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A comparative analysis of 375 patients with lateral and medial medullary infarction

Lin-Shuang Tao[1] | **Jing-Jing Lin**[1] | **Ming Zou**[1] | **Song-Fang Chen**[1] | **Yi-Yun Weng**[2] | **Ke-Yang Chen**[1] | **Bei-Lei Hu**[1]

[1] Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China

[2] Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Correspondence
Bei-lei Hu, Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Zhejiang Province, China.
Email:hubeilei902@126.com

Abstract

Background: Few studies have compared the etiology and clinical features between pure lateral medullary infarction (LMI) and pure medial medullary infarction (MMI).

Methods: All patients included were hospitalized at The First Affiliated Hospital and The Second Affiliated Hospital of Wenzhou Medical University from January 2015 to July 2020. Their risk factors, clinical manifestation, stroke mechanisms and short-term prognosis were analyzed retrospectively.

Results: Among the 387 patients enrolled, 266 (68.7%) had LMI, 109 (28.2%) had MMI, and 12 (3.1%) (nine men and three women) had LMI plus MMI. We analyzed the 375 patients of LMI and MMI. The average ages of LMI and MMI were 59.4 years and 62.69 years, respectively. Univariate analysis and multivariable logistic regression was used to investigate the existing risk factors of MMI relative to LMI. Prior infarction, poor glycemic control, and atherosclerosis were more frequently associated with MMI than with LMI. The clinical manifestation was significantly different between LMI and MMI. We used modified Rankin Scale (mRS) score as the short-term prognostic evaluation criteria, and MMI appeared worse than LMI.

Conclusions: This study reveals that: (1) patients with MMI are older than those with LMI; (2) prior infarction, poor glycemic control, and atherosclerosis are independent risk factors of MMI than that of LMI; (3) the clinical manifestations of LMI and MMI are heterogeneous; (4) short-term prognosis of MMI is worse than LMI.

KEYWORDS
manifestation, medullary infarction, prognosis, risk factors, stroke mechanism

1 | INTRODUCTION

The blood supply of medulla oblongata, located in the lower part of brainstem, comes from the vertebrobasilar system (posterior circulation) with abundant collateral circulation. Due to the great variability in the medullary blood supply and the sophistication of internal structure, different small parts lesion can cause completely different clinical manifestation. Based on the location of infarction, medullary infarction (MI) can be classified as lateral medulla infarction (LMI) and medial medulla infarction (MMI). Although previous studies have revealed the risk factors, clinical manifestation, and the pathogenesis of LMI and MMI (Aydogdu et al., 2001; Kameda et al., 2004; Kim, 2003; Kim & Han, 2009; Kim et al., 1994, 1998; Lee et al., 2012; Vuilleumier et al., 1995), some of the enrolled patients with concomitant cerebellar infarctions may not accurately reflect them. In our study, risk factors, clinical manifestation, and stroke mechanism of 375 MI patients were analyzed.
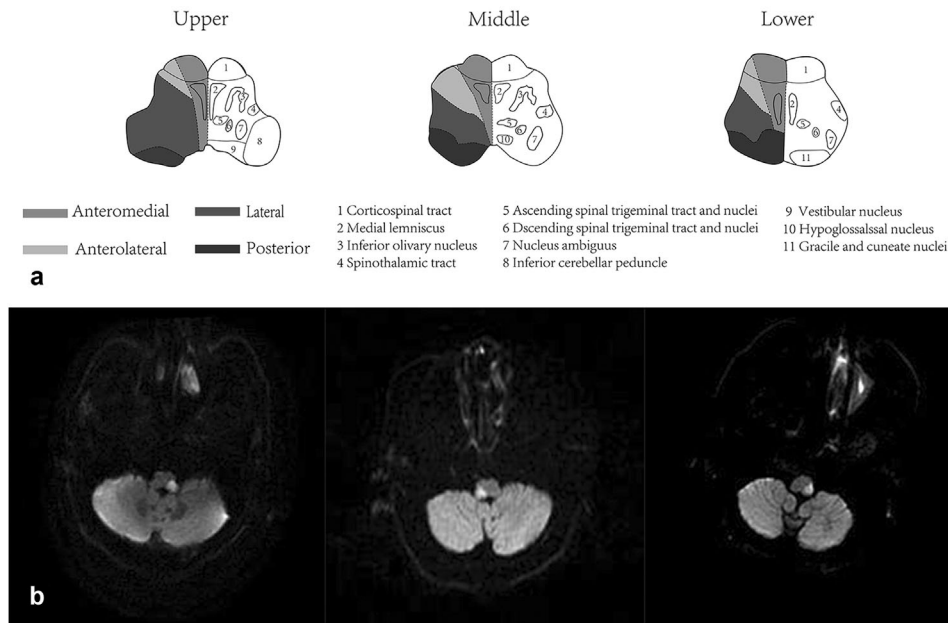
FIGURE 1 (a) The arterial territory of the medulla oblongata and important medullary structures. (b) The three levels of medulla oblongata in horizontal sections corresponding to Figure 1(a). DWI hyperintense tissues are fresh infarctions

2 | MATERIALS AND METHODS

2.1 | Subjects

Patients were included from the Department of Neurology in the First Affiliated Hospital and Second Affiliated Hospital of Wenzhou Medical University from January 2015 to July 2020. Inclusion criteria were that the symptoms of patients occurred within 14 days and lesions were confirmed by magnetic resonance imaging. Exclusion criteria were as follows: (1) concomitant cerebral hemorrhage; (2) concomitant extramedullary infarction; (3) age < 18 years; (4) neurological deficits from previous strokes or other diseases. Clinical manifestations, neurological signs and National Institute of Health Stroke Scale (NIHSS) score were recorded from the medical records of patients. The patients' demographic data (age and sex), medical history (hypertension, hyperlipidemia, diabetes mellitus, atherosclerosis, atrial fibrillation, coronary artery disease, history of smoking, and drinking), clinical features (neurological symptoms and signs, and NIHSS score in admission) were recorded. Hypertension was defined as when patients repeatedly suffered with high blood pressure (systolic ≥140 mmHg or diastolic ≥90 mmHg) or had a history of antihypertensive medication use. Hypercholesterolemia was defined as a high serum level of lipid profile (triglyceride ≥ 1.7 mmol/L, or total cholesterol ≥ 5.2 mmol/L or low-density lipoprotein cholesterol ≥3.1 mmol/L) or a history of antihypercholesterolemia medication. Diabetes mellitus was diagnosed with HbA1c% ≥6.5%, or fasting blood glucose ≥7.8 mmol/L, or nonfasting blood glucose ≥11.1 mmol/L or a history of use insulin or oral hypoglycemic drugs. Patients with diabetes mellitus were divided into two groups: (1) good glycemic control: fasting blood glucose < 7.0 mmol/L, or HbA1c% < 7.0%; (2) fasting blood glucose ≥7.0 mmol/L, or HbA1c% ≥7.0%. The NIHSS score of admission was recorded. The short-term prognosis was based on the modified Rankin Scale (mRS) score at discharge, divided into good outcome (mRS ≤ 2) and poor outcome (mRS ≥ 3).

2.2 | Topography of the lesions

Combined with the previous literature reports of arterial territories, the medullary infarctions were categorized into four groups (anteromedial, anterolateral, lateral, and posterior) in horizontal section in Figure 1(a) (Kim et al., 2012; Tatu et al., 1996). Based on the above groups, MMI included infarctions in the anteromedial and anterolateral groups, LMI included infarctions in the lateral and posterior groups (Bassetti et al., 1997). The lesions of medulla oblongata, including the area from the posterior pontine sulcus to foramen magnum, were further divided into upper, middle, and lower medulla by the level of the inferior cerebellar peduncle and the inferior olivary nucleus (Figure 1) (Kim, 2003).

2.3 | Classification of stroke mechanisms

Stroke mechanisms were modified according to the author's previous published criteria (Kim & Han, 2009; Lee et al., 2012), categorized as follows:

1. Large vessel disease (LAD): (i) when there was a significant stenosis or occlusion of the related vessel could explain the infarction; (ii) no evidence of dissection; (iii) no evidence of emboligenic heart disease.
2. Cardiogenic embolism (CE): (i) when there was emboligenic heart disease without significant atherosclerosis or stenosis of relevant vessel; (ii) no evidence of dissection.
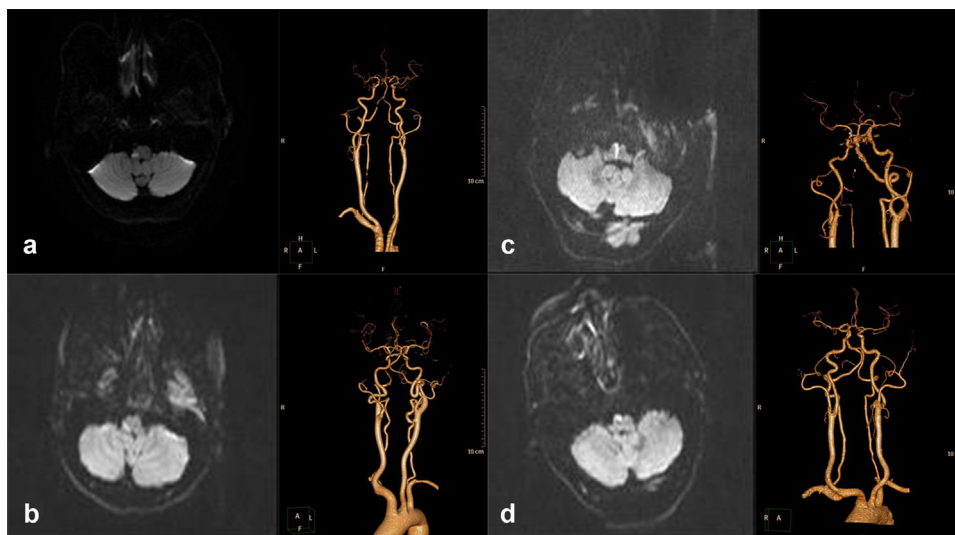
FIGURE 2 Diffusion-weighted images and conventional angiography (CTA) with different stroke mechanisms. (a) LMI infarction caused by LAD with right vertebral artery stenosis. (b) LMI infarction caused by SVD with normal vessel. (c) MMI infarction accompanied with right vertebral artery occlusion. (d) MMI infarction caused by SVD with normal vessel
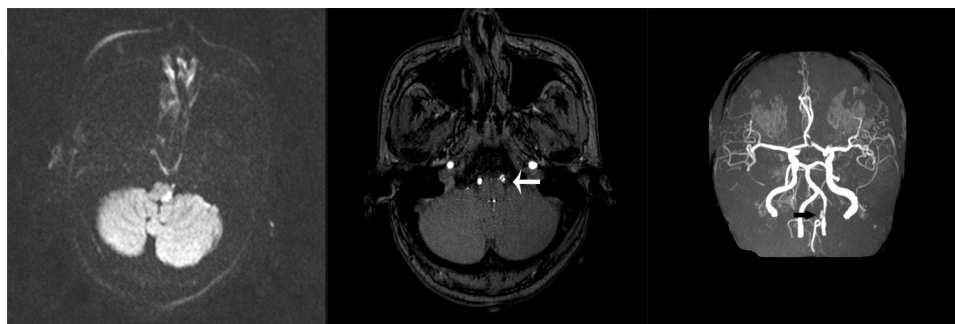
FIGURE 3 LMI infarction and double lumen (arrow) of left VA dissection on magnetic resonance angiography (MRA)

3. Small vessel disease (SVD): (i) hypertension or diabetes; (ii) no evidence of emboligenic heart disease; (iii) no evidence of stenosis or occlusion of the related vessel (Ay et al., 2007).

4. Vertebral artery (VA) dissection: (i) angiographic findings identical to dissection; (ii) concurrent neck or occipital pain.

5. Undetermined etiology was defined when: (i) two or more causes coexisted; (ii) after a thorough evaluation, it is not yet possible to determine a mechanism to meet these criteria; (iii) Some auxiliary examinations were not completed (Ay et al., 2007).

Typical examples of an abnormal diffusion-weighted MRI (DWI) finding are shown in Figures 2 and 3.

2.4 | Statistical analysis

All statistical analysis were performed using SPSS program (version 22.0). Univariate comparison of two groups was performed with student-t test, Mann–Whitney U test or Pearson's $\chi 2$ test. Kolgomorov–Smirnov test assessed continuous for distribution, with normally distributed data shown as mean $\pm$ standard deviation (SD) and skewed data shown as median with interquartile range (IQR). Normally distributed data was tested by student-t test and skewed data was compared by Mann–Whitney U test. Categorical variables were presented as numbers (%) and compared by Pearson's $\chi 2$ test. Factors which were significant in the univariate analysis ($p < 0.1$) were entered into multivariable logistic regression. p values < 0.05 were considered as significant difference.

3 | RESULTS

3.1 | Baseline clinical and laboratory features

In this study, a total of 387 patients were enrolled, where 266 (68.7%) of them (201 men and 65 women) had LMI, 109 (28.2%) (88 men and 21 women) had MMI, and 12 (3.1%) (nine men and three women) had LMI plus MMI. Baseline characteristics are shown in Table 1. Compared with patients in LMI, the patients in MMI were older ($p = .029$). The average ages of LMI and MMI were 59.40 (± 13.40) and 62.69

TABLE 1 Baseline characteristics of patients with meduallry infarction

	All patients (N = 375)	LMI (N = 266)	MMI (N = 109)	p value
Age (years)	60.35 ± 13.28	59.40 ± 13.40	62.69 ± 12.74	0.029
Sex (male) [n (%)]	289 (77.1)	201 (75.6)	88 (80.7)	0.280
The elderly (>60 years) [n%]	205 (54.7)	141 (53.0)	64 (58.7)	0.313
NIHSS in admission	3 (1–4)	2 (1–3)	4 (3–6)	<0.001
Outcome				<0.001
Good outcome	334 (89.1)	257 (96.6)	77 (70.6)	
Poor outcome	41 (10.9)	9 (3.4)	32 (29.4)	
Risk factors [n (%)]				
Hypertension	295 (78.7)	208 (78.2)	87 (79.8)	0.728
Hyperlipidemia	245 (66.4)	172 (65.9)	73 (67.6%)	0.754
Diabetes [n (%)]	369	261	108	0.026
No	218 (59.1)	162 (62.1)	56 (51.9)	
Good glycemic control	27 (7.3)	22 (8.4)	5 (4.6)	
Poor glycemic control	124 (33.6)	77 (29.5)	47 (43.5)	
Atherosclerosis	335 (90.3)	234 (88.6)	104 (97.2)	0.009
Atrial fibrillation	13 (3.5)	9 (3.4)	4 (3.7)	1.000
Prior infarction	32 (8.5)	15 (5.6)	17 (15.6)	0.002
Coronary artery disease	17 (4.5)	11 (4.1)	6 (5.5)	0.760
History of smoking	168 (44.8)	123 (46.2)	45 (41.3)	0.381
History of driking	116 (30.9)	88 (33.1)	28 (25.7)	0.160
Laboratory finding				
HBA1C%	6.1 (5.6–8.1)	6.0 (5.6–7.5)	6.6 (5.6–8.7)	0.126
D-dimer	0.40 (0.25–0.91)	0.37 (0.25–0.83)	0.48 (0.25–0.98)	0.265
Triglyceride	1.58 (1.18–2.26)	1.58 (1.14–2.28)	1.58 (1.24–2.18)	0.868
Total cholesterol	4.79 (4.02–5.65)	4.74 (4.04–5.70)	4.92 (3.95–5.47)	0.870
LDL	2.73 (2.23–3.49)	2.71 (2.18–3.50)	2.81 (2.26–3.49)	0.477

Abbreviations: LDL, low-density lipoprotein; LMI, lateral medullary infarction; MMI, media medullary infarction; NIHSS, National Institute of Health Stroke Scale.

TABLE 2 Multivariate logistic regression

	OR	95%CI	p value
Prior stroke	3.674	1.678–8.040	0.001
Atherosclerosis	4.173	1.212–14.365	0.024
Diabetes			
No	1 (reference)		
Good glycemic control	0.565	0.198–1.612	0.286
Poor glycemic control	1.653	1.013–2.698	0.044

Abbreviations: CI, confidence interval; OR, odds ratio.

(±12.74), respectively. The sex ratios for LMI and MMI group, 3.1:1 and 4.2:1 respectively, had no significant difference between males and females. In the risk factors and laboratory tests, patients with diabetes, atherosclerosis, and prior infarction were prone to have lesions in MMI. The multivariable logistic regression analysis (Table 2) shows that the medical conditions of MMI were relative to LMI. Prior stroke (odds ratio [OR]:3.674, 95% confidence interval [CI]:1.678–8.040, p = 0.001), atherosclerosis (OR:4.173, 95% CI: 1.212–14.365, p = 0.024) and diabetes with poor glycemic control (OR:1.653, 95% CI: 1.013–2.698, p = 0.044) were independent risk factors.

Symptoms and neurological signs are presented in Table 3. Among them, vertigo/dizziness was the major symptom for both of LMI and MMI groups. Besides, sensory abnormity (72.1%), ataxia (56.1%), dysphagia (44.0%), Horner's syndrome (42.9%), dysarthria/hoarseness (41.4%), nausea or vomiting (40.6%), and facial palsy (40.2%) were the major symptoms of LMI. On the other hand, limb weakness/fatigue (88.9%), facial palsy (50.5%), sensory abnormity (48.1%), and lingual palsy (43.5%) were the major symptoms of MMI. Headache/neck pain, limitation of ocular movement and blurred vision/diplopia were both uncommon symptoms for LMI and MMI. Horner's syndrome also accounted for a small proportion of MMI. The clinical manifestations between LMI and MMI were heterogeneous (Table 3), with most p values < .05. The median NIHSS scores of LMI and MMI were 2 (1–3) and 4 (3–6), which is significantly

TABLE 3 Symptoms and neurological signs, topography, presumed stroke etiology

Symptoms and signs [n (%)]	LMI (N = 266)	MMI (N = 109)	p value
Dizziness/vertigo	203 (76.3)	63 (57.8)	<0.001
Headache/neck pain	57 (21.4)	10 (9.2)	0.005
Dysarthria/hoarseness	110 (41.4)	34 (31.2)	0.066
Nausea or vomiting	108 (40.6)	26 (23.9)	0.002
Dysphagia	117 (44.0)	15 (13.8)	<0.001
Horner's syndrome	114 (42.9)	6 (5.5)	<0.001
Facial palsy	107 (40.2)	54 (50.0)	0.084
Lingual palsy	61 (23.1)	47 (43.5)	<0.001
Limb weakness/fatigue	90 (34.0)	96 (88.9)	<0.001
Sensory abnormity	191 (72.1)	52 (48.1)	<0.001
Limitation of ocular movement	9 (3.4)	11 (10.3)	0.008
Nystagmus	56 (21.1)	14 (13.1)	0.072
Blurred vision/diplopia	34 (12.8)	11 (10.2)	0.477
Ataxia	134 (56.1)	18 (34.0)	0.004
Topography			
Upper medulla	53 (19.9)	79 (72.5)	
Millde medulla	117 (44.0)	15 (13.8)	
Lower medulla	23 (8.6)		
Upper and middle	25 (9.4)	15 (13.8)	
Middle and lower	45 (16.9)		
Upper, middle and lower	3 (1.1)		
Stroke etiology			
LAD	121 (45.5)	54 (49.5)	
SVD	85 (32.0)	38 (34.9)	
CE	8 (3.0)	2 (1.8)	
VA dissection	7 (2.6)		
Undertermined	45 (16.9)	15 (13.8)	
Atherosclerosis			
Related vessel	123 (46.6)	57 (53.8)	
Other intracranial and extracranial artery	215 (81.4)	96 (90.6)	

Abbreviations: CE, cardiogenic embolism; LAD, large vessel disease; LMI, lateral medullary infarction; MMI, media medullary infarction; SVD, small vessel disease; VA, vertebral artery.

different (p <0.001). Poor outcome occurred more frequently in MMI (p <0.001).

## 3.2 | Angiographic findings and presumed mechanisms

On the brain MR images, LMI lesions were mostly located in the middle medulla (44.0%). The upper medulla, middle and lower medulla also accounted for a large part (19.9% and 16.9%, respectively). The lesions of MMI were most commonly located in the upper medulla (72.5%) (Table 3). The difference in distribution (upper, middle, and lower) of infarction was statistically significant (p <0.001). A total of 337 patients underwent vascular examination, including one or more conventional angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). The etiology attribution is shown in Table 3. LAD was the major etiology in LMI and MMI. Seven patients were diagnosed as VA dissection and ten patients were considered as CE. Among patients with undetermined etiology, three patients were suspected to have VA dissection (DSA was performed in them), three patients had atrial fibrillation, and three patients had a patent foramen ovale. The presence of intracranial and extracranial artery atherosclerosis is described in Table 3. It is in higher incidence of atherosclerosis of related vessel and other intracranial and extracranial artery in MMI patients.

4 | DISCUSSION

Due to the abundant collateral circulation, medullary infarction accounts for a small proportion of all cerebral infarction. The articles about analysis of lateral and medial medullary infarction are rare. In previous studies, there was a report about 214 patients of MI with concomitant infarction (Kameda et al., 2004), 130 patients of pure LMI (Kim, 2003), 86 patients of pure MMI (Kim & Han, 2009) and so on. Topographic evaluation (Dogan et al., 2020) and mechanism (Kim et al., 2012; Lee et al., 2012) has been described early. However, our retrospective study of the 387 cases of MI without concomitant infarction, 266 cases of LMI and 109 cases of MMI, respectively, has the largest population among the articles comparing the lateral and medial groups of pure medullary infarction so far. In our study, we found the mean age of MMI (62.69 years) was two years older than that of LMI (59.40 years), which was significantly different between two groups, and the LMI to MMI ratio was 2.4:1, which was consistent with previous reports (Kim et al., 2012; Lee et al., 2012). In terms of risk factor analysis, we found that prior stroke, poor glycemic control, and atherosclerosis are the independent risk factors for MMI relative to LMI. It was reported that patients with previous symptomatic atherothrombosis (including ischemic stroke) were at higher risk of recurrent ischemic events (Song & Ovbiagele, 2009) and patients who have had a first stroke would have another stroke six times more likely than the first time (Hardie et al., 2004). It was reported in a prior study (Kameda et al., 2004) that age and diabetes mellitus are independent risk factors of MMI relative to LMI. In our study, we further confirm that diabetes with poor glycemic control is an independent risk factor. The reason why poor glycemic control is more frequent in MMI than LMI remains unknown. We all know that diabetics have microvascular and macrovascular complications. Kosiborod et al. (2018) reported that the level of glycated hemoglobin is associated with microvascular complications, which is not an independent risk factor of macrovascular complications. The MMI lesions are mainly supplied by anterior spinal artery and the inferior cerebellar artery, and LMI lesions are mainly
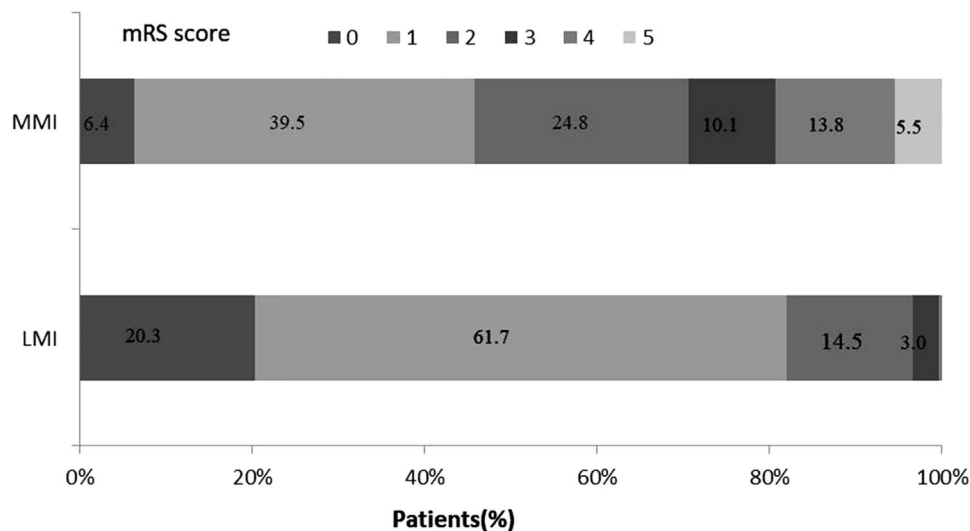
FIGURE 4 The distribution of mRS score between LMI and MMI. There is only one patient with a mRS score of 4 in LMI, which is too small to be seen in the picture

supplied by posterior spinal artery and the inferior cerebellar artery. Diabetes being more common in MMI patients may be associated with its smaller supply artery. Atherosclerosis being more common in MMI remains unclear. Hypertension, hyperlipidemia, and diabetes are major atherosclerotic risk factors, requiring strict management goals (Song & Ovbiagele, 2009). We assume that it may be associated with their higher prevalence in MMI patients. In summary, we can find that MMI patients have worse vascular conditions. Moreover, quick implementation of vascular risk reduction treatment after ischemic events can greatly reduce the risk of a secondary stroke compared to conventionally delayed follow-up treatment (Rothwell et al., 2007).

Vertigo/dizziness was a common symptom both in LMI and MMI patients, suggesting that the MI lesions often involve the vestibular nucleus or its contacted fibers. A posterior circulation infarction may cause rapid deterioration of neurological deficits, even death, so the early recognition is very important. However, dizziness, vertigo, and imbalance, quite common symptoms in posterior circulation infarction, could also be caused by other common and benign diseases. Therefore, detailed neurological examination is very important to patients with dizziness. A scale named as DEFENSIVE stroke scale with an accurate diagnosis for posterior circulation (Yamada et al., 2019) has been proposed in clinical practice. There were many patterns of sensory disturbances, including ipsilateral face, ipsilateral limb, contralateral face, contralateral limb, and cross type (ipsilateral face and contralateral limb). Among the above classifications, the contralateral limb sensory disturbance and cross type were the major forms of LMI in our study. The spinothalamic tract in the lateral area of the medulla and the dorsolateral area of the inferior olive nucleus can explain this phenomenon. The pathogenesis of ipsilateral limb paresthesia is still unknown and may be due to the involvement of the ascending medial lemniscus fibers (the posterior funiculus or secondary crossing fibers) (Kim et al., 1997). Moreover, gracile and cuneate nucleus, and the medial lemniscus composed of its crossed fibers are located near the medulla midline (Angeles Fernández-Gil et al., 2010), which can cause ipsilateral

or/and contralateral paresthesia. Dysphagia was significantly different between LMI and MMI while dysarthria was not, which is probably due to nucleus ambiguously located in the lateral medulla. Patients can present ipsilateral /contralateral facial palsy. A part of corticofacial fibers controlling the contralateral inferior facial muscles descend into the ventral part of the upper medulla, cross the midline of medulla and ascend to the facial nucleus in the dorsolateral medullary region ipsilaterally. The above pathway damage can cause ipsilateral /contralateral facial palsy (Urban et al., 2001). Lingual paralysis is more common in MMI, because of involving the corticobulbar tract more frequent than the hypoglossal nerve nucleus or its infranuclear fibers (Akimoto et al., 2017). Vertigo/dizziness, nausea/vomiting, and ataxia were prone to occur in LMI ($p = <0.001$, $p = 0.002$, and $p = 0.004$, respectively), related to the location of vestibular nucleus (Figure 1(a)). Compared to the LMI group, the MMI group had significantly higher NIHSS scores, which could be explained by the following aspects. Based on the different anatomical structure, the MMI mainly leads to weakness of limbs and deep sensory disturbance while the LMI mainly causes superficial sensory disturbance. Furthermore, in the content of NIHSS, muscle strength testing focuses on the affected body parts and severity of weakness of limbs while sensory disturbance testing only focuses on the severity, irrespective of arms or legs involved (Goldstein et al., 1989). The short-term prognosis of MMI is worse than that of LMI, because the function of exercise has a great impact on the patient's quality of life. Figure 4 shows the distribution of mRS score between LMI and MMI.

There is a predisposition that LMI was more frequently located in the middle medulla and MMI was located more in the upper medulla in our study, which was consistent with previous results (Hong et al., 2018; Kameda et al., 2004). The different infarction subtype of LMI could be explained by the anatomical course of the VA: a pair of VAs locates adjacent to the lateral surface of the lower medulla and ascends anteroinferiorly to fuse to the basilar artery (Kim, 2003). In the medial medulla, the blood supply mainly comes from VA and anterior spinal

artery (ASA). In the upper medulla, the dominant blood supply usually comes from VA and ASA, while the ASA supplies the middle and lower medulla blood supply after the coupled ASA merges into a single artery. Before the union it supplies blood to a part of the upper medulla. Therefore, the occlusion of ASA before the mergence may not cause infarction in the middle and lower medulla. This could explain why MMI is more commonly located in the upper medulla (Dogan et al., 2020; Kim et al., 2012). Previous articles reported that LAD was the major etiology both in LMI and MMI (Dogan et al., 2020; Kim, 2003; Kim & Han, 2009; Lee et al., 2012). However, several researches revealed different results on the etiology in MMI. Hong et al. (2018), Kim et al. (2012), and Shono et al. (2010) reported that SVD was the most common mechanism in MMI. Moreover, VA dissection played an equally important role in LMI and MMI in a recent study (Kameda et al., 2004). It has been reported earlier that VA dissection was more frequent in LMI compared to MMI (Kumral et al., 2002; Lee et al., 2012) and VA dissection is unusual in MMI (Kim & Han, 2009). In our study, LAD was the primary cause of LMI and MMI, while SVD also accounted for an important role. CE occurs in a small percent of patients. On the one hand, it is because that the atrial fibrillation accounts for a smaller proportion of ischemic stroke patients in China (Tsai et al., 2015), and on the other hand, most patients only do routine electrocardiograms without Holter monitoring so that some patients with arrhythmias may be diagnosed as normal. VA dissection is not an important cause of MI in our study, which might be explained by the strict criteria defining VA dissection. As a result, some patients with VA dissection may be regarded as having no dissection. Intracranial and extracranial artery atherosclerosis are more common in MMI patients, indicating that MMI patients have poor vascular conditions, consistent with stroke etiology and risk factors of two groups of patients. In addition, stroke etiology is associated with the topography of MI. It is a defect that our study did not analyze more detailed topography map of horizontal section which may explain the different etiology classification distribution compared to previous studies.

Our study has some limitations. First of all, our research is a retrospective study, which may weaken the reliability of conclusions. Second, MRA has some limitations in detecting small vessels (like posterior inferior cerebellar artery and anterior spinal artery), which may have an impact on etiology distribution. Third, the prognosis varies greatly for patients with medullary infarction, and it is our defect that we did not do further prognostic analysis. Finally, since this model is based on Asian population, the results cannot be extended to other ethnic groups directly.

In conclusion, this study reveals that: (1) patients with MMI are older than those with LMI, (2) prior infarction, poor glycemic control, and atherosclerosis are dependent risk factors of MMI than that of LMI, (3) the clinical manifestations of LM and MMI are heterogeneous, (4) short-term prognosis of MMI is worse than LMI.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Lin-Shuang Tao and Bei-Lei Hu designed the paper. Lin-Shuang Tao wrote the manuscript draft. Jing-Jing Lin, Ming Zou, Song-Fang Chen and Ke-Yang Chen screened and extracted data. Ming Zou, Song-Fang Chen, Yi-Yun Weng, Ke-Yang Chen revised the manuscript. Beilei Hu supervised study. All authors have made intellectual contributions to the manuscript and approved the submission.

ORCID

Ke-Yang Chen https://orcid.org/0000-0002-9557-0481
Bei-Lei Hu https://orcid.org/0000-0001-5429-3337

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