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ORIGINAL ARTICLE

Observational Study

Performance of the walking trail making test in older adults with white matter hyperintensities

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Abstract

BACKGROUND

Several studies have reported that the walking trail making test (WTMT) completion time is significantly higher in patients with developmental coordination disorders and mild cognitive impairments. We hypothesized that WTMT performance would be altered in older adults with white matter hyperintensities (WMH).

AIM

To explore the performance in the WTMT in older people with WMH.

METHODS

In this single-center, observational study, 25 elderly WMH patients admitted to our hospital from June 2019 to June 2020 served as the WMH group and 20 participants matched for age, gender, and educational level who were undergoing physical examination in our hospital during the same period served as the control group. The participants completed the WTMT-A and WTMT-B to obtain their gait parameters, including WTMT-A completion time, WTMT-B completion time,

speed, step length, cadence, and stance phase percent. White matter lesions were scored according to the Fazekas scale. Multiple neuropsychological assessments were carried out to assess cognitive function. The relationships between WTMT performance and cognition and motion in elderly patients with WMH were analyzed by partial Pearson correlation analysis.

RESULTS

Patients with WMH performed significantly worse on the choice reaction test (CRT) (0.51 ± 0.09 s *vs* 0.44 ± 0.06 s, P = 0.007), verbal fluency test (VFT, 14.2 ± 2.75 *vs* 16.65 ± 3.54, P = 0.012), and digit symbol substitution test (16.00 ± 2.75 *vs* 18.40 ± 3.27, P = 0.010) than participants in the control group. The WMH group also required significantly more time to complete the WTMT-A (93.00 ± 10.76 s *vs* 70.55 ± 11.28 s, P < 0.001) and WTMT-B (109.72 ± 12.26 s *vs* 82.85 ± 7.90 s, P < 0.001). WTMT-A completion time was positively correlated with CRT time (r = 0.460, P = 0.001), while WTMT-B completion time was negatively correlated with VFT (r = -0.391, P = 0.008). On the WTMT-A, only speed was found to statistically differ between the WMH and control groups (0.803 ± 0.096 *vs* 0.975 ± 0.050 m/s, P < 0.001), whereas on the WTMT-B, the WMH group exhibited a significantly lower speed (0.778 ± 0.111 *vs* 0.970 ± 0.053 m/s, P < 0.001) and cadence (82.600 ± 4.140 *vs* 85.500 ± 5.020 steps/m, P = 0.039), as well as a higher stance phase percentage (65.061 ± 1.813% *vs* 63.513 ± 2.465%, P = 0.019) relative to controls.

CONCLUSION

Older adults with WMH showed obviously poorer WTMT performance. WTMT could be a potential indicator for cognitive and motor deficits in patients with WMH.

Key Words: White matter hyperintensities; Cognitive dysfunction; Motor deficits; Gait analysis; Trail making test; Small vessel disease

Core Tip: A new modified trail making test [walking trail making test (WTMT)], was used to explore the cognitive and motor deficits in older adults with WMH. In addition, wearable sensors were selected firstly in the WTMT to analyze the gait features of subjects. The results implied that WTMT could be a potential indicator for the cognitive and motor deficits in WMH patients.

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INTRODUCTION

With continued advances in medical technologies and improvement in life expectancy in modern society, cognitive impairment and gait disturbance have become common symptoms negatively affecting the daily life of the growing elderly population. In the last decade, an increasing number of studies have confirmed that cognitive impairment and gait abnormalities in older adults should not to be explored in isolation[1]. On the contrary, impairments in cognitive and physical dimensions are frequently concurrent[2]. Kelaiditi *et al*[3] proposed the concept of "cognitive frailty" in 2013, and "motor cognitive risk syndrome" was reported by Verghese *et al*[4] a year later. Recent findings have even demonstrated the synergistic effects of cognitive and motor dysfunction in patients with cerebral small vessel disease (CSVD)[5].

White matter hyperintensities (WMH), together with cerebral microbleeds, recent subcortical lacunar infarcts (clinically symptomatic), lacunes (clinically silent), prominent perivascular spaces, atrophy lacunar infarcts, etc are known to be common signs of CSVD on conventional magnetic resonance imaging (MRI)[6]. WMH represent a common condition in older adults, occurring in approximately 80% adults in the general population over the age of 60 years[7]. Gait disorders and cognitive dysfunction (especially executive dysfunction) are the main symptoms of WMH[8]. Longitudinal studies revealed that WMH are associated with a high risk of falling, disability, and mortality due to the persistent deterioration of cognitive and motor function[9,10]. However, the early detection of the above symptoms is difficult in clinical practice. Recent studies inferred that a well-designed cognitive-motor dual walking task could be a useful tool for detecting cognitive and motor impairment in patients with WMH[11]. Under dual task conditions, the motor and/or cognitive task performance of older people can deteriorate due to competing demands when the available central resource capacity is exceeded[12].

The traditional trail making test (TMT) is a commonly used paper-and-pencil cognitive function test that can reflect a person's ability in terms of executive function, attention, and processing speed. Recent studies have attempted to modify the traditional TMT to create the walking TMT (WTMT)[13-15]. In contrast to the ordinary dual walking task tests based

on a cognitive task separate from a motor task, the WTMT incorporates a cognitive task into walking. In addition, recently published findings have implied that cognitive tasks involving internal interfering factors (*e.g.*, mental tracking) impair gait performance more than those involving external interfering factors (*e.g.*, reaction time)[13]. Multiple studies have reported that the WTMT completion time is significantly higher in patients with developmental coordination disorders and mild cognitive impairment[14,16]. Thus, the aim of the current study was to assess the gait characteristics of elderly individuals with WMH using the WTMT task.

MATERIALS AND METHODS

Study population

A total of 25 older adults with WMH (WMH group) and 20 healthy individuals matched for age, gender, and educational level (HE group) were recruited from the Department of Neurology, the Seventh Medical Center of PLA General Hospital (which also receives older individuals in Aged Cadre Convalescent subdepartments). These patients were recruited consecutively from June 1, 2021, to April 1, 2022. Participants in the HE group, who had no record of a WMH diagnosis and who had regular rest and recuperation plans, were recruited from the Aged Cadre Convalescent subdepartment. Each participant voluntarily signed an informed consent form to participate in the current study.

All participants underwent screening by 3.0 T MRI of the brain and were grouped based on a method previously described by our group[11]. White matter lesions were graded using the Fazekas scale, as previously described[17]. Briefly, we rated WMH severity as grade 1 (punctate lesions), grade 2 (early confluent lesions), or grade 3 (confluent lesions). Only individuals with a Fazekas score of 0 were included in the HE group.

The exclusion criteria were history of major stroke; presence of multiple lacunar infarcts, other reasons for leukoencephalopathy (including immune, demyelination, and genetic); major psychiatric disorders (diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); use of psychotropic medications or drugs with the side effect of risk of falling (*e.g.*, tranquillizers/sedatives, diuretics, antiparkinsonian drugs); MRI contraindications; dementia (diagnosed using an International Classification of Diseases-10 code); a mini-mental state examination (MMSE) score lower than 23 points[18]; and use of walking aids.

MRI measurements

A 3.0 T MRI brain scan (Discovery MR750; GE Healthcare, United States) displayed white matter lesions, which indicated the degree of CSVD. Brain MRI (slice and interslice thicknesses of 5 mm and 1.5 mm, respectively) was carried out as follows: T1 fluid-attenuated inversion recovery (TR, 1750 ms; TE, 23 ms; TI, 780 ms; FOV, 24 cm) and T2-weighted imaging (TR, 7498 ms; TE, 105 ms; FOV, 24 cm) sequences. The researchers who assessed gait were blinded to the imaging findings.

WTMT paradigm and gait evaluation

The WTMT was conducted in a quiet and comfortable environment. For the WTMT-A, randomly distributed coins with a 30-cm diameter and labeled with Arabic numbers (1-15) were positioned in a 16 m^2 square area (4 m × 4 m). Participants were instructed to step as quickly and accurately as possible. Experimenters instructed the participants as follows: "Please walk on numbered targets in a sequential order as rapidly as possible, joining consecutive numbers (*i.e.*, 1 to 2 to 3…15) in the coins randomly distributed on the floor." When participants stepped on an incorrect number, the experimenter indicated the error, instructing them to step on the correct number as time continued to be measured. The WTMT-A was performed only once.

For the WTMT-B, the arrangement and procedure were similar to those of WTMT-A, except the Arabic numbers 1-15 were replaced with Arabic numbers (1-8) and Chinese characters (壹, 贰, 叁, 肆, 伍, 陆, 柒). Experimenters instructed the participants as follows: "Please walk on numbered targets in a sequential order as rapidly as possible joining consecutive numbers (*i.e.*, 1 to 壹 to 2 to 贰 to 3 to 叁…8) in the coins randomly distributed on the floor."

The arrangements of numbers in the WTMT are detailed in Figure 1 and were similar to the method reported by Schott *et al*[16].

Data collection

Participants' gait characteristics during the WTMT were captured and analyzed using the Intelligent Device for Energy Expenditure and Activity (IDEEA) (Minisun, United States). The IDEEA comprises five motion sensors and a microcomputer. The device was calibrated and used as indicated by the manufacturer and as depicted previously[1].

The parameters captured by the IDEEA are detailed in Figure 2 and listed below: (1) Speed (m/s), as the mean velocity for two successive strides; (2) Step length (m), representing the half distance between consecutive points of initial contact of the same foot; (3) Cadence (steps/min), representing the number of steps/stairs per minute; and (4) Stance phase percentage (%), reflecting the duration of the stance phase (starting from initial contact and ending at toe-off for a particular foot) divided by stride time.

Neuropsychological assessment

All participants completed a series of neuropsychological assessments, including the MMSE (reflecting global cognitive level), choice reaction test (CRT, reflecting attention and concentration), digit symbol substitution test (DSST, reflecting processing speed), category verbal fluency test (cVFT, reflecting psychomotor speed, attention, and semantic memory),

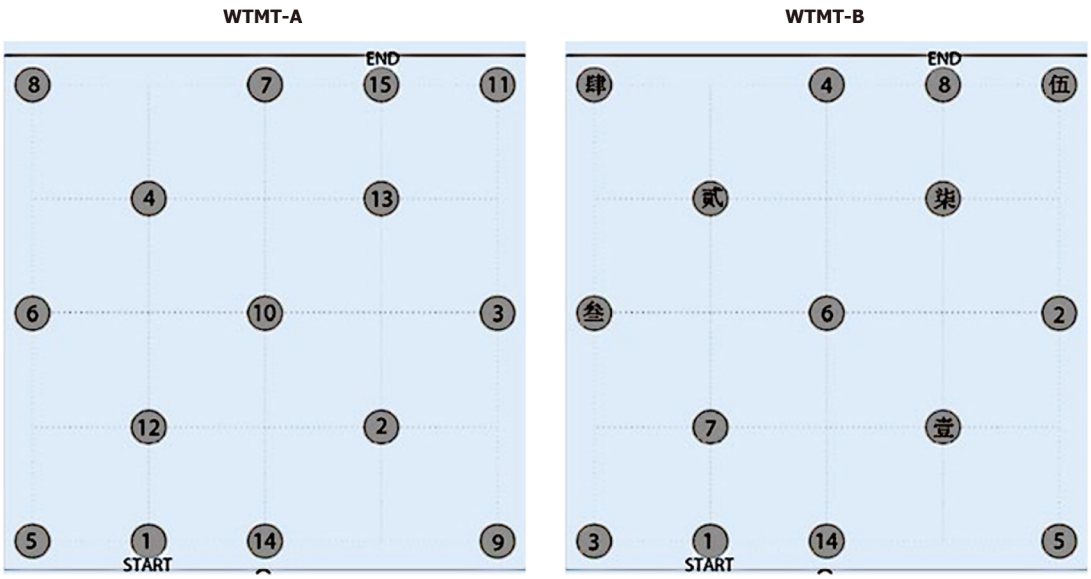

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Figure 1 The arrangements of numbers in the walking trail making test. WTMT: Walking trail making test.

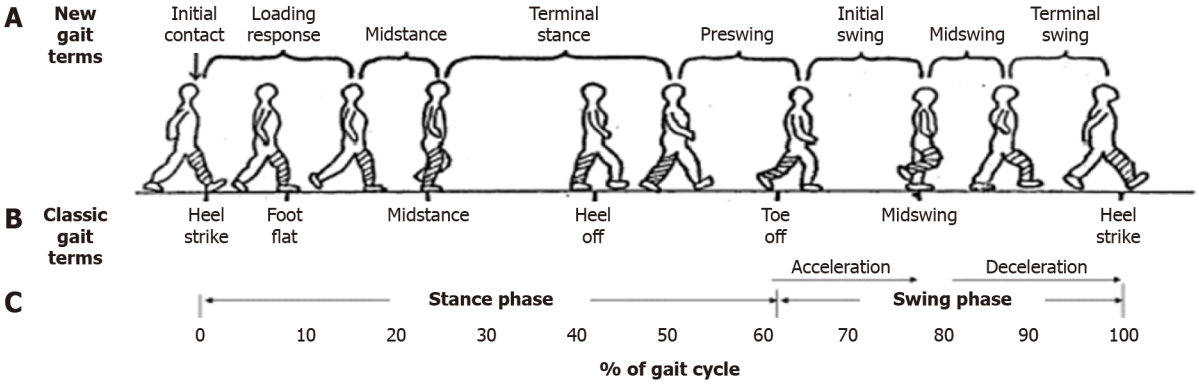

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Figure 2 The parameters captured by the Intelligent Device for Energy Expenditure and Activity. (1) Speed (m/s), as the mean velocity for two successive strides; (2) Step length (m), representing the half distance between consecutive points of initial contact of the same foot; (3) Cadence (steps/min), representing the number of steps/stairs per minute; and (4) Stance phase percentage (%), reflecting the duration of the stance phase (starting from initial contact and ending at toe-off for a particular foot) divided by stride time. A: The new gait terms of gait cycles; B: The classic gait terms of gait cycles; C: The percentage of stance/swing phase of gait cycles.

and auditory verbal learning test-huashan (AVLTh, reflecting immediate memory performance)[19].

Statistical analysis

Student's *t*-test was carried out for comparison of continuous parametric variables. Categorical variables were compared using the Chi-square or Fisher exact test. Partial Pearson correlation analysis was performed to calculate the correlation between the WTMT completion time and neuropsychological performance, controlled for age, sex, and educational level.

RESULTS

As shown in Table 1, age, sex, and educational level were similar between the WMH and HE groups ($P > 0.05$). The participants in the WMH group had an average Fazekas score of 1.52. Overall, the WMH group performed significantly worse on the CRT (0.51 ± 0.09 s *vs* 0.44 ± 0.06 s, $P = 0.007$), VFT (14.2 ± 2.75 *vs* 16.65 ± 3.54, $P = 0.012$), and DSST (16.00 ± 2.75 *vs* 18.40 ± 3.27, $P = 0.010$) than the HE group. In addition, the WHM group had significantly longer completion times for the WTMT-A (93.00 ± 10.76 s *vs* 70.55 ± 11.28 s, $P < 0.001$) and WTMT-B (109.72 ± 12.26 s *vs* 82.85 ± 7.90 s, $P < 0.001$; Table 1).

The results for the correlation between WTMT completion time and performance on neuropsychological tests for the WMH group are presented in Table 2. WTMT-A completion time was positively correlated with CRT time ($r = 0.460$, $P =$

Table 1 Clinical and demographic characteristics of the participants (mean ± SD)

	WMH group (*n* = 25)	HE group (*n* = 20)	*P* value
Age, years	74.00 ± 5.40	75.30 ± 4.26	0.385
Male, %	48%	35%	0.392
Education, years	8.00 ± 2.34	8.05 ± 2.28	0.943
MMSE, score	28.00 ± 1.15	28.10 ± 1.10	0.883
CRT, seconds	0.51 ± 0.09	0.44 ± 0.06	0.007
cVFT, words	14.20 ± 2.75	16.65 ± 3.54	0.012
DSST, counts	16.00 ± 2.75	18.40 ± 3.27	0.010
AVLTh, words	7.60 ± 1.83	8.25 ± 1.20	0.178
WTMT-A, seconds	93.00 ± 10.76	70.55 ± 11.28	< 0.001
WTMT-B, seconds	109.72 ± 12.26	82.85 ± 7.90	< 0.001
Fazekas, score	1.52 ± 0.71	0.00 ± 0.00	< 0.001

MMSE: Mini-mental state examination; CRT: Choice reaction test; cVFT: Category verbal fluency test; DSST: Digit symbol substitution test; AVLTh: Auditory verbal learning test-huashan; WTMT: Walking trail making test; WMH: White matter hyperintensities; HE: Healthy.

Table 2 Partial Pearson correlation between cognitive function and walking trail making test

	WTMT-A		WTMT-B	
	r value	*P* value	*r* value	*P* value
MMSE	0.060	0.697	0.190	0.212
CRT	0.460	0.001	0.254	0.092
cVFT	-0.157	0.303	-0.391	0.008
DSST	-0.264	0.080	-0.207	0.172
AVLTh	-0.024	0.874	-0.267	0.076

Adjustment for age, sex, and educational level. MMSE: Mini-mental state examination; CRT: Choice reaction test; cVFT: Category verbal fluency test; DSST: Digit symbol substitution test; AVLTh: Auditory verbal learning test-huashan.

0.001), while WTMT-B completion time was negatively correlated with VFT (r = -0.391, P = 0.008).

Furthermore, we explored the gait features during the WTMT, and only speed was found to differ statistically between the two groups (0.803 ± 0.096 *vs* 0.975 ± 0.050 m/s, P < 0.001). On the WTMT-B, the WMH group exhibited significantly lower speed (0.778 ± 0.111 *vs* 0.970 ± 0.053 m/s, P < 0.001) and cadence (82.600 ± 4.140 *vs* 85.500 ± 5.020 steps/m, P = 0.039), as well as a higher stance phase percentage (65.061 ± 1.813% *vs* 63.513 ± 2.465%, P = 0.019) relative to the HE group (Table 3).

DISCUSSION

The clinical presentation of WMH can be asymptomatic, silent, or covert[20] until a threshold is reached and "malignant" symptoms (such as stroke) appear[21]. Thus, much research effort has been devoted to identifying indicators for earlier recognition of WMH[19]. The present study revealed that patients with WMH exhibited remarkably worse performance on the WTMT compared with healthy individuals, as reflected in by the completion times for both the WTMT-A and WTMT-B. Considering its simplicity, non-invasiveness, and low cost, the WTMT represents a potentially useful assessment tool for patients with WMH.

Our previous studies confirmed that patients with WMH display cognitive deficits and gait abnormalities[11,22]. According to the consensus on shared measures of mobility and cognition from the Canadian Consortium on Neurodegeneration in Aging[23], both the TMT and the dual task gait speed task were included as proposed "core battery" tests. These findings, together with those of the present study, support the modification of the TMT into the WTMT, for evaluation of characteristics in aspects of gait and cognition. Furthermore, as the WTMT was designed to be an incorporated cognitive task, instead of an addition to a motor task, WTMT performance could be a better indicator of cognitive impairment than gait or cognitive tests alone[24].

Table 3 Gait analysis of the participants in walking trail making test (mean ± SD)

	WMH group (*n* = 25)	HE group (*n* = 20)	*P* value
WTMT-A			
Speed, m/s	0.803 ± 0.096	0.975 ± 0.050	< 0.001
Step length, m	0.486 ± 0.035	0.484 ± 0.038	0.820
Cadence, steps/min	86.520 ± 5.730	89.050 ± 5.671	0.127
Stance phase percentage, %	63.189 ± 1.147	63.737 ± 1.231	0.130
WTMT-B			
Speed, m/s	0.778 ± 0.111	0.970 ± 0.054	< 0.001
Step length, m	0.468 ± 0.041	0.473 ± 0.041	0.713
Cadence, steps/min	82.600 ± 4.140	85.500 ± 5.020	0.039
Stance phase percentage, %	65.061 ± 1.813	63.513 ± 2.465	0.019

WTMT: Walking trail making test; WMH: White matter hyperintensities; HE: Healthy.

The current study also investigated the relationship between WTMT completion time and cognitive function in older adults with WMH. Our analyses showed that the WTMT-A completion time was correlated with attention and concentration, while the WTMT-B completion time was correlated with psychomotor speed, attention, and semantic memory. These results should not be surprising, as the WTMT, a type of cognitive-motor dual task, is considered a useful "brain stress test" for predicting cognitive deficits[25]. For example, Perrochon and Kemoun[14] reported that poor WTMT performance is associated with executive dysfunction (in particular, mental flexibility) in patients with mid-cognitive impairment. Among community-dwelling older adults, Osuka *et al*[13] discovered that the WTMT completion time is associated with a series of executive functions, such as performance on the DSST and the traditional TMT. The disruption of crucial subcortical connections in the frontal and other lobes, as well as the basal ganglia area, following multiple pathophysiological changes could be the possible mechanism through which WMH affect cognition and WTMT performance[26,27].

To the best of our knowledge, this is the first study to assess the utility of a wearable sensor for gait analysis during the WTMT. Gait speed was not the only parameter found to be affected in the WTMT-B. Older people with WMH exhibited significantly lower speed and cadence, as well as a higher stance phase percentage. The discrepancy between the WTMT-A and WTMT-B might also imply that WTMT-B performance reflects sophisticated processing and problem solving aspects of executive functioning, which may be necessary to deal with more challenging terrain[28]. Similar trends were also reported for the traditional WTMT and other variations of the TMT[29].

Several limitations of the present study warrant consideration. First, the sample size was small. Second, some aspects, such as delayed recall of the AVLTh, were not chosen in the present study, because patients with WMH were previously found to not show deficits in this domain[30]. In addition, 3T-WMH volume should be used to quantify WMH in future research.

Notably, the TMT has been modified in different ways by multiple research groups previously (*e.g.*, WTMT, oral TMT [31], driving TMT[32]), and alternative evaluation systems for the TMT also have been reported (*e.g.*, error analysis[33], derived TMT indices[34,35]). From our point of view, delta TMT is a good indicator of executive function. Thus, delta WTMT might be another effective tool for detecting the cognitive profile of WMH and neuropsychological features of subcortical vascular dementia in the future.

CONCLUSION

In the present study, older adults with WMH showed obviously poorer WTMT performance than healthy control participants. The WTMT completion time was associated with aspects of cognitive function. Therefore, WTMT performance represents a potential indicator for early identification of the cognitive and mobility decline induced by WMH.

ARTICLE HIGHLIGHTS

Research background

The early detection of the white matter hyperintensities (WMH) is difficult in clinical practice, and dual task has been confirmed as a useful tool.

Research motivation
Trail making test (TMT), a commonly used paper-and-pencil cognitive function test, is now modified into different versions. Walking TMT (WTMT) is a modified TMT incorporates a cognitive task and concurrent walking.

Research objectives
The aim of the current study was to assess the gait characteristics of elderly individuals with WMH using the WTMT task.

Research methods
The WTMT was conducted in a 16 m^2 square area (4 m × 4 m). Each participant need to walk according to the coins randomly distributed as TMT-A and TMT-B to complete this task.

Research results
The WMH group also required significantly more time to complete the WTMT-A and WTMT-B.

Research conclusions
Older adults with WMH showed obviously poorer WTMT performance.

Research perspectives
Notably, the TMT has been modified in different ways by multiple research groups previously (*e.g.*, WTMT, oral TMT, driving TMT), and alternative evaluation systems for the TMT also have been reported (*e.g.*, error analysis, derived TMT indices). From our point of view, delta TMT is a good indicator of executive function. Thus, delta WTMT might be another effective tool for detecting the cognitive profile of WMH and neuropsychological features of subcortical vascular dementia in the future.

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FOOTNOTES

Co-first authors: Hong-Yi Zhao and Zhi-Qiang Zhang.

Author contributions: Zhao HY and Zhang ZQ were responsible for data collection, analysis and writing of the actual manuscript; Wei FY was responsible for study design; Huang YH and Li H were responsible for manuscript preparation.

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Institutional review board statement: The study was approved by the Seventh Medical Center of PLA General Hospital ethics committee, reference number: (2021) Ethics Review (015).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: The authors report no conflict of interest.

Data sharing statement: Dataset available from the corresponding author at huangyonghua2017@126.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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