

A comparison of carotid atherosclerosis in symptomatic patients between 2002–2005 and 2012–2015 cohorts using multi-contrast magnetic resonance vessel wall imaging

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ABSTRACT

OBJECTIVE To compare the morphological and compositional characteristics of carotid plaques in two cohorts (2002–2005 and 2012–2015) of Chinese patients using magnetic resonance vessel wall imaging.

METHODS Symptomatic patients with carotid atherosclerotic plaques who underwent carotid vessel wall magnetic resonance imaging between 2002–2005 and 2012–2015 were retrospectively recruited. Plaque morphology [including mean wall area, wall thickness, and maximum normalized wall index (NWI)] and composition [including calcification, intraplaque hemorrhage, and lipid-rich necrotic core (LRNC)] in symptomatic carotid arteries were evaluated and compared between patients in these two time periods.

RESULTS A total of 258 patients, including 129 patients in the 2002–2005 cohort and 129 patients in the 2012–2015 cohort, were recruited. Statin use (49.6% vs. 32.6%, $P = 0.004$) and hypertension (76.0% vs. 62.8%, $P = 0.015$) were significantly more common in the 2012–2015 cohort than in the 2002–2005 cohort. Patients in the 2012–2015 cohort also exhibited significantly low plaque burden parameters (all $P < 0.05$), as well as a lower prevalence (68.2% vs. 89.9%, $P < 0.001$) and volume percentages of LRNC (11.2% ± 14.2% vs. 25.7% ± 17.7%, $P < 0.001$). These differences remained significant after adjustment for clinical factors. The differences in the volume percentages of LRNC also remained significant after an additional adjustment for maximum NWI ($P < 0.001$).

CONCLUSIONS Patients in the 2012–2015 cohort had a lower plaque burden and volume percentages of LRNC in symptomatic carotid arteries than those in the 2002–2005 cohort. These findings indicate that carotid plaques in the recent cohort had a lower severity and vulnerability.

The morphological and compositional features of carotid plaques are closely associated with clinical risk factors and administered medications.^[1–4] As the diet,^[5] incidence of chronic diseases,^[6,7] and level of medical care^[8] have greatly changed in the Chinese population in the past decade, it is likely that the features of carotid plaques have also changed. Knowledge of the changes in carotid plaques and clinical characteristics in the

Chinese population that have taken place over a decade may provide valuable information for the prevention and treatment of carotid atherosclerosis.

A recent study of carotid plaque burden in patients from Western countries reported a decline in both stenosis and plaque area from 2002 to 2014.^[9] However, plaque morphology was assessed with carotid ultrasound, which does not provide information on compositional features related to plaque

vulnerability, such as intraplaque hemorrhage (IPH) and the lipid-rich necrotic core (LRNC).^[10–12] Therefore, it was unclear as to whether carotid plaque vulnerability varied over the ten-year period in symptomatic patients. Multi-contrast magnetic resonance imaging (MRI) has been widely used to simultaneously characterize carotid plaque burden and composition,^[13] this approach has been shown to have a good to excellent agreement with histological assessments.^[14,15]

The purpose of this study was to compare the morphology and composition of carotid plaques in Chinese patients between two time periods (2002–2005 and 2012–2015) using multi-contrast MRI of the vessel wall.

METHODS

Study Population

We retrospectively included consecutive patients from January 2002 to December 2005, and from January 2012 to December 2015. The study protocol was approved by the Institutional Review Board of Chinese PLA General Hospital (No.20010006) and Tsinghua University School of Medicine (No.2011 0017) in Beijing, China and all patients provided written informed consent. The inclusion criteria were as follows: (1) inpatients had recent stroke or transient ischemia attack; and (2) inpatients had atherosclerotic plaques in at least one carotid artery, as determined by B-mode ultrasound imaging. The exclusion criteria were: (1) no confirmed side of symptom; (2) contraindication to MRI; (3) a previous history of carotid endarterectomy; (4) a previous history of radiotherapy of the neck; and (5) claustrophobia.

Demographic and clinical information [including age, sex, body mass index (BMI), and a history of hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary heart disease, and statin use] were collected from clinical records. Hypertension was defined by a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg. A diagnosis of hyperlipidemia was based either on a low-density lipoprotein level > 1.58 mmol/L, total cholesterol level > 2.26 mmol/L, or triglyceride level > 1.69 mmol/L. Diabetes mellitus was diagnosed based on one of the following criteria: fasting blood sugar level ≥ 126 mg/dL, two-hour oral glucose tolerance test result ≥ 200 mg/dL, or hemoglobin A1c concentration $\geq 6.5\%$.

Carotid Artery MRI

All patients underwent 3.0 T MRI scanning with dedicated phase-arrayed carotid coils. MRI was performed using a GE magnetic resonance scanner (Signa HDx, General Electric Medical System, Milwaukee, WI, USA) for patients enrolled from January 2002 to December 2005 and a Philips MRI scanner (Achieva TX, Philips Healthcare, Best, the Netherlands) for patients enrolled from January 2012 to December 2015. The magnetic resonance scan was centered to the bifurcation of the symptomatic side of carotid artery. The detailed magnetic resonance parameters were listed in Table 1.

MRI Analysis

The MRI vessel wall images for the symptomatic carotid arteries were reviewed by two radiologists with more than three years of experience in cerebrovascular plaque imaging using the custom-designed software CASCADE (Vascular Imaging Lab, University of Washington).^[16] A consensus

Table 1 The magnetic resonance parameters in the cohorts of 2002–2005 and 2012–2015.

Parameters	2002–2005			2012–2015		
	T1WI	T2WI	TOF	T1WI	T2WI	TOF
Scanner	GE SignaHDx 3.0 T			Philips Achieva TX 3.0 T		
Coils	4-channel coil			8-channel coil		
Repetition time/Echo time, ms	800/10	4,800/50	800/10	800/10	4,800/50	800/10
Field of view, mm ²	140 × 140	140 × 140	140 × 140	140 × 140	140 × 140	140 × 140
Flip angle, °	90	90	20	90	90	20
Matrix size	256 × 256	256 × 256	256 × 256	256 × 256	256 × 256	256 × 256
Slice thickness, mm	2	2	2	2	2	2



between the two radiologists was obtained in the case of discrepancies. Both radiologists were blind to the date of MRI examination and imaging parameters. A 4-point scale (1 = poor and 4 = excellent), dependent on the overall signal-to-noise ratio, was utilized to assess the image quality for each slice; images with quality scores < 2 were excluded from the study. The lumen and wall boundaries were outlined manually prior to the measurement of the lumen area, wall area, and maximum wall thickness. Plaque composition (LRNC, IPH, and calcification) and the presence or absence of fibrous cap rupture were assessed.^[17,18] The volume of each plaque component as a percentage of the wall was then determined. The normalized wall index (NWI), $NWI = \text{wall area} / (\text{lumen area} + \text{wall area}) \times 100\%$, was calculated as a measure of plaque burden.

Statistical Analysis

Continuous variables are presented as mean \pm SD, and categorical variables are expressed as a percentage. Case control matching at a 1:1 ratio was performed between patients recruited from 2002 to 2005 and 2012 to 2015, according to patient age (maximum allowable difference: 2 years old) and sex (maximum allowable difference: 0). The clinical characteristics and carotid plaque measurements were compared between patients recruited during the two time periods using the independent Student's *t*-test, the Mann-Whitney *U* test, or the Pearson's chi-squared test. As the longitudinal coverage of the MRI scans obtained via the GE and Philips scanners was different, we compared measurements obtained from slices with identical coverage (10 mm in 5 slices), which were centered at the bifurcation. Multivariable linear and logistic regression models were used to determine differences in continuous and binary plaque measurements between groups, while adjusting for clinical risk factors and maximum NWI. Two-sided *P*-value < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 22.0 (SPSS Inc., IBM, Chicago, IL, USA).

RESULTS

A total of 385 patients were recruited from Chinese PLA General Hospital and Tsinghua University School of Medicine in Beijing, China between 2002 to 2005 and 2012 to 2015. Of those patients, 112 pa-

tients were excluded for the following reasons: (1) poor image quality (14 patients); (2) no confirmed side of ischemic symptoms (76 patients); and (3) insufficient longitudinal coverage (22 patients). After 1:1 matching based on patient age and sex between the two time periods (15 patients were excluded), 258 patients were included in the final analysis (Figure 1), including 129 patients (mean age: 66.4 ± 11.0 years, males: 85.3%) were included from the 2002 to 2005 cohort and 129 patients (mean age: 66.1 ± 11.1 years, males: 85.3%) from the 2012 to 2015 cohort.

Comparison of Clinical Characteristics

Hypertension, diabetes mellitus, and hyperlipidemia were diagnosed in 179 patients (69.4%), 89 patients (34.5%), and 147 patients (57.0%), respectively. A history of smoking was documented in 123 patients (47.7%), and 106 patients (41.1%) had a history of statin use. Comparisons of clinical parameters between patients in the two time periods are shown in Table 2. Patients in the 2012–2015 cohort were significantly more likely to have used statins (49.6% vs. 32.6%, *P* = 0.004), and they also had a significantly higher incidence of hypertension (76% vs. 62.8%, *P* = 0.015) than those in the 2005–2005 cohort. There were no other significant differences in clinical parameters between the two cohorts.

Comparison of Carotid Plaque Measurements

Compared with patients in the 2002–2005 cohort, those in the 2012–2015 cohort had a significantly smaller mean wall area ($50.3 \pm 19.9 \text{ mm}^2$ vs. $56.4 \pm 18.4 \text{ mm}^2$, *P* = 0.011), mean wall thickness ($2.6 \pm 1.5 \text{ mm}$ vs. $3.3 \pm 1.3 \text{ mm}$, *P* < 0.001), luminal stenosis ($50.2\% \pm 13.3\%$ vs. $54.2\% \pm 16.6\%$, *P* = 0.014), maximum NWI ($56.8\% \pm 17.2\%$ vs. $67.9\% \pm 14.9\%$, *P* < 0.001), and volume percentages of LRNC ($11.2\% \pm 14.2\%$ vs. $25.7\% \pm 17.7\%$, *P* < 0.001) (Figures 2 & 3) as well as a greater mean lumen area ($55.6 \pm 22.0 \text{ mm}^2$ vs. $45.5 \pm 23.2 \text{ mm}^2$, *P* < 0.001) and lower incidence of LRNC (68.2% vs. 89.9%, *P* < 0.001) (Table 3). Differences in the following parameters remained significant after adjustment for age, sex, BMI, a history of hypertension, and statin use: carotid mean wall area (*P* = 0.010), mean wall thickness (*P* < 0.001), luminal stenosis (*P* = 0.040), maximum NWI (*P* < 0.001), mean lumen area (*P* = 0.001), volume percentages of LRNC (*P* < 0.001), and LRNC incidence (*P* < 0.001). The difference in volume percentages of

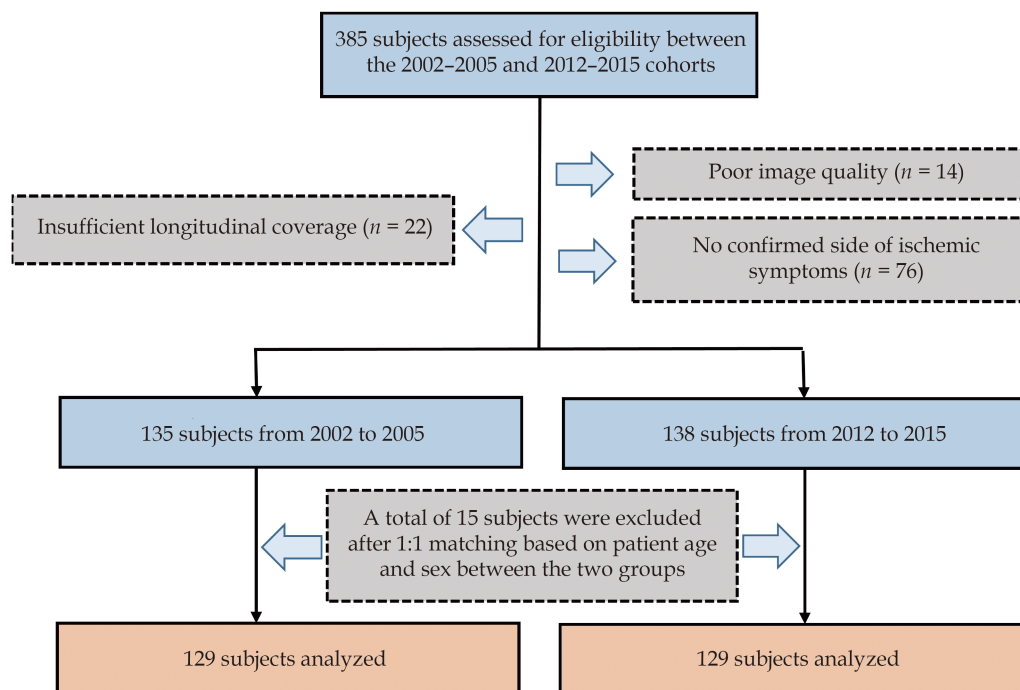


Figure 1 Flow chart of patients recruitment.

Table 2 Comparison of clinical features between patients of 2002-2005 and 2012-2015.

Characteristics	2002-2005 (n = 129)	2012-2015 (n = 129)	P-value
Male	110 (85.3%)	110 (85.3%)	> 0.999
Age, yrs	66.4 ± 11.0	66.1 ± 11.1	0.831
Body mass index, kg/m ²	24.9 ± 2.6	24.4 ± 2.9	0.102
Hypertension	81 (62.8%)	98 (76.0%)	0.015
Hyperlipidemia	80 (62.0%)	67 (51.9%)	0.131
Diabetes mellitus	41 (31.8%)	48 (37.2%)	0.432
Coronary heart disease	34 (26.4%)	31 (24.0%)	0.774
Low-density lipoprotein, mmol/L	2.6 ± 0.9	2.5 ± 0.8	0.303
High-density lipoprotein, mmol/L	1.0 ± 0.2	1.0 ± 0.2	0.310
Total-density lipoprotein, mmol/L	1.6 ± 0.8	1.5 ± 0.7	0.213
Triglyceride, mmol/L	4.2 ± 1.0	4.2 ± 1.0	0.952
Statin use	42 (32.6%)	64 (49.6%)	0.004
Smoking	56 (43.4%)	67 (51.9%)	0.213

Data are presented as means ± SD or n (%).

LRNC between the two cohorts remained significant ($P < 0.001$) after an additional adjustment for maximum NWI (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study to use multi-contrast vessel wall MRI to evaluate differences in the morphological and composi-

tional features of carotid atherosclerotic plaques between symptomatic patients in two time periods separated by a decade. We found that patients in the 2012-2015 cohort had a higher proportion of statin use and hypertension history than those in the 2002-2005 cohort. Carotid plaques in the 2012-2015 cohort exhibited a significantly smaller mean wall area, mean wall thickness, maximum NWI, and volume percentages of LRNC than those



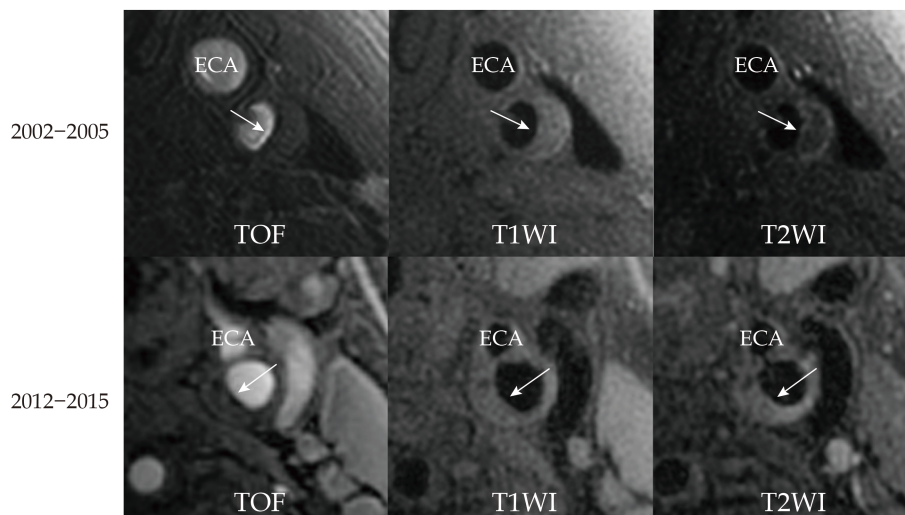


Figure 2 Atherosclerotic plaques (arrows) at the left carotid bifurcation were depicted in a patient (70-year-old male) recruited from 2003 (upper row) and a patient (72-year-old male) recruited from 2014 (lower row), respectively. The plaque of patient in 2003 shows greater plaque burden and lipid-rich component (iso-intense on TOF and T1WI and hypointense on T2WI after fat-saturation) compared with that in 2014. ECA: external carotid artery.

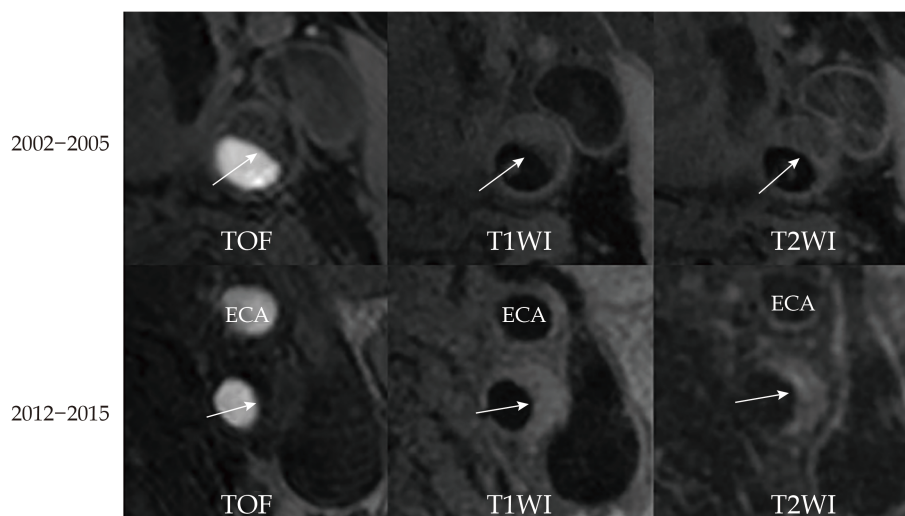


Figure 3 Atherosclerotic plaques (arrows) at the left carotid bifurcation were depicted in a patient (82-year-old male) recruited from the 2005 (upper row) and a patient (78-year-old male) recruited from the 2012 (lower row), respectively. The plaque of patient in the 2005 shows greater plaque burden and lipid-rich component (iso-intense on TOF and T1WI and hypointense on T2WI after fat-saturation) compared with that in the 2012. ECA: external carotid artery.

in the 2002–2005 cohort. Therefore, our findings suggest that carotid plaques in symptomatic patients from the more recent cohort had a lower severity and vulnerability compared to those in the earlier cohort.

The increasing trend for statin administration observed in our study is similar to that in studies conducted in other countries. A prior study reported that statin utilization increased by 121%–1 263% between 2000 and 2012 in twelve European countries.^[19] Another study conducted in India reported

that statin use increased from 0.36% to 0.74% over a ten-year period.^[20] Researchers from Western countries have attributed the increased rate of pharmaceutical expenditure (including statin use) during the past decade to an aging population, increasing incidence of chronic diseases, rising patient expectations, and greater treatment intensity. Similarly, in China, improvements in health awareness and medical conditions may have contributed to the increased prescription of statins.^[8] The present study showed that there was no difference in the low-

Table 3 Comparison of carotid plaque characteristics between patients of 2002–2005 and 2012–2015.

Characteristics	2002–2005 (n = 129)	2012–2015 (n = 129)	P-value
Plaque morphology			
Mean lumen area, mm ²	45.5 ± 23.2	55.6 ± 22.0	< 0.001
Mean wall area, mm ²	56.4 ± 18.4	50.3 ± 19.9	0.011
Mean total area, mm ²	100.4 ± 31.9	105.9 ± 25.9	0.128
Mean wall thickness, mm	3.3 ± 1.3	2.6 ± 1.5	< 0.001
Luminal stenosis	54.2 ± 16.6	50.2 ± 13.3	0.014
Maximum normalized wall index, %	67.9 ± 14.9	56.8 ± 17.2	< 0.001
Presence of plaque components			
Calcification	52 (40.3%)	65 (50.4%)	0.104
Lipid-rich necrotic core	116 (89.9%)	88 (68.2%)	< 0.001
Intraplaque hemorrhage	30 (23.3%)	33 (25.6%)	0.772
Fibrous cap rupture	12 (9.3%)	10 (7.8%)	0.656
Volume percentages of plaque components			
Calcification, %	3.1 ± 5.8	4.4 ± 6.2	0.082
Lipid-rich necrotic core, %	25.7 ± 17.7	11.2 ± 14.2	< 0.001
Intraplaque hemorrhage, %	3.0 ± 7.5	2.9 ± 7.2	0.867

Data are presented as means ± SD or n (%). All these results in Table are unadjusted for confounding factors.

Table 4 Multivariable regression models comparing plaque characteristics between patients of 2002–2005 and 2012–2015.

	Model 1			Model 2		
	Difference*	95% CI	P-value	Difference*	95% CI	P-value
Carotid plaque morphology						
Mean lumen area, mm ²	9.63	4.03–15.22	0.001	-0.17	-4.67–4.32	0.939
Mean wall area, mm ²	-6.32	-11.10–-1.54	0.010	1.28	-2.80–5.35	0.537
Mean total area, mm ²	4.81	-2.36–11.99	0.187	2.74	-4.80–10.28	0.475
Mean wall thickness, mm	-0.67	-1.01–-0.33	< 0.001	0.07	-0.16–0.29	0.552
Luminal stenosis	-3.99	-7.77–-0.32	0.040	-1.53	-5.55–2.53	0.459
Maximum normalized wall index, %	-0.11	-0.15–-0.07	< 0.001	-	-	-
Presence of plaque components						
Calcification	0.40	0.90–2.49	0.125	0.49	0.97–2.76	0.067
Lipid-rich necrotic core	0.25	0.12–0.49	< 0.001	0.65	0.28–1.51	0.313
Intraplaque hemorrhage	1.26	0.69–2.30	0.454	0.54	0.88–3.32	0.112
Fibrous cap rupture	0.81	0.33–2.00	0.648	0.73	0.28–1.85	0.501
Volume percentages of plaque components						
Calcification, %	0.6	-0.2–1.3	0.128	0.7	-0.1–1.4	0.079
Lipid-rich necrotic core, %	-9.2	-13.4–7.1	< 0.001	-6.5	-10.4–3.6	< 0.001
Intraplaque hemorrhage, %	0.3	-1.8–1.9	0.957	0.5	-1.2–2.3	0.551

Model 1: adjusted for age, sex, body mass index, history of hypertension and statin use. Model 2: adjusted for variables in Model 1 plus the maximum normalized wall index. *Refers to the values are the difference between plaques of patients in 2002–2005 and 2012–2015 in terms of the absolute mean difference for plaque morphology, odds ratio for the presence of plaque components.

density lipoprotein values between the two cohorts, although the statin use was different. The time and intensity of statin use which were not collected and included in the analysis in the present study might contribute to the inconsistent results between the

statin use and low-density lipoprotein values. In the present study, we also found that the incidence of hypertension in the 2012–2015 cohort was significantly higher than that in the 2002–2005 cohort. This is consistent with the findings of previous nation-



wide surveys in China, which have shown a significant increase in hypertension prevalence, from 18.0% in 2002 to 27.8% in 2013.^[14,21] This increase may have been associated with concurrent increases in both obesity and daily dietary salt intake over the same time period.^[22]

In the present study, patients in the 2002–2005 cohort had a greater carotid artery plaque burden than those in the 2012–2015 cohort. These findings are consistent with a western study which used carotid ultrasound to measure and compare stenosis and plaque area in 6,039 patients assessed in three time periods, from 2002 to 2014.^[9] They found that the total plaque area declined by 24% and the percentage of patients with carotid stenosis > 60% declined by 29.9% between 2002 and 2014. These results may be explained by increasingly earlier diagnoses and interventions for carotid atherosclerosis over the study period. Another explanation for the low carotid burden in the 2012–2015 cohort may be the increased use of statins since it had been reported that the utilization of statins could reduce the plaque burden.^[4]

Our results indicated that carotid plaques in the 2002–2005 cohort had a significantly greater volume percentages of LRNC compared with those in the 2012–2015 cohort. A number of studies have shown that the vulnerability of an atherosclerotic plaque to rupture is associated with LRNC size.^[23,24] Therefore, plaques in the 2012–2015 cohort were also likely to have been less vulnerable. In addition, we also found that the difference in volume percentages of LRNC between the two cohorts was slightly attenuated (from 14% to 9%) after adjusting for clinical risk factors, which included age, sex, BMI, a history of hypertension, and statin use. This suggested that these clinical risk factors may have a synergistic effect on LRNC. A higher proportion of patients were prescribed statins in the 2012–2015 cohort than in the 2002–2005 cohort. It is well-established that statins can deplete the lipid component of plaque,^[25,26] thereby reducing the LRNC volume.

LIMITATIONS

There are several limitations that must be noted. Firstly, other potential risk factors that were not investigated in the present study (such as diet, ethnicity, geography, and presence of air pollution) may have affected plaque characteristics.^[3,27,28] The evalu-

ation of additional risk factors should be considered in future studies. Secondly, the longitudinal coverage of two-dimensional vessel MRI techniques utilized in the present study was limited. Recently, three-dimensional MRI techniques for vessel walls have been developed for the characterization of carotid plaques.^[29] These techniques provide an increased longitudinal coverage, which facilitates an accurate comparison of carotid plaque characteristics. Thirdly, the post-contrast imaging was absent in the magnetic resonance protocol of the current study which might provide more valuable information of the compositional characteristics of carotid plaques. Last but not least, due to the ten-year study interval, different MRI scanners were used in the two cohorts and this may have resulted in a substantial bias in plaque measurements. Nevertheless, a previous study has shown that MRI has a good to excellent inter-scan reproducibility for the assessment of carotid plaque morphology and composition.^[30]

CONCLUSIONS

Patients in the 2012–2015 cohort had a lower plaque burden and volume percentages of LRNC in symptomatic carotid arteries than those in the 2002–2005 cohort. These suggests indicate that carotid plaques in the recent cohort had a lower severity and vulnerability.

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