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Letter to the Editor

Characteristics of Early Presenters after Intracerebral Hemorrhage

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Dear Sir:

Intracerebral hemorrhage (ICH) expansion represents an appealing therapeutic target.[1] The risk of hematoma expansion (HE) is highest in the first few hours after onset and declines with longer time to imaging.[1,2] The therapeutic window is therefore narrow and early presentation (EP) is one of the key inclusion criteria for randomized controlled trials targeting HE. The aim of our study was to describe the characteristics of ICH patients with EP.

The Institutional Review Boards approved the study procedures. Informed consent was obtained by patients, relatives, or waived by the Institutional Review Board.

We retrospectively selected ICH patients admitted at the following sites: Charité Hospital, Berlin, Germany (2014–2019), Spedali Civili, Brescia, Italy (2008–2019), Arcispedale S. Anna, Ferrara, Italy (2010–2019), IRCCS Mondino Foundation, Pavia, Italy (2017–2019), and IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy (2015–2019). We selected patients with: (1) primary, spontaneous, non-traumatic ICH; (2) age >18 years; (3) baseline non-contrast computed tomography (NCCT) within 24 hours from onset/last seen well (LSW). Patients with secondary ICH and infratentorial hemorrhages were excluded. Age, sex, history of hypertension, antithrombotic treatment, systolic blood pressure (SBP), Glasgow coma scale (GCS), NCCT timing, and 90 days mortality were collected. EP was defined as time from onset/LSW to baseline imaging <2 hours.[1,3] NCCTs were analyzed for ICH volume (semi-automated volumetric measurement), location (cortical and subcortical bleedings were classified as lobar whereas hemorrhages involving the

Table 1. Population characteristics

Characteristic	All (n=1,335)	Early presentation		*P*
		No (n=1,038)	Yes (n=297)	
Age (yr)	73 (64–80)	74 (64–81)	73 (63–80)	0.159
Male sex	717 (53.7)	556 (53.6)	161 (54.2)	0.844
History of hypertension	951 (71.2)	713 (68.7)	238 (80.1)	<0.001
History of diabetes	250 (18.7)	198 (19.1)	52 (17.5)	0.542
Statin treatment	197 (14.8)	148 (14.3)	49 (16.5)	0.337
Antiplatelet treatment	417 (31.2)	336 (32.4)	81 (27.3)	0.095
Anticoagulant treatment	255 (19.1)	184 (17.7)	71 (23.9)	0.017
SBP (mm Hg)	160 (140–180)	160 (140–180)	170 (150–190)	<0.001
GCS	14 (11–15)	14 (10–15)	15 (12–15)	<0.001
ICH volume (mL)	16 (7–37)	16 (6–37)	15 (7–36)	0.939
ICH score	1 (0–2)	1 (0–2)	1 (0–2)	0.026
Time from onset/LSW to NCCT (hr)	3.9 (2.2–9.0)	5.3 (3.2–10.9)	1.4 (1.1–1.7)	<0.001
ICH location, deep	735 (55.1)	545 (52.5)	190 (64.0)	<0.001
IVH	452 (33.9)	355 (34.2)	97 (32.7)	0.621
NCCT hypodensities	540/1,050 (51.4)	407/846 (48.1)	133/204 (65.2)	<0.001
NCCT heterogeneous density	511/1,050 (48.7)	385/846 (45.5)	126/204 (61.8)	<0.001
NCCT irregular shape	472/1,050 (45.0)	366/846 (43.3)	106/204 (52.0)	0.025
NCCT blend sign	129/1,050 (12.3)	109/846 (12.9)	20/204 (9.8)	0.229
Mortality at 90 days	287 (21.5)	223 (21.5)	64 (21.5)	0.981

Values are presented as median (interquartile range) or number (%).
SBP, systolic blood pressure; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; LSW, last seen well; NCCT, non-contrast computed tomography; IVH, intraventricular hemorrhage.

Table 2. Variables associated with early presentation

Variable	OR (95% CI)	*P*
History of hypertension	1.52 (1.10–2.10)	0.011
Anticoagulant treatment	1.41 (1.02–1.94)	0.037
GCS*	1.08 (1.04–1.13)	<0.001
SBP†	1.10 (1.06–1.15)	<0.001
ICH location, deep	1.58 (1.21–2.08)	0.001

OR, odds ratio; CI, confidence interval; GCS, Glasgow coma scale; SBP, systolic blood pressure.
*OR for one point increase; †OR for 10 mm Hg increase.

thalamus, basal ganglia, internal capsule and deep periventricular white matter were classified as deep), and the following NCCT features: hypodensities, heterogeneous density, irregular shape, and blend sign.[2]

Categorical variables were expressed as count (%) and compared with chi-square test. Continuous variables were expressed as median (interquartile range) and compared with Mann-Whitney test as all had a non-parametric distribution (Shapiro-Wilk test). Variables independently associated with EP were explored with multivariable logistic regression with backward elimination at $P<0.1$. Age, sex, ICH volume, GCS, and variables with $P<0.1$ in univariate analysis were included in the model. We also performed different sensitivity analyses. First, we excluded patients with unclear symptom onset. Second, EP was defined as time from onset/LSW within 1. Third, NCCT features with $P<0.1$ in univariate analysis were added to the logistic regression model. Fourth, the logistic regression analysis accounted also for global ICH severity, measured with the ICH score. SPSS version 21.0 (IBM Co., Armonk, NY, USA) was used for the analyses and statistical significance was set at $P<0.05$.

Amongst 1,684 patients screened, 1,335 were included, of whom 297 (22.2%) had EP. Excluded patients had smaller volume and a higher frequency of anticoagulation and hypertension. The remaining characteristics were similar (all $P>0.1$). A total of 395 (29.6%) subjects had an unclear symptom onset, of whom 13 (3.3%) presented within 2 hours from LSW.

Table 1 shows the population characteristics. EP was associated with higher GCS, deep hemorrhages, anticoagulation, history of hypertension, and higher SBP values on admission. These findings remained significant in logistic regression, as summarized in Table 2. When the analysis was restricted to patients with a clear onset (n=940, 70.4%) the same variables except anticoagulation remained associated with EP. In a sec-

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ondary analysis, 66 patients (4.9%) presented within 1 hour and the following variables were independent predictors of EP: deep ICH location (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.15 to 3.43; *P*=0.015), history of hypertension (OR, 2.58; 95% CI, 1.21 to 5.50; *P*=0.014), and admission SBP (OR per 10 mm Hg increase, 1.15; 95% CI, 1.06 to 1.24; *P*<0.001). When the logistic regression model accounted also for NCCT features, hypodensities were independently associated with EP (OR, 1.98; 95% CI, 1.43 to 2.73; *P*<0.001). SBP (OR per 10 mm Hg increase, 1.10; 95% CI, 1.05 to 1.15; *P*<0.001), GCS (OR, 1.08; 95% CI, 1.03 to 1.13; *P*<0.001), deep location (OR, 1.55; 95% CI, 1.18 to 2.04; *P*=0.002), and hypertension (OR, 1.58; 95% CI, 1.14 to 2.19; *P*<0.001) remained independently associated with EP when multivariable analysis accounted for NCCT markers as well.

Finally, the inclusion of the ICH score in multivariable logistic regression did not change our results and the ICH score was not independently associated with EP. We described the characteristics of early presenters with ICH and found that history of hypertension, SBP at presentation, and deep ICH location were associated with EP. Different mechanisms may explain our findings. Hypertension and higher SBP may be an epiphenomenon of ICH location. Alternatively, higher SBP may be associated with larger ICH volume[4] and more severe symptoms, favoring stroke recognition. The same hypothesis may apply to anticoagulation, a predictor of ICH volume.[5] However, our data do not support these speculations, as we observed similar ICH volume in early and late presenters.

Two previous studies reported earlier diagnosis in deep ICH[5,6] and our findings confirmed these observations. Deep hemorrhages are more likely to produce motor impairment,[7] a known predictor of rapid stroke recognition.[8,9] On the other hand, cortical symptoms and confusion may be more common in lobar ICH and have been linked with delayed hospital arrival.[9] Impaired consciousness has also been associated with delayed admission,[9] consistently with our results.

We observed that overall ICH severity was not associated with faster presentation, and this finding is in contrast with a previous report showing more rapid hospital admission in severely affected patients.[10] This discrepancy may be explained by the smaller sample size and inclusion of infratentorial hemorrhages in the study by Huttner et al.[10]

Another interesting finding of our analysis is the higher prevalence of NCCT features in early presenters. This observation is consistent with the hypothesis that these imaging markers may identify ICH patients with more immature bleedings in the very early natural history of the disease.[2]

Our findings may have implications for ongoing and future studies[3] targeting subjects in the ultra-early time window, as patients with hypertension, higher blood pressure values, and deep ICH location are more likely to present within 2 hours from onset. Some limitations should be acknowledged. Selection bias may have occurred, as we retrospectively selected patients and did not include subjects from intensive care units. We were not able to account for potential confounders such as geographical and racial differences, use of emergency medical system, admission during weekend and night hours.[11]

In conclusion, deep location, SBP, and history of hypertension are the main variables associated with EP and less than one in four ICH patients presented within 2 hours. These findings may inform future studies targeting ICH subjects in the ultra-early time window.

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