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

Running title: Cerebral Atherosclerosis in Cirrhosis

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Conflict of interest

The authors declare no competing interests.

Author contributions

J An and HD 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.

SO Kim contributed to the statistical analysis and critical revision of the manuscript for important intellectual content.

Hl Kim, GW Song, and HC Lee contributed to the acquisition of data and critical revision of the manuscript for important intellectual content.

JH 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.

Abbreviations

LC, liver cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; MRA, magnetic
resonance angiography; CAD, coronary artery disease; CAC, coronary artery calcium; CT, computed tomography; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar trunk artery; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease; VA, vertebral artery; SCA, subclavian artery; CCA, common carotid artery; NASCET, North American Symptomatic Trial Collaborators; BMI, bone mass index; PS, propensity score; VIF, variance inflation factor; OR, odds ratio; CI, confidence internal.
ABSTRACT

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

Methods: The study population consisted of 993 stroke-free subjects with LC who were screened by magnetic resonance angiography (MRA) of the head and neck as a pre-liver transplant workup, and 6,099 health checkup participants who underwent MRA examination. The two cohorts were matched for cerebrovascular risk factors, and the prevalence rates of atherosclerosis in the major intracranial and extracranial arteries were compared in 755 matched pairs. Also, traditional, hepatic and coronary variables related to the cerebral atherosclerosis were assessed in cirrhotics.

Results: Overall, intracranial atherosclerosis was significantly less prevalent in the LC samples than the matched controls (2.3% vs. 5.4%; \( P = 0.002 \)), whereas the prevalence of extracranial atherosclerosis were similar (4.4% vs. 5.8%; \( P = 0.242 \)). These results were maintained in multivariate analyses in the pooled samples, with the corresponding adjusted odds ratios (ORs) for LC of 0.56 and 0.77 (95% CIs, 0.36-0.88 and 0.55-1.09), respectively. In the cirrhotic series, 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 factor predicting both intra- and extra-cranial atherosclerosis (adjusted ORs, 4.06 and 5.43; 95% CIs, 1.45-11.41 and 2.68-11.00, respectively).

Conclusions: Our data suggest that LC confers protection against intracranial atherosclerosis, and that thrombocytopenia may be involved in this protection. High
CAC score could serve as a potential surrogate for cervicocerebral vascular screening in asymptomatic cirrhotics.

**Key words:** atherosclerosis; stroke; cirrhosis; transplantation

**HIGHLIGHTS**

- Prevalence rate of atherosclerosis in the intracranial territory was significantly lower in the patients with liver cirrhosis than healthy controls.
- Thrombocytopenia was found to be inversely correlated with intracranial atherosclerosis in the cirrhotic patients.
- Coronary artery calcium (CAC) score >100 was an independent predictor of both cranial and cervical stenosis.
INTRODUCTION

The cerebrovascular system may be influenced by disease-related pathophysiological changes in patients with liver cirrhosis (LC), as are renal, pulmonary, and cardiac functions.1-3 Stroke is a leading global cause of functional impairment and death, 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

The classical conception has been that LC has a protective effect on cerebral atherosclerosis, based on factors such as arterial hypotension and reduced levels of cholesterol synthesis and of bleeding tendency.5,6 A population-based cohort study in a hepatitis B virus (HBV)-endemic area reported that chronic liver disorder rather than seropositivity for HBV was linked to 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 (HCV) is reported to accelerate cerebrovascular atherosclerosis.8,9 Remarkably, it seems that, because of the general difference between the factors thought to be responsible for intracranial versus extracranial atherosclerotic plaque formation, cirrhotic patients may have different risks of occlusive events and associated infarction as a function of 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 undergoing standardized magnetic resonance angiography (MRA) of the head
and neck as pre-transplant screening, and to compare the results with those for healthy controls. In addition, we investigated whether coronary artery disease (CAD) and/or coronary artery calcium (CAC) score, detected by 64-section computed tomography (CT), was associated with cervicocephalic atherosclerosis in the cirrhotic samples. Cranial site-specific risk factors for silent atherosclerotic 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 part of pre-transplant cerebrovascular workup at the Asan Medical Center, Seoul, Korea. The patient data were collected and extracted from the database of a liver transplant registry of 1,183 potential adult recipients who were registered from October 2007 to December 2012. This database was used in a previous report. MRA was not performed in 67 of the potential transplant recipients due to poor medical condition, contraindications including metallic implants and claustrophobia, or patient refusal. Other patients excluded were 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 current structural brain parenchymal lesions (n=6). Of the 993 patients included in the study, 746 (75.1%) actually received liver transplants.
A set of controls representing healthy subjects was derived from 7,152 health check-up recipients who underwent MRA with the same protocol at the health promotion center of our institution over the same period as the cirrhotic patients. Subjects 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 subjects without stroke warning signs and symptoms were used as controls in the matching analysis. This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (IRB no. 2014-0760).

**Acquisition of MRA of the Head and Neck and Evaluation of Cerebral Atherosclerosis**

Head and neck MRA was taken using a 3-dimensional time-of-flight gradient echo technique on a 1.5T or 3.0T MR scanner (1.5T Magnetom Avanto and 3.0T Skyra [Siemens, Erlangen, Germany], or Achieva 3.0T TX [Philips Healthcare, Best, the Netherlands]) equipped with an 8-channel head coil for intracranial arteries and 3-dimensional contrast-enhanced MRA for extracranial evaluation. Intracranial large vessels comprising the intracranial portion of the internal carotid artery (Distal ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and basilar trunk artery (BA) were assessed by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method.\textsuperscript{12-14} Severe intracranial atherosclerosis was defined as $\geq 50\%$ stenosis in at least one relevant artery.\textsuperscript{13-15} Evaluation of the extracranial major vessels corresponding to the extracranial portion of the internal carotid artery (ICA), vertebral artery (VA), subclavian artery
(SCA), and common carotid artery (CCA) was based on the North American Symptomatic Trial Collaborators (NASCET) criteria.\textsuperscript{16} Severe extracranial atherosclerosis was defined as \(\geq 70\%\) stenosis in at least one of the extracranial arteries.\textsuperscript{16} Representative MRA images of intracranial and extracranial atherosclerosis were shown in Fig. S1.

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

CT scanners with 64 or more detector rows were used for coronary CT angiography and scoring CAC. Coronary artery stenosis was evaluated as described previously.\textsuperscript{11} Narrowing of \(\geq 50\%\) in at least one coronary artery was defined as obstructive coronary artery disease.\textsuperscript{11} CAC scores were calculated with an automated, computerized software program using the Agatston scoring method.\textsuperscript{17} Subjects were grouped according to the following CAC score categories: 0, 1–99, and \(\geq 100\).\textsuperscript{18,19}

**Identification of cerebrovascular risk factors**

Demographic and clinical data such as 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 of the study subjects at the time of MRA evaluation. Presence of arterial hypertension was defined as systolic blood pressure \(\geq 140\) mmHg or diastolic blood pressure \(\geq 90\) mmHg, or current use of ant-hypertensive medication.\textsuperscript{20} The use
of diuretics for the management of ascites, or of nonselective β-blockers for primary or secondary prevention of variceal bleeding, was not considered to indicate hypertension if the patient had not been diagnosed as hypertension before administration of these drugs. Diagnosis of diabetes mellitus was established when patients were on oral hypoglycemic agents or insulin, or had fasting plasma glucose levels ≥126 mg/dL on the first assay and on at least one further assay on a later day. Presence of hyperlipidemia was defined if patients were taking lipid-lowering drugs or had fasting low-density lipoprotein levels ≥190 mg/dL.

Statistical Analysis

Student’s t-test was used to compare quantitative variables, and the χ2 test was used to compare qualitative variables. Propensity score (PS) matching was implemented to reduce the effect of selection bias and potential confounding between LC patients and controls. 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 by Greedy matching using a caliper of 0.2 standard deviations of the logit of the propensity score, and statistical inference was completed with Cox regression models, with robust standard errors that accounted for the clustering of matched pairs using SAS macro, gmatch. Absolute standardized differences were used to diagnose the balance after matching. Patients with LC were subsequently compared, using McNemar’s test, with matched controls in terms of rates of intracranial and extracranial atherosclerosis, followed by atherosclerosis at any location. In order to explore factors related to cerebrovascular atherosclerosis in the samples with LC,
all clinically relevant variables with $P<0.05$ in the univariate analysis were entered into a multivariate logistic regression. The severity of multicollinearity in the regression analysis was assessed by measuring the variance inflation factor (VIF). All statistical analyses were performed using R version 4.0.3 or SAS version 9.3. All reported $P$ values were two-sided, and a $P$ value <0.05 was considered significant.

**RESULTS**

**Baseline Characteristics of the LC and Control Cohorts**

Baseline hepatic parameters of the 993 patients with LC are presented in Table 1. Most patients were male (76.9%) and had HBV infection (71.3%), which is known to be a leading cause of chronic liver disease in South Korea. Mean age was 53.3 ± 8.0 years. Child-Pugh staging was A in 298 patients (30.0%), B in 391 patients (39.4%), and C in 304 patients (30.6%). Demographics and established cerebrovascular risk factors of the patient and control sets are shown in Table S1. After PS matching, 755 matched pairs with balanced baseline profiles were generated, with post-matching absolute standardized differences of <0.25 (Table S1).

**Landscape of Cerebrovascular Atherosclerosis in the LC and Control Cohorts**

Among the entire 993 LC patients, atherosclerosis in relevant major arteries was located in the intracranial area in 24 (2.4%) patients, in the extracranial area in 47 (4.7%), and in both areas in 8 (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 the cirrhotic patients than the healthy examinees (Fig. 1A). In the matched pairs, the overall prevalence of intracranial atherosclerosis was also significantly lower in the LC group than the matched controls (2.3% vs. 5.4%, *P*=0.002), whereas there 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 multivariable regression analyses according to location of atherosclerotic lesions in the pooled cohorts were similar to those for the matched pairs (adjusted odds ratios [OR] 0.56, 95% confidence intervals [CI] 0.56 [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%, *P*=0.682; Table S1).

Among all LC patients, the MCA or distal ICA were most frequently affected by intracranial disease, and the VA or ICA by extracranial disease (Table S1). In the matched pairs, a significant difference between the rates of atherosclerosis in the two groups was noted only for the intracranial PCA (0.3% in cirrhotics vs. 1.9% in controls, *P*=0.006), and not in any extracranial arteries (Fig. 2).

The association between Cerebrovascular Atherosclerosis and Coronary Artery Disease in the LC Cohort

Coronary CT with CAC score measurement was performed in all the LC patients, apart from two with chronic kidney disease and a prior history of coronary bypass surgery, respectively, who did not have any signs or symptoms of cardiac ischemia at 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 the subjects with intra- and extra-cranial atherosclerosis than in their counterparts (Table S2). In terms of coronary calcification, CAC scores were 0 for 604 patients (60.9%), 1-99 for 235 (23.7%), and ≥100 for 152 (15.3%). Median CAC scores differed significantly between patients with and without cervico-cephalic atherosclerosis regardless of location (all \( P \text{ < 0.001} \)). Significant negative and positive correlations were also noted between the existence of atherosclerosis in both intra- and extra-cranial 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 [95% CI], 0.31 [0.13-0.76]; \( P=0.010 \)) (Fig. 4 and Table S3). In addition, CAC score ≥100, was an independent predictor of stenotic intracranial artery (adjusted OR [95% CI], 4.06 [1.45-11.41]; \( P=0.008 \)), whereas obstructive change of CAD was not.

In terms of extracranial vascular structure, CAC score ≥100 was also significantly correlated with atherosclerotic stenosis (adjusted OR 5.43 [2.68-11.00]; \( P<0.001 \)). Neither platelet count nor prothrombin time was associated with cervical atherosclerosis in the multivariate analysis. Etiology of liver disease was not significant in terms of the relationship with 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 annual carotid duplex surveillance. In this PS-matched per-location study based on full MRA evaluation of brain vascular anatomy, we found that overall stenosis in the intracranial major arteries was detected in 2.3% of the cirrhotic patients, significantly less than the 5.4% in the matched healthy controls, whereas the corresponding rates for 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 by coronary CT, rather than coronary artery obstruction, was a robust predictor of atherosclerosis at both intra- and extra-cranial sites.

Intracranial atherosclerosis is particularly prevalent in Asians; according to one report it was 7% in the Chinese population of > 40 years, a frequency similar to what we found in our healthy Koreans. Nevertheless, the prevalence of silent intracranial disease decreased 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 arteries most affected (i.e., MCA and ICA) did not differ between the LC and control groups. These observations may explain the reduced risk of overt cerebrovascular events in cirrhotics, which has been found in pathological autopsies and population-based longitudinal studies.
In general, advanced cirrhosis is accompanied by quantitative and/or functional abnormalities of platelets. It has become clear that, beside 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 they then become activated and release a variety of chemokines, which enhances 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, so protecting against cerebrovascular remodeling. This hypothesis is supported by our finding of an inverse relationship between thrombocytopenia and atherosclerotic development of intracranial vessels in the patients with LC. On the other hand, the impact of only traditional risk factors for extracranial atherosclerosis such as age ≥60 years and CAC score ≥100 even in cirrhotics may explain the similarity of the prevalence of the disease to that in non-cirrhotic populations.

As cardiac 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, as well as a strong predictor of future cardiovascular events, has been shown to be associated with co-existence of atheroma in other vascular territories including the arteries supplying blood to the brain, and also with the incidence of stroke in the general population. Our study
is the first to address the predictive value of the extent of coronary calcification for both intra- and extra-cranial atherosclerosis in a set of patients with LC. According to U.S. guidelines, carotid/vertebral testing with duplex ultrasonography should be considered for selected patients with multiple risk factors for atherosclerotic disease, such as a history of peripheral or coronary artery disease, smoking, and hypercholesterolemia, albeit not on a routine basis. Based on our findings, CAC score, a simple, safe and easily interpretable test, could be easily incorporated into one of the risk stratifiers to guide the screening for carotid artery disease in cirrhotic patients. Indeed, one normolipidemic participant with LC who had a high CAC score (i.e., 121.4) with extracranial CCA narrowing on MRA images prior to LT experienced an ischemic stroke event during the median follow-up of 5 years.

The current study has 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 for clarifying the association between cirrhosis and cerebrovascular stenosis. Second, regarding the diagnostic performance of the assessment method used in our study, while MRA tends to somewhat overestimate the severity of vascular stenosis compared to 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 in the development of
intracranial atherosclerosis, but not in extracranial atherosclerosis. The thrombocytopenia associated with cirrhosis may have an anti-atherogenic effect on the cerebral arteries in LC patients. High CAC levels could potentially be included in the criteria for cervico-cephalic vascular screening in asymptomatic cirrhotics.
Conflict of interest

The authors declare no competing interests.

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Figure 1. Prevalence of cervicocephalic atherosclerosis on MRA in (A) the pooled cohort (n=7,092) and (B) the matched cohort (n=1,510). The prevalence of atherosclerosis was consistently lower in the LC samples than the controls in the pooled cohort regardless of vascular location (all Ps<0.001). In the matched cohort, the vascular stenosis was less prevalent in the LC samples than 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)
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 was noted only in the intracranial PCA (0.3% in cirrhotics vs. 1.9% in controls, \(P=0.006\)), not in any extracranial arteries. ACA, anterior cerebral artery; BA, basilar artery; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SCA, subclavian artery; VA, vertebral artery.
Figure 3. Distribution of coronary artery calcium (CAC) scores by presence of intra- and extracranial atherosclerosis in the 991 LC patients undergoing coronary evaluation. More than half the individuals with normal cerebral arteries had 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 of $\geq 100$ were seen in 47.8% and 48.9% of individuals with Intra- and extracranial atherosclerosis, respectively. In comparison, the respective prevalences were 14.6% and 13.7% among those without cerebral atherosclerotic change ($Ps<0.001$).
Figure 4. Multivariable analysis of risk factors for intra- and extracranial atherosclerosis in the 991 cirrhotic patients (with coronary CT results) (A) CAC ≥100 was predictive of intracranial atherosclerosis, and platelet count <100K/mm³ was negatively associated with intracranial stenosis. (B) CAC ≥100 and age ≥60 years were predictors of extracranial atherosclerosis. In the multivariate analysis. Obstructive coronary artery stenosis was not independently associated with the presence of atherosclerotic change of the head and neck.
Table 1. Baseline hepatic parameters of the entire cirrhotic cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=993)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3 ± 8.0</td>
</tr>
<tr>
<td>Male gender</td>
<td>764 (76.9%)</td>
</tr>
<tr>
<td>Etiology of chronic liver disease</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus infection</td>
<td>708 (71.3%)</td>
</tr>
<tr>
<td>Hepatitis C virus infection</td>
<td>75 (7.6%)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>134 (13.5%)</td>
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<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 (x10^3/mm^3)</td>
<td>66 (45-96)</td>
</tr>
<tr>
<td>CTP classification</td>
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</tr>
<tr>
<td>A / B / C</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>

Data are presented as no. (%), or median (interquartile range), except for age presented as mean ± standard deviation.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intracranial atherosclerosis</th>
<th>Extracranial atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
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<td>0.36-0.88</td>
</tr>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.07-1.10</td>
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<tr>
<td>Male sex</td>
<td>0.82</td>
<td>0.66-1.01</td>
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<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Former</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.03</td>
<td>0.99-1.07</td>
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<tr>
<td>Hypertension</td>
<td>1.61</td>
<td>1.29-2.01</td>
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<td>Diabetes mellitus</td>
<td>1.64</td>
<td>1.26-2.12</td>
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<tr>
<td>Hyperlipidemia</td>
<td>1.15</td>
<td>0.90-1.47</td>
</tr>
</tbody>
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* Covariates with P<0.05 from univariate analysis, together with presence of cirrhosis, were included in a multivariate analysis using a logistic regression model.

** There was no significant multi-collinearity, as all VIFs measured between variables were < 5.

OR, odds ratio; CI, confidence interval; VIF, variance inflation factor.