RESEARCH ARTICLE

Effects of Heavy Alcohol Use on Acute Intracerebral Hemorrhage and Cerebral Small Vessel Disease

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Abstract

Background and Objectives

Heavy alcohol use (HAU) is a modifiable risk factor that may influence intracerebral hemorrhage (ICH) severity and cerebral small vessel disease (cSVD), but its role remains insufficiently understood. We aimed to investigate how HAU is associated with acute ICH characteristics and cSVD burden.

Methods

In this cross-sectional study, we analyzed prospectively collected data from consecutive patients admitted with spontaneous, nontraumatic ICH to Massachusetts General Hospital between 2003 and 2019. HAU was defined as regular alcohol consumption of ≥3 drinks per day. Multivariable regression models assessed associations between HAU and acute ICH clinical and radiologic features and MRI markers of cSVD.

Results

Among 1,600 patients (851 male patients [53%]; median age 75 [interquartile range 64–82] years), 104 (7%) met criteria for HAU. Compared with the non-HAU cohort, patients with HAU were significantly younger at ICH onset (median 64 vs 75 years; $p < 0.001$) and had larger hematoma volume (1.7-fold increase, $p = 0.005$) and greater odds of deep hemorrhage location (adjusted odds ratio [aOR] 2.01; 95% CI 1.11–3.64; $p = 0.021$) and intraventricular extension (aOR 1.95; 95% CI 1.02–3.70; $p = 0.045$). Among 1,195 patients with MRI (75%), analysis of markers of cSVD showed that HAU was independently associated with severe white matter hyperintensities (aOR 3.04; 95% CI 1.43–6.49; $p = 0.004$) and a hypertensive cSVD pattern (aOR 1.82; 95% CI 1.04–3.20; $p = 0.035$). No other MRI markers of cSVD were associated with HAU. HAU was also associated with lower platelet counts ($\beta = -17.73$; 95% CI −32.75 to −2.72; $p = 0.021$) and higher admission blood pressure ($\beta = 4.81$; 95% CI 0.06–9.56; $p = 0.047$).

Discussion

HAU is associated with younger age at ICH onset, larger hematoma size, and imaging features consistent with more advanced hypertensive cSVD, including a greater burden of white matter hyperintensities. These findings suggest that HAU may exacerbate acute ICH severity and accelerate long-term cerebral small vessel pathology. Study limitations include the cross-sectional design, MRI availability restricted to a subset, and lack of detailed lifetime alcohol exposure. Future studies should clarify alcohol-related mechanisms underlying cSVD progression and ICH severity and inform prevention strategies.

Introduction

Acute intracerebral hemorrhage (ICH) is a severe condition associated with high morbidity and mortality.[1] The leading cause of spontaneous ICH is cerebral small vessel disease (cSVD),

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Glossary

aOR = adjusted odds ratio; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **cSS** = cortical superficial siderosis; **cSVD** = cerebral small vessel disease; **GCS** = Glasgow Coma Scale; **HAU** = heavy alcohol use; **HTN** = hypertension; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale; **NHAU** = non–heavy alcohol use; **SSRI** = selective serotonin reuptake inhibitor; **WMH** = white matter hyperintensity.

a progressive condition characterized by chronic microvascular dysfunction of the brain, primarily driven by hypertensive arteriopathy (HTN-cSVD) and cerebral amyloid angiopathy (CAA).[2-4] Well-established risk factors such as advanced age and hypertension contribute to both ICH occurrence and cSVD progression. Lifestyle factors, including alcohol consumption, have also been associated with an increased risk of ICH.[5]

In this study, we aimed to evaluate the association between heavy alcohol use (HAU) and acute ICH characteristics and MRI markers of cSVD. We hypothesized that chronic HAU accelerates small vessel pathology, leading to more severe acute ICH characteristics and a greater cSVD burden on MRI. This effect is believed to be mediated through alcohol-related sustained hypertension, endothelial dysfunction, blood-brain barrier disruption, and impaired hemostasis, as supported by experimental and clinical studies of alcohol exposure.[6-8]

However, most studies of alcohol-related cerebrovascular injury stem from non-ICH populations or have primarily focused on ICH occurrence rather than acute hematoma severity or cSVD burden and rarely included detailed neuroimaging. Our study addresses these gaps by evaluating a large, well-characterized ICH cohort with prospectively collected clinical data and standardized MRI acquisition, including systematic evaluation of cSVD markers. This design allows for a comprehensive assessment of both acute hemorrhage features and chronic microvascular brain injury in relation to heavy alcohol consumption. A better understanding of these processes may clarify the role of HAU as a modifiable risk factor and inform targeted strategies for ICH prevention and cerebrovascular health.

Methods

Study Cohort and Data Collection

We analyzed prospectively collected data from consecutive patients admitted with spontaneous, nontraumatic ICH to Massachusetts General Hospital between 2003 and 2019. Patients with alternative bleeding etiologies—such as vascular malformations, brain tumors, or hemorrhagic transformation of an ischemic infarct—were excluded, as described elsewhere.[9,10]

Baseline demographic and clinical data were systematically collected and included information on comorbidities (hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, previous ischemic stroke, previous ICH, atrial fibrillation, and liver disease), smoking history, and current medications (including antiplatelets, anticoagulants, antihypertensive drugs, antidiabetic drugs, statins, and selective serotonin reuptake inhibitors [SSRIs]).

Admission clinical data included Glasgow Coma Scale (GCS) score, blood pressure, and laboratory values (glucose, platelet count, international normalized ratio, prothrombin time, and partial thromboplastin time). Treatment data (intubation and hematoma evacuation) and clinical outcomes (length of hospital stay, in-hospital mortality, and discharge modified Rankin Scale [mRS] score) were also recorded.

Prestroke functional status was assessed using the mRS, with a score of ≤2 indicating functional independence.

Alcohol Consumption

Information on current alcohol use, defined as the average number of alcoholic drinks consumed per week, was collected at admission, either directly from the patient or through a proxy if the patient was unable to provide the information. Alcohol intake was quantified in standard drinks, with 1 drink equivalent to 14 g (0.6 ounces) of pure alcohol.

Study participants were categorized into 2 groups based on alcohol use: HAU (≥3 drinks per day) and non–heavy alcohol use (NHAU; <3 drinks per day, including never drinkers). The threshold for HAU was based on existing literature linking this level of alcohol intake to adverse health outcomes, including elevated blood pressure, platelet dysfunction, and vascular damage.[11-13] Although this threshold is higher than the National Institute on Alcohol Abuse and Alcoholism's definition of heavy drinking (>14 drinks per week for men and >7 drinks per week for women or >2 drinks per day for men and >1 drink per day for women),[14] it was selected to isolate individuals with the most biologically relevant exposure in terms of cerebrovascular risk.

A history of alcohol abuse, defined as regular consumption of ≥5 drinks per day for 1 year or more, was also recorded. Patients with a history of alcohol abuse who did not meet criteria for current HAU were excluded to minimize misclassification and mitigate reverse causation.

No patients were excluded because of missing alcohol information.

Neuroimaging Evaluation

Admission CT scans were reviewed to determine hematoma location and volume, presence of perihematomal edema, and intraventricular hemorrhage (IVH) extension. ICH location was classified as either deep (involving the basal ganglia, thalamus, brainstem, or deep cerebellar regions) or lobar (cortico-subcortical areas in the cerebral or cerebellar hemispheres). Hematoma expansion was evaluated in patients with follow-up CT imaging within 24–48 hours and was defined as an increase in hematoma volume of ≥33% or >6 mL compared with baseline.[15,16]

MRI markers of cSVD were assessed according to the Standards for Reporting Vascular Changes on Neuroimaging 1 criteria,[17,18] including white matter hyperintensities (WMHs) rated using the Fazekas scale,[19] cerebral microbleeds (CMBs),[20] cortical superficial siderosis (cSS),[21] and lacunes.[22-24] WMHs were classified as severe if the Fazekas score was ≥2. Based on hemorrhagic MRI markers, ICH etiology was categorized as CAA, HTN-cSVD, or mixed-location ICH. CAA classification was based on the modified Boston criteria[25] and included patients with lobar ICH and, if present, strictly lobar CMBs and/or cSS. Patients with strictly deep ICH and, if present, deep CMBs (without cSS) were classified as HTN-cSVD. Mixed etiology included patients with either (1) both deep and lobar ICH (with or without CMBs in any location), (2) deep ICH with at least 1 lobar CMB, (3) lobar ICH with at least 1 deep CMB, or (4) deep ICH with cSS.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. Comparisons between the HAU and NHAU groups were performed using bivariate analyses: χ^2 tests or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables, as appropriate. To assess the association between HAU and predefined study outcomes, we performed multivariable regression analyses, selecting model types based on the outcome variable. Linear regression was used for continuous outcomes (age at onset, hematoma volume, platelet count, and blood pressure) and logistic regression for binary outcomes (hemorrhage location, MRI markers of cSVD, ICH etiology, discharge mRS score, and in-hospital mortality). All models were adjusted for predefined baseline covariates, including age, sex, race, smoking, hypertension, diabetes mellitus, hyperlipidemia, previous stroke/TIA, previous hemorrhage, coronary artery disease, atrial fibrillation, and liver disease. For models with hemorrhage location or hematoma volume as the outcome, we further adjusted for medication use (antiplatelets, anticoagulants, statins, antihypertensives, antidiabetics, and SSRIs) and time from ICH onset to CT scan and mutually adjusted for hemorrhage location (in the hematoma volume model) and hematoma volume (in the hemorrhage location and IVH extension models).

Model assumptions were assessed using residual diagnostic plots to evaluate linearity, homoscedasticity, and normality. Multicollinearity was assessed using the variance inflation factor. For skewed outcomes or nonlinear relationships, log transformation was applied and results are presented as back-transformed coefficients. Patients with missing data were excluded from the multivariable analyses using listwise deletion.

Supplementary Analysis

To explore the association between varying levels of alcohol consumption and ICH characteristics and severity with greater granularity, we conducted supplementary analyses by stratifying patients into 5 categories based on average daily alcohol intake: no alcohol use, <1 drink per day, 1 drink per day, 2 drinks per day, and ≥3 drinks per day (eTable 1). Multivariable regression models were repeated using the "no alcohol use" group as the reference category.

This stratification aimed to determine whether intermediate levels of alcohol consumption were associated with differences in ICH characteristics or cSVD markers and to evaluate potential dose-response relationships.

A 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed using Stata SE software, version 17.0.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board of our hospital. Informed consent was waived because of the retrospective design of the study and minimal risk to participants.

Data Availability

Anonymized data not published within this article may be made available by request from any qualified investigator.

Results

We identified 1,600 patients eligible for the study (851 male patients [53%]; median age 75 [interquartile range (IQR) 64–82] years, 1,363 White [85%]), with a median (IQR) ICH volume of 17.7 (5.6–46.2) mL. Among these, 104 patients (7%) were classified as having HAU. The median (IQR) time from ICH onset to initial brain CT was 187 (89–426) minutes. Brain MRI was performed in 1,194 (75%) at a median (IQR) of 2 (1–11) days after ICH onset. Baseline characteristics and comparisons between the HAU and NHAU groups are presented in Table 1. Heavy alcohol users had significantly fewer cardiovascular comorbidities (hyperlipidemia: 32% vs 49%; coronary artery disease: 11% vs 21%; atrial fibrillation: 13% vs 23%) and were less likely to be dependent before admission (4% vs 21%) compared with non–heavy alcohol users. Conversely, patients with HAU were more likely to smoke (33% vs 9%) and had a higher prevalence of liver disease (12% vs 3%).

Association Between HAU and Acute ICH Onset and Severity

Patients with HAU were significantly younger at the time of ICH compared with patients with NHAU (median age 64 [IQR 58–71] vs 75 [IQR 65–83] years; $p < 0.001$) (Table 1).

Table 1 Baseline Characteristics of Patients With ICH by Alcohol Use Category[a]

	Non–heavy alcohol use (n = 1,496)	Heavy alcohol use (n = 104)	*p* Value[b]
Age, y, median (IQR)	75.0 (65.0–83.0)	64.0 (58.0–70.5)	<0.001
Sex, male	770 (51.5)	81 (77.9)	<0.001
Race			
White	1,272 (85.0)	91 (87.5)	0.066
Black	80 (5.4)	4 (3.9)	
Asian	107 (7.2)	3 (2.9)	
Hispanic	32 (2.1)	6 (5.8)	
Other	5 (0.3)	0 (0.0)	
Smoking[c]	130 (8.7)	34 (32.7)	<0.001
BMI, median (IQR)[d]	26.6 (23.5–30.3)	26.6 (24.2–30.7)	0.536
Hypertension	1,201 (80.3)	79 (76.0)	0.287
Diabetes	346 (23.1)	17 (16.4)	0.110
Hyperlipidemia	734 (49.1)	33 (31.7)	0.001
Previous stroke/TIA	316 (21.1)	19 (18.3)	0.489
Previous ICH	122 (8.2)	4 (3.9)	0.115
Coronary artery disease	316 (21.1)	11 (10.6)	0.010
Atrial fibrillation	337 (22.5)	13 (12.5)	0.017
Liver disease	44 (2.9)	12 (11.5)	<0.001
Prestroke mRS score ≥3	315 (21.1)	4 (3.9)	<0.001
Drug use at time of admission			
Antiplatelet	589 (39.4)	30 (28.9)	0.033
Anticoagulants	308 (20.6)	13 (12.5)	0.046
Statins	599 (40.0)	24 (23.1)	0.001
Antidiabetic drugs	227 (15.2)	12 (11.5)	0.315
Antihypertensive drugs	985 (65.8)	52 (50.0)	0.001
SSRIs	173 (11.6)	13 (12.5)	0.773

Abbreviations: BMI = body mass index; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale; SSRI = selective serotonin reuptake inhibitor.
[a] Data are presented as numbers (percentages) of patients, unless otherwise indicated.
[b] Bivariate analyses were performed using the χ^2 test or the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.
[c] Includes both current and former smokers.
[d] Data missing for 392 patients.

This difference remained significant after adjustment for baseline covariates (adjusted β = −4.88; 95% CI −7.31 to −2.45; $p < 0.001$).

The median (IQR) time from symptom onset to initial CT was 146 (75–325) minutes in the HAU group and 191 (90–432) minutes in the NHAU group ($p = 0.102$). Radiologic characteristics of the acute hemorrhage in HAU and NHAU groups are provided in Table 2. Patients with HAU presented with significantly larger hematoma volumes (median 28.7 [IQR 10.7–57.8] vs 17.0 [IQR 5.2–44.7] mL; $p = 0.002$) and were more likely to have hemorrhages in deep brain regions (61.5% vs 46.5%; $p = 0.003$). These findings reflect a more severe hemorrhage pattern in the HAU group. In adjusted models (Table 3), HAU was independently associated with a 1.7-fold increase in hematoma volume (95% CI 1.17–2.41; $p = 0.005$) and higher odds of deep hemorrhage location (adjusted odds ratio [aOR] 2.01; 95% CI 1.11–3.64; $p = 0.021$) and presence of IVH extension (aOR 1.94; 95% CI 1.02–3.71; $p = 0.045$).

Table 2 Radiologic and Clinical Characteristics at Admission and Outcomes in Patients With Intracerebral Hemorrhage by Alcohol Use Category[a]

	Non–heavy alcohol use (n = 1,496)	Heavy alcohol use (n = 104)	*p* Value[b]
Imaging characteristics on admission			
Time to initial CT[c], min, median (IQR)	191 (90–432)	146 (75–325)	0.102
Hemorrhage volume[d], mL, median (IQR)	17.0 (5.2–44.7)	28.7 (10.7–57.8)	0.002
Deep hematoma location	696 (46.5)	64 (61.5)	0.003
Hematoma expansion[e,f]	229 (21.2)	14 (18.9)	0.644
Perihematomal edema	1,319 (88.2)	93 (89.4)	0.701
Intraventricular extension	667 (44.6)	65 (62.5)	<0.001
Clinical characteristics on admission			
GCS[g] score, median (IQR)	14 (8–15)	14 (9–15)	0.306
MAP[h], mm Hg, median (IQR)	116 (102–133)	127 (109–142)	<0.001
Intubation[i]	525 (35.4)	45 (43.3)	0.105
Hematoma evacuation	101 (6.8)	7 (6.7)	0.994
Laboratory data on admission			
Glucose[j], mg/dL, median (IQR)	133 (111–168)	139 (116–176)	0.155
Platelets[k], $\times 10^3$/μL, median (IQR)	222 (181–272)	208 (162–264)	0.025
PT[l], s, median (IQR)	12.7 (11.9–13.4)	12.9 (11.8–13.7)	0.256
PTT[m], s, median (IQR)	25.8 (23.6–28.2)	26 (24.0–29.0)	0.471
INR[n], median (IQR)	1.1 (1.0–1.2)	1.0 (1.0–1.2)	0.255
Outcomes			
Length of hospital stay[o], median (IQR)	7 (4–12)	11 (4–18)	0.006
Dependent at discharge[p,q]	1,285 (87.7)	90 (86.5)	0.739
Loss of independency at discharge[p]	977 (66.8)	86 (82.7)	<0.001
In-hospital mortality	385 (25.7)	19 (18.3)	0.090

Abbreviations: GCS = Glasgow Coma Scale; INR = international normalized ratio; MAP = mean arterial pressure; mRS = modified Rankin Scale; PT = prothrombin time; PTT = partial thromboplastin time.
Système International Conversion Factors: to convert glucose from mg/dL to mmol/L, multiply by 0.055; to convert platelet count from $\times 10^3$/μL to $\times 10^9$/L, use a 1:1 conversion.
[a] Data are presented as numbers (percentages) of patients, unless otherwise indicated.
[b] Bivariate analyses were performed using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables.
Data missing for [c]561, [d]96, [e]447, [g]13, [h]31, [i]12, [j]91, [k]75, [l]78, [m]336, [n]83, [o]16, and [p]34 patients.
[f] Hematoma expansion defined as an increase in hematoma volume of at least ≥33% or >6 mL on follow-up head CT within 24–48 hours compared with baseline head CT.
[q] Defined as mRS score ≥3.

Additional clinical and laboratory characteristics at admission and outcomes are summarized in Table 2, with results of multivariable analyses presented in Table 3. HAU was associated with lower platelet counts (median 208 [IQR 162–264] vs 222 [IQR 181–272] $\times 10^3$/μL; p = 0.025), which remained significant after adjustment (adjusted β = −17.73; 95% CI −32.75 to −2.72; p = 0.021), and higher mean arterial pressure (median 127 [IQR 109–142] vs 116 [IQR 102–133] mm Hg; p < 0.001), also significant in adjusted analysis (adjusted β = 4.81; 95% CI 0.06–9.56; p = 0.047).

Patients with HAU had longer hospital stays (median 11 [IQR 4–18] vs 7 [IQR 4–12] days; p = 0.006), an association that persisted after adjustment (adjusted β = 1.22; 95% CI 1.02–1.45; p = 0.033). While overall rates of dependency at discharge did not differ significantly between groups (86.5% vs 87.7%; p = 0.739), a significantly greater proportion of patients with HAU transitioned from pre-ICH independency to post-ICH dependency (82.7% vs 66.8%; p < 0.001), an association confirmed in adjusted analysis (aOR 1.92; 95% CI 1.12–3.31; p = 0.018). In-hospital mortality did not differ significantly between groups after adjustment.

Table 3 Univariate and Multivariable Regression Analyses of the Association Between Heavy Alcohol Use and Admission Radiologic and Clinical Characteristics and Outcomes in Patients With ICH

	Regression analysis	Crude β-coefficients/OR (95% CI)	*p* Value	Adjusted β-coefficients/OR[a] (95% CI)	*p* Value
CT imaging characteristics					
ICH volume[b]	Linear regression	1.61[b] (1.19–2.18)	0.002	1.68 (1.17–2.41)	0.005
ICH location (nonlobar)	Logistic regression	1.84 (1.22–2.77)	0.003	2.01 (1.11–3.64)	0.021
Intraventricular extension	Logistic regression	2.07 (1.37–3.12)	<0.001	1.94 (1.02–3.71)	0.045
Clinical characteristics on admission and outcomes					
Platelets	Linear regression	−16.57 (−31.44 to −1.70)	0.029	−17.73 (−32.75 to −2.72)	0.021
MAP on admission	Linear regression	7.33 (2.53–12.13)	0.003	4.81 (0.06–9.56)	0.047
Length of hospital stay[b]	Linear regression	1.30 (1.09–1.54)	0.003	1.22 (1.02–1.45)	0.033
Loss of dependency at discharge	Logistic regression	2.37 (1.41–3.99)	0.001	1.92 (1.12–3.31)	0.018
In-hospital mortality	Logistic regression	0.65 (0.39–1.07)	0.092	0.71 (0.42–1.22)	0.219

Abbreviations: ICH = intracerebral hemorrhage; MAP = mean arterial pressure; OR = odds ratio; SSRI = selective serotonin reuptake inhibitor.
[a] Adjusted for age, sex, smoking status, race, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, diabetes mellitus, previous stroke/TIA, previous hemorrhage, and liver disease. Models of CT imaging characteristics also adjusted for use of medications (antiplatelets, anticoagulants, SSRIs, and statins), time from symptom onset to CT, and ICH location (in the model with ICH volume as the outcome) and ICH volume (in the model with ICH location or intraventricular extension as the outcomes).
[b] ICH volume and length of hospital stay were log-transformed in the models; the reported β-coefficient is back-transformed.

Association Between HAU and Markers of cSVD

Brain MRI was available for 1,121 patients (75%) in the NHAU group and 73 patients (70%) in the HAU group (p = 0.283). Patients without MRI were older and had more severe ICH, including larger hematoma volumes, lower admission GCS scores, and higher in-hospital mortality rates (eTables 2 and 3). In bivariate analyses, no significant differences were observed in cSVD imaging markers between groups (Table 4). However, after adjustment for baseline covariates, including age and sex, HAU was significantly associated with severe WMHs (aOR 3.04; 95% CI 1.43–6.49; p = 0.004) (Figure 1). No other cSVD markers showed significant group differences in adjusted models.

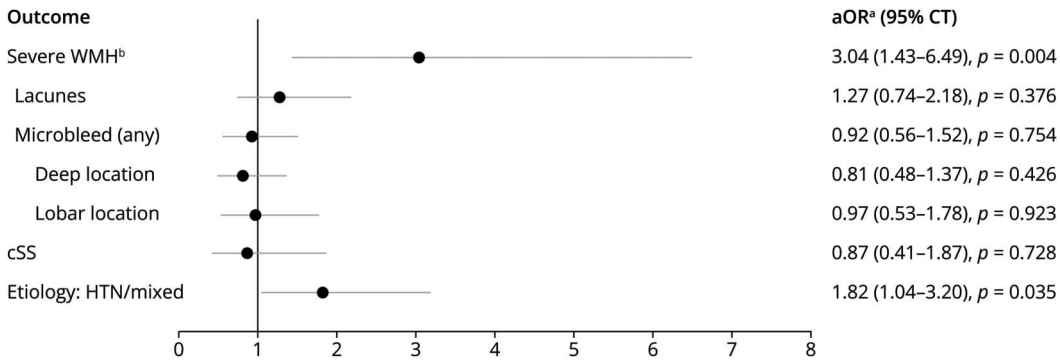
Analysis of ICH etiology showed that patients with HAU were more frequently classified as having hypertensive or mixed cSVD-related ICH compared with patients with NHAU (72.2% vs 54.4%; p = 0.003) (Table 4). This association

Table 4 MRI Markers of Cerebral Small Vessel Disease and Classification of Intracerebral Hemorrhage Etiology by Alcohol Use Category[a]

	Non–heavy alcohol users (n = 1,121)	Heavy alcohol users (n = 73)	*p* Value
Severe WMHs[b,c]	899 (80.3)	64 (87.7)	0.120
Lacunes[c]	371 (33.1)	25 (34.3)	0.844
Microbleeds, any[d]	582 (52.5)	35 (48.6)	0.524
Lobar	467 (42.1)	25 (34.7)	0.218
Deep	242 (21.8)	16 (22.2)	0.936
Cortical superficial siderosis[d]	198 (17.9)	9 (12.5)	0.247
Etiology[d]			
HTN/mixed	603 (54.4)	52 (72.2)	0.003

Abbreviations: HTN = hypertensive; WMHs = white matter hyperintensities.
[a] Data are presented as numbers (percentages) of patients, unless otherwise indicated.
[b] Severe WMH defined as Fazekas score ≥2.
Missing data for [c]1 patient (fluid-attenuated inversion recovery sequence of poor quality and not usable) and [d]13 patients (no susceptibility-weighted imaging/gradient-echo/T2* sequence available for analysis).

Figure 1 Adjusted Odds Ratios for the Association Between Heavy Alcohol Use and MRI Markers of Cerebral Small Vessel Disease and Intracerebral Hemorrhage Etiology



Multivariable logistic regression models were adjusted for age, sex, smoking status, hypertension, race, hyperlipidemia, coronary artery disease, atrial fibrillation, diabetes mellitus, previous stroke/TIA, previous hemorrhage, and liver disease. Odds ratios >1 indicate a higher likelihood of the outcome in the heavy alcohol use group (reference: non–heavy alcohol use); odds ratios <1 indicate a lower likelihood. Error bars represent 95% confidence intervals. aOR = adjusted odds ratio; cSS = cortical superficial siderosis; HTN = hypertension; WMH = white matter hyperintensity.
[a]Model adjustments are described above. [b]Severe WMH was defined as a Fazekas score ≥2.

persisted after adjustment (aOR 1.82; 95% CI 1.04–3.20; p = 0.035) (Figure 1).

Supplementary Analysis: Association of Alcohol Consumption Levels With ICH Characteristics and cSVD Markers

Results of the adjusted regression analyses comparing varying levels of alcohol consumption (<1 drink per day, 1 drink per day, 2 drinks per day, and ≥3 drinks per day) with the reference group (no alcohol use) are presented in eFigures 1–3. Outcomes assessed included age at ICH onset, hematoma volume, hemorrhage location, IVH extension, platelet count, and presence of severe WMHs.

Across all outcomes, no significant associations were observed for intermediate levels of alcohol consumption (<3 drinks per day) except for age at ICH onset. Specifically, patients consuming 2 drinks per day experienced ICH at a significantly younger age compared with abstainers (adjusted β = −4.04; 95% CI −6.65 to −1.25; p = 0.015) (eFigure 1).

Significant associations with hematoma volume, deep hemorrhage location, IVH, lower platelet count, severe WMHs, and hypertensive ICH etiology were observed only in patients consuming ≥3 drinks per day, consistent with findings from the primary analysis comparing HAU with NHAU.

Discussion

In this cross-sectional study of 1,600 patients with spontaneous ICH, HAU was associated with greater acute ICH severity and more advanced imaging markers of cSVD. Specifically, patients with HAU presented with ICH at a younger age; had significantly larger hematoma volumes; and were more likely to present with deep, hypertensive hemorrhages and severe white matter disease compared with those with NHAU. HAU was also associated with higher admission blood pressures and lower platelet counts. These findings indicate an association between HAU and ICH severity, possibly through mechanisms involving blood pressure dysregulation, platelet dysfunction, and accelerated small vessel pathology.

The younger age at ICH onset, larger hematoma volumes, and predominance of deep hemorrhages observed among patients with HAU align with those of previous studies linking HAU to earlier ICH onset and nonlobar locations.[12,26] Experimental evidence from animal models has shown that chronic alcohol exposure led to increased hematoma volume, supporting a potential mechanistic link.[27] These findings likely reflect the deleterious vascular effects of HAU and its impact on platelet function.[6] In our study, patients with HAU had significantly higher admission blood pressure and lower platelet counts than patients with NHAU. While the hemostatic effects of alcohol are believed to stem primarily from impaired platelet aggregation,[28,29] a mechanism not directly assessed in our study, the observed reduction in platelet count may have further exacerbated bleeding severity in the HAU group. Because blood pressure was recorded only at admission, we cannot determine whether chronic blood pressure dysregulation mediated the observed associations. The higher incidence of IVH extension in the HAU group likely reflects a combination of larger hematoma volumes, deep hemorrhage locations, and platelet dysfunction—all established risk factors of IVH extension.[30,31] Collectively, these findings suggest that HAU may be an important contributor to both occurrence and expansion of ICH.

Of interest, despite larger hematoma volumes, patients with HAU had similar admission GCS scores and in-hospital mortality rates compared with those with NHAU. This apparent paradox may be partly explained by the younger age and lower burden of cardiovascular comorbidities in the HAU

group, potentially conferring greater physiologic resilience during the acute phase. However, a significantly larger proportion of patients with HAU transitioned from pre-ICH independence to post-ICH dependency compared with patients with NHAU (83% vs 67%), and they had longer hospital stays, suggesting a more complex clinical course. These findings may reflect greater hemorrhage severity and systemic complications associated with chronic alcohol use not captured in this analysis. While long-term outcomes were not available in our cohort, previous observational data suggest that HAU is associated with worse functional outcomes at 3 and 12 months, despite similar initial severity.[32]

Although bivariate analyses did not identify significant differences in cSVD markers between groups, we conducted separate multivariable logistic regression analyses for each cSVD marker to account for the significant age difference, given the strong age dependence of cSVD. The adjusted analyses revealed a significant association between HAU and severe WMHs while no other cSVD markers differed significantly between groups. This pattern suggests that alcohol-related vascular dysfunction may primarily contribute to diffuse white matter damage rather than focal lesions. The selective association with WMHs may reflect the particular vulnerability of deep white matter to chronic hypoperfusion and blood-brain barrier dysfunction—processes that are exacerbated by long-term alcohol exposure through mechanisms such as endothelial dysfunction, oxidative stress, and hypertension.[6] Supporting this hypothesis, a previous advanced neuroimaging study linked lacunes to focal vascular effects rather than global ischemia resulting from widespread vessel dysfunction.[33] By contrast, other cSVD markers such as lacunes and CMBs may arise from more focal arteriolar occlusions or hemorrhagic changes, which might be less directly influenced by alcohol-related injury or may require different pathologic thresholds to manifest. In addition, it is possible that some cSVD manifestations are less sensitive to detection in a cross-sectional design. Nonetheless, the relationship between alcohol use and cSVD remains complex and is likely multifactorial, with previous studies reporting inconsistent findings. For instance, a Mendelian randomization study found a positive association between alcohol use and cSVD risk while an observational study in a cohort similar to ours reported an inverse relationship with WMH burden.[26,34] Future studies should incorporate quantitative metrics of cSVD burden, including longitudinal WMH volumetric assessment, to better elucidate the impact of alcohol on microvascular brain integrity.

Previous research has shown that strictly lobar ICH and CMBs are strongly indicative of CAA, whereas deep ICH and CMBs are characteristic of HTN-cSVD.[35-37] Mixed ICH is believed to represent a more severe form of HTN-cSVD, a hypothesis supported by data from multiple lines of advanced neuroimaging studies.[38-40] In our detailed assessment of cSVD markers, HAU was disproportionately associated with HTN-cSVD or mixed-pattern cSVD-related ICH rather than CAA. This finding further supports the hypothesis that chronic alcohol consumption accelerates hypertensive small vessel pathology, contributing to the deep hemorrhagic phenotype typical of HTN-cSVD.

In supplementary analyses evaluating varying levels of alcohol consumption, only individuals consuming ≥2 drinks per day were significantly younger at ICH onset. No other significant associations were observed for intermediate intake levels (<3 drinks per day) and ICH characteristics or cSVD markers. These findings may suggest a threshold effect, whereby alcohol-related cerebrovascular risk becomes clinically apparent only at higher levels of intake (≥3 drinks per day). However, given the relatively small sample sizes of the intermediate alcohol intake groups, these findings should be interpreted with caution. Future studies with larger cohorts and more granular alcohol exposure metrics are warranted to confirm these observations.

A key strength of this study is its large, well-characterized cohort with comprehensive clinical and imaging data, enabling a detailed assessment of the effects of HAU on both acute ICH characteristics and chronic cSVD. The substantial proportion of patients with available MRI (75%) allowed for an in-depth evaluation of cSVD markers—an aspect rarely captured in previous studies.

However, several limitations should be considered. First, alcohol use was self-reported, which may introduce recall or reporting biases. Nonetheless, alcohol consumption is more likely to be underreported, potentially leading to a conservative bias and an underestimation of the true effects of HAU. Alcohol use was captured as a current behavior without distinguishing long-term chronic consumption from recent heavy intake, precluding assessment of cumulative lifetime exposure and raising the possibility of reverse causation. In addition, the NHAU group included a heterogeneous mix of never drinkers and mild-to-moderate drinkers, which may have introduced residual confounding and attenuated group differences. Nonetheless, data were collected prospectively at admission from both patients and proxies, with no missing alcohol information, enhancing overall reliability.

Second, the relatively low prevalence of HAU (7%) may have limited statistical power to detect certain associations and precluded more granular subgroup analyses. The potential influence of other substance use, such as cocaine and amphetamines, known contributors to cerebrovascular pathology,[41] could not be fully assessed because of limited data. Moreover, information on treatment limitation decisions and temporal changes in ICH care was unavailable, which may have influenced length of stay and mortality. However, because our main analyses focused on acute ICH characteristics and cSVD markers, these limitations are unlikely to have substantially affected the main findings.

Third, MRI was not performed randomly; patients without MRI were older and had more severe ICH. Although MRI availability did not differ significantly by alcohol use, minimizing the likelihood of differential selection, this potential selection bias may limit the generalizability of our findings on cSVD burden.

Fourth, this study was conducted at a single academic tertiary-care hospital, which may limit the external validity of our findings. Referral patterns could have resulted in an overrepresentation of more severe or complex ICH cases. Moreover, the cohort was predominantly White and socioeconomic data, including insurance status, were unavailable, limiting applicability to more diverse populations and introducing the possibility of residual confounding.

Finally, the cross-sectional design prevents evaluation of long-term alcohol consumption patterns and cumulative dose-response relationships. Given the multiple outcomes analyzed, the risk of type I error is increased. However, because the outcomes were correlated and prespecified, strict multiple-testing corrections were not applied to avoid overly conservative results and potential type II errors. Therefore, these findings should be interpreted with caution.

The observed association underscores excessive alcohol consumption as a modifiable cerebrovascular risk factor with significant public health implications. The notable prevalence of HAU in this hospital-based cohort further reinforces its relevance. Implementing routine alcohol screening and counseling in both primary care and hospital settings could facilitate early identification and intervention for high-risk individuals. From a preventive neurology perspective, reducing heavy alcohol consumption may not only decrease the risk of ICH but also slow the progression of cSVD, with potential downstream benefits in reducing stroke recurrence, cognitive decline, and long-term disability. These findings highlight the need to integrate lifestyle-focused interventions into comprehensive stroke prevention strategies, particularly for patients with coexisting vascular risk factors.

HAU is associated with earlier onset of ICH, larger hematoma volumes, deep hemorrhage locations, and more severe manifestations of cSVD, particularly hypertensive arteriolosclerosis. These findings suggest that chronic HAU may accelerate cerebral small vessel pathology and contribute to both occurrence and severity of ICH, possibly through alcohol-related vascular injury and hemostatic alterations. HAU was also linked to greater functional decline and prolonged hospitalization, underscoring its broader clinical impact. These results highlight the need for targeted public health strategies to reduce alcohol-related cerebrovascular risk and mitigate its long-term effect on brain health.

Author Contributions

M.F. Hindsholm: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A.S. Das: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Gokcal: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Morotti: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. O. Rotschild: drafting/revision of the manuscript for content, including medical writing for content. C.Z. Simonsen: drafting/revision of the manuscript for content, including medical writing for content. Z. Dipucchio: drafting/revision of the manuscript for content, including medical writing for content. A. Viswanathan: drafting/revision of the manuscript for content, including medical writing for content. S.M. Greenberg: drafting/revision of the manuscript for content, including medical writing for content. C.D. Anderson: drafting/revision of the manuscript for content, including medical writing for content. J. Rosand: drafting/revision of the manuscript for content, including medical writing for content. J.N. Goldstein: drafting/revision of the manuscript for content, including medical writing for content. M.E. Gurol: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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