Functional Long-Term Outcome after Left- versus Right-Sided Intracerebral Hemorrhage

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Key Words

Intracerebral hemorrhage · Hemisphere · Location · Outcome · Epidemiology

Abstract

Background and Purpose: Hemispheric location might influence outcome after intracerebral hemorrhage (ICH). INTERACT suggested higher short-term mortality in right hemispheric ICH, yet statistical imbalances were not addressed. This study aimed at determining the differences in long-term functional outcome in patients with right- vs. left-sided ICH with a priori-defined sub-analysis of lobar vs. deep bleedings. **Methods:** Data from a prospective hospital registry were analyzed including patients with ICH admitted between January 2006 and August 2014. Data were retrieved from institutional databases. Outcome was assessed using the modified Rankin Scale (mRS) score. Outcome measures (long-term mortality and functional outcome at 12 months) were correlated with ICH location and hemisphere, and the imbalances of baseline characteristics were addressed by propensity score matching. **Results:** A total of 831 patients with supratentorial ICH (429 left and 402 right) were analyzed. Regarding clinical baseline characteristics in the unadjusted overall cohort, there were differences in disfavor of right-sided ICH (antiplatelets: 25.2% in left ICH vs. 34.3% in right ICH; $p < 0.01$; previous ischemic stroke: 14.7% in left ICH

vs. 19.7% in right ICH; $p = 0.057$; and presence/extent of intraventricular hemorrhage: 45.0% in left ICH vs. 53.0% in right ICH; $p = 0.021$; Graeb-score: 0 [0–4] in left ICH vs. 1 [0–5] in right ICH; $p = 0.017$). While there were no differences in mortality and in the proportion of patients with favorable vs. unfavorable outcome (mRS 0–3: 142/375 [37.9%] in left ICH vs. 117/362 [32.3%] in right ICH; $p = 0.115$), patients with left-sided ICH showed excellent outcome more frequently (mRS 0–1: 64/375 [17.1%] in left ICH vs. 43/362 [11.9%] in right ICH; $p = 0.046$) in the unadjusted analysis. After adjusting for confounding variables, a well-balanced group of patients ($n = 360$ /hemisphere) was compared showing no differences in long-term functional outcome (mRS 0–3: 36.4% in left ICH vs. 33.9% in right ICH; $p = 0.51$). Sub-analyses of patients with deep vs. lobar ICH revealed also no differences in outcome measures (mRS 0–3: 53/151 [35.1%] in left deep ICH vs. 53/165 [32.1%] in right deep ICH; $p = 0.58$). **Conclusion:** Previously described differences in clinical end points among patients with left- vs. right-hemispheric ICH may be driven by different baseline characteristics rather than by functional deficits emerging from different hemispheric functions affected. After statistical corrections for confounding variables, there was no impact of hemispheric location on functional outcome after ICH.

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Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for about 15% of strokes and is associated with high mortality, severe disability, and unfavorable functional outcome [1, 2]. The hemispheric location of ischemic and hemorrhagic stroke and its impact on clinical end points has only been studied insufficiently, yet this field is of special interest since both hemispheres comprise a complex variety of different functions, and therefore, lateralization of lesions may result in different disabilities. In ischemic stroke, worse functional outcome has been reported in left hemispheric as compared to right-sided ischemia [3]. Contrarily, in ICH, higher mortality rates at 3 months have recently been demonstrated for right-sided ICH upon a sub-analysis of the INTERACT trial, while functional outcome at 3 months was not significantly different among left- and right-sided ICH [4].

However, these analyses did not sufficiently address the baseline confounding variables, possibly influencing the reported results. Moreover, influence of site of ICH (lobar vs. deep) in relation to hemispheric location has not been linked to long-term functional outcome. This study investigated whether hemispheric location and site of ICH is associated with outcome measures – specifically long-term mortality and functional outcome – after spontaneous supratentorial ICH.

Methods

Patient Selection

The study was approved by the Institutional Review Board of the University of Erlangen-Nuremberg. Informed consent was obtained from all patients or legal representatives. Based on a prospective hospital registry, we initiated a retrospective analysis including patients with spontaneous ICH who were admitted to the Department of Neurology between January 2006 and August 2014. A total of 831 patients with supratentorial ICH were analyzed. Patients with infratentorial ICH and secondary ICH, for example, trauma, arteriovenous malformations, tumor, or ICH after acute thrombolysis or coagulopathy were excluded from the study. For 94 patients, information on long-term functional outcome was not available.

Data Collection and Outcome Analysis

As described previously, we retrieved demographic and clinical baseline characteristics from our prospective hospital registry and institutional databases [5, 6]. We evaluated mortality and functional outcome by standardized mailed questionnaires and semi-quantitative phone interviews 12 months after onset of ICH. Functional outcome was assessed using the modified Rankin Scale (mRS) score [7]. Favorable outcome was defined as mRS 0–3, excellent outcome as mRS 0–1, and unfavorable outcome as mRS 4–6.

Imaging

Patients with spontaneous ICH were identified by cranial imaging using CT (SOMATOM VolumeZoom or SOMATOM Definition AS+, Siemens Healthcare, Germany). CT scans were evaluated independently by 2 neuroradiologists. Hemorrhage location was scored as either deep or lobar. ICH volume was estimated according to the formula of ellipsoids [8, 9]. Hematoma growth (>33% of initial ICH volume) was assessed by CT scan at approximately 24 ± 6 h after primary imaging [10]. Intraventricular hemorrhage (IVH) was graded using the Graeb score [11].

Statistics

Statistical analyses were performed using IBM® SPSS® (Statistics version 21, Chicago, IL, USA). Continuous variables were tested for distribution using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean $\pm$ SD and compared using one-way analysis of variance, non-normally distributed data are presented as median and interquartile range and were compared using the Mann–Whitney U test. The chi-square test was used to compare dichotomized variables. Statistical significance was assumed for a p value of <0.05 upon 2-sided testing. A trend toward significance was defined for a p value of <0.1 . All analyses were calculated as complete case analyses, and missing variables (missing data of all investigated parameters was $<5\%$) were evaluated as appropriate by this methodology [12]. A total of 94 patients were excluded only from analyses on functional outcome as there were no follow-up information on outcome measures available at 1 year. Online supplemental Table I (for all online suppl. material, see www.karger.com/doi/10.1159/000454775) displays the baseline characteristics of these patients who were lost to follow-up dichotomized by ICH location. To adjust for imbalances in baseline characteristics, a propensity score matching using a balanced, parallel, 1:1 ratio nearest-neighbor approach was conducted in which parameters showing a statistical trend in univariate analysis were taken into consideration ($p < 0.1$) [6].

Results

Baseline Characteristics

Of 831 patients with supratentorial ICH, there were 429 (51.6%) with left-sided (203 deep and 226 lobar) and 402 (48.4%) with right-sided (201 deep and 201 lobar) ICH. When comparing baseline characteristics of patients with left vs. right ICH, there were significant differences in the proportion of patients with prior use of antiplatelets (108/424 [25.2%] in left ICH vs. 138/396 [34.3%] in right ICH; $p = 0.003$), presence and extent of IVH (IVH: 192/427 [44.8%] in left vs. 213/402 [52.9%] in right ICH; $p = 0.017$; Graeb score: 0 [0–4] in left vs. 1 [0–5] in right ICH; $p = 0.017$) as well as a statistical trend toward a history of prior ischemic stroke (63/429 [8.9%] in left vs. 79/402 [19.7%] in right ICH; $p = 0.057$), all in disfavor of right hemispheric ICH (Table 1).

Table 1. Admission status, demographic, neuroradiological, and treatment characteristics as well as complications of patients with supratentorial spontaneous ICH left vs. right

	ICH left (n = 429)	ICH right (n = 402)	p value
Demographic and clinical characteristics			
Gender*, female	199 (46.4)	177 (44.0)	0.495
Age†, years	70.2±12.9	71.5±12.0	0.138
Pre-mRS‡	0 (0–2)	1 (0–2)	0.267
Congestive heart disease*	68 (15.9)	64 (15.9)	0.978
Hypertension*	354 (82.5)	327 (81.3)	0.660
Diabetes*	106 (24.7)	106 (26.4)	0.583
Hypercholesterolemia*	143 (33.3)	120 (29.9)	0.281
Ischemic stroke*	63 (14.7)	79 (19.7)	0.057
Hemorrhagic stroke*	38 (8.9)	32 (8.0)	0.642
Myocardial infarction*	59 (13.8)	54 (13.4)	0.893
Alcoholics*	57 (13.3)	48 (11.9)	0.559
Smoking*	104 (24.2)	99 (24.6)	0.887
Antiplatelets*	108 (25.2)	138 (34.3)	0.003
Atrial fibrillation*	84 (19.6)	91 (22.6)	0.280
Oral anticoagulation*	81 (18.9)	94 (23.4)	0.112
Hemorrhage characteristics			
Location basal ganglia*	203 (47.3)	201 (50.0)	0.440
Location lobar*	226 (52.7)	201 (50.0)	0.440
Initial ICH volume†, cm ³	29.9±35.7	32.5±38	0.317
Hematoma growth*	40 (9.3)	34 (8.5)	0.662
IVH*	192 (44.8)	213 (52.9)	0.017
Graeb score‡	0 (0–4)	1 (0–5)	0.017
Midlineshift†, mm	4.23±5.6	4.6±5.7	0.349
Admission status			
GCS‡	13 (6–15)	13 (5–15)	1.0
NIHSS‡	14 (6–25)	14 (5–27)	0.797
Treatment characteristics			
EVD*	104 (24.2)	115 (28.6)	0.154
Duration of EVD†, days	2.32±4.9	2.82±6.5	0.217
Ventilation*	168 (39.2)	174 (43.3)	0.226
Duration of ventilation†, days	4.28±8.1	5.23±10	0.137
Tracheotomy*	65 (15.2)	64 (15.9)	0.764
Complications			
Pneumonia*	135 (31.5)	141 (35.1)	0.269
Sepsis*	71 (16.6)	66 (16.4)	1.000
Ventriculitis*	4 (0.9)	6 (1.5)	0.535
Length of stay†, days	11.69±9.6	12.34±10.5	0.356

ICH, intracerebral hemorrhage; CCT, cerebral computed tomography; IVH, intraventricular hemorrhage; EVD, external ventricular drain; mRS, modified Rankin Scale; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.

* n (%), † mean ± SD, ‡ median (IQR 25th–75th percentile).

Regarding lobar ICH location, there were overall similar findings among patients with left and right hemispheric ICH (Table 2). However, the presence and extent of IVH were increased in right-sided ICH (IVH: 70/225 [30.9%] in lobar left ICH vs. 85/201 [42.3%] in lobar right ICH; $p = 0.015$; Graeb score: 0 [0–2] in lobar left vs. 0

[0–3] in lobar right ICH; $p = 0.030$). The number of male patients tended to be lesser (119/226 [52.7%] in lobar left ICH vs. 89/201 [44.3%] in lobar right ICH; $p = 0.084$), and a more frequent use of oral anticoagulation (40/226 [17.7%] in lobar left ICH vs. 49/201 [24.4%] in lobar right ICH; $p = 0.09$) was observed in right-sided ICH (Table 2).

Table 2. Admission status, demographic, neuroradiological, and treatment characteristics as well as complications of patients with lobar/deep ICH left vs. right

	Lobar left ICH (n = 226)	Lobar right ICH (n = 201)	p value	Deep left ICH (n = 203)	Deep right ICH (n = 201)	p value
Demographic and clinical characteristics						
Gender*, female	119 (52.7)	89 (44.3)	0.084	80 (39.4)	88 (43.8)	0.373
Age†, years	71.3±13.2	72.5±12.3	0.349	68.9±12.5	68.8±11.7	0.202
Pre-mRS‡	1 (0-2)	1 (0-2)	0.838	0 (0-1)	1 (0-2)	0.040
Congestive heart disease*	42 (18.6)	35 (17.4)	0.753	26 (12.8)	29 (14.4)	0.635
Hypertension*	174 (77)	154 (76.6)	0.927	180 (88.7)	173 (86.1)	0.431
Diabetes*	57 (25.2)	50 (24.9)	0.934	49 (24.1)	56 (27.9)	0.394
Hypercholesterolemia*	81 (33.3)	71 (29.9)	0.911	62 (30.5)	49 (24.4)	0.165
Ischemic stroke*	32 (14.2)	34 (16.9)	0.432	31 (15.3)	45 (22.4)	0.067
Hemorrhagic stroke*	28 (12.4)	20 (10.0)	0.426	10 (4.9)	12 (6.0)	0.644
Myocardial infarction*	35 (15.5)	27 (13.4)	0.548	24 (11.8)	27 (13.4)	0.626
Alcoholics*	24 (10.6)	48 (23.9)	0.001	33 (16.3)	27 (13.4)	0.423
Smoking*	56 (24.8)	49 (24.4)	0.920	48 (23.6)	50 (24.9)	0.777
Antiplatelets*	58 (25.7)	82 (40.8)	0.001	50 (24.6)	56 (27.9)	0.462
Atrial fibrillation*	42 (19.6)	43 (22.6)	0.468	42 (20.7)	48 (23.9)	0.441
Oral anticoagulation*	40 (17.7)	49 (24.4)	0.090	41 (20.2)	45 (22.4)	0.591
Hemorrhage characteristics						
Initial ICH volume†, cm ³	36.8±39.9	40.9±42.9	0.312	22.3±28.5	24.3±30.3	0.509
Hematoma growth*	14 (6.2)	17 (8.5)	0.368	26 (12.8)	17 (8.5)	0.156
IVH*	70 (30.9)	85 (42.3)	0.015	122 (60.0)	128 (63.7)	0.458
Graeb-score‡	0 (0-2)	0 (0-3)	0.030	2 (0-6)	3 (0-8)	0.317
Midlineshift†, mm	4.4±6.3	4.8±6.3	0.564	4.0±4.8	4.5±5.0	0.409
Admission status						
GCS‡	13 (7-15)	13 (5-15)	0.730	12 (5-14)	12 (5-14)	0.624
NIHSS‡	12 (4-23)	11(3-26)	0.989	17 (8-28)	16 (9-29)	0.889
Treatment characteristics						
EVD*	31 (13.7)	31 (15.4)	0.617	73 (13.7)	84 (15.4)	0.229
Duration of EVD†, days	1.2±3.6	1.4±3.9	0.586	3.6±5.8	4.3±8.1	0.347
Ventilation*	65 (28.8)	70 (34.8)	0.178	103 (50.7)	104 (51.7)	0.841
Duration of ventilation†, days	2.4±5.9	2.3±7.5	0.193	6.4±9.6	7.0±11.7	0.535
Tracheotomy*	15 (6.6)	18 (8.9)	0.371	50 (24.6)	46 (22.9)	0.680
Complications						
Pneumonia*	51 (22.6)	54 (26.9)	0.303	84 (41.4)	87 (43.3)	0.823
Sepsis*	30 (13.3)	21 (10.4)	0.368	41 (20.2)	45 (22.4)	0.590
Ventriculitis*	2 (0.9)	1 (0.5)	1.000	2 (0.9)	5 (2.5)	0.261
Length of stay†, days	10.3±7.3	10.5±8.9	0.784	13.2±11.5	14.1±11.6	0.410

ICH, intracerebral hemorrhage; CCT, cerebral computed tomography; IVH, intraventricular hemorrhage; EVD, external ventricular drain; mRS, modified Rankin Scale; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.
 * n (%), † mean ± SD, ‡ median (IQR 25th–75th percentile).

Comparison of hemispheric location in patients with deep ICH also revealed very similar findings (Table 2). Indeed, patients with right-sided ICH showed a significantly poorer pre-existing clinical status (mRS prior to ICH: 0 [0–1] in deep left ICH vs. 1 [0–2] in deep right ICH; $p = 0.04$) alongside a statistical trend toward a history of prior ischemic stroke (31/203 [15.3%] in deep left ICH vs. 45/201 [22.4%] in deep right ICH; $p = 0.067$), as compared to left hemispheric deep ICH patients.

Long-Term Functional Outcome in Left versus Right Hemispheric ICH – Unadjusted Analysis

Long-term functional outcome of the entire cohort is shown in Figure 1. There was no difference in long-term mortality among patients with left vs. right ICH (168/375 [44.8%] in left ICH vs. 163/362 [45%] in right ICH; $p = 0.950$), and the proportion of patients with favorable vs. unfavorable outcome also did not differ among patients with left vs. right hemispheric ICH (mRS 0–3: 142/375 [37.9%] in left ICH vs. 117/362 [32.3%] in right ICH; $p =$

Fig. 1. Distribution of long-term functional outcome at 1 year after ICH. A favorable functional outcome (mRS 0–3 vs. 4–6) is shown as a bold line. An excellent functional outcome (mRS 0–1 vs. 2–6) is shown as a thin line.

0.115). However, the proportion of patients with excellent outcome was significantly higher in patients with left-sided ICH (mRS 0–1: 64/375 [17.1%] in left ICH vs. 43/362 [11.9%] in right ICH; $p = 0.046$) (Fig. 1; online supplemental Table II for various dichotomized outcome analyses [13]).

Outcome analysis of patients with deep ICH revealed no significant differences in the proportion of patients with favorable vs. unfavorable outcome among patients with left and right hemispheric ICH (mRS 0–3: 65/176 [36.9%] in left ICH vs. 57/184 [31.0%] in right ICH; $p = 0.233$; mRS 0–1: 24/176 [13.6%] in left ICH vs. 17/184 [9.2%] in right ICH; $p = 0.189$; online suppl. Fig. I). Outcome analysis of patients with lobar ICH revealed no significant differences in the proportion of patients with favorable vs. unfavorable outcome among patients with left and right hemispheric ICH (mRS 0–3: 77/199 [38.7%] in left ICH vs. 60/178 [33.7%] in right ICH; $p = 0.315$; mRS 0–1: 40/199 [20.1%] in left ICH vs. 26/178 [14.6%] in right ICH; $p = 0.161$; online suppl. Fig. II).

Long-Term Functional Outcome in Propensity Score Matched Cohort – Adjusted Analysis

To account for imbalances in baseline characteristics (Table 1, i.e., prior use of antiplatelets, history of ischemic stroke, presence and extent of IVH), we performed a propensity score matching that provided evenly balanced cohorts (overall: $n = 360$ for left and right-sided ICH, see online supplemental Table III, $n = 187$ for lobar left and $n = 178$ for lobar right as well as $n = 173$ for deep left and $n = 182$ for deep right ICH, see online supplemental Table IV). Neither mortality nor favorable or excellent long-term functional outcome was different among the overall pro-

Fig. 2. Distribution of long-term functional outcome in the propensity score matched cohort at 1 year after ICH. A favorable functional outcome (mRS 0–3 vs. 4–6) is shown as a bold line. An excellent functional outcome (mRS 0–1 vs. 2–6) is shown as a thin line.

pensity score matched cohort of patients with left- vs. right-sided ICH (mortality: 147/319 [46.1%] in left ICH vs. 136/322 [42.2%] in right ICH; $p = 0.33$; mRS 0–3: 116/319 [36.4%] in left ICH vs. 109/322 [33.9%] in right ICH; $p = 0.51$; mRS 0–1: 50/319 [15.7%] in left ICH vs. 40/322 [12.4%] in right ICH; $p = 0.24$; Fig. 2; online suppl. Table V).

In patients with deep ICH, there were no significant differences in outcome measures (mortality: 69/151 [45.7%] in deep left ICH vs. 60/165 [36.4%] in deep right ICH; $p = 0.09$; mRS 0–3: 53/151 [35.1%] in deep left ICH vs. 53/165 [32.1%] in deep right ICH; $p = 0.58$; mRS 0–1: 17/151 [11.3%] in deep left ICH vs. 16/165 [9.7%] in deep right ICH; $p = 0.65$; online suppl. Fig. III). In patients with lobar ICH, there were no differences in outcome measures (mortality: 78/168 [46.4%] in lobar left ICH vs. 76/157 [48.4%] in lobar right ICH; $p = 0.72$; mRS 0–3: 63/168 [37.5%] in lobar left ICH vs. 56/157 [35.7%] in lobar right ICH; $p = 0.73$; mRS 0–1: 33/168 [19.6%] in lobar left ICH vs. 24/157 [15.3%] in lobar right ICH; $p = 0.30$; online suppl. Fig. IV).

Discussion

This study investigated the impact of hemispheric location and site of ICH on clinical end points in a large cohort of patients with spontaneous supratentorial ICH. In essence, significant and clinically relevant differences in baseline characteristics existed for hemispheric location and site of ICH in disfavor of patients with right-sided ICH. However, significant differences in mortality and long-term functional outcome were not observed among patients with left vs. right hemispheric ICH. Given the

implications for both invasive treatment as well as treatment restrictions which were raised by previous studies that reported on differences in ICH locations, it appears important to provide evidence that no outcome differences were observed. Some aspects emerge from the data.

First, there are quite a few studies that deal with the issue of laterality of stroke lesions and its impact on patients' long-term functional outcome and mortality after ischemic stroke [14–17]. Regarding ICH, the largest study recently published was a post-hoc analysis of the INTERACT trial reporting on increased rates of mortality in right-sided ICH [4]. However, the methodological approach of this study lacked a strong enough statistical design to rule out baseline confounders possibly accounting for the described mortality differences. Moreover, only short-term outcome was assessed and the ethnic decent of included patients undermined extrapolation of these findings to European Caucasians. Furthermore, INTERACT included about 90% of deep ICH and reported an unrepresentatively low rate of mortality (about 10%), usually amounting up to 40% at 3 months [18]. We have correlated hemispheric location and site of ICH to long-term functional outcome using established statistical approaches to minimize bias. As demonstrated for ischemic stroke [15], and in line with findings from Sato et al. [4] in ICH, we were unable to verify differences in outcome measures among patients with left- vs. right-sided ICH.

Second, while it does not appear surprising that adjusted outcome analysis revealed no differences among left and right ICH for the overall population, differences were expected in the subgroup analyses regarding the site of ICH, specifically in lobar ICH [19]. On the one hand, from a pathophysiological point of view, hemispheric differences were not expected in deep ICH as corticospinal tracts and projection neurons are more affected [20]. On the other hand, given the various cognitive and executive functions located within cerebral lobes, outcome differences may be anticipated in lobar ICH when comparing left- vs. right-sided bleedings [21, 22]. In cerebral ischemia, such differences have been reported for malignant middle cerebral artery infarctions (e.g., speech impairment in left-sided vs. cognitive impairment and depression in right-sided infarctions [23–25]). However, we were not able to detect possible outcome differences in lobar ICH between left and right hemispheric ICH, an aspect that either reflects very small patient numbers or insufficient discriminatory power of the mRS in evaluation of cognitive and other end points [7].

Third, the reason for differences in baseline characteristics among left- and right-sided ICH need to be discovered,

and also for their crystallization to predominantly occur in disfavor of right-sided ICH. Although not significant, one explanation may be the gender distribution with more male patients – having usually more comorbidities than women [26, 27] – in the group of right-sided ICH. Only systematically designed prospective registries including longitudinal cranial imaging and careful assessment of lifestyle factors may be able to address whether additional physiological aspects may be the bottom of different comorbidities among left- and right-sided stroke [3].

Limitations of the present study are its retrospective and single-center design and – compared to INTERACT – fewer patient numbers. Furthermore, we have only assessed functional outcome and mortality and did not obtain cognitive or quality-of-life end points to possibly detect subtle differences not displayed in dichotomized mRS outcome. Moreover, long-term complications, such as new ischemic or hemorrhagic stroke and their secondary complications, have not been assessed as our observational study design did not allow to obtain valid information on such complications.

Conclusion

Long-term functional outcome after ICH most likely is not influenced by hemispheric location. It remains questionable whether data from the INTERACT trial have been affected by confounding baseline variables. Nonetheless, further analyses, especially those of lobar ICHs, are warranted since differences in functional outcome in respect to specific lesions are conceivable.

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Disclosure Statement

All authors have no conflicts of interest to report and have read the article, agree with the contents, and approved the final version of the article.

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