General Practice in China

Volume 1 | Issue 1 Article 30

2022

Effect of Periodic Limb Movements in Sleep on Sleep Structure

Yaya Hu

GENERAL PRACTICE IN CHINA

Effect of Periodic Limb Movements in Sleep on Sleep Structure in Stroke Patients

HU Yaya，ZHU Ning*，XUE Mengzhou

Department of Neurological Rehabilitation，the Second Affiliated Hospital of Zhengzhou University，Zhengzhou 450000，China

Corresponding author：ZHU Ning，Associate chief physician；E-mail：zhuning96@163.com

Recommended Citation

HU Y Y，ZHU N，XUE M Z. Effect of periodic limb movements in sleep on sleep structure in stroke patients［J］. Chinese General Practice，2022，25（35）：4389-4393.

Available at: https://gpinchina.net

Effect of Periodic Limb Movements in Sleep on Sleep Structure in Stroke Patients

HU Yaya，ZHU Ning，XUE Mengzhou*

【**Abstract**】 **Background** Sleep disorder is a common complication of stroke with various clinical manifestations. Among them，periodic limb movements in sleep （PLMS） are characterized by repetitive and stereotyped limb movements during sleep. Due to limited clinical date，the pathogenesis of PLMS and their impact on prognosis of stroke are still in the exploratory stage. Studies about the effect of PLMS on sleep in stroke patients are few in worldwide. **Objective** To explore the sleep structure of stroke patients with PLMS. **Methods** From December 2020 to February 2022，a total of 81 stroke patients with sleep disorders were selected from the Second Affiliated Hospital of Zhengzhou University，in which polysomnography （PSG） was performed. The clinical information and PSG sleep monitoring data of patients were collected. According to the Periodic Limb Movement Index （PLMI），the patients were divided into non-PLMS patients （control group，PLMI<15 times/h） and PLMS patients（experimental group，PLMI ⩾ 15 times/h）. The parameters between two groups were compared. These parameters include awake PLMI，sleep efficiency，proportion of stage N1 sleep in total sleep time，proportion of stage N2 sleep in total sleep time，proportion of stage N3 sleep in total sleep time，REM sleep in total sleep time，sleep apnea hypopnea index（AHI），sleep latency，arousal index，and periodic limb movement arousal index （PLMAI）. Moreover，the correlation between PLMS and sleep structure and related parameters was analyzed. **Results** There were 42 cases in the control group and 39 cases in the experimental group. The awake PLMI，proportion of stage N1 sleep in total sleep time，proportion of stage N2 sleep in total sleep time，arousal index and PLMAI in experimental group were higher than those in control group（P<0.05）. However，the sleep efficiency and proportion of stage N3 sleep in total sleep time of experimental group were lower than those of control group （P<0.05）. There was no significant difference between two groups in sleep latency，AHI and REM stage sleep in total sleep time （P>0.05）. The results of Spearman rank correlation analysis showed that PLMS was positively correlated with awake PLMI，proportion of stage N2 sleep in total sleep time，sleep latency，arousal index，and PLMAI （rs values were 0.619，0.250，0.271，0.312，0.828，respectively；P values were <0.001，0.024，0.014，0.005，<0.001），which were negatively correlated with sleep efficiency （rs=-0.345，P=0.002）. **Conclusion**

Stroke patients with PLMS have objective sleep disturbance and reduced sleep efficiency， and PLMS may be one of the signs of poor prognosis of stroke.

【Key words】 Nocturnal myoclonus syndrome；Periodic limb movements in sleep；Periodic limb movement disorder；Stroke；Sleep structure

【Chinese Library Classification Number】 R 749.79 R743 【Document Identification Code】 A

Periodic limb movements disorder in sleep (PLMS) is defined as repetitive limb movements during non-rem sleep, it is characterized by a short, rigid and repetitive period of sleep toe extension, foot and ankle dorsiflexion, sometimes involving the knee, hip and upper limbs. Periodic limb movement of sleep index (PlMI) is the number of times that regular limb movements are detected during sleep monitoring. Periodic limb movements disorder (PLMD) was defined as PLMI,PLMI ≥15 times/h and the sleep symptoms caused by other diseases were excluded[1].The prevalence of PLMD in adults was 4% ~ 11% and increased with age[2-3]. Studies have shown that PLMS may be a risk factor of stroke and may aggravate functional impairment in stroke patients [increased National Institutes of Health stroke scale (NIHSS)][4]. The above results are supported and verified by the Lin et al[5]. Although PLMS is clearly associated with stroke severity and recurrence rates, current cross-sectional studies can not answer the question of temporal and causal relationships between the two[6].Because there are few data about the effect of PLMS on sleep in stroke patients, the purpose of this study was to observe the sleep architecture of stroke patients by polysomnography (PSG) , and to analyze the sleep architecture of stroke patients with PLMS.

1 Information and methods

1.1 General data A total of 81 stroke patients with sleep disorders who received PSG from December 2020 to February 2022 in the second affiliated hospital of the Zhengzhou University were selected. The diagnose of stroke was based on the diagnostic criteria of Chinese guidelines for the diagnosis and treatment of acute ischemic stroke 2018[7]. PLMS diagnosis was based on the International Classification of Sleep Disorders, 3rd edition criteria for sleep-related dyskinesia: at least 4 consecutive leg events; The shortest period of leg movement events (including leg movement events) is 5s, and the maximum interval (including leg movement events) is 90s (if the interval between the starting points of both leg movement events is < 5s, the single leg movement is counted)[1]. Patients who met the above diagnostic criteria with different degrees of sleep disorders were included in the study, excluding restless leg syndrome, rapid eye movement sleep behavior disorder (RBD) , narcolepsy, heart failure, essential hypertension, end-stage renal disease, spinal cord injury, alcohol dependence, Parkinson's disease, and Tourette syndrome.

The study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Zhengzhou University (approval number: 2022174) , and the informed consent was signed by the patient or his legal representative.

1.2 Method

1.2.1 Data collection The basic information of patients (age, sex, height, weight, type of stroke) and PSG monitoring data were collected by the doctors who were engaged in sleep medicine, and BMI was calculated. Patient privacy is strictly protected during information collection.

1.2.2 PSG method Before PSG, patients were informed to avoid the intake of sleep-regulating drugs and drinking of alcohol, coffee, Cola, tea, etc on the monitor day; too much daily sleep and emotional function. In accordance with the above conditions, the patients entered the sleep monitoring room before 19:00 and underwent PSG after acclimatization until 7:00 the next day. The recording time was≥7 hours. Automatic recording and analysis of electroencephalogram (EEG) , electroencephalogram(EEG), lower limb electromyography (EMG) and nasal and oral airflow by sleep detection and analysis system, psg-trained physicians read the sleep and related events manual of the American Academy of Sleep Medicine Version 2.6[8].Record relevant monitoring data, the sleep efficiency, PLMI, sleep efficiency, proportion of N1 sleep to total sleep time, proportion of N2 sleep to total sleep time, proportion of N3 sleep to total sleep time, proportion of REM sleep to total sleep time, sleep apnea hypopnea index (Ahi), sleep latency, wakefulness index, and cyclic limb movement wakefulness index were measured.

According to PLMI, patients were divided into non-PLMS patients (control group, PLMI < 15 times/h) and PLMS patients (trial group, PLMI ≥15 times/h) .

1.3 Observation index The sleep structure and related parameters were compared between the two groups, and the correlation between PLMS and sleep structure and related parameters was analyzed.

1.4 Statistical methods SPSS26.0 statistical software was used to analyze the data. The normality test was carried out for the measurement data, and the normal distribution was expressed as (x±s). The variance between the two groups was compared by group t-test, otherwise it was expressed by M (P25 ,P75), the rank sum test was used for the comparison between the two groups, and the counting data was expressed as relative numbers, and the comparison between the two groups was compared with χ2 test. Correlation analysis is based on Spearman rank correlation analysis.P<0.05 was considered statistically significant.

2 Results

2.1 Comparison of the general data between the groups There were 42 cases in the control group and 39 cases in the test group. There was no significant difference in age, sex, BMI and stroke type between the two groups (P>0.05), as shown in table 1.

2.2 Comparison of sleep structure and related parameters between experimental group and control group Compared with the control group, the experimental group had higher PLMI, the proportion of N1 sleep to total sleep time, the proportion of N2 sleep to total sleep time, the wakefulness index and the cyclic limb movement wakefulness index, the sleep efficiency and the proportion of N3 sleep in total sleep time were lower than those in the control group, the difference was statistically significant (P<0.05).There was no significant difference in the proportion of REM sleep to total sleep time, AHI and sleep latency between the two groups (P>0.05), as shown in table 2.

2.3 Correlation Analysis of PLMS with sleep structure and related parameters PLMS was positively correlated with PLMI in wakefulness, N2 sleep proportion in total sleep time, sleep latency, wakefulness index, and periodic limb movement wakefulness index, and sleep efficiency was negatively correlated (P<0.05), as shown table 3.

Table 1 Comparison of general information between two groups

Group	Case	Case〔M（P25,P75）,years〕	Sex (Male/female）	BMI [M（P25,P75),kg/m2]	Types of stroke (hemorrhagic stroke/ischemic stroke)
Control Group	42	49.0（44.8，61.3）	24/18	25.3（22.4，27.8）	6/36
Experimental Group	39	58.0（48.0，64.0）	28/11	25.6（23.7，28.4）	5/34
Z（χ2Value		-1.854	1.889a	-5.060	0.037a
PValue		0.064	0.169	0.613	0.847

Note:[a] represents χ^2 value; BMI = Body Mass Index

Table 2 Comparison of sleep structure and related parameters between experimental group and control group

Group	Case	PLMI(M (P25, P75), times / h)	sleep efficiency [(M (P25, P75),%)]	N1 sleep to total sleep time [(M (P25, P75),%)]	N2 sleep to total sleep time [($\bar{x}$ ±s),%]	N3 sleep to total sleep time [(M (P25, P75),%)]	REM sleep to total sleep time ratio [($\bar{x}$±s). %)]	AHI (M [(P25,p75), times / h)]	sleep latency [(M (P25,P75), min)]	arousal index [(M (P25,P75), times / h)]	periodic limb movement arousal index [(M (P25,P75), times / h)]
Control Group	42	24.0(4.1，49.9)	74.8(65.0,85.7)	7.3(3.6，10.9)	51.32±11.07	20.9(12.4,28.0)	18.59±7.68	6.6(2.0,27.6)	12.3(5.5,23.0)	14.9(10.2,25.9)	0.1（0，0.6）
Experimental Group	39	65.5（51.3，96.0）	64.3（55.8，78.3））	10.1（4.3，19.9	57.51±12.32	12.7（6.8，19.7）	16.53±6.69	13.4(2.5,33.2)	15.0(8.5,32.5)	29.9(12.7,41.1)	1.9(1.0,4.6)
Z（tValue		-4.713	-2.874	-1.971	2.379a	-2.685	-1.283a	-1.191	-1.432	-2.387	-6.111
P Value		<0.001	0.004	0.049	0.020	0.007	0.203	0.234	0.152	0.017	<0.001

Table 3 Spearman rank correlation analysis of PLMS with sleep structure and related parameters

Project	Case	PLMI	sleep efficiency	N1 sleep to total sleep time	N2 sleep to total sleep time	N3 sleep to total sleep time	REM sleep to total sleep time ratio	AHI	sleep latency	arousal index
rsValue	0.619	-0.345	0.216	0.250	-0.172	-0.259	0.144	0.271	0.312	0.828
PValue	<0.001	0.002	0.053	0.024	0.125	0.059	0.200	0.014	0.005	<0.001

3 Discussion

Sleep disorder is a common complication of stroke with various clinical manifestations, which is the focus of neurology and many other disciplines. PLMS has entered the public view because of its repeated stereotyped movements, but the etiology is not clear. It has been reported that it may be related to the damage of dopaminergic system and increase the risk of cardiovascular and cerebrovascular diseases[9-10]. At present, little attention has been paid to the prevention and treatment of limb movement caused by cerebral vessels, and there are few related reports and lack of clinical experience. When bed companions find abnormal limb movement during sleep, they are often treated with cerebrovascular complications without further exploration of the etiology, and often induce or aggravate some patients' symptoms and delay the disease due to poor drug selection. For this reason, 81 patients were included in this study to observe their sleep structure, provide theoretical support and data support for clinic, promote the development of sleep medicine, scientifically guide the use of drugs, and reduce the burden of patients.

It was found that PLMS was associated with decreased sleep efficiency, increased frequency of wakefulness, and dysregulation of sleep structure(rs= 0.828) . Benbir et al[4] evaluated the patients with ischemic stroke aged 50-80 years, finding that 54.3% of the patients had periodic leg movements during sleep, and the mean PLMI was higher. It has been proved that brain destructive injury can lead to the damage of motor pathway, which results in subcortical depression, causing the functional decrease of A11 dopaminergic in brainstem and spinal cord pathway, and promoting the progression of PLMS[9]. These pathways also dominate the preganglionic sympathetic nervous system, and their reduced function can lead to sympathetic nervous system, leading to an increased risk of heart attack and stroke[10].

In a recent, prospective study, elevated PLMS was found to be associated with small-vessel disease in the brain by analyzing the imaging relationship between PLMS and small-vessel disease in the brain[11]. It was confirmed again that organic lesions of the brain can aggravate the development of PLMS and can be an important risk factor for cardiac cerebrovascular disease in stroke patients.

Regarding the neurological function of PLMS patients, Kim et al[12] found that the central and peripheral areas of the individual's brain changed first before the onset of the PLMS, then followed by frontal and parietal regions by analyzing the incremental bands of the EEG source localization, and based on the topographic data of the delta band. A Positron emission tomography study showed that prior to PLMS, the bilateral pericentral and right posterior cingulate regions of the brain corresponded to the activation of motor imagery associated with movement[13]. A growing body of neuroimaging and neuroanatomy evidence supported that, the activation of PLMS is associated with electrical activity in the pericentral, dorsolateral prefrontal, and cingulate regions, where the dorsolateral prefrontal cortex is responsible for motor control and the posterior cingulate cortex serves as the central node, playing a role in executive motion control associated with the frontal parietal control network[14-15] During monitoring sleep, we also observed the corresponding amplitude changes in EEG before PLMS, which supports the correlation between PLMS and frontal cortex and cingulate gyrus.

In terms of sleep architecture, PLMS is generally considered to be a wake-up response and the cause of sleep fragmentation[16-17]. However, the extent to which PLMS are affected by sleep architecture disorders is controversial [18]. PLMS can be broadly divided into two categories, one is the result of PSG observation alone, which is not related to arousal and has no practical significance, and the other is related to arousal[19]. Among them, PLMS with

EEG arousal has been shown to be associated with sympathetic nervous system-mediated increases in pulse rate and blood pressure, affecting the prognosis of patients with ischemic stroke [4, 10, 20] . In summary of this, the results showed that there was a strong correlation between PLMS and arousal induced by PLMS, but a weak correlation with overall arousal, although there was no clinical data related to prognosis in this study, the PSG results showed that the sleep structure of patients in the trial group was more disturbed than that in the control group, and the sleep pattern of patients in the trial group was more disturbed than that in the control group, consistent with the findings of HUANG et al[21]. Therefore, this study suggests that the limb movement with wakefulness may aggravate the degree of sleep structure disorder in stroke patients, which is a sign of poor prognosis in stroke patients.

However, the causes of PLMS are complex. A pharmacological study showed that pramipexole significantly reduced PLMS without affecting the frequency of arousal, while clonazepam reduced sleep arousal but had no effect on PLMS[22]. This evidence suggests that selective pharmacological approaches can separate PLMS from arousal events A growing number of research suggest that PLMS may not have a direct causal relationship with arousal, the relationship between the two is not simple and may be subject to more complex regulatory mechanisms, including the possible presence of other sleep-phase events, which is a combination of influencing factors[23-24].Analysis of the results of this experiment, it was found that the disorder of sleep structure may be caused by the combined causes of obstructive sleep apnea, limb movement with wakefulness, stroke and potential risk factors, which were revealed by PLMI. Studies have shown that PLMI ≥15 times/h is a strong predictor of stroke recurrence and can make the brain BMI and NIHSS scores increased[4, 25] .The clinical symptoms were aggravated by the increase of wakefulness and the decrease of sleep efficiency.

The results of PSG showed that the proportion of N 1 and N 2 phase sleep to total sleep time was increased and that of N 3 phase sleep to total sleep time was decreased in the experimental group as compared with the control group. To rule out sleep disorders caused by physical movement, the sleep structure disorder may be caused by the decrease and redistribution of cerebral blood flow, the imbalance of central neurotransmitters and cytokines, and the defect of nerve function[26-27]. At the same time, in this study, we also found that PLMS was correlated with PLMI in wakefulness period and the index of periodic limb movement arousal. We can not rule out that pathological changes could cause corresponding limb movement, but the limb movement in wakefulness period was affected by various factors, did not reduce the ability of daily living, casing clinical neglect and less clinical data, further improvement the collection of relevant clinical data is needed. It should be noted that this study can not dynamically observe the causal relationship between PLMS and wakefulness due to the rigid monitoring data; Meanwhile, the patients in this study only came from one sleep disorder center, which may lead to potential sample bias and sampling bias. In the future, more large-scale and multi-center studies are needed to explore the effect of PLMS on stroke patients, and to provide new theoretical support for better identification, intervention and treatment of PLMS.

In conclusion, the pathogenesis of PLMS is not clear, and the relationship between PLMS and various conditions is difficult to be explained by a single mechanism. But for stroke patients, PLMS may increase the sleep structure disorder and the risk of stroke recurrence, which is a sign of poor prognosis of stroke. Therefore, it is necessary to analyze the types of sleep disorders, observe PLMI and limb movement with or without wakefulness, and select appropriate drugs according to the clinical needs of patients, and follow-up whether there are other adverse reactions after taking medicine, improve sleep, reduce the recurrence of stroke and aggravating factors, so as to improve the quality of life.

Author's contributions: Hu Yaya was responsible for the conception and design of the research program, data collection, collation, statistics, analysis and interpretation of the results, and the writing of the thesis. Zhu Ning was responsible for the interpretation of the sleep report and the revision of the thesis, xue Mengzhou was responsible for the quality control and revision of the article, and was responsible for the overall supervision and management of the article. Xue Mengzhou analyzed the implementation and feasibility of the study, and reviewed the paper.

There is no conflict of interest here.

References

［1］SATEIA M J. International classification of sleep disorders-third edition：highlights and modifications［J］. Chest,2014,146(5)： 1387-1394. DOI：10.1378/chest.14-0970.

［2］HORNYAK M,TRENKWALDER C. Restless legs syndrome and periodic limb movement disorder in the elderly［J］. J Psychosom Res,2004,56(5)：543-548. DOI：10.1016/ S0022- 3999(04)00020-0.

［3］WANG Q J,LI Y Z,LI J,et al. Low arousal threshold：a potential bridge between OSA and periodic limb movements of sleep［J］. Nat Sci Sleep,2021,13：229-238. DOI：10.2147/NSS.S292617.

［4］BENBIR G,KARADENIZ D. Influence of periodic limb movements in sleep on stroke outcome［J］. Sleep Biol Rhythms,2013,11(3)：194-199. DOI：10.1111/sbr.12021.

［5］LIN J,MORRONE K,MANWANI D,et al. Association between periodic limb movements in sleep and cerebrovascular changes in children with sickle cell disease［J］. J Clin Sleep Med,2019, 15(7)：1011-1019. DOI：10.5664/jcsm.7884.

［6］NANNAPANENI S,RAMAR K. Periodic limb movements during sleep and their effect on the cardiovascular system：is there a final answer? ［ J］. Sleep Med,2014,15(4)：379-384. DOI： 10.1016/j.sleep.2013.12.014.

［7］Chinese Society of Neurology，Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018［J］. Chinese Journal of Neurology，2018，51（9）：666- 682. DOI：10.3760/cma.j.issn.1006-7876.2018.09.004.

［8］The AASM manual for the scoring of sleep and associated events Summary of Updates in Version 2.6［EB/OL］.（2020-01- 10）［2022-08-14］. https://aasm. org/clinical-resources/scoring- manual/.

［9］DRAKATOS P，OLAITHE M，VERMA D，et al. Periodic limb movements during sleep：a narrative review［J］. J Thorac Dis， 2021，13（11）：6476-6494. DOI：10.21037/jtd-21-1353.

［10］LIN C Y，TSAI S J，PENG C K，et al. Sleep state instabilities in patients with periodic limb movements in sleep - detection and quantification with heart rate variability［J］. Psychiatry Res， 2020，293：113454. DOI：10.1016/j.psychres.2020.113454.

［11］OUYANG F B，WANG M，LIAO M S，et al. Association between periodic limb movements during sleep and neuroimaging features of cerebral small vessel disease：a preliminary cross-sectional study［J］. J Sleep Res，2022：e13573. DOI：10.1111/jsr.13573.

［12］KIM T J，CHA K S，LEE S H，et al. Brain regions associated with periodic limb movements during sleep in restless legs syndrome［J］. Sci Rep，2020，10（1）：1615. DOI：10.1038/ s41598-020-58365-0.

［13］YU H L，BA S D，GUO Y X，et al. Effects of motor imagery tasks on brain functional networks based on EEG mu/beta rhythm［J］. Brain Sci，2022，12（2）：194. DOI： 10.3390/brainsci12020194.

［14］MOGAVERO M P，MEZZAPESA D M，SAVARESE M，et al.Morphological analysis of the brain subcortical gray structures in restless legs syndrome［J］. Sleep Med，2021，88：74-80. DOI：10.1016/j.sleep.2021.10.025.

［15］SI R G，ROWE J B，ZHANG J X. Functional localization and categorization of intentional decisions in humans：a meta-analysis of brain imaging studies［J］. Neuroimage，2021，242：118468. DOI：10.1016/j.neuroimage.2021.118468.

［16］KIM H，YANG K I，SUNWOO J S，et al. Association between self-perceived periodic limb movement during sleep and excessivedaytime sleepiness depend on restless leg symptoms in Korean adolescents［J］. Int J Environ Res Public Health，2022，19（8）： 4751. DOI：10.3390/ijerph19084751.

［17］ZHOU X B，ZHOU B，LI Z，et al. Periodic limb movements in patients with obstructive sleep apnea syndrome［J］. Sci Rep， 2021，11（1）：15341. DOI：10.1038/s41598-021-95018-2.

［18］KIM H J，LEE S A. Periodic limb movements during sleep may reduce excessive daytime sleepiness in men with obstructive sleep apnea［J］. Schlaf Atmung，2020，24（4）：1523-1529. DOI：10.1007/s11325-020-02024-1.

［19］WALTERS A S. Pro：assessment of periodic limb movements is an essential component of an overnight sleep study［J］. Am J Respir Crit Care Med，2001，164（8 pt 1）：1339-1340. DOI： 10.1164/ajrccm.164.8.2107127a.

［20］WIPPER B，WINKELMAN J W. The long-term psychiatric and cardiovascular morbidity and mortality of restless legs syndrome and periodic limb movements of sleep［J］. Sleep Med Clin，2021，16（2）：279-288. DOI：10.1016/j.jsmc.2021.02.005.

［21］HUANG J Y，SHEN Y，HAN F，et al. Preliminary clinical analysis for acute cerebral infarction with periodic limb movements［J］. Chinese Journal of Cerebrovascular Diseases，2020，17（5）： 231-236. DOI：10.3969/j.issn.1672-5921.2020.05.002.

［22］MANCONI M，FERRI R，ZUCCONI M，et al. Dissociation of periodic limb movements from arousals in restless legs syndrome［J］. Ann Neurol，2012，71（6）：834-844. DOI： 10.1002/ana.23565.

［23］SPEKTOR E，FIETZE I，POLUEKTOV M G. Periodic limb movements syndrome in patients with cerebral small vessel disease： protocol for a prospective observational study［J］. Front Neurol， 2021，12：700151. DOI：10.3389/fneur.2021.700151.

［24］FULDA S. Periodic limb movements during sleep［J］. Sleep Med Clin，2021，16（2）：289-303. DOI：10.1016/ j . jsmc.2021.02.004.

［25］HAN S H，PARK K Y，KIM J M，et al. Restless legs syndrome is associated with arterial stiffness and clinical outcome in stroke patients［J］. Sleep Med，2019，60：219-223. DOI：10.1016/j. sleep.2019.03.027.

［26］LI W F，ZHANG X Y. Analysis of the relationship between the changes of monoamine neuro-transmitters and sleep disorders after stroke in patients with hypoxemia after brainstem stroke［J］. China Modern Doctor，2021，59（36）：45-48.

［27］YUAN X J. Study on the influence of sleep disturbance on prognosis after stroke [J] . Chinese medicine and clinical medicine, 2021,21(22):3747-3749. DOI: 10.11655/zgywylc2021.22.039.