Nonalcoholic fatty liver disease in pregnancy
Cerebral atherosclerosis in cirrhosis
NAFLD and prediction of gestational diabetes
Low urea level and hepatic decompensation
Cost-effectiveness of HCV screening in Korea
Cervicocerebral atherosclerosis and its hepatic and coronary risk factors in patients with liver cirrhosis

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Graphical Abstract

Abbreviations:
BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; HBV, hepatitis B virus; ICA, internal carotid artery; LC, liver cirrhosis; MRA, magnetic resonance angiography; OR, odds ratio; PS, propensity score

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Editor: Sang Gyune Kim, Soonchunhyang University College of Medicine, Korea

Received: Jul. 15, 2021 / Revised: Sep. 24, 2021 / Accepted: Oct. 11, 2021

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INTRODUCTION

Disease-related pathophysiological changes in patients with liver cirrhosis (LC) may influence the cerebrovascular system, in addition to the renal, pulmonary, and cardiac functions. Stroke is a leading cause of functional impairment and death worldwide, and atherosclerotic stenosis of a major cranial artery is one of the most common causes of in situ ischemic stroke, with a substantial risk of recurrent stroke episodes. However, it is unclear whether there is an association between LC and cerebrovascular atherosclerotic lesions.

LC has been traditionally believed to have a protective effect against cerebral atherosclerosis, based on factors such as arterial hypotension and reduced cholesterol synthesis and bleeding tendency. A population-based cohort study in an hepatitis B virus (HBV)-endemic area reported that chronic liver disorder, rather than seropositivity for HBV, was linked to a decreased risk of ischemic stroke. However, patients with decompensated cerebral autoregulation have been shown to maintain adequate arterial flow to the brain in response to hemodynamic changes, and, as a result, to be more vulnerable to cerebral ischemia. In addition, infection with hepatitis C virus is reported to accelerate cerebrovascular atherosclerosis.

Remarkably, it seems that because of the general differences in factors believed to be responsible for intracranial versus extracranial atherosclerotic plaque formation, cirrhotic patients may have different risks of occlusive events and associated infarction depending on the cerebral vascular site.

This study aimed to measure the comprehensive risk of subclinical cerebral atherosclerosis according to the cranial site in potential transplant recipients with LC who underwent standardized magnetic resonance angiography (MRA) of the head and neck as a pre-transplant assessment and to compare the results with those obtained in healthy controls. In addition, we investigated whether coronary artery disease (CAD) or coronary artery calcium (CAC) score, detected using 64-section computed tomography (CT), was associated with cervicocephalic atherosclerosis in cirrhotic patients.

Study Highlights
- The prevalence of atherosclerosis in the intracranial territory was significantly lower in patients with LC than in healthy controls.
- Thrombocytopenia was found to be inversely correlated with intracranial atherosclerosis in cirrhotic patients.
- CAC score ≥100 was an independent predictor of both cranial and cervical stenosis.

Background/Aims: We aimed to investigate the silent atherosclerotic burden of cervicocephalic vessels in cirrhotic patients compared with the general population, as well as the relevant risk factors including coronary parameters.

Methods: This study included 993 stroke-free patients with liver cirrhosis (LC) who underwent magnetic resonance angiography (MRA) of the head and neck as a pre-liver transplant assessment and 6,099 health checkup participants who underwent MRA examination. The two cohorts were matched for cerebrovascular risk factors, and the prevalence of atherosclerosis in major intracranial and extracranial arteries was compared in 755 matched pairs. Moreover, traditional, hepatic, and coronary variables related to cerebral atherosclerosis were assessed in cirrhotic patients.

Results: Overall, intracranial atherosclerosis was significantly less prevalent in the LC group than in the matched control group (2.3% vs. 5.4%, P=0.002), whereas the prevalence of extracranial atherosclerosis was similar (4.4% vs. 5.8%, P=0.242). These results were maintained in multivariate analyses of the pooled samples, with corresponding adjusted odds ratios [ORs] of LC of 0.56 and 0.77 (95% confidence intervals [CIs], 0.36–0.88 and 0.55–1.09). In the LC group, lower platelet count was inversely correlated with intracranial atherosclerosis (adjusted OR, 0.31; 95% CI, 0.13–0.76). Coronary artery calcium (CAC) score ≥100 was the only predictive factor for both intracranial and extracranial atherosclerosis (adjusted ORs, 4.06 and 5.43, respectively).

Conclusions: LC confers protection against intracranial atherosclerosis, and thrombocytopenia may be involved in this protective effect. High CAC score could serve as a potential surrogate for cervicocerebral vascular screening in asymptomatic cirrhotic patients. (Clin Mol Hepatol 2022;28:67-76)

Keywords: Atherosclerosis; Stroke; Liver cirrhosis; Transplantation
sclerotic changes in the cerebrovascular system were also exam-
ined in patients with CAD.

**MATERIALS AND METHODS**

**Study population**

This retrospective study included 993 cirrhotic patients with no
signs or symptoms of brain ischemia who underwent MRA of the
head and neck as a routine component of the pre-transplant cere-
brovascular assessment at Asan Medical Center, Seoul, Korea.
The patients’ data were collected and extracted from the data-
base of a liver transplant registry including 1,183 potential adult
recipients who were registered between October 2007 and De-
cember 2012. This database has been used in a previous study.11
MRA was not performed in 67 of the potential transplant recipi-
ents because of poor medical condition, contraindications includ-
ing metallic implants and claustrophobia, or patient refusal. Non-
cirrhotic patients with acute liver failure (n=32), chronic hepatitis
(n=41), idiopathic portal hypertension (n=6), and other liver dis-
ases such as polycystic liver disease (n=14), as well as patients
with prior or current histories of ischemic cerebrovascular accident
(n=24) or those with current structural brain parenchymal lesions
(n=6) were also excluded. Of the 993 patients included in the
study, 746 (75.1%) actually received a liver transplant.

A set of controls representing healthy individuals was derived
from 7,152 health checkup participants who underwent MRA with
the same protocol at the health promotion center of our institu-
tion during the same period as the cirrhotic patients. Individuals
who had a history of cerebrovascular attack (n=287), brain paren-
chymal lesions (n=31), or any prior or current hepatic disease in-
cluding nonalcoholic fatty liver disease (n=735) were excluded.
The remaining 6,099 participants without warning signs and
symptoms of stroke were used as controls in the matching analy-
sis. This study was reviewed and approved by the Institutional Re-
view Board of Asan Medical Center (approval No. 2014-0760).

**MRA of the head and neck and evaluation of cerebral
atherosclerosis**

Head and neck MRA was performed using a three-dimensional
time-of-flight gradient echo technique in a 1.5- or 3.0-T magnetic
resonance scanner (1.5-T Magnetom Avanto and 3.0-T Skyra [Sie-
mens, Erlangen, Germany] or Achieva 3.0-T TX [Philips Health-
care, Best, Netherlands]) equipped with an eight-channel head
coil for the intracranial arteries and three-dimensional contrast-
enhanced MRA for extracranial evaluation. Intracranial large ves-
sels comprising the intracranial portion of the internal carotid ar-
tery (distal ICA), middle cerebral artery, anterior cerebral artery,
posterior cerebral artery, and basilar trunk artery were assessed
using the Warfarin-Aspirin Symptomatic Intracranial Disease
method.12–14 Severe intracranial atherosclerosis was defined as
≥50% stenosis in at least one relevant artery.13–15 The extracranial
major vessels corresponding to the extracranial portion of the
ICA, vertebral artery, subclavian artery, and common carotid ar-
tery were evaluated according to the North American Symptomat-
ic Trial Collaborators criteria.16 Severe extracranial atherosclerosis
was defined as ≥70% stenosis in at least one of the extracranial
arteries.16 Representative MRA images of intracranial and extra-
cranial atherosclerosis are shown in Supplementary Figure 1.

**Assessment of coronary artery stenosis and calcium
score**

CT scanners with ≥64 detector rows were used for coronary CT
angiography and CAC scoring. Coronary artery stenosis was eval-
uated as described previously.11 A ≥50% narrowing in at least
one coronary artery was defined as obstructive CAD.17 CAC scores
were calculated with an automated, computerized software pro-
gram using the Agatston scoring method.17 The participants were
grouped according to the following CAC score categories: 0,
1–99, and ≥100.18,19

**Identification of cerebrovascular risk factors**

Demographic and clinical data, including age, sex, family history
of cerebrovascular accident, smoking status, body mass index
(BMI), presence of hypertension, diabetes mellitus, and hyperli-
pidemia, together with other blood test results, were collected
from all study participants at the time of MRA evaluation. Arterial
hypertension was defined as systolic blood pressure ≥140 mmHg
or diastolic blood pressure ≥90 mmHg, or current use of antihy-
pertensive medications.20 The use of diuretics for the management
of ascites, or of nonselective β-blockers for the primary or sec-
ondary prevention of variceal bleeding, was not considered to indicate
hypertension if the patient had not been diagnosed with hyper-
tension before the administration of these drugs. Diabetes melli-
tus was diagnosed when patients were using oral hypoglycemic
agents or insulin or had a fasting plasma glucose level of ≥126
mg/dL on the first assay and on at least one further assay on a later day.\textsuperscript{21} Hyperlipidemia was defined as fasting low-density lipoprotein levels $\geq$ 190 mg/dL or use of lipid-lowering drugs.\textsuperscript{22}

**Statistical analysis**

Student’s t-test was used to compare quantitative variables, and the chi-square test was used to compare qualitative variables. Propensity score (PS) matching was implemented to reduce the effect of selection bias and potential confounding between patients with LC and controls. The variables used for PS matching were age, sex, smoking status, family history of cerebrovascular incident, hyperlipidemia, hypertension, diabetes mellitus, and BMI. PS matching was performed through greedy matching using a caliper of 0.2 standard deviation of the logit of the PS, and statistical inference was completed with Cox regression models, with robust standard errors that accounted for the clustering of matched pairs using the SAS macro gmatch “gmatch”\textsuperscript{23}. Absolute standardized differences were used to assess the balance after matching. Subsequently, McNemar’s test was used to compare patients with LC and the matched controls in terms of the rates of intracranial and extracranial atherosclerosis, followed by the rate of atherosclerosis at any location. To explore factors related to cerebrovascular atherosclerosis in patients with LC, all clinically relevant variables with $P < 0.05$ in the univariate analysis were entered into a multivariate logistic regression analysis. The severity of multicollinearity in the regression analysis was assessed by measuring the variance inflation factor. All statistical analyses were performed using R version 4.03 (R Foundation for Statistical Computing, Vienna, Austria) or SAS version 9.3 (SAS Institute, Cary, NC, USA). All reported $P$ values were two-sided, and $P < 0.05$ was considered significant.

**RESULTS**

**Baseline characteristics of the LC and control cohorts**

The baseline hepatic parameters of the 993 patients with LC are presented in Table 1. Most patients were men (76.9%) and had HBV infection (71.3%), which is a leading cause of chronic liver disease in South Korea.\textsuperscript{24} The mean patient age was 53.3±8.0 years. The Child-Pugh class was A in 298 patients (30.0%), B in 391 patients (39.4%), and C in 304 patients (30.6%). The demographics and established cerebrovascular risk factors of the LC and control cohorts are shown in Supplementary Table 1. After PS matching, 755 matched pairs with balanced baseline profiles were generated, with post-matching absolute standardized differences of $<0.25$ (Supplementary Table 1).

**Landscape of cerebrovascular atherosclerosis in the LC and control cohorts**

Among all 993 patients with LC, atherosclerosis in relevant major arteries was located in the intracranial area in 24 patients (2.4%), in the extracranial area in 47 patients (4.7%), and in both areas in eight patients (0.8%) (Fig. 1A). An analysis of the pooled cohorts ($n=7,092$) showed that the rates of atherosclerosis of intracranial and extracranial arteries were significantly lower in cirrhotic patients than in the healthy examinees (Fig. 1A). In the matched pairs, the overall prevalence of intracranial atherosclerosis was also significantly lower in the LC group than in the matched control group (2.3% vs. 5.4%, $P=0.002$), whereas there

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value ($n=993$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3±8.0</td>
</tr>
<tr>
<td>Male sex</td>
<td>764 (76.9)</td>
</tr>
<tr>
<td>Etiology of chronic liver disease</td>
<td></td>
</tr>
<tr>
<td>HBV infection</td>
<td>708 (71.3)</td>
</tr>
<tr>
<td>HCV infection</td>
<td>75 (7.6)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>134 (13.5)</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>40 (4.0)</td>
</tr>
<tr>
<td>Others</td>
<td>36 (3.6)</td>
</tr>
<tr>
<td>INR</td>
<td>1.38 (1.19–1.62)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.9 (1.2–4.0)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.9 (2.5–3.4)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.75 (0.63–0.90)</td>
</tr>
<tr>
<td>Platelet count (10$^3$/µL)</td>
<td>66 (45–96)</td>
</tr>
<tr>
<td>CTP classification</td>
<td>298 (30.0)/391 (39.4)/304 (30.6)</td>
</tr>
<tr>
<td>MELD score</td>
<td>13 (10–18)</td>
</tr>
<tr>
<td>Presence of HCC</td>
<td>547 (55.1)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation, median (interquartile range), or number (%). HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; CTP, Child-Turcott-Pugh; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.
was no significant between-pair difference in terms of extracranial vascular disease (4.4% vs. 5.8%, \( P=0.242 \); Fig. 1B). The results of the multivariate regression analyses according to the location of atherosclerotic lesions in the pooled cohorts were similar to those for the matched pairs (adjusted odds ratio [OR], 0.56; 95% confidence interval [CI], 0.36–0.88; \( P=0.011 \) for intracranial atherosclerosis and OR, 0.77; 95% CI, 0.55–1.09; \( P=0.139 \) for extracranial atherosclerosis; Table 2). The rates of severe atherosclerosis in intracranial and extracranial vessels were comparable in the matched pairs (0.4% vs. 0.8%, \( P=0.504 \) and 0.3% vs. 0.5%,

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**Table 2.** Independent predictive factors of cervicocephalic atherosclerotic disease in the pooled cohort (n=7092)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intracranial atherosclerosis</th>
<th>Extracranial atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI  ( P )-value</td>
<td>OR 95% CI  ( P )-value</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0.56  0.36–0.88  0.011</td>
<td>0.77  0.55–1.09  0.139</td>
</tr>
<tr>
<td>Age</td>
<td>1.08  1.07–1.10  &lt;0.001</td>
<td>1.09  1.08–1.10  &lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.82  0.66–1.01  0.066</td>
<td>1.57  1.21–2.04  0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>Current</td>
<td>-</td>
<td>1.52</td>
</tr>
<tr>
<td>Former</td>
<td>-</td>
<td>1.07</td>
</tr>
<tr>
<td>BMI</td>
<td>1.03  0.99–1.07  0.119</td>
<td>1.01  0.98–1.04  0.514</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.61  1.29–2.01  &lt;0.001</td>
<td>1.42  1.17–1.72  &lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.64  1.26–2.12  &lt;0.001</td>
<td>1.81  1.46–2.25  &lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.15  0.90–1.47  0.255</td>
<td>1.60  1.31–1.96  &lt;0.001</td>
</tr>
</tbody>
</table>

Covariates with \( P<0.05 \) in univariate analysis, together with the presence of cirrhosis, were included in a multivariate analysis using a logistic regression model.

There was no significant multicollinearity, as all variance inflation factor values measured between variables were <5.

OR, odds ratio; CI, confidence interval; BMI, body mass index.
Among all patients with LC, the most frequently affected site by intracranial disease was the middle cerebral artery or distal ICA and that by extracranial disease was the vertebral artery or ICA (Supplementary Table 1). In the matched pairs, a significant difference between the rates of atherosclerosis in the two groups was noted only in the intracranial posterior cerebral artery (0.3% in cirrhotic patients vs. 1.9% in controls, \( P=0.006 \)) and not in any extracranial arteries (Fig. 2).

### Association between cerebrovascular atherosclerosis and CAD in the LC cohort

Coronary CT with CAC score measurement was performed in all patients with LC, excluding one patient with chronic kidney disease and one patient with a prior history of coronary bypass surgery, both of whom did not have any signs or symptoms of cardiac ischemia at the time of coronary evaluation. Obstructive coronary stenosis was found in 79 of the other 991 patients (8.0%). The prevalence of obstructive coronary disease was significantly higher in patients with intracranial and extracranial atherosclerosis than in their counterparts (Supplementary Table 2). In terms of coronary calcification, the CAC score was 0 in 604 patients (60.9%), 1–99 in 235 patients (23.7%), and \( \geq 100 \) in 152 patients (15.3%). The median CAC scores significantly differed between...
patients with and without cervicocephalic atherosclerosis regardless of location (all \(P<0.001\)). Significant negative and positive correlations were also observed between the existence of atherosclerosis in both intracranial and extracranial sites and CAC scores of 0 and \(\geq 100\), respectively (Fig. 3).

**Risk factors for cerebrovascular atherosclerosis in the LC cohort according to location**

Of the factors that were significant in the univariate analysis of the 991 cirrhotic patients, the association of thrombocytopenia with intracranial atherosclerosis remained significant in a multivariate model (adjusted OR, 0.31; 95% CI, 0.13–0.76; \(P=0.010\)) (Fig. 4, Supplementary Table 3). In addition, CAC score \(\geq 100\) was an independent predictor of a stenotic intracranial artery (adjusted OR, 4.06; 95% CI, 1.45–11.41; \(P=0.008\)), whereas obstructive CAD was not.

In terms of the extracranial vascular structures, CAC score \(\geq 100\) was also significantly correlated with atherosclerotic stenosis (adjusted OR, 5.43; 95% CI, 2.68–11.00, \(P<0.001\)). Neither platelet

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**Figure 4.** Multivariate analysis of risk factors for intracranial and extracranial atherosclerosis in the 991 cirrhotic patients with coronary computed tomography results. (A) CAC \(\geq 100\) is predictive of intracranial atherosclerosis, and platelet count <1x10^5/µL is negatively associated with intracranial stenosis. (B) CAC \(\geq 100\) and age \(\geq 60\) years are predictors of extracranial atherosclerosis. In the multivariate analysis, obstructive coronary artery stenosis is not independently associated with the presence of atherosclerotic change in the head and neck. OR, odds ratio; CI, confidence interval; CAC, coronary artery calcium.

count nor prothrombin time was associated with cervical atherosclerosis in the multivariate analysis. The etiology of liver disease was not significant in terms of the relationship to atheroma at either location.

**DISCUSSION**

The effect of LC per se on the formation or prevention of atheroma in the brain vasculature remains uncertain. Given the tendency of cerebral atherosclerotic disease to lead to transient or permanent ischemic attacks, individuals with any grade of stenosis are recommended to receive treatment for risk factors and undergo carotid duplex surveillance annually. In this PS-matched per-location study based on full MRA evaluation of the brain vascular anatomy, overall stenosis in the intracranial major arteries was detected in 2.3% of cirrhotic patients, which is a significantly lower rate than that observed in the matched healthy controls (5.4%), whereas the corresponding rates for the cervical vessels were not significantly different. Intracranial stenosis was inversely associated with lower platelet count, which usually correlates with cirrhosis-induced portal hypertension. Importantly, CAC scores detected with coronary CT, rather than coronary artery obstruction, was a robust predictor of atherosclerosis in both intracranial and extracranial sites.

Intracranial atherosclerosis is particularly prevalent in Asians. In one report, it was detected in 7% of a Chinese population aged >40 years, a rate similar to that observed in our healthy Korean cohort. Nevertheless, the prevalence of silent intracranial disease decreased by almost 3-fold in our cirrhotic patients, to a severe stenosis rate of 0.3% at most, although the frequency of atheromatous changes in the most affected arteries (i.e., middle cerebral artery and ICA) did not differ between the LC and control groups. These observations may explain the reduced risk of overt cerebrovascular events in cirrhotic patients, which has also been observed in pathological autopsies and population-based longitudinal studies.

In general, advanced cirrhosis is accompanied by quantitative or functional abnormalities of platelets. It has become clear that, besides their primary role in hemostasis, platelets are key cellular components of inflammatory-dependent atherothrombosis. In vitro and in vivo studies have found that platelets adhere to the vascular endothelium of the arteries as an initial step in chronic vascular damage and thereafter become activated and release a variety of chemokines, which enhance inflammatory processes and localized cell recruitment. Thus, this crosstalk between platelets, recruited myeloid and immune cells, and the vascular endothelium creates an atherogenic milieu and promotes plaque formation. Therefore, it is likely that such platelet-induced chronic inflammatory processes within the vascular wall are impaired in cirrhotic patients with their innate thrombocytopenia or thrombocytopathy, thus protecting against cerebrovascular remodeling. This hypothesis is supported by our finding of an inverse relationship between thrombocytopenia and atherosclerotic development in intracranial vessels in patients with LC. Conversely, the impact of only traditional risk factors for extracranial atherosclerosis, such as age ≥60 years and CAC score ≥100, even in cirrhotic patients may explain their similar prevalence of the disease to that in noncirrhotic populations.

As cardiac atherosclerosis and cerebral atherosclerosis share similar risk factors and pathogenic mechanisms, they have repeatedly been found together in post-mortem examinations and general population-based studies. CAC score, which is an established surrogate for coronary atherosclerosis and a strong predictor of future cardiovascular events, has been shown to be associated with the coexistence of atheroma in other vascular territories, including the arteries supplying blood to the brain, as well as with the incidence of stroke in the general population. This is the first study to address the predictive value of the extent of coronary calcification for both intracranial and extracranial atherosclerosis in a set of patients with LC. According to USA guidelines, carotid/vertebral testing with duplex ultrasonography should be considered in selected patients with multiple risk factors for atherosclerotic disease, such as a history of peripheral artery disease or CAD, smoking, and hypercholesterolemia, although not on a routine basis. According to our findings, CAC score measurement, a simple, safe, and easily interpretable method, could be used as a risk stratification tool in screening for carotid artery disease in cirrhotic patients. In our study, one normolipemic patient with LC who had a high CAC score (i.e., 121.4) and extracranial common carotid artery narrowing on MRA before liver transplant experienced an ischemic stroke event during the median follow-up of 5 years.

The current study had certain limitations. First, chronic viral hepatitis as the cause of LC in our Korean cohort was mostly due to HBV. Although the individual causes of liver disease per se were not found to be associated with the occurrence of cerebral atherosclerosis in our multivariate analysis, additional studies of samples of different ethnic origins and with different distributions of the causes of hepatic disease would be helpful in clarifying the
association between cirrhosis and cerebrovascular stenosis. Second, with respect to the diagnostic performance of the assessment method used in our study, although MRA tends to somewhat overestimate the severity of vascular stenosis compared with conventional digital angiography, it can provide accurate structural information on the cervical and cerebral arteries and yield measurements of the diameters of the stenotic lesions, unlike carotid or transcranial Doppler tests. In conclusion, our data point to a protective role of LC against the development of intracranial atherosclerosis, but not of extracranial atherosclerosis. The thrombocytopenia associated with cirrhosis may have an anti-atherogenic effect on the cerebral arteries in patients with LC. High CAC levels could potentially be included in the criteria for cervicocephalic vascular screening in asymptomatic cirrhotic patients.

Authors' contribution
J. An and H.D. Kim contributed to the study concept and design; the acquisition, analysis, and interpretation of data; statistical analysis; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.
S.O. Kim contributed to the statistical analysis and critical revision of the manuscript for important intellectual content.
H.I. Kim, G.W. Song, and H.C. Lee contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.
J.H. Shim contributed to the study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervision of the study.

Acknowledgements
This study was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2017R1E1A1A01074298) and the research fund of Hanyang University (HY-201900000002619).

Conflicts of Interest
The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL
Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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