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경동맥 죽상경화반의 전산화 단층촬영 혈관조영술 상 감약계수 측정을 통한 주요 심혈관 사건의 예측

Hounsfield Unit of Carotid Plaque on CT angiography for the Prediction of Major Adverse Cardiovascular Events

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최 얼

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이 논문을 의학박사 학위 논문으로 제출함

2020 년 2 월

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국문요약

목적: 이 연구의 목적은 중등도 이상의 경동맥 협착증 환자에서 전산화 단층촬영 혈관조영술을 통한 경동맥 죽상경화반의 감약계수 측정이 미래의 주요 심혈관 사건을 예측할 수 있는지 조사하는 데에 있다.

방법: 이 연구는 50% 이상의 중등도 이상 경동맥 협착증을 가진 환자로, 2010 년 1 월부터 2017 년 12 월 사이에 단일 대학병원에서 경부 및 두부에 대하여 전산화 단층촬영 혈관조영술을 시행한 환자들을 대상으로 진행되었다. 연구의 일차 결과는 주요 심혈관 사건으로 이는 비열공성 뇌경색, 일과성 뇌허혈, 심근경색, 불안정 협심증, 심혈관 재관류 치료를 받은 경우, 모든 원인에 의한 사망 등을 포함하였다. 분석은 인구 통계학적 변수와 전산화 단층촬영 상 감약계수, 고위험 경동맥 죽상경화반의 특징들, 예를 들면 냅킨 고리 징후, 점상 석회화, 궤양 등의 변수를 포함하였다.

결과: 판독 결과에서 “경동맥”과 “협착증” 이라는 단어가 들어간 두경부 전산화 단층촬영 혈관조영술 사진을 모았고 879 개의 전산화 단층촬영 혈관조영술 사진이 골라졌다. 제외 기준에 따라 일부가 제외되었고, 최종적으로 117 개의 경동맥 죽상경화반이 연구에 포함되었다. 중앙값 58 개월 (사분위수 범위 32.5-79 개월) 간의 추적관찰 기간 동안 44 명의 환자 48 개의 경동맥 죽상경화반에서 주요 심혈관 사건이 발생하였다. 콕스 비례위험 모델 분석에서 뇌졸중 과거력 (p=0.012), 점상 석회화 (p=0.031), 저음영 죽상경화반 (p=0.001>) 등이 의미 있는 인자로 나타났다. 생존분석 및 로그-순위 검정에서도 저음영 죽상경화반은 주요 심혈관 사건의 의미 있는 위험인자로 나타났다. 로그 상대위험 그래프에서 감약계수가 감소할수록 주요 심혈관 사건의 위험도는 높아지는 것으로 나타났다.

결론: 기존의 몇몇 연구들에서 전산화 단층촬영 혈관조영술 상의 경동맥 죽상경화반의 감약계수가 뇌졸중이 발생한 환자에서 뇌졸중이 발생하지 않은 환자보다 낮았음을 보여준 적이 있다. 이 연구에서는 감약계수의 측정을 통해 미래에 발생할 수 있는 주요 심혈관 사건을 예측할 수 있음을 보여주었다. 이 결과는 중등도 이상의 경동맥 협착증 환자들에서 감약계수 측정을 통해 예후를 예측하고 위험도에 따라 환자들을 층

화시킬 수 있다는 것에 의미가 있다.

차 례

표 및 그림목차

Introduction

Investigations of the predictive value of carotid plaque (CP) to predict cardiovascular (CV) risk have continued up to recently. Such research is based on the hypothesis that atherosclerosis affecting different vascular beds could be interdependent.(1, 2) Some large studies have shown that carotid intima-media thickness (IMT) could predict CV risk, and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines suggested that the measurement of carotid artery IMT is reasonable for CV risk assessment in asymptomatic adults at intermediate risk (class IIa recommendation).(3, 4)

More recently, with improved imaging modality, researchers have been interested in plaque characteristics, not just stenotic degree. High-risk morphologies of CP on computed tomography angiography (CTA) including low attenuation plaque, spotty calcium, napkin ring sing, and ulceration have been studied by several researches comparing symptomatic CP with asymptomatic CP. Furthermore, many studies have been performed to differentiate plaque composition and to compare vulnerable CP with stable CP using histologic analysis through HU measurement on CTA. (5-8) However, as far as we know, there have been few studies that investigate whether CP actually affect to future CV and cerebrovascular events.

The aim of this study is to investigate whether Hounsfield unit (HU) of CP on CTA is associated with future major adverse cardiovascular events (MACE).

Materials and Methods

Study population and design

CTAs performed in single teaching hospital between January 2010 and December 2017, including the words "carotid" and "stenosis" on reports were collected. After the extraction of actual carotid stenosis, 449 carotid stenosis from 337 consecutive patients who underwent neck CTA were included in this study. Exclusion criteria were as follows: 1) mild stenosis (<50%) or total occlusion; 2) previous ipsilateral carotid endarterectomy or carotid artery stenting; 3) cases for which it was impossible to measure HU, such as calcified plaque, diffuse stenosis, or thin plaque. After exclusion, 117 CPs from 90 patients were included in the final analysis (Fig 1).

The hospital records of each patient were reviewed for demographics and CV risk factors, including hypertension, diabetes, dyslipidemia, smoking history, and history of coronary artery disease and stroke. CTA reports were recorded by specialized neuro-radiologists, and CTA images were re-evaluated for determination of plaque characteristics including HU, percentage of stenosis, presence of spotty calcium, presence of napkin ring sign, and ulceration. Measurement of HU was conducted independently by two observers without knowledge of the outcomes of another observer for estimation of inter-observer reliability. All patients were followed from the date that they underwent CTA and divided into groups based on whether MACE occurred. According to AHA / ACC guideline, antiplatelet therapy was routinely prescribed unless contraindication existed.(9) This study was approved by the institutional review board of same hospital.

CTA protocol

CTA was performed using a Somatom Definition Edge (Siemens, Erlangen, Germany) with the following acquisition protocol: 128 × 0.6-mm collimation, slice thickness, 1.0 mm; reconstitution width, 0.5 mm; gantry rotation time, 0.5/s rotation; table speed, 5 mm/s; voltage, 120 kV; and current, 300 mA. Sixty milliliters of nonionic contrast medium Iopamidol injection (Bracco imaging, Milan, Italy) (370 mg/ml) was bolus-injected intravenously at 4.5 ml/s with an injector via a 20-gauge catheter placed in the cubital vein. The scan was conducted from the

aortic root to 3cm above the skull before and after contrast injection.

Plaque characterization

HUs were measured using a width of 850 and length of 300 as window-level settings on enhanced images to distinguish plaque from vascular lumen. Regions of interests (ROIs) were selected on the visually least attenuated area of the plaque at the most stenotic level on axial image. Five separate HU measurements were performed on a $2mm^2$ circular areas of ROI and mean value was calculated and recorded (Fig 2). Diameter reduction was calculated by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Each plaque was categorized as follows: 1) Calcified plaque which was composed with predominant calcification (>130 HU), 2) Mixed plaque which had calcified and non-calcified component either, 3) Soft plaque which had lower density without calcification. High-risk features of CP which were defined as presence of spotty calcium, napkin ring sign, ulceration were evaluated in each plaque. Spotty calcium was defined as the presence of calcium in the plaque with a diameter <3mm in any direction on curved multiplanar reformation images and occupied only one side on cross-sectional images.(10) Napkin ring sign was defined as presence of low attenuation plaque surrounded by ring of high attenuation which was not >130HU.(11) Ulceration was defined as the presence of large obvious excavation (>2mm in depth) on the surface of the plaque (Fig 3).(8)

Clinical outcome

The outcome of this study was the occurrence of MACE including stroke, transient ischemic attack, acute coronary syndrome (ACS) and all-cause mortality. Stroke as an outcome was defined as non-lacunar ischemic stroke that had evidence of brain ischemia on magnetic resonance image or CT. ACS was defined as acute MI or unstable angina pectoris according to the AHA / ACC Guidelines.(12)

Statistical analysis

SPSS 18.0 (SPSS, Chicago, IL, US) and R software (www.r-project.org) were used for statistical analysis. Continuous variables are presented as mean ± SD and categorical variables are presented as number (%). Cox proportional hazard analysis was performed to

identify predictors of MACE on per CP. Demographic characteristics that were considered to be related with MACE and features of CP on CTA were included in this analysis. Kaplan-Meier survival method and log-rank test was used to compare occurrence of MACE between low attenuation plaque and the others. HU was modelled as restricted cubic splines to evaluate log relative hazards in Cox regression. Time dependent receiver-operating characteristics (ROC) curve was used to quantify the discriminatory accuracy of HU for predicting MACE. Intra- and inter-observer reproducibility of HU measurement was analyzed through the calculation of the intra-class correlation coefficient (ICC). The ICC ranged from 0 to 1.00, and measurement reliability was classified as excellent (ICC > 0.9), good (0.75 – 0.9), moderate (ICC = 0.5 – 0.75), poor (ICC<0.5).(13)

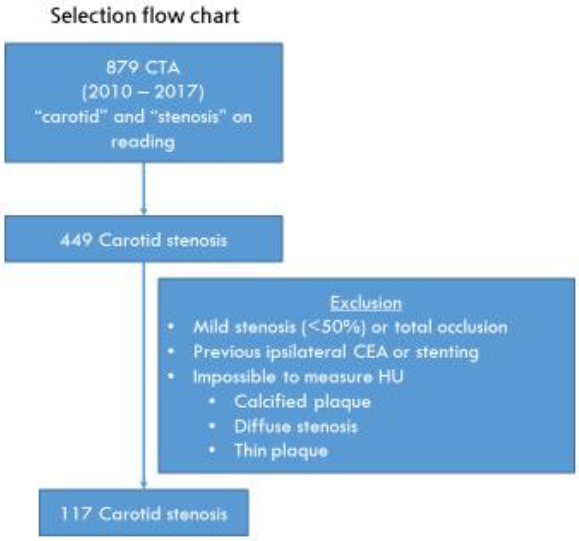


Fig 1. Selection flow chart

CEA, carotid endarterectomy; CTA, computed tomography angiography; HU, Hounsfield unit

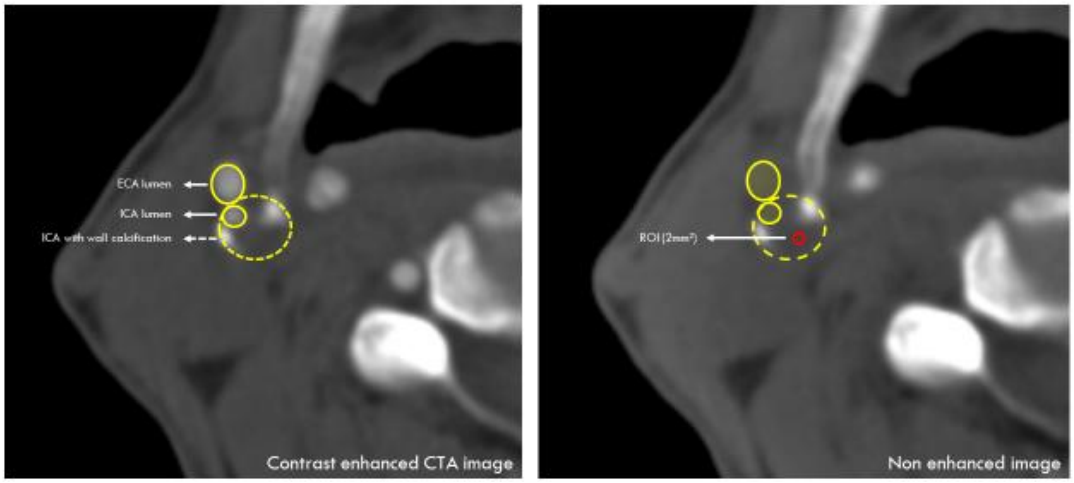


Fig 2. Method of Hounsfield unit measurement

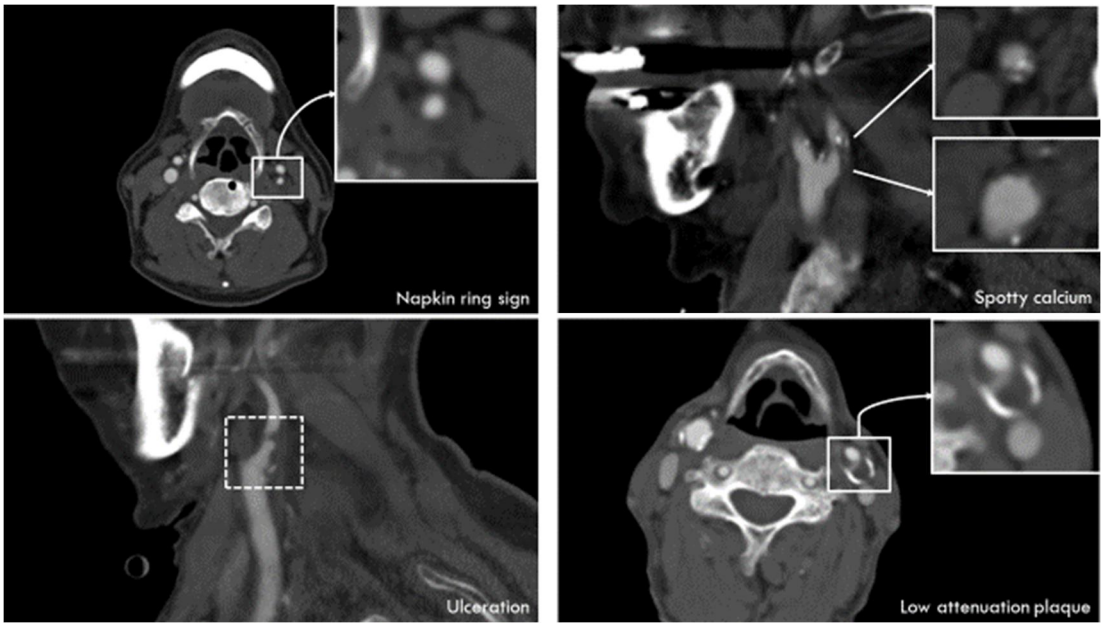


Fig3. High-risk features of carotid plaque on CTA

Results

A total of 117 consecutive CPs were identified using pre-defined inclusion and exclusion criteria for further analysis and follow up. Their demographic and plaque characteristics were showed as total study subjects (Table 1). Among them, 58 MACEs occurred in 48 CPs, comprising 8 cardiac events, 22 strokes and 28 mortalities. Median follow-up of CPs with and without MACE was 54.5 months (20.25 – 75.75) and 65 months (40.5 – 81.5), respectively.

Clinical outcomes by demographics and plaque characteristics

Association of clinical demographics and plaque characteristics with occurrence of MACE were analyzed using univariate and multivariate Cox proportional hazard regression analysis (Table 2). Among demographic variables including age, sex, underlying diabetes, hypertension and history of cardiovascular disease, history of ischemic stroke was significantly associated with MACE occurrence in univariate and multivariate analysis.

In a comparison of the plaque characteristics on CTA between CPs with and without MACE, CPs resulting in MACE had an increased prevalence of napkin ring sign ($p=0.014$), spotty calcium ($p=0.012$), low attenuation plaque ($p<0.001$) than those not associated with occurrence of MACE. In multivariate analysis, spotty calcium ($p=0.029$), history of stroke ($p=0.011$) and low attenuation plaque ($p<0.001$) were significant predictors of MACE.

Clinical outcomes by HU

Kaplan-Meier curves for MACE based on the presence of low attenuation plaque are shown in Fig 4. In multivariate analysis using HU as a continuous variable instead of low attenuation plaque, HU ($p<0.001$), spotty calcium ($p=0.013$) and history of stroke ($p=0.003$) were significant predictors of MACE. The mean HU of CPs with and without MACE were 31.8 ± 9.6 and 41.2 ± 12, respectively. The time-dependent area under the ROC curve for HU predicting 5-year MACE probability was 0.68 (Fig 5). HU was modelled as a restricted cubic spline in a Cox regression model and plotted against the log relative hazard with a 95% confidence interval, and the risk of MACE decreased when HU increased (non-linear

p=0.162) (Fig 6).

Intra- and inter-observer reproducibility

The intra-observer ICC for HU measurement were 0.972 (95% CI = 0.96 – 0.981), and the inter-observer ICC for HU measurement were 0.919 (95% CI = 0.885 – 0.943). According to the classification, both intra- and inter-observer reproducibility was excellent. (Table 3)

Table 1. Demographics and plaque characteristics (n=117)

Demographics		
Sex	Female	15 (12.8%)
	Male	102 (81.2%)
Age		69.6±7.6
BMI		24±3
DM		50 (42.7%)
HTN		86 (73.5%)
Hyperlipidemia		58 (49.6%)
Stroke history		31 (26.5%)
CAD history		37 (31.6%)
Smoking	None	35 (29.9%)
	Past	41 (35%)
	Current	41 (35%)
Plaque characteristics		
Diameter reduction		69.9±12.2
Soft or mixed plaque	Soft plaque	39 (33.3%)
	Mixed plaque	78 (66.7%)
Napkin ring sign		46 (39.3%)
Spotty calcium		31 (26.5%)
Ulceration		15 (12.8%)
Hounsfield unit		37.37±11.97
LAP (HU<40)		70 (59.8%)

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; HU, Hounsfield unit; LAP, low attenuation plaque

Table 2. Cox proportional hazards model for occurrence of MACE

	MACE		Univariable		Multivariable	
	Non MACE (n=69)	MACE (n=48)	HR (95% CI)	P value	HR (95% CI)	P value
Demographics						
Age	69.3±7.7	70.1±7.6	1.01 (0.98-1.05)	0.559		
Sex (M:F)	59:10	43:5	1.35 (0.53-3.43)	0.527		
BMI	23.9±2.7	24.2±3.5	1.04 (0.94-1.14)	0.487		
DM	29	21	1.16 (0.65-2.05)	0.618		
HTN	47	39	1.66 (0.81-3.43)	0.17		
Hyperlipidemia	33	25	1.57 (0.89-2.8)	0.123		
Stroke history	15	16	1.8 (0.98-3.3)	0.058	2.23 (1.2 – 4.15)	0.011
CAD history	20	17	1.17 (0.65-2.11)	0.611		
Smoking						
Current	23	18	0.81 (0.4-1.6)	0.538		
Past	26	15	1.02 (0.49-2.1)	0.967		
Plaque characteristics						
Diameter reduction	69.9±11.3	69.9±13.5	1 (0.97-1.02)	0.791		
Soft : Mixed plaque	20:49	19:29	1.51 (0.85-2.69)	0.165		
Napkin ring Sign	20	26	2.03 (1.15-3.59)	0.014		
Spotty calcium	12	19	2.11 (1.18-3.77)	0.012	1.91 (1.07 – 3.44)	0.029
Ulceration	8	7	1.39 (0.62-3.11)	0.421		
LAP (HU<40)	31	39	3.94 (1.91-8.16)	0.001>	4.08 (1.95 – 8.54)	0.001>

MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; HU, Hounsfield unit; LAP, low attenuation plaque

Table 3. Intra-class correlation values for HU measurement

Variable	Intra-class correlation (95% CI)	
	Intra-observer reliability	Inter-observer reliability
HU	0.972 (0.960-0.981)	0.919 (0.885-0.943)

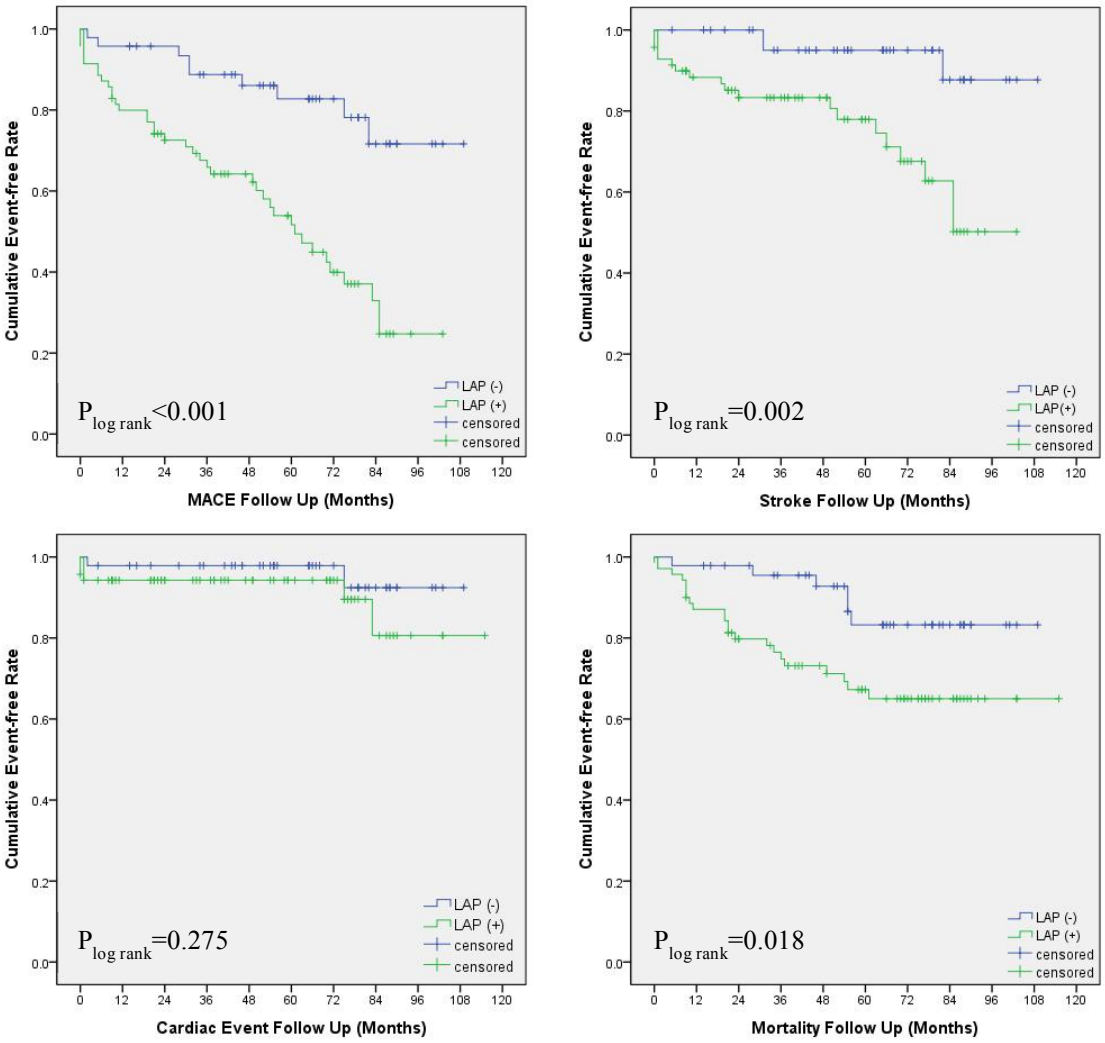


Fig 4. Kaplan-Meier curve for MACE of patients with and without low attenuation plaque

CAD, coronary artery disease; MACE, major adverse cardiovascular events

Fig 5. Time-dependent ROC curve for 5 year MACE

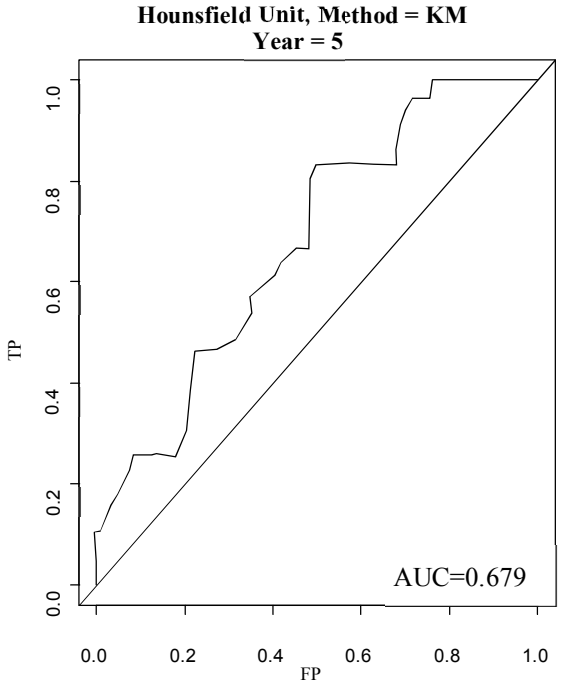
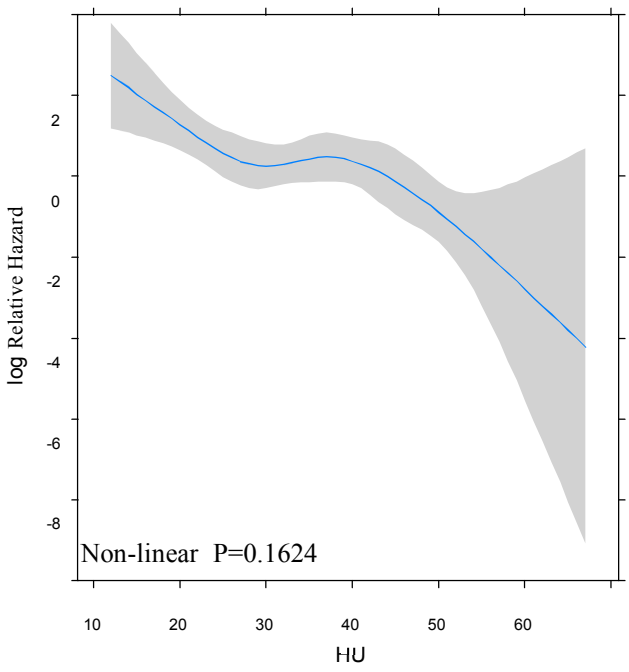


Fig 6. Log relative hazard plot of MACE by HU using regression cubic spline



Discussion

In this study, we demonstrated that HUs of CPs on CTA were associated with future MACE in patients with moderate to severe carotid artery stenosis (>50%). Several previous studies have investigated the association between HUs and plaque vulnerability. The interest in the usefulness of CT for evaluating vulnerable plaques has increased with development of the multidetector row CT (MDCT). In an earlier study aiming to assess the composition and characteristics of CPs using MDCT angiography, CTA classification by HU showed good correlation with histologic examination when large lipid cores or large hemorrhages were considered.(8) According to a recent pilot study from Italy evaluating 31 CPs, CPs with multiple high-risk features on histology, including ulceration, the presence of lipids, fibrosis, thrombotic deposits, hemorrhage, neovascularization, and inflammation, had higher proportion of soft tissue with density ≤40, 60, 80, 100HU.(6) In those studies, the discrimination of lipid core from connective tissue or intraplaque hemorrhage (IPH) was challenging. However, despite some overlap between those components, several studies showed that IPH (AHA type VIb) had the lowest attenuation value compared with other components.(14, 15) Other several studies demonstrated the association between HU and symptomatic plaque. Serfaty et al. reported that HU was significantly related with neurologic event. In that report, they found an odds ratio of 1.54 for neurologic events associated with a 10-point decrease in attenuation (p=0.002), showing an association between plaque attenuation and neurologic events.(16)

The correlation between carotid and coronary atherosclerosis was well-established through several retrospective studies.(2, 17) According to these studies, atherosclerosis is a systemic disease and the presence of atherosclerosis in a particular vascular bed is frequently associated with disease in other vascular territories. Steinvil et al. demonstrated that carotid artery stenosis to be an independent predictor of MACE in 1391 patients undergoing coronary angiography.(18) Furthermore, CPs seemed to affect not only ipsilateral stroke but contralateral stroke regardless of location. In our study, 66 of 117 CPs underwent carotid endarterectomy or radiologic intervention through trans-femoral cerebral angiography during the study period. However, HU was independent predictor for the occurrence of

MACE including stroke whether or not surgery or intervention was performed. This finding suggests that CP characteristics, including HU, are associated with stroke, irrespective of their location. The Rotterdam study, with 4217 asymptomatic patients with CPs in various location, found similar results.(19)

Our study is unique in several ways. First, as far as we know, this study is the first study that is designed as case-control study investigating HU. Previous studies investigating HUs of CPs were generally cross-sectional studies comparing stable plaques with vulnerable plaques, or symptomatic plaques with asymptomatic plaques. However, in this study, we reviewed hospital records and collected follow-up data for identifying occurrence of MACE. We believe that this difference supports the strength of this study. Second, we demonstrated the increasing trend of MACE with decreasing HU. The lower the HU value, the more likely that IPH or a lipid-rich necrotic core exists.(5, 14) This result suggests that HU could be utilized as a biomarker for risk stratification of future MACE.

Our study had several limitations. First, this study was based on a small number of patients from a single center. Particularly, the number of cardiac events was small, and we did not achieve statistical significance in the survival analysis between cardiac events and HU. However, the correlation between coronary artery disease and high-risk plaque features, including spotty calcium and low-attenuation plaque, was considered to be with high probability.(10) Further research is needed to verify this discrepancy. Second, we did not take plaque volume into account. Relative or absolute area of low attenuation of CP on CTA image could be associated with plaque vulnerability.(20, 21) However, the measurement of volume according to HU usually requires expensive software and a complicated process compared with our method, which only required general clinical imaging software. Furthermore, both of intra- and inter-observer reproducibility of our measuring method was classified as excellent.

In conclusion, several previous studies have shown that the HU values of symptomatic plaques are lower than those of asymptomatic plaques. This study demonstrated that HU of carotid plaque could predict future MACE. This finding could be helpful in predicting prognosis and risk stratification of patients with moderate to severe carotid stenosis.

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영문요약

Purpose: This study was aim to investigate that Hounsfield units (HUs) of the carotid plaque could predict future major cardiovascular events (MACE) in the patients with moderate to severe carotid artery stenosis.

Methods: The research subject was the patients with moderate to severe carotid artery stenosis (50%≤) who underwent computed tomography angiography (CTA) from January 2010 to December 2017 at a single academic hospital. The primary outcome was a MACE (non-lacunar ischemic stroke, transient ischemic attack, myocardial infarct, unstable angina pectoris, revascularization of coronary artery or all-cause mortality). The analysis included demographic factors, HU and other high-risk features of carotid plaque on CTA: napkin-ring sign, spotty calcification, and ulceration.

Results: Reports from 879 CTAs conducted during the study period, including the word "carotid" and "stenosis" were screened. Among these cases, 117 carotid plaques were included in the analysis. During a median follow-up period 58 months (interquartile range 32.5 – 79 months), 44 patients with 48 (41%) carotid plaques experienced MACE. Cox proportional hazards model analysis revealed previous history of stroke (p=0.012), spotty calcification (p=0.031) and low attenuation (HU≤40) (p=0.001>) of carotid plaque as significant risk factor for MACE. Kaplan–Meier analysis and log rank test showed that low attenuation plaques were associated with a higher risk for MACE (p=0.001>). The log relative hazard plot showed that the risk of MACE decreased with HUs increased.

Conclusion: Several previous studies have shown that the HUs of symptomatic plaques are lower than those of asymptomatic plaques. This study demonstrated that HUs of carotid plaques could predict future MACE risk. This finding could be helpful in risk stratification of patients with moderate to severe carotid plaques.

Keywords: carotid stenosis, plaque, atherosclerosis, computed tomography, stroke, acute coronary syndrome.