

## Influence of Prior Nicotine and Alcohol Use on Functional Outcome in Patients after Intracerebral Hemorrhage

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*Background:* The influence of prior nicotine or alcohol use (legal drug use [LDU]) on outcome measures after intracerebral hemorrhage (ICH) is insufficiently established. We investigated drug-specific associations with (1) neuroradiologic and clinical parameters and (2) functional long-term outcome after ICH. *Methods:* This observational cohort study analyzed consecutive spontaneous patients with ICH (n = 554) from our prospective institutional registry over a 5-year study period (January 2010 to December 2014). We compared no-LDU patients with LDU patients, and patients using only nicotine, only alcohol, or both. To account for baseline imbalances, we reanalyzed cohorts after propensity score matching. *Results:* Prevalence of prior LDU was 197 of 554 (35.6%), comprising 94 of 554 (17.0%) with only nicotine use, 33 of 554 (6.0%) with only alcohol use, and 70 of 554 (12.6%) with alcohol and nicotine use. LDU patients were younger (65 [56-73] versus 75 [67-82],  $P < .01$ ), less often female (n = 61 of 197 [31.0%] versus n = 188 of 357 [52.7%],  $P < .01$ ), had more often prior myocardial infarction (n = 29 of 197 [14.7%] versus n = 24 of 357 [6.7%],  $P < .01$ ), and in-hospital complications (sepsis or systemic inflammatory response syndrome: n = 95 of 197 [48.2%] versus n = 98 of 357 [27.5%],  $P < .01$ ; pneumonia: n = 89 of 197 [45.2%] versus n = 110 of 357 [30.8%],  $P < .01$ ). Except for an increased risk of pneumonia (odds ratio 2.22, confidence interval [1.04-4.75],  $P = .04$ ) in patients using both nicotine and alcohol, we detected no significant differences upon reanalysis after propensity score matching of neuroradiologic or clinical parameters, complications, or long-term outcome between patients with and without LDU (mortality: n = 48 of 150 [32.0%] versus n = 45 of 150 [30.0%],  $P = .71$ ; favorable outcome [modified Rankin Scale 0-3]: n = 56 of 150 [37.3%] versus n = 53 of 150 [35.3%],  $P = .72$ ). *Conclusions:* Prior nicotine use, alcohol use, and their combination were associated with significant differences in baseline characteristics. However, adjusting for unevenly balanced baseline parameters revealed no differences in functional long-term outcome after ICH. **Key Words:** Intracerebral hemorrhage—stroke—alcohol—nicotine—drug use—prognostication. © 2017 National Stroke Association. Published by Elsevier Inc. All rights reserved.

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## Introduction

Nicotine and alcohol use (legal drug use [LDU]) represent common preventable risk factors for several diseases including intracerebral hemorrhage (ICH).<sup>1-3</sup> Nevertheless, little is known about the influence of prior LDU on ICH severity, on potentially triggered complications, and on functional long-term outcome. Although 2 previous studies—limited by smaller sample size, male patients only, or only conservative statistical adjustments—reported an absent influence of alcohol intake on functional outcome,<sup>4,5</sup> there are no data on the impact of nicotine use on ICH. Moreover, in light of relevant comorbidities and coincidences between nicotine and alcohol use (combined legal drug use [cLDU]), a differentiated view of the particular and intrinsic risk of each drug itself, and their combination, respectively, remains complicated.<sup>4</sup> Using propensity score (PS) matching to adjust for any confounding variables, we here investigated drug-specific associations of nicotine and alcohol use with clinical baseline parameters and explored their impact on long-term functional outcome after ICH.

## Material and Methods

### *Patient Selection*

We identified consecutive spontaneous patients with ICH treated at the University Hospital Erlangen, Germany, from our prospective institutional ICH registry over a 5-year study period (January 2010 to December 2014). The study was approved by ethics committee and informed consent was obtained from all individual participants or legal representatives. We excluded secondary ICH etiologies, that is, ICH related to trauma, tumor, arteriovenous malformations, platelet count  $<50.000/\mu\text{L}$  or ICH post thrombolysis. Overall, 593 patients with ICH were identified, of which 39 patients were excluded because of missing data ( $n = 14$ ), loss to follow-up ( $n = 13$ ), refusal of consent ( $n = 9$ ), and comorbid illegal drug use ( $n = 3$ ). Altogether, 554 patients of central European descent remained for final analysis.

### *Parameter Acquisition*

Demographics, prior comorbidities (including liver dysfunction defined as known liver cirrhosis, alcoholic liver disease, acute or chronic hepatitis, or initial serum aminotransferase levels exceeding  $\geq 5$  times upper reference limit<sup>6</sup>), in-hospital parameters, and treatment characteristics, including decisions about early care limitations ( $<24$  hours), were retrieved from our prospective database, as previously described.<sup>7,8</sup> We specifically assessed a relevant nicotine use (defined as current smoker or recent [ $<2$  years] history of smoking with more than 20 cumulative pack-years), and risky alcohol use (defined according to the National Institute on Alcohol Abuse and Alcoholism<sup>9</sup> as  $>4$  standard drinks [12 g of ethanol] per day or  $>14$

drinks/week on average concerning men  $<65$  years and  $>3$  drinks/day or  $>7$  drinks/week concerning women and adults  $\geq 65$  years) by personal interview of patients and relatives. Neuroradiologic parameters and 12-month outcome data were assessed as previously described.<sup>7</sup> Functional outcome was evaluated using modified Rankin scale (mRS), dichotomized as favorable (mRS 0-3) and unfavorable (mRS 4-6).<sup>7</sup>

## Statistics

Statistical analyses were performed with SPSS Statistics 20.0 (SPSS Inc, Chicago, IL) and R version 2.12.0 (<https://www.r-project.org/>). We computed 2-sided statistical tests, set the significance level at  $\alpha = .05$ , and corrected for multiple comparisons using the Bonferroni method. Kolmogorov-Smirnov test was applied to determine data distribution. Data are shown as mean  $\pm$  standard deviation, compared using Student's *t* test, or as median and interquartile range, compared using Mann-Whitney *U* test, as appropriate.<sup>7</sup> Pearson's  $\chi^2$  and Fisher's exact tests were applied to compare frequency distributions of categorized variables between patients without and with LDU, respectively, only nicotine use, only alcohol use, or cLDU. We performed a 2-stage PS matching using a parallel, balanced, 1:1 ratio nearest-neighbor approach to match LDU patients to no-LDU patients according to basic and outcome-relevant parameters showing at least a statistical trend ( $P < .10$ ) for differences between groups. In a first step, we controlled for differences in demographics, that is, age, sex, and comorbidities, that is, prior myocardial infarction leading to a (first) post-match cohort of 320 (160:160) patients. Imbalances in rates of liver dysfunction were excluded from matching procedure because of known strong causal linkage to alcohol use.<sup>10</sup> In a second step, we additionally adjusted for differences in admission status, that is, National Institutes of Health Stroke Scale (NIHSS), resulting in a (second) post-match cohort of 300 (150:150) patients. Please see e-Figure 1, visualizing both cohorts equally balanced for adjusted confounder with no statistically significant differences between groups. Generated cohorts were used to analyze LDU-related differences in (first) admission status respectively (second) in-hospital parameters and functional long-term outcome. We further conducted multivariable logistic regression modeling to specifically investigate associations between LDU status and in-hospital complications.

## Results

The present study cohort consisted of 554 spontaneous patients with ICH, and median age was 72 (61-80), median ICH volume was  $14.2\text{ cm}^3$  (5.5-38.8), median NIHSS was 13 (5-25), and 49.8% ( $n = 276$  of 554) of patients had intraventricular hemorrhage (IVH).

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