

Original Article

Application of 3D-ASL in hemodynamic analysis and prognosis evaluation of vascular cognitive impairment

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Abstract: Objective: To investigate the application of magnetic resonance 3D arterial spin labeling (3D-ASL) imaging in the hemodynamic analysis and prognostic assessment of vascular cognitive impairment (VCI). Methods: Using a retrospective research method, 108 patients with ischemic cerebrovascular disease diagnosed in the Department of Neurology of Lianyungang Hospital of Traditional Chinese Medicine from January 2021 to April 2022 were chose as the research subjects. The Montreal cognitive assessment (MoCA) was used to evaluate cognitive function. The patients were divided into a VCI group (n=54, 28 males and 26 females) and a normal cognitive function group (NCF group, n=54, 30 males and 24 females). The 3D-ASL cerebral perfusion imaging was performed on the two groups of patients using different post label delay (PLD) (1525 ms, 2525 ms). The cerebral blood flow (CBF) values of bilateral frontal lobe, temporal lobe, temporal parietal junction, parietal lobe, and hippocampus were analyzed under different PLDs in the two groups. The two sets of MoCA scale scores were compared. The receiver operating characteristic curve (ROC) of CBF of VCI patients was drawn, and the area under curve (AUC), specificity and sensitivity under different PLDs was compared. Results: There was no statistical significance between the two groups in terms of sex, average age, hypertension, diabetes, coronary heart disease, smoking history, and drinking history ($P>0.05$). CBF 1525 values and CBF 2525 values in the bilateral frontal lobes, temporal lobes, temporoparietal junction, parietal lobes, and hippocampus were significantly reduced in the VCI group under different PLD (all $P<0.05$). There was no significant difference in the CBF 1525 value and CBF 2525 value of the bilateral frontal lobe and temporal lobe in the VCI group (all $P<0.05$). The language, delayed memory, executive ability, attention and calculation ability, naming, abstract thinking, orientation, and total scores of the VCI group were significantly lower than those of the NCF group (all $P<0.05$). The ROC analysis revealed that the AUC, specificity, and sensitivity of CBF (bilateral frontal, temporal, temporoparietal junction, parietal, and hippocampus) at PLD 1525 ms were lower than those of CBF at PLD 2525 ms ($P<0.05$). Conclusion: Non-invasive 3D-ASL technology can be used to detect cerebral hemodynamics and predict prognosis in VCI patients. PLD 1525 ms was more sensitive to detect cerebral hypoperfusion. PLD 2525 ms showed a more accurate hypoperfusion range. This guides and adjusts treatment methods.

Keywords: 3D-ASL, vascular cognitive impairment, hemodynamics, post label delay, cerebral blood flow, prognosis

Introduction

Vascular cognitive impairment (VCI) is manifested by cognitive dysfunction caused by vascular factors. The prevalence rate of VCI among people over 65 years old in China is 8.7% [1]. With the aging process of the population, VCI and dementia have become key issues in public health. Many cerebral lesions are accompanied by changes in cerebral blood supply. Evaluation of the cerebral tissue perfusion is

an important basis for disease diagnosis, identification, treatment, and prognosis. In recent years, the evaluation of cerebral hemodynamics has relied on imaging techniques, such as digital subtraction angiography. This has been the gold standard for evaluating cerebral blood flow, but it is an invasive, complex, and expensive examination [2]. Computed tomography angiography can visually display the anatomy of intracranial vessels and evaluate the location and extent of vascular stenosis, but it is not

good for small vessels [3]. Magnetic resonance angiography is non-invasive and simple. It can show good intracranial and cervical large blood vessels, but it is not good for small arteries. The detection sensitivity for distal blood vessels is poor [4]. The newly launched magnetic resonance three-dimensional arterial spin labeling (3D-ASL) imaging is a non-invasive, simple, and repeatable method for measuring cerebral perfusion without contrast agent [5]. This study aimed to explore the application of 3D-ASL imaging in the hemodynamic analysis and prognostic assessment in VCI patients, to provide reference for early clinical diagnosis.

Materials and methods

Basic information

The medical records of 108 patients with ischemic cerebrovascular disease diagnosed in the Department of Neurology of Lianyungang Fourth People's Hospital from January 2021 to April 2022 were retrospectively analyzed. Inclusion criteria: patients met the diagnosis of VCI [6], with obvious cognitive dysfunction in learning, memory, language, or action; patients who were attacked by stroke at least 3 months ago, with MRI showing cerebral infarction and white matter lesions; patients aged 40-80 years old. Exclusion criteria: patients with neurodegenerative diseases; patients with white matter lesions from sarcoidosis and multiple sclerosis; patients with cognitive impairment caused by non-vascular diseases such as intracranial infection or traumatic brain injury; patients with malignant tumors, severe neurological diseases, history of poisoning, reverse blood flow or other factors that cannot be evaluated for cognitive function or vascular disease; patients with hemorrhagic diseases such as cerebral hemorrhage, subarachnoid hemorrhage, or hemangioma rupture; patients with MRI contraindications or severe claustrophobia. This study was approved by the Medical Ethics Committee of Lianyungang Hospital of Traditional Chinese Medicine (2021-[KY]-09).

Methods

Cognitive function test: The Montreal Cognitive Assessment (MoCA) scale [7] was used for testing cognitive function. The scale included attention, language, delayed recall, visuospatial and executive function, naming, abstract thinking, and orientation, with a total score of 30 points.

After being assessed by the MoCA scale, patients were divided into a cognitive impairment group and a cognitive normal group. The cut-off value of the MoCA scale was 26 points. The higher the score, the better the cognitive status. Patients with a score of 26 points or lower were divided into a vascular cognitive impairment group (VCI group, n=54, 28 males and 26 females). Patients with a score over 26 were divided into a normal cognitive function group (NCF group, n=54, 30 males and 24 females). The NCF group had independent behavioral ability, no cognitive dysfunction and memory decline, and no obvious abnormal signs in neurological examination and head MRI.

MRI examination: All patients underwent 3D-ASL magnetic resonance imaging for cerebral blood perfusion using a GE Discovery 750 3.0T MRI scanner (32-channel head and neck phased coil). Scanning sequence: T1WI, T2WI, T2FLAIR, DWI, and 3D ASL. 3D ASL specific parameters: TR: 4632 ms (post label delay (PLD): 1525), TR: 5327 ms (PLD: 2525), TE: 10.5 ms, FOV: 24 cm × 24 cm, NEX: 3, acquisition times once. The scanning time was 3 min 3 s.

Image processing

The 3D ASL raw data were post-processed with Functool software. The cerebral blood flow (CBF) values of bilateral hippocampus, basal ganglia, thalamus, and frontoparietal lobe were measured in CBF pseudocolor map. We selected the same level for the measurement. The selection range of region of interest was 200 ± 20 mm². Each area was measured three times and an average value was taken. We avoided ventricles, sulci, and old infarct softening foci when outlining the range.

The CBF parameters of each brain region were recorded and analyzed in the two groups. The scores of the MoCA were evaluated and compared. The receiver operating characteristic (ROC) curve of CBF in VCI patients was drawn. The area under the curve (AUC), specificity and sensitivity were compared.

Statistical processing

SPSS 26.0 statistical software was used for statistical analysis. Count data were expressed as frequency and percentage (n%) and pro-

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Table 1. Comparison of clinical data between the two groups ($\bar{x}\pm s$)

Group	n	Sex (male/female)	Mean age (years)	Hypertension (%)	Diabetes (%)	Coronary heart disease (%)	History of smoking (%)	History of drinking (%)
VCI group	54	28/26	69.48±2.67	32 (59.26)	27 (50.00)	24 (44.44)	20 (37.04)	33 (61.11)
NCF group	54	30/24	68.93±2.72	31 (57.41)	30 (55.56)	25 (46.30)	22 (40.74)	30 (55.56)
χ^2/t		0.149	1.060	0.038	0.334	0.037	0.156	0.343
P		0.700	0.291	0.845	0.563	0.847	0.693	0.558

Note: vascular cognitive impairment (VCI), normal cognitive function (NCF).

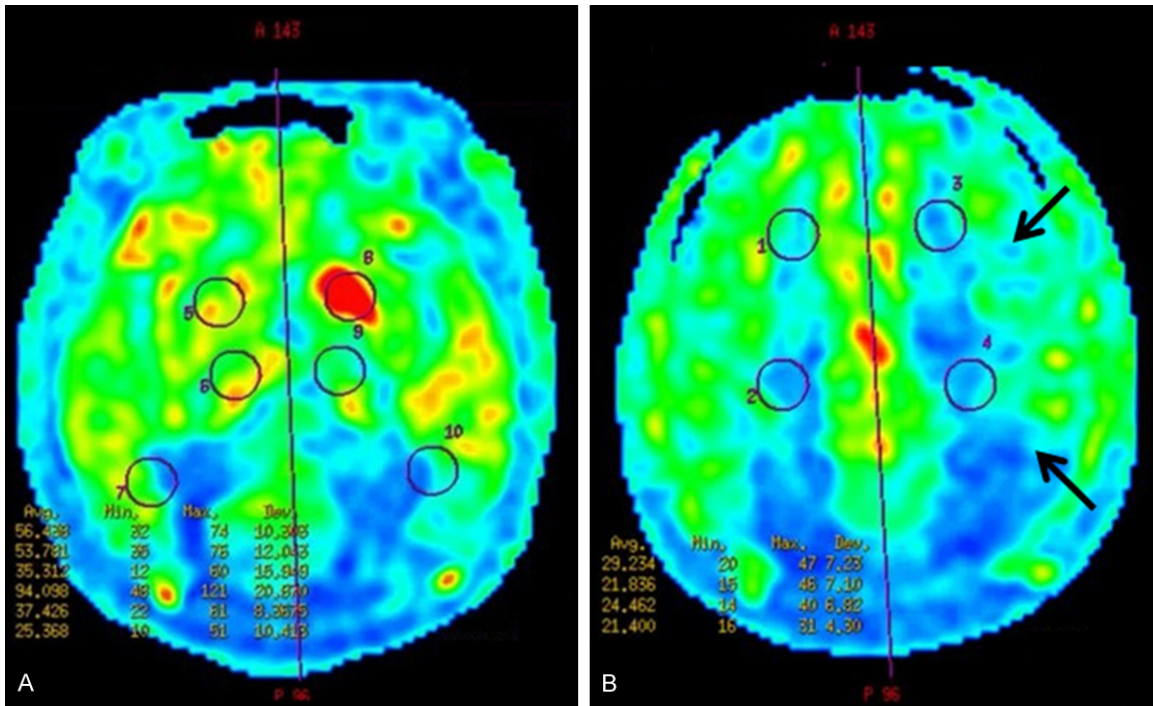


Figure 1. A, B. Shows brain perfusion at PLD=1525 ms. Note: post label delay (PLD).

cessed by χ^2 test. Measured data were expressed as mean \pm standard deviation ($\bar{x}\pm s$) and compared between the groups with the use of the student t test. The prognosis of 3D-ASL in VCI patients was evaluated by ROC curve analysis, with test level at $\alpha=0.05$.

Results

Clinical characteristics of the two groups

There was no statistical difference between the two groups in terms of sex, average age, hypertension, diabetes, coronary heart disease, smoking history, and drinking history ($P>0.05$), as shown in **Table 1**.

Analysis of 3D-ASL in CBF of VCI patients

Among the 54 VCI patients, the 3D-ASL sequences clearly showed the CBF perfusion under different PLDs. The typical imagines of

the cerebral perfusion when PLD=1525 ms and PLD=2525 ms are shown in **Figures 1** and **2**, respectively.

CBF values in different PLD brain regions of the two groups

The CBF parameters of different brain regions of the two groups were analyzed under different PLD conditions. It was found that the CBF 1525 and CBF 2525 of bilateral frontal lobes, temporal lobes, temporoparietal junctions, parietal lobes, and hippocampus in the VCI group were significantly decreased (both $P<0.05$), as shown in **Table 2**.

Comparison of brain regions under different PLD in VCI group

The CBF values of different brain regions of the two groups were analyzed under different PLDs.

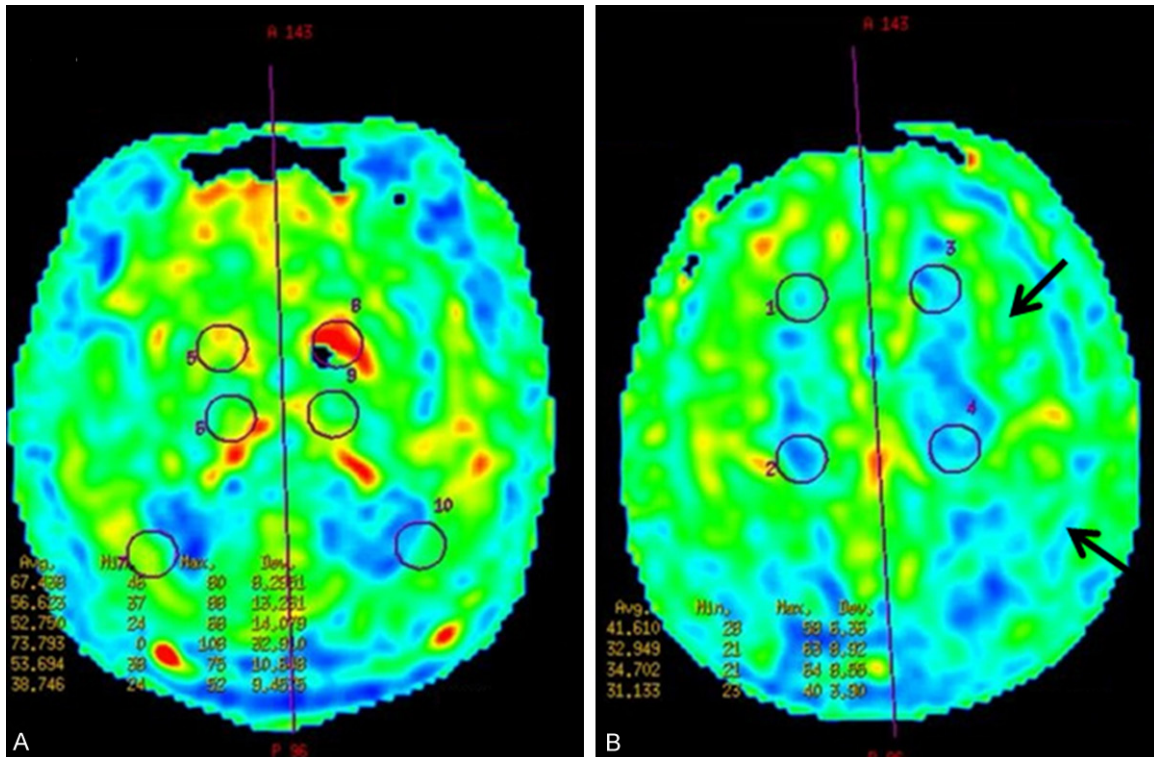


Figure 2. A, B. Shows brain perfusion at PLD=2525 ms. Note: post label delay (PLD).

Table 2. Comparison of different PLD brain regions of the two groups of subjects ($\bar{x} \pm s$)

Index (n=54)	PLD=1525 ms (mL/(min·100 g))		P	PLD=2525 ms (mL/(min·100 g))		P
	VCI group	NCF group		VCI group	NCF group	
Left frontal lobe	42.13±5.39	51.91±6.35	<0.001	44.80±5.78	54.66±6.54	<0.001
Right frontal lobe	43.28±5.37	57.69±8.54	<0.001	45.42±4.39	57.7±7.32	<0.001
Left temporal lobe	36.82±4.74	54.29±5.83	<0.001	39.24±4.45	55.02±6.43	<0.001
Right temporal lobe	39.45±5.13	47.59±7.98	<0.001	42.45±3.69	50.12±6.43	<0.001
Left temporoparietal junction	41.89±4.63	50.59±5.61	<0.001	43.16±5.91	54.45±5.35	<0.001
Right temporo-parietal junction	43.62±5.39	54.39±7.95	<0.001	44.85±5.74	54.55±6.06	<0.001
Left parietal lobe	45.97±7.13	54.02±9.14	<0.001	46.73±7.82	55.91±7.11	<0.001
Right parietal lobe	46.91±7.96	56.52±8.40	<0.001	47.59±8.56	56.67±7.37	<0.001
Left hippocampus	39.42±5.83	45.32±6.75	<0.001	38.61±5.97	47.56±6.02	<0.001
Right hippocampus	39.26±5.95	48.67±6.83	<0.001	40.24±6.11	49.28±5.03	<0.001

Note: post label delay (PLD), vascular cognitive impairment (VCI), normal cognitive function (NCF).

The CBF 1525 values and CBF 2525 values of bilateral frontal lobe and temporal lobe in the VCI group were compared. The differences were statistically significant between the two study groups (all $P < 0.05$), as shown in **Table 3**.

Comparison of MoCA scores between the two groups

The language, delayed memory, executive ability, attention and calculation ability, naming, 7963

abstract thinking, orientation, and total scores of the VCI group were significantly lower than those of the NCF group. The differences were statistically significant between the two groups (all $P < 0.05$), as shown in **Table 4**.

ROC analysis under different PLDs

The AUC, specificity and sensitivity (bilateral frontal lobe, temporal lobe, junction, parietal lobe, and hippocampus) of CBF at PLD 1525

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Table 3. Comparison of brain regions in VCI group under different PLD ($\bar{x} \pm s$)

Index	Left frontal lobe	Right frontal lobe	Left temporal lobe	Right temporal lobe	Left temporoparietal junction	Right temporo-parietal junction	Left parietal lobe	Right parietal lobe	Left hippocampus	Right hippocampus
PLD=1525 ms	42.13±5.38	43.28±5.37	36.82±4.74	39.45±5.13	41.89±4.63	43.62±5.39	45.97±7.13	46.91±7.96	39.42±5.83	39.26±5.95
PLD=2525 ms	44.80±5.78	45.42±4.39	39.24±4.45	42.45±3.69	43.16±5.91	44.85±5.74	46.73±7.82	47.59±8.56	38.61±5.97	40.24±6.11
t	2.485	2.267	2.735	3.489	1.243	1.148	0.528	0.428	0.713	0.805
P	0.014	0.025	0.007	<0.001	0.217	0.253	0.599	0.669	0.477	0.400

Note: post label delay (PLD), vascular cognitive impairment (VCI), normal cognitive function (NCF).

Table 4. Comparison of MOCA scores between two groups ($\bar{x} \pm s$)

Index	n	Language	Delayed memory	Executive ability	Attention and Computation	Name	Abstract thinking	Orientation force	Total score
VCI group	54	1.57±0.41	1.42±0.35	3.13±0.80	4.52±0.93	1.62±0.39	0.78±0.42	4.73±0.65	17.79±3.84
NCF group	54	2.14±0.59	2.62±0.68	3.98±0.36	5.85±0.56	2.45±0.60	1.49±0.31	5.59±0.76	24.35±3.97
t		5.830	11.530	7.120	9.003	8.523	9.995	6.319	8.994
P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Montreal Cognitive Assessment scale (MoCA), vascular cognitive impairment (VCI), normal cognitive function (NCF).

ms were lower than those of CBF at PLD 2525 ms ($P < 0.05$). See **Table 5** and **Figure 3**.

Discussion

In recent years, the prevalence of cerebrovascular disease and cognitive dysfunction has been increasing each year with the prolongation of life expectancy. VCI, as the most common type of cognitive impairment, brings a heavy burden to the patients and their families. According to the pathological characteristics, VCI can be divided into non-dementia VCI, cortical vascular dementia, hypoperfusion dementia, cerebral hemorrhagic dementia, and dementia due to specific arterial disease [8]. VCI diseases are clinically classified as non-vascular dementia and vascular dementia according to the progression trend. Non-vascular dementia is the early stage of VCI. In this stage, patients have mild clinical symptoms, but can develop vascular dementia and/or stroke, as the disease advances. Vascular dementia is a severe stage of VCI. The 5-year survival rate of the patients is 39.00% [9]. The pathogenesis of VCI is believed to be closely related to cerebrovascular disease, which leads to decreased cerebral perfusion, white matter injury, metabolic slowdown, inflammatory response, neurovascular damage, and cognitive dysfunction. The treatment effect is not good after VCI develops to dementia, early identification, and treatment. It is important to delay cognitive deterioration.

With the gradual development of imaging technology, the use of ASL techniques in clinical has increased. Compared with the traditional perfusion examination, ASL technology has the advantages of non-invasive, reproducible, non-radiation hazard, easy to operate, and short examination time [10]. The 3D-ASL adopts three-dimensional pseudo continuous arterial spin labeling. This can be used for large-scale whole brain volume perfusion imaging and can repeatedly measure the CBF value of brain regions of interest in a short time [11]. In the application of 3D-ASL technology, one of the parameters that determines the success is the PLD. The PLD in this study was scanned with 1525 ms and 2525 ms. In this study, the CBF of bilateral frontal lobes, temporal lobes, temporo-parietal junctions, parietal lobes, and hippocampus were significantly decreased in the VCI

group. It shows that in the early stage of cognitive impairment, the patient has hypoperfusion, or has focal hypoperfusion and hypometabolism before the co-invasion symptoms of dementia. The reason for this can be that damage to small arteries in VCI patients causes cerebral blood flow to slow down. This makes it difficult to reach the acquisition level in a short period of time, and reduces cerebral perfusion. This causes neuroglial and neuronal cell death, reduced brain volume, and impaired neurological function [12]. PLD is an important parameter that can be controlled in 3D-ASL cerebral blood perfusion imaging. When the PLD is less than or greater than the arterial arrival time, the CF value cannot express the real cerebral perfusion state of the brain region of interest and accurately assess cerebral blood perfusion [13]. Studies have shown that [14], PLD 1525 ms reflects the establishment of rapid blood flow and rapid collateral circulation. PLD 2525 ms reflects the establishment of secondary collateral circulation. In ischemic cerebrovascular disease, it is believed that the disease can prolong the arterial arrival time. It was found that the disease perfusion was more realistic at 2525 ms of PLD. When Suo et al. [15] studied Alzheimer's disease and early cognitive dysfunction, they found that arterial arrival times in the right parietal and right thalamus were significantly prolonged. This can be related to pathology such as small artery damage. In studies on non-Parkinsonian diseases, prolonged arterial arrival time can reflect age-related structural cerebrovascular changes, such as increased vascular sparsity, increased tortuosity, and damage to small arterial walls [16]. In the analysis of CBF 1525 and CBF 2525 values in the VCI group in this study, only the differences in the CBF values of bilateral frontal lobes and bilateral temporal lobes were statistically significant. A study [17] analyzed the changes of cerebral blood flow in VCI patients and found that frontal lobe, temporal lobe, and parietal lobe perfusion decreased in the non-dementia stage. This suggested that the frontal lobe and temporal lobe brain regions are important areas for cognitive function. Early monitoring of cerebral hemodynamics can help delay cognitive deterioration and prognosis.

In this study, analysis of the MoCA scale revealed that the VCI group had statistically significant lower scores in language, delayed

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Table 5. ROC characteristic analysis under different PLDs

Index	Left frontal lobe	Right frontal lobe	Left temporal lobe	Right temporal lobe	Left temporoparietal junction	Right temporoparietal junction	Left parietal lobe	Right parietal lobe	Left hippocampus	Right hippocampus
PLD=1525 ms										
AUC	0.895	0.888	0.881	0.880	0.898	0.864	0.720	0.778	0.824	0.858
Specificity	0.833	0.831	0.816	0.759	0.870	0.852	0.704	0.796	0.759	0.852
Sensitivity	0.889	0.870	0.759	0.836	0.833	0.741	0.788	0.722	0.778	0.741
PLD=2525 ms										
AUC	0.918	0.894	0.902	0.891	0.914	0.876	0.809	0.779	0.843	0.875
Specificity	0.815	0.870	0.819	0.762	0.878	0.852	0.815	0.848	0.796	0.889
Sensitivity	0.907	0.815	0.778	0.848	0.852	0.759	0.796	0.833	0.852	0.815

Note: Receiver operating characteristic curve (ROC), Area under curve (AUC), post label delay (PLD).

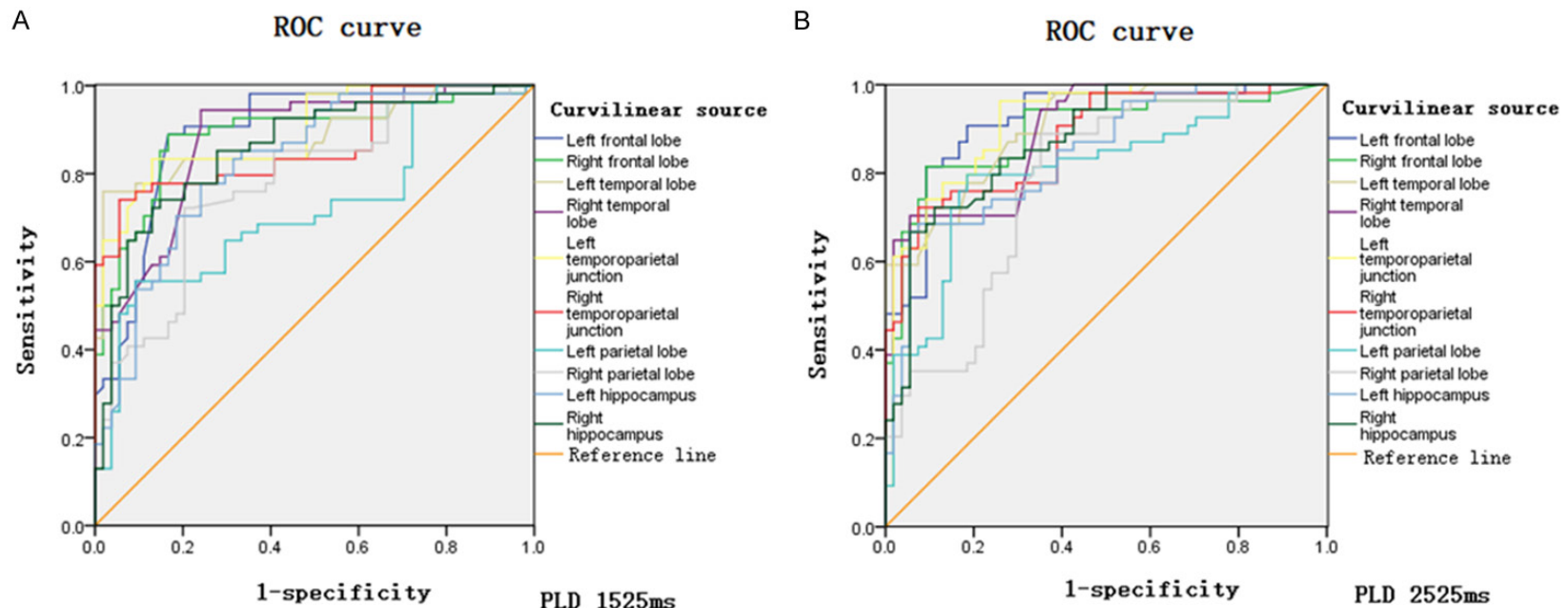


Figure 3. A, B. ROC curve under different PLDs (PLD=1525 ms, PLD=2525 ms). Note: Receiver operating characteristic curve (ROC), post label delay (PLD).

memory, executive ability, attention and computational ability, naming, abstract thinking, orientation, and total score than the NCF group. Early stage of VCI affects performance in language, memory, executive ability, attention, and computational ability and naming, with less damage to abstract thinking and orientation. This indicated that VCI involves a wide range of relevant cognitive domains. This result is in partial agreement with the meta-analysis of Vasquez et al. [18], suggesting the need for close perfusion of changes in these areas in people with high risk of cerebrovascular disease. It is clinically believed that the cognitive function of patients is significantly related to the blood supply level of the cerebral artery. The blood supply system of the cerebral artery includes the vertebrobasilar artery and the internal carotid artery blood supply system. The body's internal carotid artery blood supply system is directly connected to the temporal lobe region, frontal lobe region, and hippocampal region of the brain. The above regions are directly related to the body's intelligence, memory, and executive functions [19]. The vertebrobasilar artery blood supply system connects the occipital lobe, thalamus, cerebellum, and inner ear of the body and regulates respiration, balance, body muscle tone, coordination of information transmission in brain regions, language function, and orientation of the body. Abnormal changes in the blood supply system can directly affect the cognitive function of the body [20]. The middle cerebral artery is the main source of blood perfusion in the cerebral cortex. The increase in the vascular resistance of the middle cerebral artery will reduce the CBF. This reduces the blood supply to the temporal lobe, frontal lobe, parietal lobe, and other parts of the body, resulting in cognitive dysfunction.

The ROC area can be used to evaluate the effectiveness of diagnostic tests, with larger values indicating higher diagnostic value. Another analysis of this study found that, the AUC, specificity and sensitivity of CBF at PLD 1525 ms (bilateral frontal, temporal, temporo-parietal junction, parietal, and hippocampus) were lower than those of CBF at PLD 2525 ms. AUC in the range of 0.70~0.90 indicated that the prediction accuracy was medium, and above 0.90 indicated that the diagnostic value was high. It showed that the CBF value of VCI

patients was quite accurate in diagnosing the severity of cognitive impairment. The choice of PLD 1525 ms in the 3D-ASL technique improves the sensitivity to brain hypoperfusion in VCI patients and is suitable for screening. PLD 2525 ms improves the specificity of hypoperfusion in VCI patients and is more accurate in showing the extent of hypoperfusion. Using multiple PLDs can provide richer and more accurate cerebral blood flow information. The smaller the CBF value, the higher the prevalence of VCI and the degree of cognitive impairment. In the clinical prevention of VCI, 3D-ASL cerebral blood perfusion imaging technology can be used to closely monitor the hemodynamic level of the patient's cerebral arteries and make judgments and interventions.

There were some limitations in this study. The number of patients in this study was small. The patients with VCI were not subgrouped. Only the two most used PLDs values were chosen in this study. We did not use more PLDs for comparison. In the future, a large sample, multi-parameter, and prospective related study is expected.

In conclusion, the noninvasive 3D-ASL technique can be used to detect cerebral hemodynamics and predict prognosis in VCI patients. PLD 1525 ms is more sensitive to detect cerebral hypoperfusion in VCI. PLD 2525 ms shows a more accurate range of hypoperfusion, which can guide and adjust clinical treatments.

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Disclosure of conflict of interest

None.

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