

# Color-coded duplex sonography vs. 3.0 Tesla magnetic resonance angiography for detection of intracranial stenosis of the internal carotid artery: A prospective cohort study

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**Abstract.** Hemodynamic changes may provide important information for clinical decision-making in internal carotid artery (ICA) stenosis. The degree of stenosis is responsible for the hemodynamic changes. For detection of intracranial stenosis, each diagnostic method has its own advantages and disadvantages. The goal of the present study was to compare the sensitivity and accuracy of color-coded duplex sonography with that of magnetic resonance angiography (MRA) for the detection of intracranial stenosis. Patients with 3 vessels and/or left stem coronary artery disease were subjected to transcranial and extracranial color-coded duplex sonography (n=998), MRA (n=998) and invasive catheter angiography (n=939). The degree of stenosis was defined according to the Warfarin-Aspirin Symptomatic Intracranial Disease methodology. A  $\geq 50\%$  reduction in artery diameter was considered as a positive obstructive lesion. The benefits of each imaging method were assessed by clinical decision-making analysis. Color-coded duplex sonography and MRA, had sensitivities of 0.935 and 0.957 and accuracies of 0.92 and 0.974, respectively, when using invasive catheter angiography as a gold standard. The number of false-positive obstructive lesions detected by MRA was significantly higher than that for color-coded duplex sonography (53 vs. 13,  $P < 0.0001$ ). Color-coded duplex sonography was able to detect an obstructive lesion in one single image for ICAs with  $\geq 57\%$  stenosis, while MRA was only capable of detecting an obstructive lesion in one single image for ICAs with  $\geq 80\%$  stenosis. In conclusion, color-coded duplex sonography is a reliable method for the detection of intracranial stenosis in patients with coronary artery disease.

## Introduction

Intracranial stenosis may result in ischemic infarction (1) and is associated with a risk of ischemic stroke (2). Extracranial and intracranial carotid artery stenosis is common among symptomatic patients in China (3). Autopsy studies have proved that cerebral vascular occlusion is the major cause of stroke (4). The most common location for intracranial stenosis is the internal carotid artery (ICA) (5) and it is accessed by evaluation of the degree of luminal stenosis on angiography (6). Hemodynamic changes may provide important information for clinical decision-making, but the degree of ICA stenosis, which is responsible for hemodynamic changes, may not be properly determined by using imaging modalities (7).

Application of suitable diagnostic methods for intracranial stenosis remains challenging (8). The diagnostic methods currently used for detection of intracranial stenosis are transcranial Doppler ultrasound (9), digital subtraction angiography, high-resolution magnetic resonance imaging (MRI) (10), conventional catheter angiography (9), CT angiography (10) and magnetic resonance angiography (MRA) (5). CT angiography is less prone to movement artifacts within the blood vessels and has a shorter signal-to-noise ratio than MRA, but has the risk of degradation of image quality and limitations of post-processing artifact interpretations (9). High-resolution MRI is suitable for diagnosis of the C1, C3 and C5 segments only due to the inherent signal-intensity loss of parallel imaging in the other segments (5) but it cannot be applied for patients with pacemakers (9). MRA facilitates the determination of stenosis grade (5). Digital subtraction angiography is usually performed after MRA (5). Transcranial Doppler ultrasound is only effective when the blood flow pattern is abnormal (5). Overall, each diagnostic method has its own advantages and disadvantages.

The purpose of the present prospective study was to compare the sensitivities and accuracies of color-coded duplex sonography with those of MRA for the detection of intracranial stenosis while using conventional catheter angiography as a reference standard in Chinese patients with coronary artery disease.

## Materials and methods

**Inclusion/exclusion criteria.** Patients aged  $\geq 18$  years with angiographic confirmation of 3 vessels and/or left stem coronary artery disease, as well as symptoms of a transient

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ischemic attack and cerebral ischemia with/without neurologic deficits were included in the study. Only patients with isolated intracranial stenosis were included. Patients who had impairments of the brain, spinal cord or nerve function, or diseases associated with functional deterioration of organs (according to clinical diagnostic parameters and MRI) were excluded from the study. Patients with inadequate image quality for interpretation were also excluded from the analysis. Prior to transcranial diagnosis, plaques (atherosclerotic lesions) present in the extracranial vessels were excluded by standard extracranial color-coded duplex sonography.

**Color-coded duplex sonography.** All color-coded duplex sonographies were performed using 19" LED up and down 90° foldable color-duplex ultrasound systems equipment (LOGIQ e; GE Healthcare) with a 2.4-10.0 MHz linear array transducer (9L-D; GE Healthcare) for the extracranial examination and a 4-10 MHz phased array (PA6-8 H46701J; GE Healthcare) for the transtemporal examination.

Transcranial color-coded duplex sonographies were performed with a 4 MHz center transmit frequency in color mode, linear post-processing, highest transmit power, at intermediate resolution and the pulse repetition frequency for the central focal zone. The gain of color was maintained as per the acoustic bone window of the proband to avoid colored speckles outside the borders of vessels. The gate of Doppler was set at 5 mm and 0° angles in all the measurements of blood flow. If the angle was <60°, it was corrected in the segment of the arteries with a minimum of 20 mm. Transcranial color-coded duplex sonographies were started from the axially-oriented transtemporal approach. The butterfly-shaped hypoechogenic mesencephalic brainstem was located. As illustrated in Fig. 1, a P1 segment (indicated in red) and P2 segment (red and blue) were identified for the assessment of the posterior cerebral artery. The transducer was moved slightly upwards, and the M1 segment (indicated in red) of the middle cerebral artery and anterior cerebral artery (indicated in blue) was visualized. Finally, the transducer was moved slightly toward the posterior part of the brain and a cross-sectional view of the terminal ICA (the C1 segment) was visualized. The transducer was made perpendicular in an anti-clockwise direction towards the frontal planes. During the anterior scanning, the C1 segment (indicated in red) of the ICA, the A1 segment of the anterior cerebral artery and the M1 segment of the middle cerebral artery were visualized. Slightly frontal towards the posterior frontal plane, the basilar artery was visualized at the top, and the posterior cerebral arteries and C5 segment (blue color) near the carotid canal were also visualized. Subsequently, in a slightly lateral view, the C4 segment was identified (blue color; Fig. 1) (1).

For the siphon segments, the axial mesencephalic image plane was preferred. For the diagnosis, the coronal planes were used for the middle cerebral artery. The M1 segment in the middle cerebral artery and the carotid siphon C1 and C5 segments were diagnosed on the bilateral sides (1).

The end-diastolic blood flow velocities, peak systolic blood flow velocities and mean blood flow velocities were recorded. The pulsatility index, resistance index and C1/ICA index were calculated for each vessel segment as per Equations i, ii and iii (1).

$$\text{Pulsatility index} = \frac{\text{Peak systolic blood flow velocity} - \text{End diastolic blood flow velocity}}{\text{Mean blood flow velocity}} \quad (\text{i})$$

$$\text{Resistance index} = \frac{\text{Peak systolic blood flow velocity} - \text{End diastolic blood flow velocity}}{\text{Peak systolic blood flow velocity}} \quad (\text{ii})$$

$$\frac{C1}{ICA} \text{ index} = \frac{\text{Mean blood flow velocity of C1}}{\text{Mean blood flow velocity of the ICA}} \quad (\text{iii})$$

**MRA.** 3.0 Tesla MRI equipment (GE Healthcare) was used to visualize the cervical intracranial artery, petrous intracranial artery, cavernous intracranial artery, supraclinoid portions, anterior cerebral artery, segment A1, segment A2, middle cerebral artery, segment M1, segment M2, posterior cerebral artery, segment P1, segment P2, intracranial vertebral artery, the proximal basilar artery and distal basilar artery. The field of view was as small as possible over the middle cerebral artery and 512x512 mm<sup>2</sup> matrices. T1-weighted imaging (T1WI) was performed with a repetition time/echo time (RT/ET) of 565/15.79 msec, T2WI with fast-spin-echo array coil spatial sensitivity encoding and a RT/ET of 2,884/50 msec, proton density-weighted imaging with a RT/ET of 6,241/32.6 msec and short T1 inversion recovery imaging with a RT/ET of 3,701/56.3 msec were acquired for determination of the middle cerebral artery lumen diameter. A total of 16 MR slices (2 mm slice thickness x 0.5 mm slice interval) with 6-fold signal averaging including stenosis were acquired (11).

**Invasive catheter angiography.** The patients who exhibited stenosis on color-coded duplex sonography and/or MRA were subjected to invasive catheter angiography. Femoral punctures were given to patients by injection of vehicles using Ultravist (Bayer Healthcare AG). In late venous phase with standard anteroposterior, lateral and oblique images were acquired with 1,024x1,024 matrix, pixel size of 0.21x0.21 and a field of view of 22 cm with 5 ml/sec of the contrast agent inflow rate (12).

**Image analysis.** All Digital Imaging and Communications in Medicine files were uploaded onto a workstation (version 4.0; GE Healthcare). The artery diameter of the maximal stenosis side and non-stenosis region were measured. The proximal and distal views were examined. The analysis was performed orthogonal to the long axis of the artery and the stenosis was evaluated in segment M1 for comparison (12). The degree of stenosis was considered as per Equation iv, in accordance with the Warfarin-Aspirin Symptomatic Intracranial Disease methodology (9) under consultation of a neuroradiologist (25 years of experience).

$$\% \text{ Stenosis} = \left[ 1 - \frac{\text{Artery diameter of the maximal stenosis side}}{\text{Artery diameter of the non-stenosis region}} \right] \times 100 \quad (\text{iv})$$

A reduction in diameter of ≥50% of the artery was considered as a positive obstructive lesion; otherwise, the diagnosis of obstructive lesion was negative (13).

**Advantage score analysis.** The advantages of each of the modalities adopted were evaluated by clinical decision-making analysis. The advantage score of each diagnostic method adopted was evaluated as per Equations v and vi (14):

$$\text{Advantage score} = \frac{\text{Number of patients with a true positive obstructive lesion}}{\text{Number of patients subjected to diagnosis}} - \left( \frac{\text{Number of patients with false positive stenosis}}{\text{Number of patients were subjected to diagnosis}} \times \text{Risk of overdiagnosis} \right) \quad (\text{v})$$

$$\text{Risk of overdiagnosis} = \frac{\text{Threshold probability}}{1 - \text{Threshold probability}} \quad (\text{vi})$$

The invasive catheter angiography was used as the gold standard to determine the true- and false-positive rates of the other methods.

**Cost.** The cost of each diagnostic modality was calculated.

**Statistical analysis.** InStat, version 3.0 for Windows (GraphPad Inc.) was used for statistical analysis. Categorical data were compared using the Wilcoxon matched-pairs test (12). All variables were considered significant at a 99% confidence level. The mean reader difference values were calculated for each diagnostic method adopted to assess interobserver reliability (15). Continuous data were compared using the Friedman test followed by the Nemenyi test (considering a critical value  $q$  of  $>3.314$  as indicative of significance). The cost was analyzed by one-way analysis of variance (16) followed by the Tukey-Kramer multiple-comparisons test.

## Results

**Patient characteristics.** Between January 2015 and December 2017, a total of 1,005 patients with 3 vessels and/or left stem coronary artery disease were available at Luoyang Central Hospital Affiliated to Zhengzhou University (Luoyang, China) and the referring hospitals. All patients were subjected to interview (panel of a cardiologist, a neurologist and a physician of the institute, all with a minimum of 3 years of experience) and the cardiovascular risk of each patient was estimated based on demographic, clinicopathological and laboratory data (Table I). Among those patients, three had impairments of the brain, one had impairments of the spinal cord, one had impairments of nerve function, one had diseases associated with functional deterioration of organs and for one patient, the image quality of color-coded duplex sonography was inadequate for interpretation. Therefore, these patients were excluded from the analysis. A total of 998 neurologically asymptomatic patients were subjected to color-coded duplex sonography and MRA. The flow diagram for inclusion of patients in the present study is provided in Fig. 2.

**Obstructive lesions of the ICA.** In the transcranial and extracranial portions, stenosis was detected in 909 patients by color-coded duplex sonography and in 939 patients by MRA. Therefore, a total of 939 patients were subjected to invasive catheter angiography. Invasive catheter angiography was superior in the detection of stenosis compared with color-coded duplex sonography ( $P<0.0001$ ;  $q=4.144$ ) and MRA ( $P<0.0001$ ;  $q=7.301$ ). The results of the different diagnostic modalities regarding evaluation of obstructive lesions are provided in Table II. The pulsatility index, resistance index and C1/ICA index were higher for obstructive lesions than for normal lesions ( $P<0.0001$  for all; data not shown). The intracranial stenosis in the other intracerebral arteries were mostly found in M1 and M2 segments of middle cerebral arteries, the vertebral artery and the anterior cerebral artery. The distribution of intracranial stenosis in the other intracerebral arteries assessed is presented in Table III.

Table I. Demographic and clinicopathological characteristics and laboratory parameters of the patients enrolled ( $n=998$ ).

Item	Value
Ethnicity	
Han Chinese	912 (92)
Mongolian	73 (7)
Tibetan	13 (1)
Age (years)	
Range	19-85
Mean $\pm$ SD	59.85 $\pm$ 8.89
Sex	
Male	633 (63)
Female	365 (37)
Blood pressure (mmHg)	
Diastolic	86.52 $\pm$ 5.45
Systolic	135.12 $\pm$ 14.12
Diabetes	201 (20)
Time from onset of transient ischemic symptoms (days)	41.12 $\pm$ 5.45
Transient ischemic symptoms	
Mild paralysis in side of body	55 (6)
Garbled speech	101 (10)
Double vision	52 (5)
Dizziness	173 (17)
Headache	203 (20)
Dyslipidemia	173 (17)
Body mass index ( $\text{kg}/\text{m}^2$ )	
18.5-24.9 (normal)	308 (31)
25-29.9 (overweight)	545 (55)
$\geq 30$ (obese)	145 (14)
Smoking	
Never	790 (79)
Previously	145 (15)
Currently	63 (6)
Alcohol intake	
Never	888 (89)
Previously	65 (6)
Currently	45 (5)
Hyperuricemia	38 (4)
Sleep apnea syndrome	21 (2)
Pulmonary artery pressure (mmHg)	23.12 $\pm$ 1.25
Claudication	5 (1)
Painful cramping in hips	3 (1)
Leg numbness	15 (2)
Coldness in lower legs	8 (1)
Sores on toes	11 (1)
Hair loss on feet	17 (2)
Slower growth of toenails (self-reported by patients)	16 (2)
Shiny skin of legs	42 (4)
Erectile dysfunction in males	52 (5)
Complaints of disrupted sleep	15 (2)

Values are expressed as the mean  $\pm$  SD and or as n (%). SD, standard deviation.

Table II. Comparison of evaluation of obstructive lesions of the internal carotid artery using different imaging modalities.

Obstructive lesion parameters	Diagnostic modality adopted						
	Invasive catheter angiography (n=939)	Color-coded duplex sonography (n=998)			Magnetic resonance angiography (n=998)		
		Value	P-value <sup>a</sup>	q-value <sup>a</sup>	Value	P-value <sup>a</sup>	q-value <sup>a</sup>
Normal (0%)	66 (7)	89 (9)	<0.0001	4.144	59 (6)	<0.0001	7.301
<50% stenosis	780 (83)	809 (81)			797 (80)		
50-69% stenosis	65 (7)	38 (4)			77 (8)		
70-99% stenosis	9 (1)	41 (4)			40 (4)		
Occlusion (no flow detected; 100%)	19 (2)	21 (2)			25 (2)		

Values are expressed as n (%). <sup>a</sup>Comparison with invasive catheter angiography. The degree of stenosis was defined as per the Warfarin-Aspirin Symptomatic Intracranial Disease methodology under consultation of a neuroradiologist (25 years of experience).

Table III. Distribution of intracranial stenosis in the other intracerebral arteries assessed.

Artery	Invasive catheter angiography (n=939)	Color-coded duplex sonography (n=998)	Magnetic resonance angiography (n=998)
Internal carotid artery			
Petrous segment	7 (1)	8 (1)	9 (1)
Cavernous segment	7 (1)	8 (1)	9 (1)
Cerebral segment	4 (0.4)	5 (0.5)	3 (0.3)
Vertebral artery	15 (1.5)	14 (1)	13 (1)
Anterior cerebral artery	13 (1)	15 (1.5)	14 (1)
Middle cerebral artery			
M1 segment	45 (5)	41 (4)	40 (4)
M2 segment	39 (4)	40 (4)	41 (4)
Basilar artery	5 (0.5)	4 (0.4)	4 (0.4)
Posterior communicating artery	1 (0.1)	0 (0)	0 (0)
Posterior cerebral artery	1 (0.1)	1 (0.1)	1 (0.1)

Values are expressed as n (%).

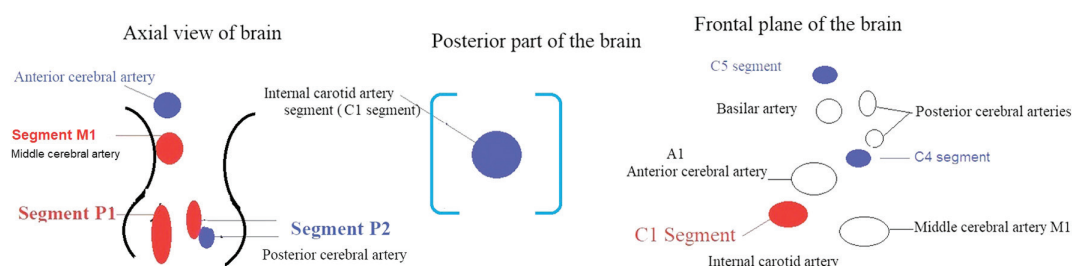


Figure 1. Regions of interest for transcranial color-coded duplex sonography.

**Interobserver reliability.** The quality of the acoustic window was categorized as excellent (1,550-1,300 HU), intermediate (1,299-1,150 HU) and poor ( $\leq 1,149$  HU), and  $<1,000$  HU was considered to indicate transtemporal window insufficiency. Color-coded duplex sonography had

fewer readers' errors than invasive catheter angiography ( $P<0.0001$ ; Table IV).

**Diagnostic parameters.** MRA ( $P=0.390$ ) and color-coded duplex sonography ( $P=0.484$ ) detected the same number of

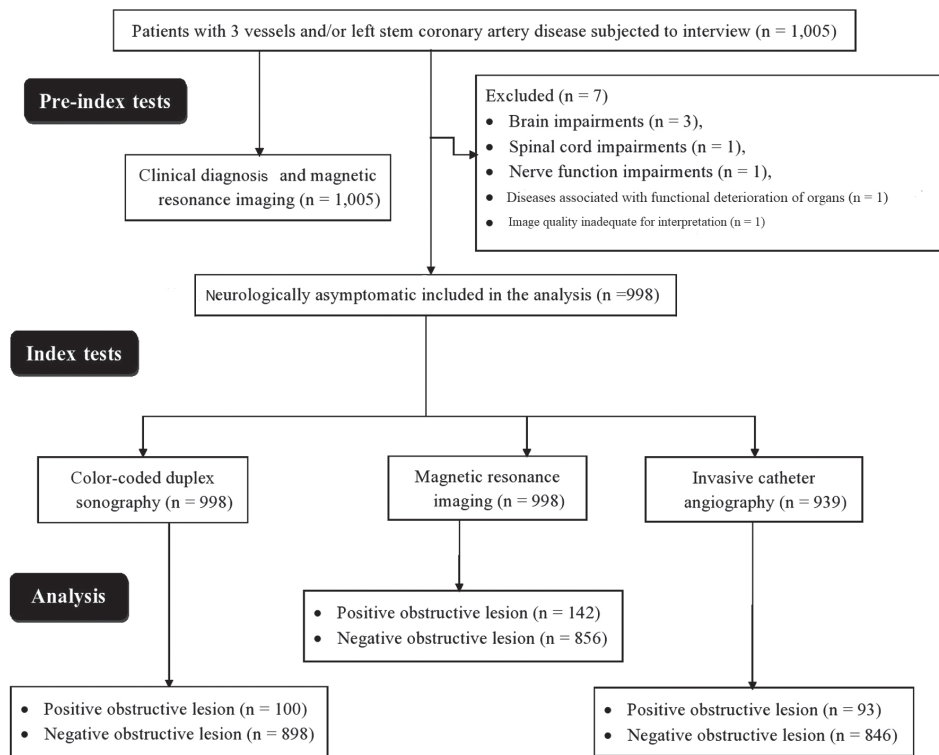


Figure 2. Flow diagram of the study.

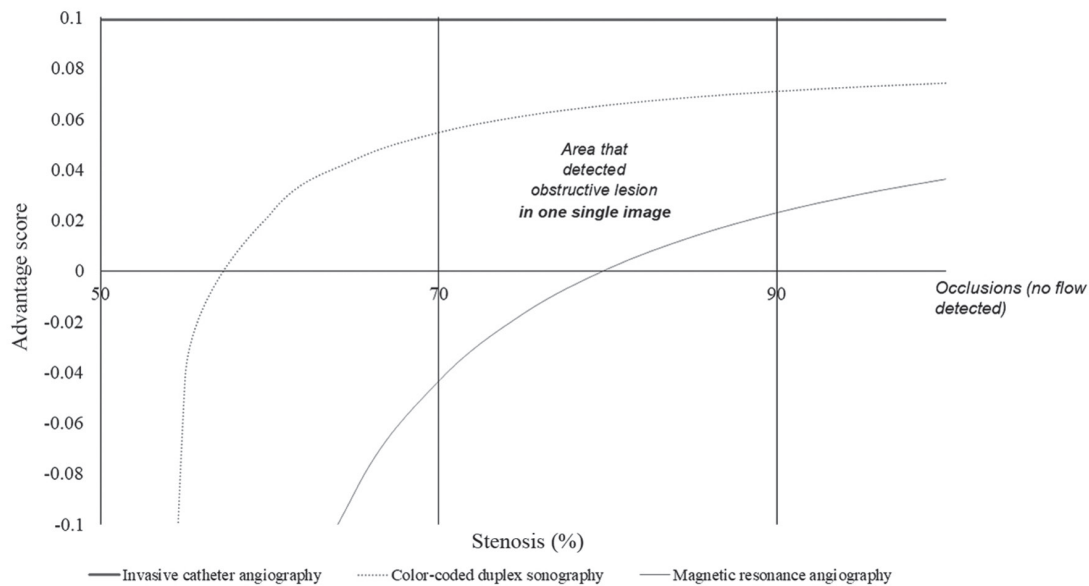


Figure 3. Clinical decision-making curve. The degree of stenosis was defined according to the Warfarin-Aspirin Symptomatic Intracranial Disease methodology under consultation of a neuroradiologist (25 years of experience).

true-positive obstructive lesions with invasive catheter angiography set as the gold standard. As compared to invasive catheter angiography, the sensitivities of color-coded duplex sonography and MRA were 0.935 and 0.957 and the accuracies were 0.920 and 0.974, respectively (Table V).

**Clinical decision-making analysis.** Color-coded duplex sonography was able to detect an obstructive lesion in one single image for ICAs with  $\geq 57\%$  stenosis, while MRA was capable of

detecting an obstructive lesion in one single image for ICAs with  $\geq 80\%$  stenosis. For ICAs that had  $< 57\%$  of stenosis, color-coded duplex sonography had a risk of overdiagnosis and for ICAs that had  $< 80\%$  of stenosis, MRA had a risk of overdiagnosis (Fig. 3).

**Cost.** Color-coded duplex sonography was the cheapest of the 3 methods applied, and the cost per patient was significantly lower than that of invasive catheter angiography ( $P < 0.0001$ ,  $q = 419.81$ ) and MRA ( $P < 0.0001$ ,  $q = 330.21$ ; Fig. 4).



Table IV. Mean reader differences.

Parameter	Invasive catheter angiography (n=939)	Color-coded duplex sonography (n=998)		Magnetic resonance angiography (n=998)	
		Value	P-value <sup>a</sup>	Value	P-value <sup>a</sup>
Number of readers	8	7	N/A	5	N/A
Number of readers' errors	47 (5)	9 (1)	<0.0001	31 (3)	0.037

Values are expressed as n or n (%). <sup>a</sup>Comparison with invasive catheter angiography. N/A, not applicable.

Table V. Diagnostic parameters.

Item	Invasive catheter angiography (n=939)	Color-coded duplex sonography (n=998)		Magnetic resonance angiography (n=998)	
		Value	P-value <sup>a</sup>	Value	P-value <sup>a</sup>
True-positive obstructive lesion	93 (10)	87 (9)	0.3900	89 (9)	0.4840
True-negative obstructive lesion	846 (90)	778 (78)	<0.0001	824 (83)	<0.0001
False-positive obstructive lesion	0 (0)	13 (1)	0.0003	53 (5)	<0.0001
False-negative obstructive lesion	0 (0)	120 (12)	<0.0001	32 (3)	<0.0001
Sensitivity	1	0.935	<0.0001	0.957	<0.0001
Accuracy	1	0.920	<0.0001	0.974	<0.0001

Values are expressed as n (%) or ratio. A reduction in diameter of  $\geq 50\%$  was considered to indicate a positive obstructive lesion. <sup>a</sup>Comparison with invasive catheter angiography. N/A, not available.

**Complications.** After invasive catheter angiography, three patients suffered injuries to the catheterized artery, one patient had an irregular heart rhythm, two patients reported allergic reactions to the medications used during the procedure, one patient had increased bleeding and one patient suffered an infection.

## Discussion

In the present study, color-coded duplex sonography, MRA and invasive catheter angiography were used to assess the degree of stenosis in patients with coronary artery disease with satisfactory sensitivity and accuracy, as well as manageable readers' errors and diagnostic costs. The results were consistent with those of previous prospective studies (1,5). Catheter angiography provides excellent visualization but it is risky, invasive, expensive (15) and requires contrast agent injection (7). In addition, invasive catheter angiography has a risk of false-negative predictions in the chronic stage of the disease or segmental stenosis in young patients (16). For MRA, the use of 3.0 and 1.5 Tesla been debated, e.g. 1.5 Tesla MRA has higher sensitivity and accuracy than 3.0 Tesla MRA but 3.0 Tesla has a higher spatial resolution and signal-to-noise ratio (17). All in all, the present study was successful in the pre-operative evaluation of risk factors for coronary artery bypass grafting surgery.

Compared to invasive catheter angiography, the color-coded duplex sonography detected a similar number of

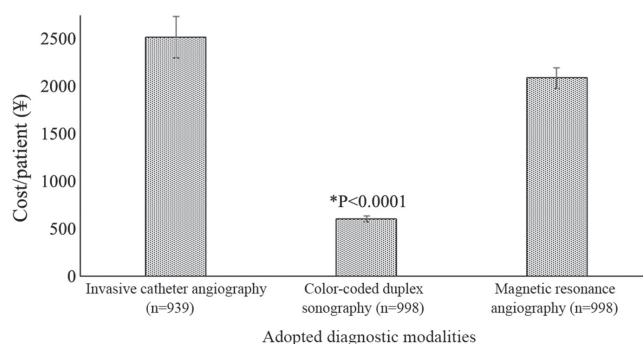


Figure 4. Cost of the diagnostic modalities adopted. Values are expressed as the mean  $\pm$  standard deviation.

obstructive lesions (93 vs. 100,  $P=0.363$ ), but MRA reported higher numbers of obstructive lesions (142 vs. 100,  $P=0.019$ ). 3.0 Tesla MRA imaging has limitations in the detection of decreased velocity of inflowing blood (17). Therefore, MRA should be applied to detect occluded lesions, while detection of the degree of stenosis in lesions using this technique remains challenging. The higher numbers of positive obstructive lesions detected indicated a reduced accuracy of 3.0 Tesla MRA.

The present study reported significantly higher numbers of false-positive obstructive lesions for MRA than color-coded duplex sonography (53 vs. 13,  $P<0.0001$ ). These results were not in line with those of one previous study (17) but were

consistent with those of retrospective studies (15,18). 3.0 Tesla MRA image resolution or image artifacts are responsible for the false-positive results (19), particularly for vasculitis (16). The present study reported that MRA overestimates the prevalence of incidental aneurysms in patients with coronary artery disease.

In the present study, a clinical decision-making curve indicated that color-coded duplex sonography has a higher working area and a lower risk of overdiagnosis than MRA. These results study were in line with those of a previous prospective study (5). Color-coded duplex sonography is a more suitable approach for the evaluation of cerebrovascular diseases than MRA.

Of note, the present study had several limitations, for instance, all patients included were Chinese. Due to certain diseases, the condition is more prevalent in Asians and the results may not be completely generalized to Caucasian patients. The sensitivity (0.935) of color-coded duplex sonography was lower than that of MRA (0.957). Insufficient transcranial acoustic bone windows (20) and tandem stenosis (5) were responsible for the lower sensitivity of color-coded duplex sonography in the present study, while MRA provided clearer images with lower blood fluctuation of arteries (17).

In conclusion, invasive catheter angiography, MRA and color-coded duplex sonography were used to assess the risk for coronary artery bypass grafting surgery. Invasive catheter angiography is risky, inaccurate for segmental stenosis in young patients ( $\leq 45$  years) and expensive. Color-coded duplex sonography was able to detect an obstructive lesion in one single image for ICAs with  $\geq 57\%$  stenosis, while MRA was only capable of detecting an obstructive lesion in one single image for ICAs with  $\geq 80\%$  stenosis. Color-coded duplex sonography is a reliable method for the detection of intracranial stenosis in patients with coronary artery disease.

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#### Availability of data and materials

The datasets used and/or analyzed during the present study available from the corresponding author on reasonable request.

#### Authors' contributions

All authors had read and approved the manuscript prior to submission for publication. LX was the project administrator and contributed to the conceptualization, formal analysis and literature review of the study. WC contributed to resources, software and literature review of the study and drafted and edited the manuscript for intellectual content. HW contributed to resources, formal analysis, data curation and literature review of the study. The authors agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

#### Ethics approval and consent to participate

The protocol (no. LCH/CL/11/15 dated 1 January 2015) of the study was approved by the Luoyang Central Hospital Affiliated to Zhengzhou University human ethics committee (Luoyang, China). Informed consent forms were signed by all participants, which included consent for biopsy, radiology and to an additional procedure for research purposes only. The study adhered to the law of China, the STrengthening the Reporting of OBservational studies in Epidemiology statement and the Declaration of Helsinki (version from 2008).

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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