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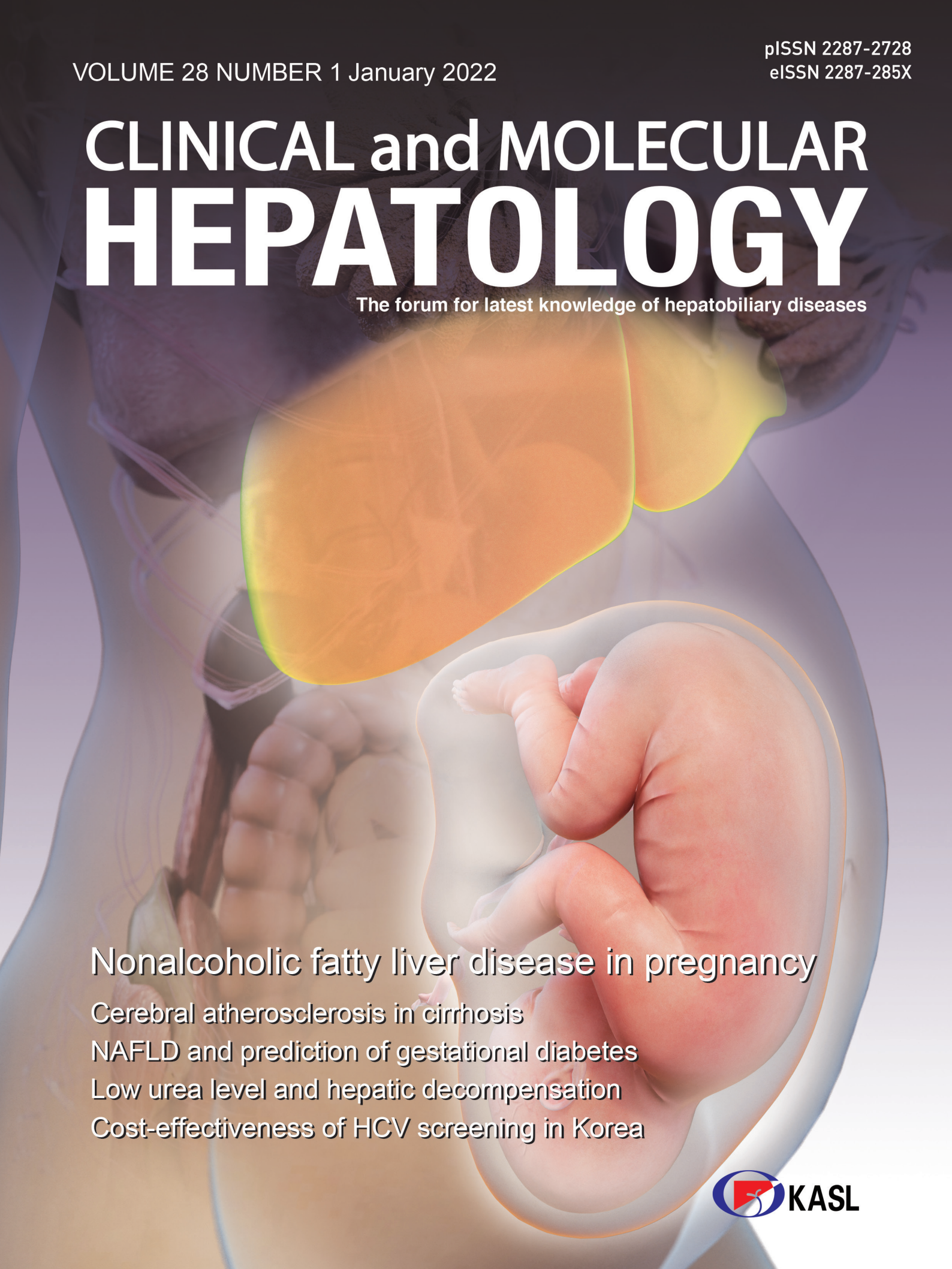

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Original Article

Cervicocerebral atherosclerosis and its hepatic and coronary risk factors in patients with liver cirrhosis

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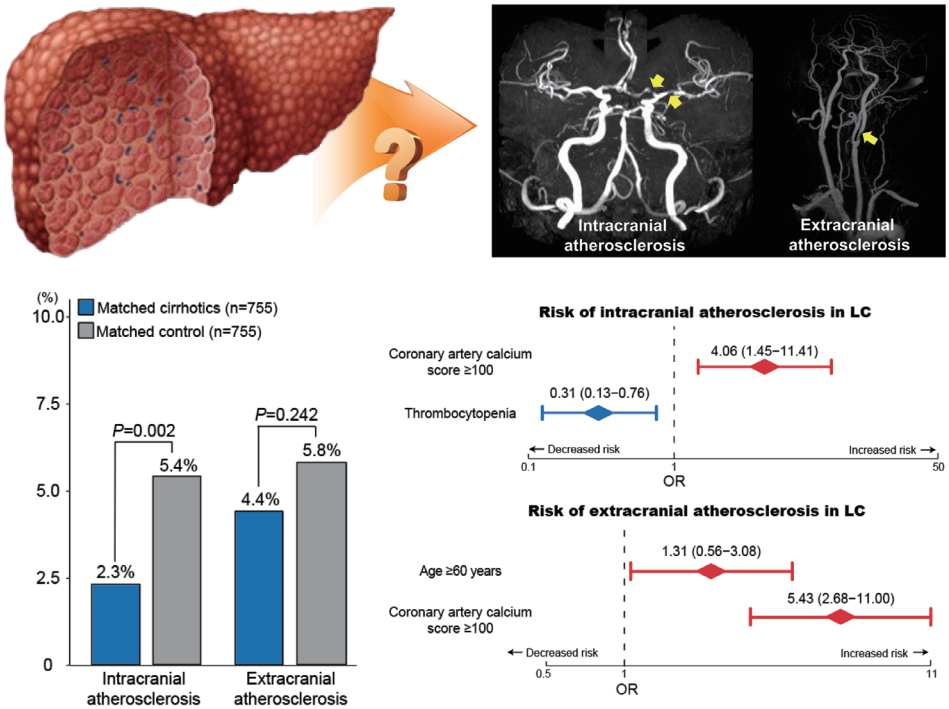
Graphical Abstract



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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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

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.

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.[1-3] 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.[4]

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.[5,6] 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.[7] 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.[8,9]

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.[10]

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. Cranial site-specific risk factors for silent athero-

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sclerotic changes in the cerebrovascular system were also examined 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 cerebrovascular assessment at Asan Medical Center, Seoul, Korea. The patients' data were collected and extracted from the database of a liver transplant registry including 1,183 potential adult recipients who were registered between October 2007 and December 2012. This database has been used in a previous study.[11] MRA was not performed in 67 of the potential transplant recipients because of poor medical condition, contraindications including 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 diseases 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 institution during the same period as the cirrhotic patients. Individuals who had a history of cerebrovascular attack (n=287), brain parenchymal lesions (n=31), or any prior or current hepatic disease including 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 analysis. This study was reviewed and approved by the Institutional Review 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 [Siemens, Erlangen, Germany] or Achieva 3.0-T TX [Philips Healthcare, Best, Netherlands]) equipped with an eight-channel head coil for the intracranial arteries and three-dimensional contrast-enhanced MRA for extracranial evaluation. Intracranial large vessels comprising the intracranial portion of the internal carotid artery (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 artery were evaluated according to the North American Symptomatic 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 extracranial 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 evaluated as described previously.[11] A ≥50% narrowing in at least one coronary artery was defined as obstructive CAD.[11] CAC scores were calculated with an automated, computerized software program 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 hyperlipidemia, 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 antihypertensive medications.[20] The use of diuretics for the management of ascites, or of nonselective β-blockers for the primary or secondary prevention of variceal bleeding, was not considered to indicate hypertension if the patient had not been diagnosed with hypertension before the administration of these drugs. Diabetes mellitus 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.[21] Hyperlipidemia was defined as fasting low-density lipoprotein levels ≥190 mg/dL or use of lipid-lowering drugs.[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".[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.[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 1. Baseline hepatic parameters of the entire cohort of cirrhotic patients

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

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.

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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%,

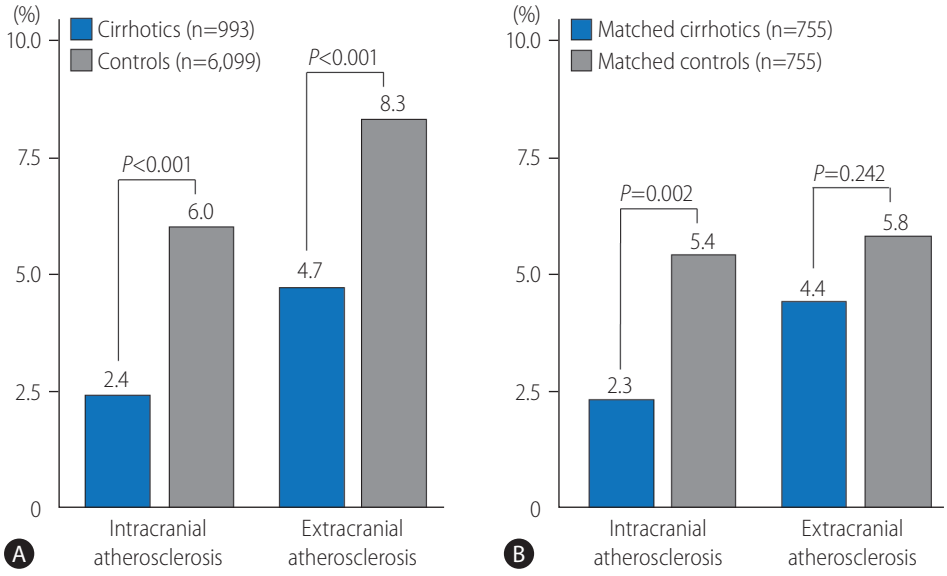

Figure 1. Prevalence of cervicocephalic atherosclerosis on magnetic resonance angiography in the (A) pooled cohort (n=7,092) and (B) matched cohort (n=1,510). The prevalence of atherosclerosis is consistently lower in patients with liver cirrhosis (LC) than in controls in the pooled cohort regardless of the vascular location (all *P*<0.001). In the matched cohort, vascular stenosis is less prevalent in patients with LC than in the matched controls in terms of intracranial disease (2.3% vs. 5.4%, *P*=0.002) but not extracranial disease (4.4% vs. 5.8%, *P*=0.242).

Table 2. Independent predictive factors of cervicocephalic atherosclerotic disease in the pooled cohort (n=7,092)

Variable	Intracranial atherosclerosis			Extracranial atherosclerosis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Liver cirrhosis	0.56	0.36–0.88	0.011	0.77	0.55–1.09	0.139
Age	1.08	1.07–1.10	<0.001	1.09	1.08–1.10	<0.001
Male sex	0.82	0.66–1.01	0.066	1.57	1.21–2.04	0.001
Smoking status						
Never	-	-	-	1.0		
Current	-	-	-	1.52	1.14–2.02	0.005
Former	-	-	-	1.07	0.84–1.36	0.602
BMI	1.03	0.99–1.07	0.119	1.01	0.98–1.04	0.514
Hypertension	1.61	1.29–2.01	<0.001	1.42	1.17–1.72	<0.001
Diabetes mellitus	1.64	1.26–2.12	<0.001	1.81	1.46–2.25	<0.001
Hyperlipidemia	1.15	0.90–1.47	0.255	1.60	1.31–1.96	<0.001

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.

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P=0.682; Supplementary Table 1).

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 ≥100 in 152 patients (15.3%). The median CAC scores significantly differed between

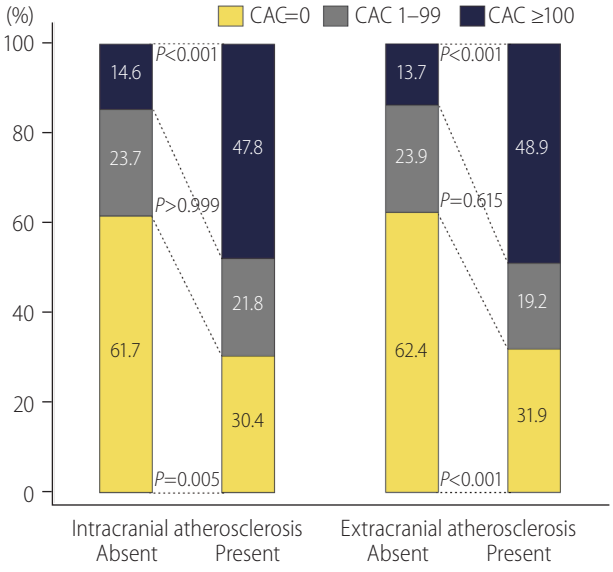

Figure 3. Distribution of CAC scores according to the presence of intracranial and extracranial atherosclerosis in the 991 patients with liver cirrhosis who underwent coronary evaluation. More than half of the individuals with normal cerebral arteries have CAC=0, whereas those with either cervical or cephalic atherosclerosis were less likely to have CAC=0 (*P*=0.005 and *P*<0.001, respectively). CAC scores ≥100 are observed in 47.8% and 48.9% of individuals with intracranial and extracranial atherosclerosis, respectively. In comparison, the respective prevalence is 14.6% and 13.7% among those without cerebral atherosclerotic change (*P*<0.001). CAC, coronary artery calcium.

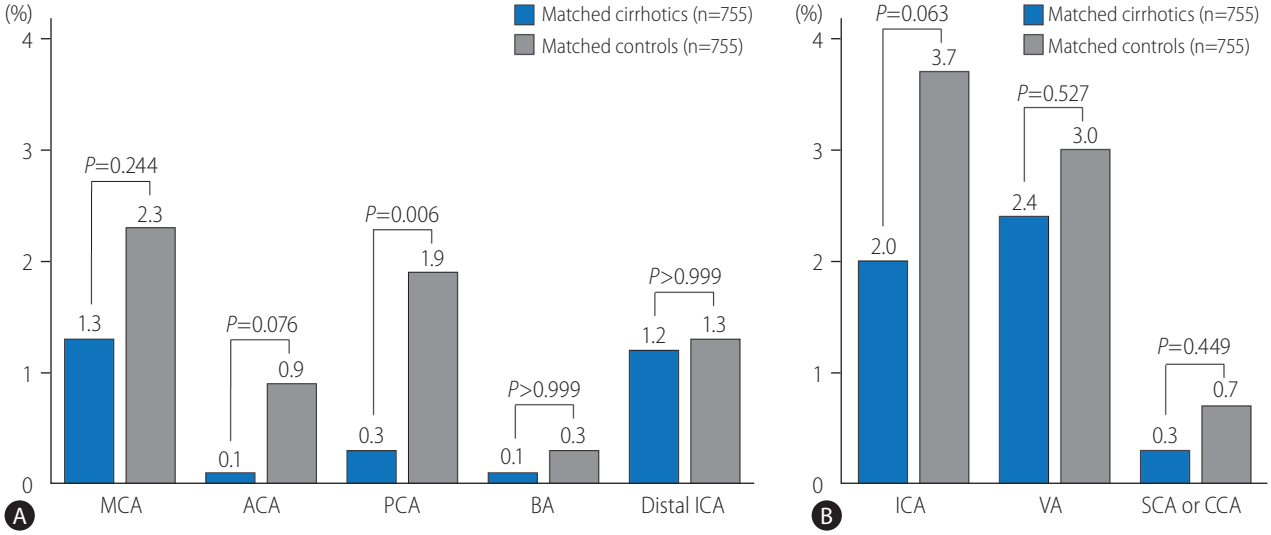

Figure 2. Distribution of cervicocephalic atherosclerosis in the matched cohort (n=1,510) according to vascular anatomy. (A) Intracranial atherosclerotic disease. (B) Extracranial atherosclerotic disease. A significant difference in the rate of atherosclerosis between the two groups is noted only in the intracranial PCA (0.3% in cirrhotic patients vs. 1.9% in controls, *P*=0.006) and not in any extracranial arteries. MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; VA, vertebral artery; SCA, subclavian artery; CCA, common carotid artery.

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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 ≥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 ≥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 ≥100 was also significantly correlated with atherosclerotic stenosis (adjusted OR, 5.43; 95% CI, 2.68–11.00, $P<0.001$). Neither platelet

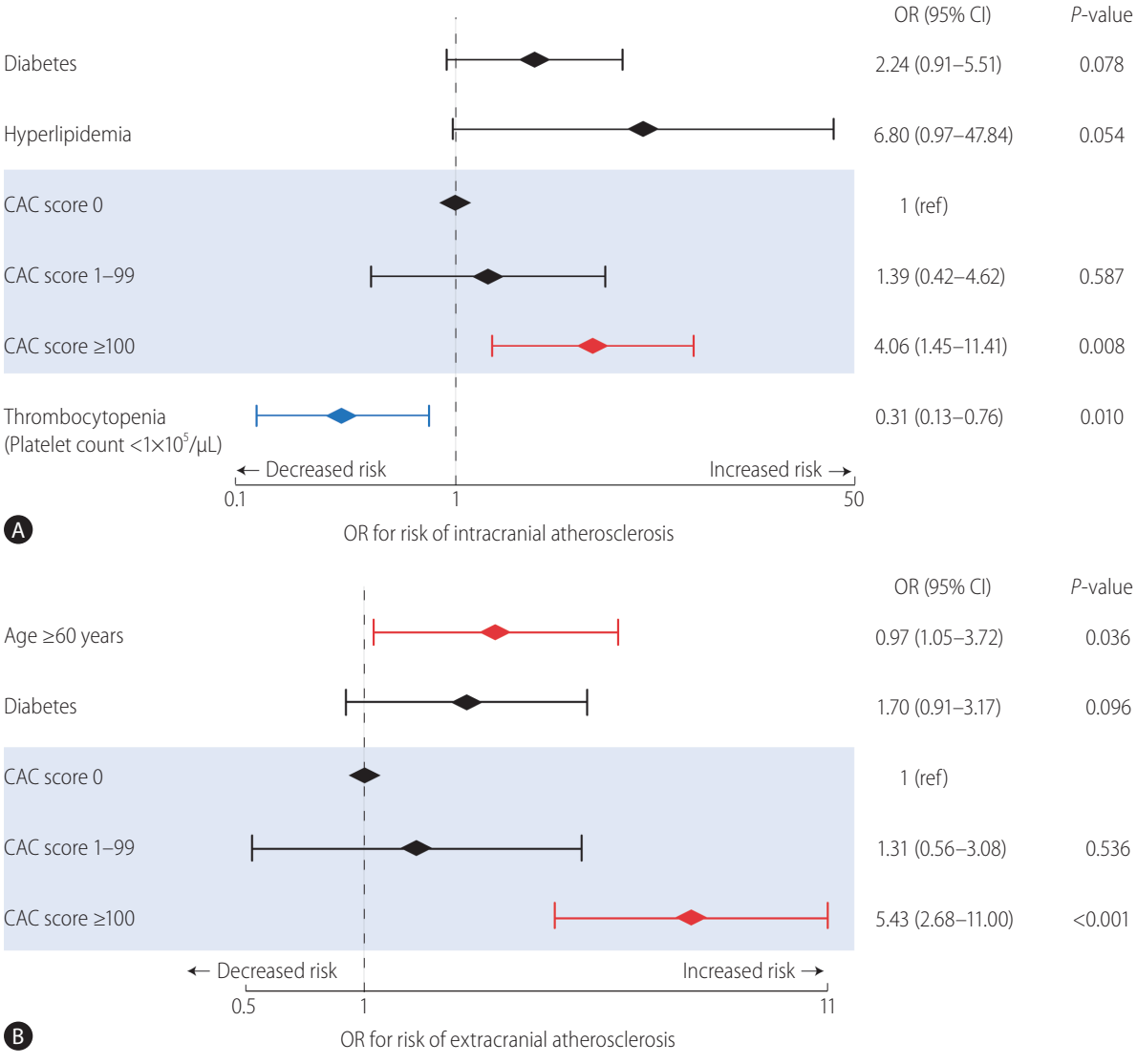

Figure 4. Multivariate analysis of risk factors for intracranial and extracranial atherosclerosis in the 991 cirrhotic patients with coronary computed tomography results. (A) CAC ≥100 is predictive of intracranial atherosclerosis, and platelet count <100,000/mm^3 is negatively associated with intracranial stenosis. (B) CAC ≥100 and age ≥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.

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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.[8,25] 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.[26] 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,[27] a rate similar to that observed in our healthy Korean cohort.[28] 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.[4,29]

In general, advanced cirrhosis is accompanied by quantitative or functional abnormalities of platelets.[30] It has become clear that, besides their primary role in hemostasis, platelets are key cellular components of inflammatory-dependent atherothrombosis.[31] *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.[32] Thus, this crosstalk between platelets, recruited myeloid and immune cells, and the vascular endothelium creates an atherogenic milieu and promotes plaque formation.[31] 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.[33,34] CAC score, which is an established surrogate for coronary atherosclerosis and a strong predictor of future cardiovascular events,[35] 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.[36,37] 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.[38] 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 normolipidemic 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.[24] 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

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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.[39]

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.

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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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