the quality of life.

There are several limitations of this study. The participants were relatively small and recruited from one center. And the data were obtained by self-report. We only investigated the adult MG patients because the questionnaire required to be completed by the patients themselves in order to ensure the reality and

reliability of the information. In addition, we were unable to directly to compare the individual participants longitudinally according to their previous medical records because the questionnaires were anonymous.

In summary, this study has shown that the COVID-19 outbreak has a significant impact on the quality of life and psychological status in adult MG patients. Compared to the general population, they are more likely to be influenced by the COVID-19 epidemic. Health care institutions will not only have to pay attention to control the MG disease severity, but also provide psychosocial supports in time.

Abbreviations

MG

Myasthenia gravis

MGQOL15

Questionnaire of Life Quality Specific for Myasthenia Gravis-15 items

MGQOL15r

Revised 15-item Myasthenia Gravis Quality of Life Questionnaire

SARS

Severe acute respiratory syndrome

PTSD

Posttraumatic symptoms

NMJ

Neuromuscular junction

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were acquired patient's electronic informed consent and in accordance with the ethical standards of the Ethics Committee for Human Research, Xiangya Hospital approved this study and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Individual patient data is not reported in this study.

Consent for publication

Not applicable: individual patient data is not reported in this study.

Competing interests

The authors report no competing interests.

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Authors' contributions

YYP, ZBL, QMZ and HY were involved in the collection of data, drafting and editing of the manuscript. All authors have read and approved the final manuscript. The author YYP and ZBL contributed to this work equally. The content of the manuscript has not been published, nor submitted for publication, elsewhere.

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