Intraventricular hemorrhage expansion in patients with spontaneous intracerebral hemorrhage

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ABSTRACT

Objective: To evaluate whether delayed appearance of intraventricular hemorrhage (dIVH) represents an independent entity from intraventricular hemorrhage (IVH) present on admission CT or is primarily related to the time interval between symptom onset and admission CT.

Methods: A total of 282 spontaneous intracerebral hemorrhage (ICH) patients, admitted February 2009–March 2014 to the neurological intensive care unit of a tertiary care university hospital, were prospectively enrolled in the ICH Outcomes Project. Multivariate logistic regression was used to determine associations with acute mortality and functional long-term outcome (modified Rankin Scale).

Results: A cohort of 282 ICH patients was retrospectively studied: 151 (53.5%) had intraventricular hemorrhage on initial CT scan (iIVH). Of the remaining 131 patients, 19 (14.5%) developed IVH after the initial CT scan (dIVH). The median times from symptom onset to admission CT were 1.1, 6.0, and 7.4 hours for the dIVH, iIVH, and no IVH groups (Mann-Whitney U test, dIVH vs iIVH, $p < 0.001$) and median time from onset to dIVH detection was 7.2 hours. The increase in ICH volume following hospital admission was larger in dIVH than in iIVH and no IVH patients (mean 17.6, 0.2, and 0.4 mL). After controlling for components of the ICH score and hematoma expansion, presence of IVH on initial CT was associated with discharge mortality and poor outcome at 3, 6, and 12 months, but dIVH was not associated with any of the outcome measures.

Conclusions: In ICH patients, associated IVH on admission imaging is commonly encountered and is associated with poor long-term outcome. In contrast, dIVH on subsequent scans is far less common and does not appear to portend worse outcome. *Neurology*® 2015;84:989–994

GLOSSARY

CI = confidence interval; **CUMC** = Columbia University Medical Center; **dIVH** = delayed intraventricular hemorrhage; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **ICHOP** = ICH Outcomes Project; **iIVH** = initial IVH; **IQR** = interquartile range; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale; **OR** = odds ratio.

Intracerebral hemorrhage (ICH) is associated with high mortality and unfavorable outcome.[1] In order to improve clinical outcomes, research efforts have primarily been directed towards understanding modifiable factors that worsen outcome, e.g., hematoma expansion after hospital admission.[2,3] One recent study showed that delayed intraventricular hemorrhage (dIVH; intraventricular hemorrhage [IVH] that is not present on the initial admission CT but happens during hospitalization) occurs in up to every fifth ICH patient without IVH on initial CT and is independently associated with in-hospital mortality.[4] These results from one single-center study suggest that this subgroup of ICH patients is both at increased risk of unfavorable outcome and a promising target group, in which unfavorable outcome might potentially be prevented by frequent follow-up CTs and aggressive intervention. Before embarking on costly clinical trials to test this hypothesis, we thought it prudent to investigate if these observations can be confirmed in an independent patient sample. We tested the hypothesis that dIVH to a large extent is an

Supplemental data at Neurology.org

artifact of the timing of obtaining the initial CT scan and does not represent a separate clinical entity.

METHODS **Patient selection and data collection.** A total of 401 consecutive patients with spontaneous nontraumatic ICH were admitted to the Neurological Intensive Care Unit at Columbia University Medical Center (CUMC) between February 2009 and March 2014 and prospectively enrolled in an institutional review board–approved study, the ICH Outcomes Project (ICHOP).

Patients were treated according to current guidelines.[5] Details of clinical management and imaging analysis are presented in the e-Methods on the *Neurology*® Web site at Neurology.org. We studied 282 patients with spontaneous ICH. The presumed ICH etiology and presence/absence of IVH were determined by consensus among treating physicians during a weekly meeting.

Patients with ICH attributed to trauma or hemorrhagic conversion of an ischemic stroke were not included in ICHOP. Patients excluded from ICHOP are described in the e-Methods. From the available subjects included in ICHOP, we excluded a priori 50 patients with arteriovenous malformation–associated ICH from our study, and 48 patients whose admission CT was later than 48 hours after symptom onset, as well as an additional 21 patients who did not receive an admission CT scan, resulting in a final cohort of 282 patients with spontaneous, nontraumatic ICH.

dIVH was defined as any newly occurring IVH during hospitalization, i.e., IVH that was not present on admission CT but was present on any CT scan thereafter. Demographics (patient age, sex, ethnicity), clinical variables (e.g., Glasgow Coma Scale [GCS] score, hospital complications), and outcome measures were prospectively recorded by a dedicated study investigator. Missing outcome data were imputed using a predefined SPSS algorithm (SPSS Inc., Chicago, IL) in order to account for sampling bias.

Standard protocol approvals, registrations, and patient consents. The Institutional Review Board at CUMC approved the study protocol. Written informed consent was obtained from patients or, if neurologically impaired, from family members.

Neuroimaging. Per hospital protocol, patients underwent a noncontrast CT scan on admission, followed by CT scans at 12 and 24 hours after admission. Most comatose patients or patients with a high ICH score on admission underwent additional CT scans 4–6 hours after admission. Additional CT scans were obtained in case of clinical worsening.

Parenchymal hemorrhage size (ICH) and IVH volumes were measured semiautomatically (MIPAV software, NIH, Bethesda, MD). Hematoma volume change after admission was calculated using a follow-up CT (≥24 hours after admission CT) as reference. Outcome was determined using the modified Rankin Scale (mRS). Methodologic details are presented in the supplementary material.

Outcome assessment. Mortality (score of 6 on the mRS) was determined on hospital discharge or postbleed day 14, whichever occurred first. Follow-up mRS scores at 3, 6, and 12 months after the ICH were determined by trained study staff using standardized telephone interviews. Poor outcome was defined as a mRS score of 4–6.

Statistical analysis. All analyses were performed using SPSS version 21 software package and R (version 3.0.2, R Project). Data are expressed either as median and interquartile range (IQR) or mean and SD. Mann-Whitney U and Student t tests were used to assess the differences between groups for non-normally and normally distributed data, respectively. To assess correlations between baseline variables (for more than 2 groups), we used Pearson χ^2 and the independent samples Kruskal-Wallis tests (for non-normally distributed data) and one-way analysis of variance (for normally distributed data), as appropriate. In the multivariate logistic regression analysis, we included those binary input variables included in the ICH score[6] and hematoma expansion as continuous variable. A p value of <0.05 was considered statistically significant.

RESULTS Baseline characteristics of the 3 study subgroups are shown in table 1 and table e-1. Table e-2 shows a direct comparison of the baseline characteristics

Table 1	Baseline characteristics of patients with IVH on initial CT, delayed IVH, and no IVH			
Variable	**Initial IVH**	**Delayed IVH**	**No IVH**	**p Value**
Patients, n	151	19	112	—
Age, n (IQR)	64 (52–75)	74 (49–83)	65 (53–81)	0.27
Female, n (%)	59 (39.1)	7 (36.8)	52 (46.4)	0.44
Anticoagulation at admission, n (%)	20 (13.2)	6 (31.6)	14 (12.5)	0.19
Clinical/CT findings admission				
Glasgow Coma Scale score	7 (4–13)	9 (4–13)	13 (9–15)	<0.001
ICH score	3 (2–4)	2 (1–3)	1 (0–2)	<0.001
Hemorrhage location				
Deep (thalamus/basal ganglia)	86 (57.0)	10 (52.6)	42 (37.5)	0.007
Lobar	38 (25.2)	7 (36.8)	43 (38.4)	0.06
Infratentorial	18 (11.9)	1 (5.3)	19 (17.0)	0.28
Therapy				
EVD placement	67 (44.4)	4 (21.1)	5 (4.5)	<0.001
Surgical evacuation	20 (13.2)	2 (10.5)	8 (7.1)	0.29

Abbreviations: EVD = external ventricular drain; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage.
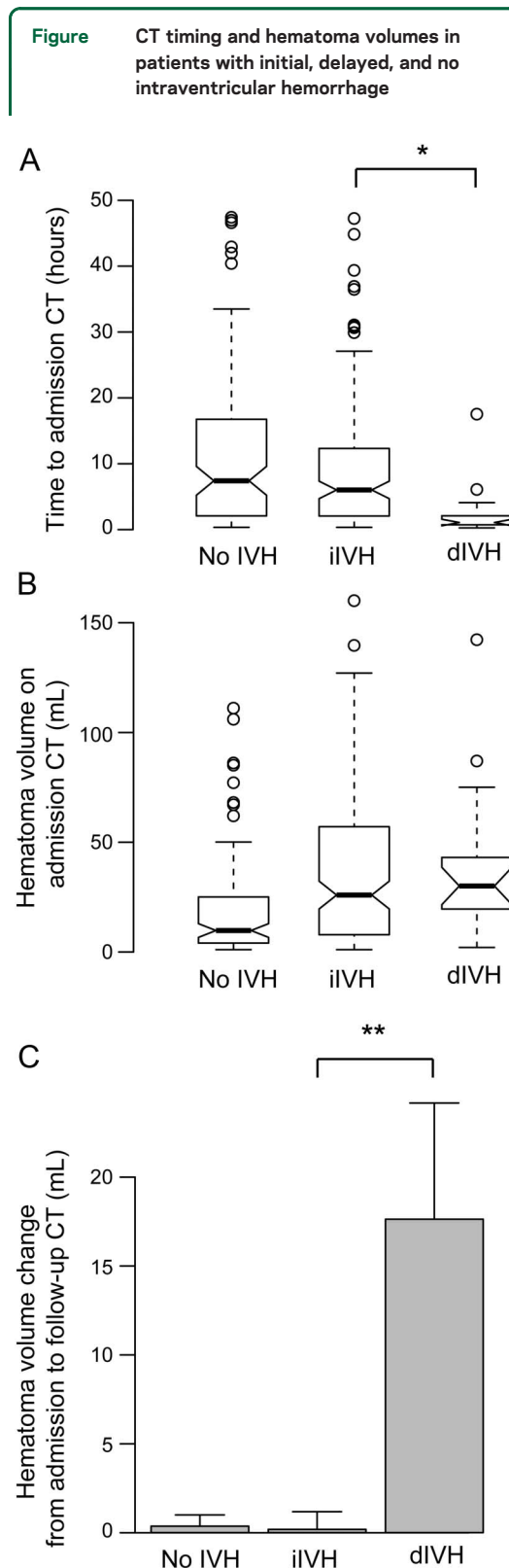
of patients with initial and dIVH. A total of 151 of the patients had IVH on admission CT scan (initial IVH [iIVH]). In 19 (14.5%) of the patients with no IVH on initial CT, IVH was seen on follow-up CT scan. The median time from symptom onset to detection of dIVH was 7.2 hours (IQR 3.4–13.2), and the median time between the initial imaging study and the follow-up study showing IVH was 4.7 hours (IQR 2.4–10.0).

In 14 out of 19 patients, dIVH was detected until 7.4 hours after the initial CT (second scan after admission), in 2 patients 11 hours (both third scan after admission), in 1 patient 21 hours (second scan), and in 2 patients 34 and 36 hours (both third scan) after the initial CT scan. Among the 5 patients with late IVH discovery (>8 hours after admission CT), 2 were coagulopathic, 2 had hyperglycemic crises potentially associated with intraventricular ICH expansion,[7] and in the remaining patient no potential cause of dIVH could be found. Two of 5 died during hospitalization; one was dead at 12 months. The remaining 2 had mRS scores of 3 and 4 at 12 months follow-up.

The median time from symptom onset to first CT scan was shorter in dIVH patients (1.1 hours) than in iIVH patients (6.0 hours) and no IVH patients (7.4 hours) (figure, A; Mann-Whitney U test iIVH vs dIVH groups, $p < 0.001$). Hematoma volumes on initial CT were similar between iIVH and dIVH patients (median 25.9 mL in iIVH, 30.0 mL in dIVH, and 9.7 mL in no IVH; figure, B). However, the mean ICH increase from initial CT to follow-up CT was far larger in dIVH patients than in the other 2 groups (no IVH 0.4 mL, iIVH 0.2 mL, dIVH 17.6 mL; t test dIVH vs no dIVH: $p < 0.001$; figure, C). dIVH patients underwent external ventricular drainage less often than iIVH patients (21.1% vs 44.4%). The rate of hematoma surgery was similar between both IVH groups (13.2% in iIVH and 10.5% in dIVH patients). The median IVH volume in the dIVH group was 2.7 mL (IQR 1.1–8.8 mL) and in the iIVH group 6.5 mL (IQR 2.3–21.1 mL). This difference was significant on statistical testing ($p = 0.025$).

The short onset to admission CT time in the 19 dIVH patients was plausible in all cases: 6 cases of ICH occurred in-hospital, 11 experienced symptom onset at home in the presence of relatives (in 3/11 in the presence of health care professionals), and 2 patients had symptom onset while in the emergency department accompanying a relative.

A total of 72%, 71%, and 72% of patients in our cohort had poor outcome (mRS 4–6) at 3, 6, and 12 months after the ICH, respectively. After controlling for age (>80 years), admission hematoma size (≥30 mL), decreased level of consciousness (GCS < 13), hematoma expansion, and infratentorial hematoma location,[4,6] the presence of IVH on initial CT was

Figure CT timing and hematoma volumes in patients with initial, delayed, and no intraventricular hemorrhage

(A) Time from symptom onset to admission CT. (B) Hematoma volume on admission CT scan. (C) Change of hematoma volume from admission CT to follow-up CT (>24 hours after admission CT). dIVH = patients with intraventricular hemorrhage on follow-up CT; iIVH = patients with intraventricular hemorrhage on admission CT; no IVH = patients without intraventricular hemorrhage. */** = significant difference on statistical testing.

associated with 14-day mortality (odds ratio [OR] 3.95, confidence interval [CI] 1.79–8.72; p = 0.001) and poor outcome at 3 months (OR 2.84, CI 1.42–5.66; p = 0.003), 6 months (OR 2.16, CI 1.13–4.12; p = 0.02), and 12 months (OR 2.7, CI 1.37–5.33; p = 0.004). dIVH was not significantly associated with any of these outcome measures (table 2, table e-3). There was a trend for worse functional outcome at 3 months for those with dIVH (OR 8.38, CI 0.86–81.35; p = 0.07). However, when including both the time from symptom onset to the initial CT and the presence of dIVH as independent variables in the multivariate model, dIVH was not associated but timing of CT (OR 2.48, CI 1.44–4.28) was associated with poor 3-month functional outcome (table e-4).

DISCUSSION Our study confirms that ICH-associated IVH that occurs after hospital admission is not uncommon (14.5% compared to 21% in a previous study[4]) but is far less frequent than IVH on admission CT. dIVH was predominantly seen in those who underwent very early admission CT scans. Two characteristics of the dIVH group, the markedly shorter onset to CT time and greater hematoma expansion, suggest that dIVH patients represent a specific subgroup of ICH patients with associated IVH, and that the categorization into initial and dIVH is mainly driven by CT timing, which confirms our initial hypothesis.

Comparing our cohort with the one studied by Maas and coworkers,[4] we found similar baseline characteristics with higher rates of atrial fibrillation, heart disease, and a higher rate of anticoagulation before admission (p = 0.08) in dIVH when compared to iIVH patients. Accordingly, our dIVH patients had a higher partial thromboplastin time on admission compared to iIVH patients (p = 0.03). In both studies, the initial serum glucose levels were higher among iIVH patients compared to the other groups, which has been described to be associated with

intraventricular extension of intracerebral hemorrhages.[7] Expectedly and in line with the previous study, patients who never developed IVH were less likely to have a deep location (thalamus/basal ganglia) of the hematoma, both dIVH and iIVH patients had similar hematoma baseline volumes, and hematoma extension was overwhelmingly larger in patients with dIVH. In both studies, ventriculostomy was less frequent among dIVH compared to iIVH patients. However, dIVH patients in our study had a lower rate of surgical hematoma evacuation (11% and 30%, respectively), which might reflect different neurosurgical practice at both study sites.

Notably, and in contrast with the previous study, we did not find an association between dIVH and acute or long-term outcome. Although this finding was consistent over the outcome measures at different time points (discharge and 3, 6, and 12 months after), it is important to note that neither the present cohort (n = 282) nor the one in the previous study (n = 216) are large enough to demonstrate or reject an association between dIVH and outcome.[4] The fact that Maas et al.[4] found dIVH to be associated with mortality and poor outcome and we did not is most likely a consequence of insufficient power in both studies. Studies in larger patient cohorts are needed to conclusively answer this question.

Both hematoma expansion and early hospital admission are known to be more frequent in stroke patients with poor initial clinical status and low GCS score.[8–10] Thus, short latency between symptom onset and hospital admission is likely a surrogate marker for low GCS score, which in turn is a strong predictor of mortality and poor outcome. Accordingly, the trend level association of dIVH and poor outcome at 3 months did not prevail when tested in a model with CT timing (CT ≤8 hours vs CT >8 hours after symptom onset) and hematoma expansion as covariates. The previous study neither quantified nor controlled for the time from symptom onset to initial imaging.

Furthermore it is of note that dIVH in our cohort was detected 2 hours earlier than in the cohort described previously, which we believe is due to differing local guidelines. In the previous study, patients per protocol were supposed to get a follow-up CT after 6 hours (the exact timing of CT scans was not separately reported for those with iIVH and dIVH in this study), while at our institution those with large hematomas or poor clinical state tend to receive follow-up imaging earlier than those with small bleeds and clinically stable patients.

Bias introduced by variable imaging time relative to the onset of acute disease is a well-known phenomenon. Examples in ICH research include the spot sign that may or may not be detectable, depending on the

Table 2	Multivariate regression analysis of poor outcome (modified Rankin Scale score 4-6) at 12 months		
Variable	**OR**	**95% CI**	***p* Value**
Delayed IVH	2.87	0.46-17.90	0.26
Initial IVH	2.70	1.37-5.33	0.004
Hematoma expansion	1.04	1.02-1.06	0.001
GCS <13	5.29	2.70-10.36	<0.001
Age >80 y	14.20	4.41-45.71	<0.001
Hematoma ≥30 mL	5.30	1.91-14.71	0.001
Infratentorial hematoma	2.03	0.80-5.17	0.14

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale; IVH = intraventricular hemorrhage; OR = odds ratio.

time interval from symptom onset to CT angiography,[11] estimation of ICH size that is strongly confounded by hematoma expansion,[12] and the quantification of perihematomal edema size, which is markedly dynamic during the first 14 days after the ICH.[13] Conversely, imaging may be used to guide therapeutic decisions in the absence of a reliable neurologic history, provided that imaging characteristics can be correlated well enough with changes of the underlying pathophysiology over time.[14] In order to control for bias arising from timing of imaging studies, clinical data acquisition has to be thorough and CT time in relation to preceding and subsequent events has to be documented and accounted for in the analysis. In our study, a dedicated investigator gathered all available data including history information for each patient. The onset time was documented after discussion with the treating attending and fellow taking all information into account. Future studies investigating dIVH should ideally prospectively also include only patients with a reliable history regarding bleed onset.

The strengths of our study include a relatively large sample size and a prospective mode of data collection. Furthermore, all CT scans were evaluated in an interdisciplinary meeting. Limitations might arise from a less rigid imaging protocol in comparison to the previous study.[4] Our imaging protocol did not include routine follow-up CTs before 12 hours after admission, since awake and cooperative patients can be sufficiently evaluated by neurologic examination alone. Importantly, because all patients received an admission and follow-up CT scan, we do not believe we underestimated the incidence of IVH after hospital admission. Though a longer latency to follow-up CT after admission may prolong the time to dIVH detection, it would most likely not prevent dIVH detection.

It is conceivable that ICH patients with IVH may be subdivided into 2 clinically meaningful groups: one that develops IVH simultaneously with the ICH, and one in which IVH occurs after the ICH as a consequence of hematoma expansion. Our findings of CT timing–dependent detection of IVH illustrate the latter pathomechanism. However, the significantly smaller IVH volumes in the dIVH group compared to the iIVH group indicate that possibly another mechanism of dIVH, e.g., rebleeding in coagulopathic patients during the hospital course, might account for some dIVH cases, possibly leading to smaller IVH volumes than in patients who develop IVH initially.

Our findings challenge recent observations associating dIVH with acute mortality. Moreover, they suggest that the timing of obtaining the admission CT scan is the main driver for categorizing IVH into early vs delayed. Future studies should test these hypotheses in larger patient samples in order to account for the overall relatively low incidence of dIVH. The CT timing aspect of intraventricular expansion in ICH should ideally be studied in an ICH cohort with a short onset to CT time (e.g., ≤2 hours).

Comment: Intraventricular hemorrhage— It's the blood that matters, not the timing

Intracerebral hemorrhage (ICH) is a highly morbid form of stroke. Recent research has sought to identify pathologic processes that continue to evolve after patients present for medical care, with the hope that those delayed injuries may be effectively detected and intervened upon to improve outcomes. Our group recently reported an observation that delayed intraventricular hemorrhage (dIVH) developed in 21% of ICH subjects with no intraventricular hemorrhage (IVH) present on initial imaging.[1] IVH has been characterized as an independent contributor to poor outcomes, and recognizing that delayed development of IVH was fairly common, along with the more widely recognized phenomenon of parenchymal hematoma growth, advanced it as another potential candidate for hemostatic treatments. Moreover, dIVH showed approximately the same effect size in contributing to death within 2 weeks and poor outcomes at 3 months as IVH on initial imaging, suggesting that IVH posed similar morbid consequences regardless of when it occurred.

The present work by Witsch and colleagues[2] provides additional insight into this phenomenon. A substantial number of patients in their cohort had dIVH (15%), and they similarly found that the discovery of dIVH was related to the scan timing, reinforcing the concept that intraventricular extension is a phenomenon that evolves for several hours after hemorrhage ictus. The effect of dIVH on outcomes did not reach statistical significance in their multivariate model, perhaps due to a lower observed incidence and a regression technique that dichotomized the modified Rankin Scale (mRS) rather than using an ordinal regression shift analysis. Ordinal statistical approaches to analyzing the mRS have become favored over dichotomization because they increase statistical power by using information from every stratum of the scale, and can identify clinical and significant effects not identified by simple binary regression.[3] That 20%–30% of patients with dIVH in these studies required ventriculostomy placement itself is notable and important. Their and our outcome analyses should not be interpreted as attempts to demonstrate or refute that dIVH is physiologically novel and distinct from initial IVH, but rather to confirm that they are similar and similarly morbid. What is remarkable from the data of Witsch et al. is how the effect estimates from the regression models confirm the similar morbidity of initial and delayed IVH: odds ratio of 2.70 and 2.87, respectively, for poor outcome (mRS 4–6 vs 0–3).

These findings are physiologically intuitive: Why would IVH affect outcomes differently when it occurs a few hours later, or when discovered in a patient who arrives at the hospital a few hours earlier? The key message for practicing clinicians is that important pathologic processes continue to evolve while patients are under our observation and care. The challenge ahead lies in elucidating the most effective methods for preventing, detecting, and treating these evolving and harmful processes.

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AUTHOR CONTRIBUTIONS

Jens Witsch drafted, revised, and gave final approval for the manuscript and conducted the statistical analysis. Eliza Bruce provided suggestions

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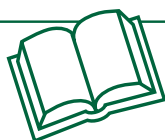
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