

The Value of Subjective Visual Vertical in Diagnosis of Vestibular Migraine*

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[Abstract] Objective: To study the value of the subjective visual vertical (SVV) in the diagnosis of vestibular migraine (VM). **Methods:** This study recruited 128 VM patients and 64 age-matched normal subjects. We detected the SVV during the interval between attacks in both groups, in sitting upright, and the head tilted at 45° to the left or right. We then examined the correlation between the SVV results with the vestibular evoked myogenic potential (VEMP) and canal paresis (CP). **Results:** It was found there was a significant difference in SVV at the upright position between VM patients and normal controls ($P=0.006$) and no significant difference was found at the tilts of 45° to the left or right between the two groups. The SVV results at the upright position were significantly correlated with cervical VEMP ($P=0.042$) whereas not significantly correlated with CP and VEMP. There existed no significant difference in the conformity to the Müller effect (M effect) between the two groups. ROC analysis exhibited that the sensitivity, specificity of SVVs at the upright were 67.200% and 62.500% respectively. The diagnostic value of SVV at the upright position was significantly higher than that at tilts of 45° to the left and right ($P=0.006$). Nonetheless the diagnostic accuracy was relatively low. **Conclusion:** Abnormality in SVV possibly stems from the lasting functional disorder of cerebellar or high-level cortical centers in VM patients or is linked to the vestibular compensation. The SVV is of low diagnostic value for VM and the value of SVV in VM warrants further study.

Key words: vestibular migraine; subjective visual vertical; diagnostic value evaluation

Vestibular migraine (VM) is a common paroxysmal vestibular syndrome and, so far, the pathological mechanism of VM remain poorly understood^[1]. The results of the vestibular function tests in VM patients

tend to vary substantially. Some VM patients presented normal results while some have findings indicating central or peripheral impairment, such as abnormal caloric test results or abnormal eye movement of central origin^[2-6]. A prior study showed that patients with migraine had sub-clinical disorders of the vestibular-spinal reflex system. These abnormalities might, in part, originate from the damage to the otolith organ. These aberrant messages might affect the sensory information used for posture control, thereby resulting in postural instability^[7]. Moreover, migraine-related vascular spasm might lead to inner-ear ischemia of some regions, which results in transient or permanent vestibular disorder^[8]. The amplitude in cervical vestibular evoked myogenic potential (cVEMP)^[9] and ocular VEMP (oVEMP)^[10] were lowered in VM patients and these findings support the theory that otolith

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organ impairment is implicated in VM pathogenesis. Nonetheless, some studies also found that there existed abnormalities in high-level cortical function of brain in VM patients. For instance, a study exhibited that VM patients were more sensitive to low-frequency dynamic roll tilting^[11] and an imaging study supported the assumption that the “high-level” vestibular perception was dysfunctional in VM patients^[12].

Subjective visual vertical (SVV) refers to the perceptual judgment of gravitational vertical when visual references are deprived. SVV is currently believed to be an effective technique for assessing the function of the otolith organ and the central pathways of gravity perception. It has been well established that, in normal population, when sitting upright at rest, SVV deviation should be within a range of $\pm 2.5^\circ$ ^[13, 14]. SVV deviation is a sensitive measure for the vestibular tone imbalance in roll plane^[15]. When the vestibular periphery or nucleus sustained damage, SVV tilted to the affected side; if the damage was in or above the pons, SVV tilted contralaterally; with damage in thalamus or cerebellar dental nucleus, SVV tilted in random directions^[16]. The study found that the SVV might have different presentations at different phases of condition: in patients with peripheral damage, SVV deviation might return to normal when the disease stabilizes, suggesting that central compensation might impact the SVV results^[17]. At static head tilt, SVV may work better in reflecting the functions of higher-level control centers, such as the thalamus or cerebral cortex than dynamic SVV during off-vertical axis rotation^[18].

Previous studies on VM patients revealed that SVV was not altered when the head was in the upright position^[19, 20]. In these patients, however, errors of upright perception have hardly been investigated during static head tilt, when the brain has to maintain a common multisensory reference frame for orientation constancy. We hypothesized that the disorder of spatial perception is associated with the disorder of gravity perception pathways of the otolith organ in VM patients. Our hypothesis is premised on the following reasoning: When the head tilts, the brain has to integrate sensory information that encodes the positions of the eye, head and body to maintain perception of upright status. As a result, SVV errors are more likely at head tilts due to the integration errors. Since the head tilt of 45° is within the physiologic range of neck positions and near the upper limit of compensation (60°), if a VM patient suffers from disorder of deep and vestibular sensations, the 45° head tilt suffices to bring about SVV errors.

This study examined the SVV presentations in VM patients who sat upright or tilted head 45° to the right or left during the intervals of VM attacks and analyzed their association with VEMP. We aimed to understand the features of otolith impairments and provide added data for the study of the pathogenesis of VM.

1 MATERIALS AND METHODS

1.1 Data and Subjects

This study initially included 135 VM patients (meeting ICVD diagnostic criteria)^[21] who visited the vertigo clinic of Changzheng Hospital of Shanghai (China) from June 2019 to December 2020. Also recruited were 68 healthy subjects with no prior history of migraine, dizziness, or other neurological disorders, serving as normal controls.

This study was approved by the hospital ethics committee of Shanghai Changzheng Hospital, Naval Medical University (CZ2019-SJNK-005) and all patients signed an informed consent for this study.

Inclusion criteria were as follows: (1) having no organic neurological or aural diseases; (2) having good neck movement; (3) having normal eyesight or corrected version of 1.0 or above; (4) electric otoscopy, pure tone audiometry, acoustic immittance measurement, video head impulse test and eye movement test yielded normal results; (5) understanding and cooperating with the relevant examinations and agreeing to sign an informed consent.

Exclusion criteria were as follows: (1) having dizziness, vertigo or hearing abnormalities not in line with the characteristics of VM; (2) having seriously aberrant vestibular functions, such as abnormalities revealed by video head impulse test and eye movement test; (3) having vertical deviation of eyes, eye diseases and serious cervical spondylopathy or limited cervical movement; (4) those who couldn't understand and cooperate during the experiment.

After elimination of ineligible candidates against the aforementioned criteria, eventually 128 patients were included. Four subjects whose SVV at upright position didn't fall into the range of reference value $\pm 2.5^\circ$ were excluded and, in the end, 64 healthy controls were recruited. The patient selection process is illustrated in fig. 1.

1.2 Methodologies

The patients and normal controls all received video nystagmography, caloric test, video head impulse test, VEMP, static SVV test. The tests were performed by senior technicians who had been engaged in vestibular examination.

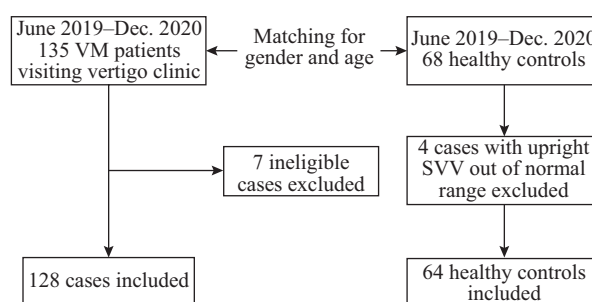


Fig. 1 Subject selection process

Video nystagmography, caloric test, video head impulse test and VEMP were all conducted in accordance with the expert consensus on vestibular function tests (Version 2019)^[22, 23].

SVV test was carried out as follows. Each subject was examined for the following fixed head positions: (a) upright head position (0°); (b) head tilt of 45° to the right; (c) head tilt of 45° to the left. SVV test was conducted in all three head positions. For each head position, 6 tests were performed and the average result of the 6 tests was obtained. Participants were asked to wear VR goggles (VertiGoggles®ZT-VNG-I, ZEHNIT, China). Afterwards, the participant actively avoided light and entered a dark environment. The participant could see a yellow-green light band on a black background. The light band was randomly presented to the participant at an angle in the range from 20° to 90°, either from the right or left. The participant, by using a remote controller, turned the light band, clockwise or counterclockwise, to what he or she believed the position of “gravitational vertical” and confirmed the adjustment by pressing the “Confirm” button. In the meantime, the computer recorded his or her head position and the deviation of the light band position (in angles) from the actual gravitational vertical. For each head position, the test was repeated 6 times and the computer automatically calculated the means and the standard deviations. In the test, the computer monitored the head position in real time mode to make sure the participant kept his or her head in desired position. Under a gyroscope, the actual gravitational vertical was detected and its position defined as 0°. The value was recorded as positive (+) if the upper segment went to the right and the lower segment to the left and as negative (–), if the line went the opposite direction.

1.3 Statistical Analysis

SPSS23.0 software package was employed for statistical analysis. Measurement data were presented as mean±standard deviation (SD) ($\bar{x}\pm s$) and enumeration data were expressed as percentage (%). For measurement data, inter-group comparison was made by using homogeneity test of variance and normal distribution test. If variance was homogeneous and in normal distribution, *t*-test was used. On the other hand, if variance was not homogeneous or not in normal distribution, the rank sum test was employed. The numeration data between groups were compared

by using χ^2 test or Fisher’s exact test. To set reference values, the range between 2.5 centile to 97.5 centile (95% reference range) was taken as normal range for non-normally distributed data while for the normally-distributed data, mean±1.96 standard deviation was set as the normal range ($\bar{x}\pm 1.96s$). The correlation among analysis results was evaluated by employing Spearman rank correlation test. The receiver operating characteristic (ROC) curve was utilized for assessing the diagnostic value of SVVs at different positions in the diagnosis of VM. Test level was set at $\alpha=0.05$. A $P<0.05$ was considered to be statistically significant.

2 RESULTS

2.1 Basic Features and Determination of Reference Values in the Controls

The patient group contained 107 female subjects (83.594%), with an average age of 52.210±11.242 years. The control group had 47 females (73.438%), with an average age of 48.91±10.977 years. There were no statistically significant differences in gender ($P=0.096$) and age ($P=0.054$) between the two groups (table 1).

Table 1 Basic features

Features	Cases (n=128)	Controls (n=64)	F/ χ^2	P
Age	52.21±11.242	48.91±10.977	3.745	0.054
Gender				
Female (n, %)	107 (83.594)	47 (73.438)	2.772	0.096
Male (n, %)	21 (16.406)	17 (26.562)		

Continuous data are shown as mean±standard deviation and categorical data as count (percentage). *P*-value represents the comparison between cases and controls.

Our tests showed that, in the healthy controls, the values at tilt of 45° to the right and values at tilt of 45° to the left all conformed to a normal distribution ($P>0.05$). The 95% reference range of the right title at 45° was (–15.125, 7.807) and the 95% reference range of the left tilt at 45° was (–10.048, 15.174) (table 2). Against the 95% reference ranges of values at the upright position, tilt of 45° to the right and head tilt of 45° to the left right, we found that the upright head position had a higher error rate (47 cases, accounting for 36.719%). Tilt of 45° to the right and tilt of 45° to the left yielded significantly lower error rates ($n=21$, 16.406% with the right tilt and, $n=16$, 12.500% with the left tilt, respectively).

Table 2 Normality test and 95% reference range in healthy controls

Positions	Normality test			Quartile test			Mean	SD
	Skewness	Kurtosis	P	Median	$P_{2.5}$	$P_{97.5}$		
Upright position	–0.395	–0.917	0.002	0.450	–2.313	2.275	0.223	1.260
Tilt of 45° to right	–0.224	0.144	0.200	–3.800	–17.800	7.938	–3.659	5.850
Tilt of 45° to left	0.020	–0.155	0.200	2.200	–10.700	15.688	2.563	6.434

To set the reference values at SVV of the normal control group, the normal distribution test and the quartile test of the data were carried out. Normality test: normal distribution test. $P_{2.5}$: data of 2.5 centile. $P_{97.5}$: data of 97.5 centile. SD: standard deviation

Analysis revealed that there existed no correlation in SSV test results among the three head positions, i.e., the upright position, the tilts of 45° to the right and the left. Moreover, no correlation was found between the SVV results and the age (table 3).

2.2 Comparison between Patients and Controls in Terms of SSV Results at Three Head Positions

There were significant differences in the SVV

Table 3 Correlation between SVV test results and three head positions in the controls

Indicator 1	Indicator 2	Spearman correlation coefficient	P
Age	Upright position	-0.11	0.386
	Tilt of 45° to the right	0.227	0.072
	Tilt of 45° to the left	-0.218	0.083
Upright position	Tilt of 45° to the right	0.123	0.331
	Tilt of 45° to the left	0.243	0.053
Tilt of 45° to the right	Tilt of 45° to the left	-0.168	0.185

results at the upright position between the two groups ($P=0.006$), with the values in the patients being significantly less than those in the controls. There were also significant differences in the absolute values of the three positions between the two groups ($P=0.003$). No significant difference was revealed between the two groups when the head tilted 45° to the left or right (table 4).

Analysis showed that there were no significant differences in the conformity to the Müller (M effect) between the two groups, neither unilaterally nor bilaterally ($P>0.05$) (table 5).

2.3 Correlation between SVV Test Results and CP, cVEMP, oVEMP in Patients

Our analysis exhibited that only SVV results at the upright position were significantly correlated with cVEMP ($P=0.042$). SVVs at tilts of 45° to the right and the left were not significantly correlated with CP, cVEMP and oVEMP (table 6).

Table 4 Comparison between patients and controls in terms of test result errors

Positions	Groups	Median (lower and upper quartiles)	Z	P
Upright	Patients	-0.700 (-2.500, 1.175)	-2.769	0.006
	Controls	0.450 (-0.800, 1.300)		
45° tilt to right	Patients	-5.00 (-9.600, 0.100)	-1.404	0.160
	Controls	-3.800 (-6.800, 0.300)		
45° tilt to left	Patients	2.100 (-2.500, 7.425)	-0.264	0.791
	Controls	2.200 (-1.100, 7.250)		
Absolute values at three positions	Patients	15.100 (9.025, 20.825)	-2.995	0.003
	Controls	11.200 (8.800, 15.125)		

Table 5 Conformity to the M effect in two groups

Conformity	Patients (n, %)	Controls (n, %)	χ^2	P
Yes at right side	95 (74.219)	47 (73.437)	0.014	0.907
Yes at left side	83 (64.844)	47 (73.437)	0.574	0.449
Yes at both sides	70 (54.687)	36 (56.250)	0.042	0.837
Not at neither side	20 (15.625)	8 (12.500)	0.334	0.563

P-value represents the comparison on the conformity of the Müller (M effect) between patients group and controls group.

Table 6 Correlation between SVV and the peripheral vestibular function in patients

Indicator 1	Indicator 2	Spearman correlation coefficient	P
Upright position	CP	0.026	0.791
	cVEMP	0.199	0.042
	oVEMP	-0.033	0.745
Tilt of 45° to the right	CP	0.055	0.579
	cVEMP	-0.043	0.660
	oVEMP	-0.040	0.691
Tilt of 45° to the left	CP	-0.016	0.875
	cVEMP	-0.050	0.615
	oVEMP	0.081	0.427

CP: canal paresis; cVEMP: cervical vestibular evoked myogenic potential; oVEMP: ocular vestibular-evoked myogenic potential

2.4 Value of SVV Test in the Diagnosis of VM

Our analysis showed that the sensitivity and specificity of SVV test at upright position for the diagnosis of VM were 67.200% and 62.500%, respectively. The area under the ROC curve (AUC) was 0.623 (0.545–0.700) and cut-off value was -0.350. The diagnostic value of SVV was significantly higher at the upright position than at tilts of 45° to the right or left ($P=0.006$). Since $AUC<0.7$, the diagnostic accuracy was relatively low (table 7). The working curve analysis revealed that even adding the absolute values at the three positions together failed to increase the diagnostic power ($AUC<0.7$) (table 7) (fig. 2).

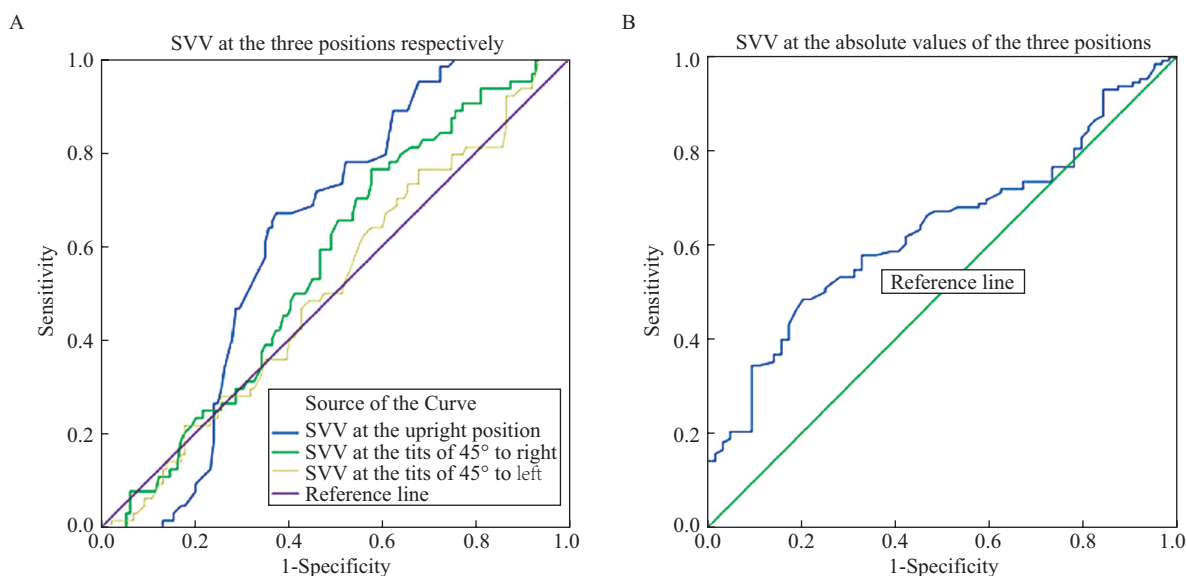
3 DISCUSSION

Patients with VM often complain of dizziness with changes in the head or body position. Such symptoms mean the spatial orientation may not function properly in these patients. Currently, it is generally believed that any abnormality along the otolith pathways, including utricle, saccule, brain stem, thalamus, vestibular cortex, leads to errors of spatial orientation^[24]. Mechanistically, the development and progression of VM involve both peripheral vestibular system and central nerve

Table 7 The value of SVV test for the VM diagnosis

Indicators	AUC	Sensitivity	Specificity	cut-off value	<i>P</i>	95% IC
Upright	0.623	0.672	0.625	-0.350	0.006	0.545–0.700
Tilt of 45° to right	0.562	0.766	0.422	-6.900	0.160	0.480–0.644
Tilt of 45° to left	0.512	0.766	0.322	-1.250	0.791	0.427–0.597
Sum of the absolute of values at three positions	0.633	0.484	0.797	15.650	0.003	0.554–0.712

AUC: area under ROC curve. 95% IC: 95% confidence interval

**Fig. 2** ROC curves of SVV in the study

A: SVV at the three positions respectively. blue line, SVV at the upright position; green line, SVV at the tilts of 45° to right; pink line, SVV at the tilts of 45° to left; purple line, reference line. B: SVV at the absolute values of the three positions, blue line. The green line is reference line.

system^[25]. To further understand the features of otolith pathway damage in VM patients, this study examined the static SVV at the upright position, at head tilts of 45° to the right and left during intervals of VM attacks and compared the SVV results with findings of VEMP and CP.

According to previous reports, in normal populations, the deviation of the static SVV at the upright position should be within $\pm 2.5^\circ$ ^[13, 18]. Nonetheless, no consensus has been arrived at concerning the normal range of SVV at tilts. In this study, we recruited subjects, as normal controls, who previously had no dizziness, vertigo, migraine and other neurological, otological and ophthalmological conditions and whose SVV at the upright position was within $\pm 2.5^\circ$. Our detection showed that the 95% reference range of the right tilt at 45° was (-15.125, 7.807) and the 95% reference range of the left tilt at 45° was (-10.048, 15.174) (table 2). The error rates at the upright position and at tilts of 45° to the right and the left were 36.719%, 16.406%, 12.500%, respectively. There was statistically significant difference in the SVV result at the upright position between the two groups ($P=0.006$) and the SVV values were significantly less in patients than in controls, i.e., the perception of VM patients to the gravitational vertical tended to

tilt to the left at the upright position. No statistically significant difference was found in the SVV result at tilts of 45° to the right or left between the two groups. In this study, VM patients had higher abnormality rate in terms of SVV at the upright position, with diagnostic sensitivity and specificity being 67.200% and 62.500%, respectively, suggesting that it can serve as a complementary indicator for the diagnosis of VM. The conclusion reached in this study is not fully consistent with the conclusions of previous researches on SVV tests in VM patients. Prior studies found no SVV deviation in VM patients at the upright position^[19, 20]. This discrepancy might be attributed to the phase of the condition during which the patients were recruited. In our cohort, most patients had clinical VM episodes 1 week before the recruitment and some even had attacks 1 day before SVV test. We retrieved only one study which found that in patients whose symptoms persisted for over 24 hours^[26]. Given the differences between the two studies in patient selection and symptoms, which indicated that the mechanisms and locations involved in the two studies were different, we believe that this discrepancy might also be ascribed to the sample selection bias. Moreover, this study showed that there was no significant difference in SVV at tilt of 45° between VM patients and controls. On the other hand,

Winnick *et al* found that the static SVV deviation at a tilt of 20° was less in VM patients than in normal subjects^[27]. Our finding was not in agreement with their results. The study by Winnick *et al* included only 27 VM patients and their sample size was small and sampling errors were very alike. In addition, their tilt angle (20°) differed from ours (45°). The two factors might largely explain the discrepancy between the two studies.

To further know if SVV abnormalities result from vestibular damage of peripheral or of central origin, we examined the correlations among CP, oVEMP, cVEMP and the SVVs at three head positions. Our study demonstrated that SVV at the upright position was correlated with cVEMP ($P=0.042$). Considering that cVEMP is indicative of function of saccular pathways whereas SVV reflects, to a greater extent, the function utricular pathways, we believe its clinical implications await further exploration. Moreover, in this study, CP, which measures the function of semicircular canal, and oVEMP, an indicator of utricular function, bore no significant correlation with SVVs at the three positions, suggesting that SVV abnormalities in VM patients are not directly linked to the functions of the semi-circular canal and utricule, indicating that SVV abnormalities could not be solely attributed to the damage of peripheral otolith organs. VM patients had no signs of vestibular or ocular motor dysfunction that could lead to abnormal SVV deviations. This prompted us to hypothesize that SVV deviations in these patients might be related to a “higher-order” dysfunction in multisensory integration for spatial orientation and to the vestibular compensation secondary to peripheral damage. This hypothesis is mechanistically in line with the potential role that the multisensory integration plays in migraine pathophysiology^[28].

In a dark room, a normal subject develops delusion when he or she inclines head about the nasal-occipital axis, towards to the left or right shoulder and when his or her body system tries to adjust subjective vertical to the gravitational vertical. When the head tilt is less than 60°, the subjective vertical is away from the head tilt direction while the tilt angle is greater than 60°, the subjective vertical is in line with the head tilt direction. Howard dubbed these two phenomena as Müller (M) effect and Aubert (A) effect^[29, 30].

In this study, SVV test was conducted in static state, with a head tilt of 45° and comparison was made between two groups to see if they were in conformity with M effect. Our results revealed no significant differences in the conformity with the M effect between the two groups, neither unilaterally nor bilaterally. These results suggested that during the interval of VM episodes, adding input of deep sensation information did not increase the error rate of verticality perception. Given that there were no significant differences in

SVV values at head tilts between patients and healthy controls, we believe that the deep sensation does not weigh heavily in the disorder of spatial orientation in VM patients. The errors in sensory integration of the spatial orientation stem more from the disorder of signal redundancy processing of visual or vestibular senses.

This study also found that there was a substantial individual variation in SVV results among VM patients. We inferred that, if the patients in our series had been further sub-grouped in terms of clinical features, in terms of type of dizziness, presence or absence of visual vertigo, tolerance or intolerance to head movement, presence or lack of premonitory symptoms, the subgroup analysis might have yielded more valuable findings. Nonetheless, the sample size of our cohort was too small to allow further sub-grouping. This is a limitation of the study.

To sum up, this study found that SVV exerted complementary value for the diagnosis of VM. Nevertheless, since the ROC analysis showed that the AUC was less than 0.7, its diagnostic accuracy is low. So far, we don't recommend that SVV result can be used as an indicator for the diagnosis of VM and further studies are warranted to further explore the value of SVV in the diagnosis of VM.

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Conflict of Interest Statement

All authors declare no conflicts of interest.

Author Su-ling ZHANG is a young member of the Editorial Board for Current Medical Science. The paper was handled by the other Editor and has undergone rigorous peer review process. Author Su-ling ZHANG was not involved in the journal's review of, or decisions related to, this manuscript.

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