ORIGINAL RESEARCH

Low levels of serum magnesium are associated with poststroke cognitive impairment in ischemic stroke patients

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Purpose: Population-based studies have revealed a high prevalence of cognitive impairment after stroke. We aimed to determine the impact of serum magnesium (Mg^{2+}) levels on the occurrence of poststroke cognitive impairment (PSCI).

Patients and methods: Acute ischemic stroke patients (n = 327) were enrolled in our study and serum Mg^{2+} levels were assessed on admission. The cognitive performance of each patient was evaluated using the Mini–Mental State Examination (MMSE) at a 1-month follow-up visit.

Results: One hundred five (32.1%) patients were diagnosed with PSCI at 1-month poststroke. The serum Mg^{2+} levels in both the PSCI group and the non-PSCI group were significantly lower than those in normal control group ($P<0.001$). In addition, the PSCI group had lower levels of serum Mg^{2+} compared to the non-PSCI group ($P=0.003$). In the binary logistic regression analysis, a serum Mg^{2+} level of ≤ 0.82 mmol/L was significantly associated with an increased risk of developing PSCI by the 1-month follow-up (OR 2.236, 95% CI 1.232–4.058, $P=0.008$), as was age (OR 1.043, 95% CI 1.014–1.073, $P=0.003$).

Conclusion: Our results demonstrate the existence of a significant association between low levels of serum Mg^{2+} and the occurrence of PSCI 1-month poststroke, and these results suggest that low levels of serum Mg^{2+} on admission may serve as a risk factor for developing PSCI by 1-month poststroke.

Keywords: cognition, magnesium, stroke, risk factor

Introduction

Poststroke cognitive impairment (PSCI) is one of the frequent residual sequelae of stroke worldwide. The prevalence of PSCI reported in previous studies varied from 20 to 80% in various countries.[1,2] Cognitive impairments in stroke survivors not only raise the risk of disability and mortality[3] but also lead to the recurrence of vascular events.[4] Recently, an increasing number of studies have focused on the role of risk factors in the development of dementia after stroke; although older age and sex have been reported to be risk factors for PSCI,[5] these factors are not preventable. Thus, there is an urgent need to identify novel and preventable risk factors of PSCI.

In recent years, it has been found that there was a significant drop in serum magnesium (Mg^{2+}) levels in acute ischemic stroke (AIS) patients.[6,7] In addition, studies have indicated that low serum Mg^{2+} levels contributed to unsatisfactory short-term functional outcomes after stroke.[8,9] Contrarily, Mg^{2+}-enriched dietary intake has been proved to reduce the incidence of ischemic stroke,[10] and moderate amount of Mg^{2+} dietary approaching the Dietary Reference Intake (DRI) even could improve functional outcomes after stroke.[11,12]

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Evidence for a role of serum Mg^{2+} on cognitive function comes from both clinical and animal studies. Clinical studies have shown that low levels of serum Mg^{2+} exerted negative effects on cognitive function,[13] while Mg^{2+} supplements attenuated cognitive impairment.[14] In animal models, Mg^{2+} also was found to be involved in cognitive impairment; increasing Mg^{2+} in the brain was found to led to enhancements in learning and memory in rats via improved functional connectivity and synaptic plasticity,[15] which had been demonstrated to be involved in cognitive impairment.[16,17] Besides, Mg^{2+} was found to boost the memory restorative effect by reducing the synaptic loss and restoring the N-methyl-D-aspartic acid receptor (NMDAR) signaling pathway in Alzheimer's disease mice.[18]

Considering the important role of Mg^{2+} in both stroke and cognition, it is plausible that serum Mg^{2+} levels may play an important role in the development of PSCI. However, no study to date has examined the association between Mg^{2+} and cognitive function in a stroke setting, and additional studies in this area are urgently needed. Therefore, the aim of our study was to explore the role of serum Mg^{2+} levels in PSCI and we hypothesized that low levels of serum Mg^{2+} are associated with an increased incidence of PSCI.

Patients and methods
Patients and study design
All first-ever or recurrent AIS patients hospitalized in the Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, from October 2013 to June 2015 were consecutively screened for this observational prospective cohort study. The inclusion criteria included the following: 1) patients were between the age of 18 and 80 years; 2) diagnosis of AIS was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) on admission; 3) onset of AIS events was less than 2 weeks on admission; and 4) patients had the ability and willingness to give informed consent. The exclusion criteria applied to patients included the following: 1) a history of dementia or cognitive impairment; 2) present or past psychiatric disorders, such as depression; 3) neurodegenerative diseases such as Parkinson's disease; 4) a history of a malignant tumor; 5) a history of nootropic or antipsychotic drug use; 6) severe aphasia, visual or auditory impairment, or a chaotic conscious state that made them unable to complete neuropsychological assessments; 7) a fasting state or severe renal failure with acute oliguresis or diuresis; 8) severe metabolic abnormalities, such as calcium metabolism disorder and diabetes mellitus ketoacidosis; and 9) ongoing use of Mg^{2+} supplement drugs, diuretics, dehydrants, or insulin after the

stroke onset. Meanwhile, 110 healthy control subjects were recruited from a health survey conducted at The First Affiliated Hospital of Wenzhou Medical University. Subjects with any personal or familial history of psychiatric illness were excluded. All subjects were free of severe physical diseases including AIS.

This study protocol was performed in accordance with the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Medical Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University, and written informed consent was provided by all participants or their relatives.

Clinical variables and assessments
Demographic and clinical characteristics were collected via standardized questionnaires through face-to-face interviews. Education levels were categorized as illiterate, primary school, and secondary school and above according to years of education.

Cognitive function assessment was performed at a 1-month follow-up by using the Mini–Mental State Examination (MMSE). The MMSE is a traditional and well-accepted scale for detecting current cognitive dysfunction. Based on the education level, an MMSE score of ≤19 points (illiterate), ≤22 points (primary school education level), and ≤26 points (secondary school and above education level) was adopted as the diagnostic cutoff value for cognitive impairment.[19] A lower MMSE score means more severe cognitive dysfunction. The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the stroke severity on admission. The Hamilton Depression Rating Scale 17-item (HAMD-17) was used to screen depressive symptoms at the 1-month follow-up. The Hamilton Anxiety Rating Scale (HAMA) was used to screen anxiety symptoms at the 1-month follow-up. Besides, we assessed the poststroke functional outcomes at 1-month follow-up with the modified Barthel Index (BI) and modified Rankin Scale (mRS; a score of greater than 2 was defined as poor outcome). All the evaluations were carried out by trained neurological physicians who were blind to the other clinical data of the patients.

Definition of PSCI
PSCI is a series of syndromes that occurs within 6 months of a stroke event and meets the diagnostic criteria for cognitive impairment.[20,21] PSCI includes not only the cognitive impairment resulting from various new stroke events but also the deterioration of cognitive function within 6 months of a new stroke event in Alzheimer's disease patients. Currently, the

diagnostic criteria for cognitive impairments mainly based on the results of neuropsychological assessment scales, such as the MMSE,[22] Montreal Cognitive Assessment (MoCA),[23] and mini-cognitive (Mini-Cog) assessment.[24] In this study, the diagnosis of cognitive impairment was established when the MMSE scores were below the diagnostic cutoff value described earlier.[25]

Serum Mg^{2+} measurements

Peripheral blood samples were acquired within 12–18 hours after admission. The serum Mg^{2+} concentration was measured by dimethylaniline blue colorimetry using a Beckman Coulter automatic analyzer (AU5800) at our hospital's laboratory. Patients were divided into the following three groups based on serum Mg^{2+} levels: ≤ 0.82, 0.83–0.88, and ≥ 0.89 mmol/L.

Statistical analyses

For continuous variables with a normal distribution or a skewed distribution, results were described as the mean $\pm$ SD or median (IQR), respectively, while for categorical variables, the results were described using proportions. For univariate comparisons between groups, proportions were compared by using Chi-squared tests and one-way ANOVA, and Student's t-tests were used for variables normally distributed; for variables with an asymmetrical distribution,

the Mann–Whitney U-test and Kruskal–Wallis test were used. When ANOVA showed significant differences among the groups, Bonferroni corrections were used for pairwise comparisons. When Kruskal–Wallis tests showed significant differences among the groups, pairwise multiple comparisons followed. Binary logistic regression analysis was performed to quantify the association between serum Mg^{2+} levels and the development of PSCI. All potential confounders with a P-value of <0.05 in the univariate analyses and variables such as NIHSS score and history of stroke were introduced into the regression models. These results are represented as adjusted ORs and their 95% CIs. All statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA), and a P-value of <0.05 was considered statistically significant.

Results

The flowchart of our study is shown in Figure 1. During the screening period, 476 consecutive patients with AIS were screened and 327 patients were enrolled in our study. No significant differences were found between patients who dropped out from our study and patients who enrolled in terms of age (62.12±10.43 vs 62.50±10.19; P=0.614), sex (male/female) (55/26 vs 207/120; P=0.191), NIHSS score (3 [1–6] vs 3 [1–4]; P=0.094), and serum Mg^{2+} levels (0.85 [0.80–0.90] vs 0.85 [0.81–0.90]; P=0.736).
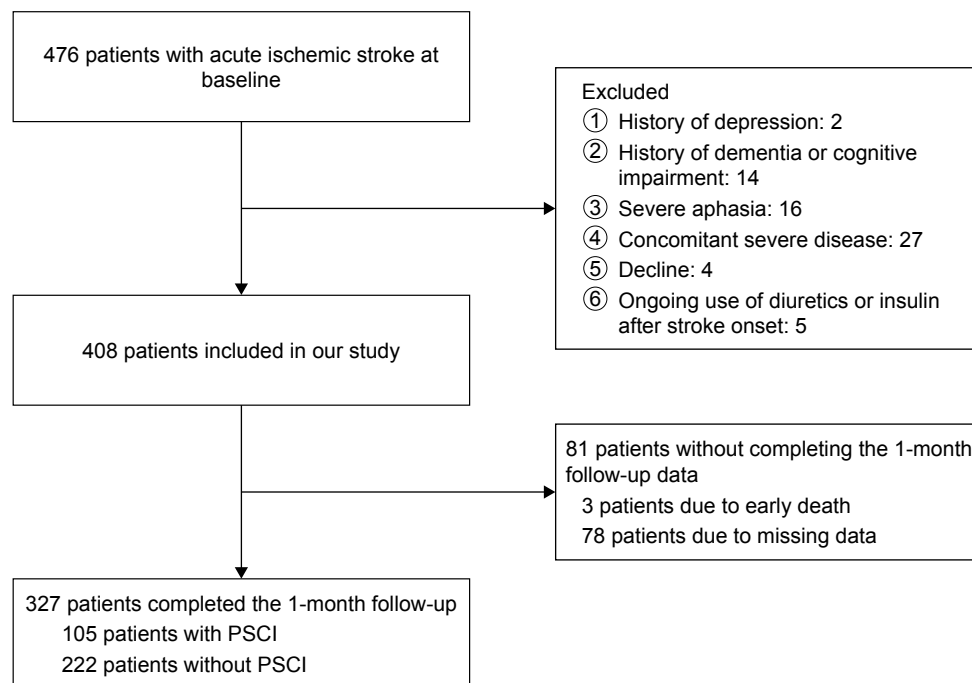

Figure 1 Study recruitment profile.
Abbreviation: PSCI, poststroke cognitive impairment.

Baseline characteristics of patients are shown in Table 1. The mean (± SD) age of the stroke patients who enrolled was 62.50±10.19 years. Their median (IQR) NIHSS score was 3 (1–4). Of the 327 patients who formed the study sample, 105 (54 men, 51 women) patients were diagnosed with PSCI at the 1-month follow-up and the incidence of PSCI at 1-month poststroke was 32.1%. The average serum Mg^{2+} concentrations in all stroke patients and the normal control group were 0.85±0.08 and 0.96±0.17 mmol/L, respectively ($P<0.001$), and the average serum Mg^{2+} concentrations

in the non-PSCI and PSCI groups were 0.86±0.07 and 0.83±0.09 mmol/L, respectively. The overall serum Mg^{2+} concentration of all stroke patients was significantly lower than the concentration in normal controls ($P<0.001$). Furthermore, there was a significant intergroup difference in terms of the serum Mg^{2+} levels ($P<0.001$) among PSCI, non-PSCI, and normal control groups. The serum Mg^{2+} concentration in normal subjects was significantly higher than both non-PSCI patients ($P<0.001$) and PSCI patients ($P<0.001$), and the PSCI group showed a lower serum Mg^{2+} levels than the

Table 1 Baseline clinical characteristics in non-PSCI and PSCI patients at 1 month

	Non-PSCI (n=222)	PSCI (n=105)	*P*-value
Demographic characteristics			
Age (years), mean ± SD	61.14±9.97	65.39±10.08	<0.001
Male/female	153/69	54/51	0.003
Married status, n (%)	202 (91.0)	90 (85.7)	0.180
Education levels, n (%)			0.029
Illiterate	55 (24.8)	41 (39)	
Primary school	103 (46.4)	38 (36.2)	
Postsecondary school	64 (28.8)	26 (24.8)	
TOAST classification, n (%)			0.741
LA	180 (81.1)	84 (80)	
CE	12 (5.4)	6 (5.7)	
SA	23 (10.8)	11 (10.5)	
SOE	4 (1.8)	1 (1.0)	
SUE	2 (0.9)	3 (2.9)	
Lesion location, n (%)			0.840
Left hemisphere	69 (31.1)	37 (35.2)	
Right hemisphere	79 (35.6)	31 (29.5)	
Brainstem	36 (16.2)	18 (17.1)	
Cerebellum	10 (4.5)	4 (3.8)	
Others	28 (12.6)	15 (14.3)	
Multiple infarcts, n (%)	85 (38.3)	52 (49.5)	0.056
Vascular risk factors, n (%)			
Hypertension	157 (70.7)	73 (69.5)	0.897
Diabetes mellitus	63 (28.4)	37 (35.2)	0.247
Hyperlipidemia	21 (9.5)	10 (9.5)	1.000
Coronary artery disease	14 (6.3)	8 (7.6)	0.814
History of stroke	17 (7.7)	12 (11.4)	0.299
Current smoking	73 (32.9)	20 (19.0)	0.012
Current drinking	89 (40.1)	38 (36.2)	0.544
NIHSS score, median (IQR)	2.5 (1–4)	3 (1.5–5)	0.210
HAMA score, median (IQR)	4 (1–7)	4 (1–8)	0.800
HAMD score, median (IQR)	4 (2–7)	5 (1–9)	0.616
Poor outcome, n (%)	31 (14.2)	22 (21.0)	0.148
BI score, median (IQR)	100 (98–100)	100 (91–100)	
Laboratory data			
Mg^{2+} (mmol/L), mean ± SD	0.86±0.07	0.83±0.09	0.003
HbA1c (mmol/L), mean ± SD	6.36±1.59	6.28±1.26	0.707
FBG (mmol/L), mean ± SD	5 (4.4–5.9)	4 (4.6–6.4)	0.257
PBG (mmol/L), mean ± SD	7.6 (6.0–10.6)	8.1 (6.0–12.4)	0.391

Abbreviations: BI, Barthel Index; CE, cardioembolism; FBG, fasting blood glucose; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; HbA1c, hemoglobin A1c; LA, large-artery atherosclerosis; Mg^{2+}, magnesium; MMSE, Mini–Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; PBG, postprandial blood glucose; PSCI, poststroke cognitive impairment; SA, small-artery occlusion lacunar; SOE, stroke of other determined etiology; SUE, stroke of other undetermined etiology; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
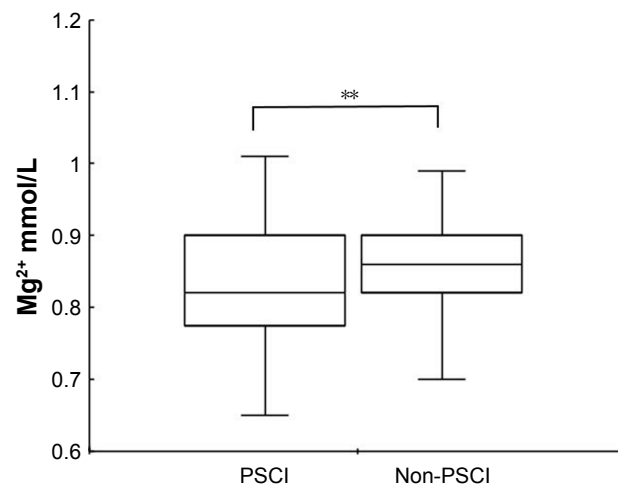
Figure 2 Comparisons of serum Mg^{2+} levels in patients with PSCI and non-PSCI.
Notes: In the box-and-whisker plots, the horizontal line in the middle of each box indicates the median value; the lower and upper ends of the box represent the 25th and 75th percentiles, and the peripheral lines extending to the outer fences represent 10th and 90th percentiles, respectively. **$P < 0.01$ compared with the non-PSCI group via the Mann–Whitney U-test.
Abbreviations: Mg^{2+}, magnesium; PSCI, poststroke cognitive impairment.

non-PSCI group (0.83 ± 0.09 vs 0.86 ± 0.07; $P < 0.05$). Besides, there was no significant difference in terms of age and sex between normal control group and non-PSCI group. Meanwhile, there was also no difference in terms of age and sex between normal control group and PSCI group. Compared to non-PSCI group, PSCI group had significant lower levels of serum Mg^{2+} concentration ($P = 0.003$, Figure 2), were significantly older (65.39 ± 10.08 vs 61.14 ± 9.97; $P < 0.001$), had a higher proportion of female (54/51 vs 153/69; $P = 0.003$), and were more likely to be less educated, female, and a current smoker. No significant differences were observed in the other variables, such as lesion location, vascular risk factors, poor functional outcome, and blood glucose levels on admission.

As shown in Table 2, further comparisons revealed that there were significant differences between the non-PSCI group and the PSCI group in serum Mg^{2+} levels across tertiles of patients ($P < 0.001$). In addition, the proportion of patients in the low tertile (≤ 0.82 mmol/L) was significantly higher in the PSCI group than in the non-PSCI group (51.4 vs 29.3%, respectively, $P < 0.001$) and the proportion of patients in the

intermediate tertile (0.83–0.88 mmol/L) was lower in the PSCI group than in the non-PSCI group ($P = 0.011$).

In an analysis using all participants, with the high tertile (≥ 0.89 mmol/L) taken as a reference and PSCI occurrence as a dependent variable in the binary logistic regression analysis, after adjusting for potential confounders, there remained an independent association between the lowest tertile of serum Mg^{2+} level and the occurrence of PSCI (OR 2.236, 95% CI 1.232–4.058, $P = 0.008$). In addition, age was significantly associated with the occurrence of PSCI at the 1-month follow-up (OR 1.043, 95% CI 1.014–1.073, $P = 0.003$) (Table 3).

Discussion
In this study, we observed that a low level of serum Mg^{2+} was independently associated with the occurrence of PSCI at

Table 2 Magnesium levels across tertiles of patients

	Non-PSCI patients (n=222)	PSCI patients (n=105)	P-value
Magnesium, n (% of total population)			<0.001
Tertile 1 (≤0.82 mmol/L)	65 (29.3)	54 (51.4)	<0.001
Tertile 2 (0.83–0.88 mmol/L)	81 (36.5)	23 (21.9)	0.011
Tertile 3 (≥0.89 mmol/L)	76 (34.2)	28 (26.7)	0.204

Abbreviation: PSCI, poststroke cognitive impairment.

Table 3 Multivariate logistic model of the clinical determinants of PSCI

Variables	OR (95% CI)	P-value
Magnesium		0.001
Tertile 1	2.236 (1.232–4.058)	0.008
Tertile 2	0.765 (0.395–1.480)	0.426
Age	1.043 (1.014–1.073)	0.003
Sex	1.614 (0.885–2.943)	0.118
Education levels		0.527
Illiterate	0.776 (0.412–1.460)	0.431
Primary school	1.083 (0.515–2.276)	0.833
Current smoking	0.747 (0.385–1.449)	0.389
NIHSS score	1.094 (0.994–1.205)	0.066
History of stroke	1.648 (0.709–3.827)	0.246

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; PSCI, poststroke cognitive impairment.

1-month poststroke. To the best of our knowledge, this is the first report exploring the correlations between serum levels of Mg^{2+} on admission and PSCI in AIS patients.

In our study, 32.1% of AIS patients developed PSCI by a 1-month follow-up visit, which is in line with previous studies.[1,2] Meanwhile, age was shown to be a risk factor for the development of PSCI, which is in accordance with the existing literature.[5]

There are two hypotheses regarding the role of Mg^{2+} in cognitive impairment. One hypothesis is the direct regulating effect of neuronal Mg^{2+} on the NMDAR,[13] which is well-known to be the predominant molecule involved in synaptic plasticity and learning and memory.[26–28] Neuronal Mg^{2+} is essential in the regulation of the excitability of NMDAR by modulating the open duration and coincidence detection ability of the NMDAR via pore blockade.[29,30] Furthermore, experimental studies indicated that increased extracellular Mg^{2+} upregulated and enhanced activity-dependent NMDAR-dependent signaling and, thus, resulted in an enhancement of synaptic plasticity in cultured neurons.[15,31] When Mg^{2+} is deficient, fewer NMDA channels are blocked by the extracellular Mg^{2+} and the NMDAR becomes hyperexcitable,[29] which might impair synaptic plasticity and learning and memory function.[31,32]

Other hypothesized pathways are oxidative stress and chronic inflammation.[33,34] Mg^{2+} deficiency has been found to increase the production of free oxygen radicals, stimulate the excessive production and release of proinflammatory molecules such as tumor necrosis factor-α (TNF-α), interleukins, and nitric oxide, all of which are responsible for triggering the development of a proinflammatory state both in experimental animals and in humans,[33,35–37] and thereby, increase the risk of cognitive impairment. In addition, it has been reported that Mg^{2+} deficiency may impair cell membrane integrity and function and increase susceptibility of the body to oxidative stress.[38] Similar to the results documented in previous studies,[39,40] our previous study found that the concentrations of serum 8-hydroxydeoxyguanosine (8-OHdG) and malondialdehyde (MDA), both of which are widely perceived as markers of oxidative stress, were significantly higher in the PSCI group than in the non-PSCI group. Previous studies also suggested that increased levels of interleukin-6 and C-reactive protein (CRP) are associated with PSCI.[41,42]

In addition, serum concentrations of Mg^{2+} are remarkably constant in healthy subjects and correlate well with intracellular free Mg^{2+},[43] a physiologically active form of the element Mg^{2+}; therefore, serum Mg^{2+} could be regarded as the most applicable clinical indicator of Mg^{2+} metabolic disorders.

Given the above findings, we put forward the view that low levels of serum Mg^{2+} are associated with the occurrence of PSCI and may predict its development at 1-month poststroke.

Several limitations of our study should be mentioned. First, according to our inclusion/exclusion criteria, patients recruited in our study cohort were limited to those without severe aphasia and other serious conditions, which may result in a bias in the estimates of PSCI incidence. Second, serum Mg^{2+} levels were measured only on admission in our study; it would be better to measure serum Mg^{2+} at the time of the cognitive screening to further explore how serum Mg^{2+} levels change over time following the stroke. Third, as Mg^{2+} can be found in many common foods, diet may have an impact on Mg^{2+} levels in the human body. Information on the dietary intake of patients was not collected, and thus, there may have been an influence of differing diets on the results. Fourth, 1-month follow-up was chosen for the assessment of PSCI rather than 3- or 6-month follow-up, which might be more appropriate to assess the cognitive impairment after stroke. Fifth, cognition function may not be fully reflected with MMSE; other neuropsychological tests should be evaluated together with MMSE to better assess the cognition function of patients.

Conclusion

Despite these limitations, our study demonstrated that low levels of serum Mg^{2+} on admission were independently associated with the development of PSCI at 1-month poststroke. The result suggested that low levels of serum Mg^{2+} were predictive of the subsequent PSCI by 1-month poststroke, and for patients with AIS, the determination of serum Mg^{2+} levels after admission is necessary. Further multicenter and randomized controlled trials are critical to confirm the causal relationship between serum Mg^{2+} levels and PSCI.

Acknowledgments

Author contributions

Xinjie Tu and Jincai He designed the study and wrote the protocol. Xinjie Tu, Huihua Qiu, Shasha Lin, Weilei He,

Guiqian Huang, Xingru Zhang, and Yuemin Wu collected the data of the study. Xinjie Tu conducted literature searches and provided summaries of previous research studies. Xinjie Tu conducted the statistical analysis. Xinjie Tu and Huihua Qiu wrote the first draft of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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