Early Seizures Are Predictive of Worse Health-Related Quality of Life at Follow-Up After Intracerebral Hemorrhage

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OBJECTIVES: Early seizures are a common complication of intracerebral hemorrhage, occurring in ~10% of patients. However, the independent effect of early seizures on patient outcomes, particularly health-related quality of life, is unclear. Without a potential benefit to patient outcomes, the widespread use (~40%) of prophylactic seizure medications has no reasonable chance of improving patient outcomes. We tested the hypothesis that health-related quality of life at follow-up is different between patients with and without early seizures (and secondarily, with nonconvulsive status epilepticus) after intracerebral hemorrhage.

DESIGN: Patients with intracerebral hemorrhage were enrolled in an observational cohort study that prospectively collected clinical data and health-related quality of life at follow-up.

SETTING: Academic medical center.

PATIENTS: One-hundred thirty-three patients whose health-related quality of life was assessed 3 months after intracerebral hemorrhage onset.

MEASUREMENTS AND MAIN RESULTS: Health-related quality of life was obtained at 3 months after intracerebral hemorrhage onset. T Scores of health-related quality of life were modeled with multivariable linear models accounting for severity with the intracerebral hemorrhage Score and hematoma location. Health-related quality of life was measured with National Institutes of Health Patient Reported Outcomes Measurement Information System/Neuroquality of life, expressed in T Scores (U.S. normal 50 ± 10). The modified Rankin Scale (a global measure) was a secondary outcome. There were 12 patients (9%) with early seizures. T Scores of health-related quality of life at follow-up were lower (worse) in patients with early seizure compared with patients without an early seizure (44 [32.75–51.85] vs 30.25 [18.9–39.15]; $p = 0.04$); results for other domains of health-related quality of life were similar. The association persisted in multivariable models. There was no association between early seizures and prophylactic seizure medications ($p = 0.4$). Results for patients with nonconvulsive status epilepticus were similar. There was no association between early seizures and the modified Rankin Scale at 3 months.

CONCLUSIONS: Early seizures and nonconvulsive status epilepticus were associated with lower health-related quality of life at follow-up in survivors of intracerebral hemorrhage.

KEY WORDS: health-related quality of life; intracerebral hemorrhage; outcomes; seizures; seizure medications

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Early seizures are a common and morbid complication of spontaneous intracerebral hemorrhage (ICH). Of the approximately hundred thousand Americans in whom ICH occurs each year, a seizure will occur in approximately 10% during the first week after ICH (defined as "early seizures") and up to 35–50% of patients months to years later ("late seizures") (1). Early seizures are plausibly associated with worse outcome after ICH. Early seizures increase the risk of subsequent brain herniation, poor outcome (2), and may progress to nonconvulsive status epilepticus (NCSE). The longer seizures and NCSE persist, the worse the patient's outcome is likely to be (3–5). If the patient survives the hospitalization, early seizures predict late seizures (1). Preventing early seizures is a rational therapeutic strategy to improve patient outcomes.

Previous investigations have found no association between early seizures and patient outcomes (6). Several potential explanations for this reported lack of association exist. Early seizures may be insufficient to independently worsen patient outcomes, particularly in patients with already have high severity of ICH (2), who are likely to have a dismal prognosis regardless of whether early seizures occur or not. Further, measurements of global patient outcomes are fairly crude and may not detect meaningful differences in patient outcomes that do not include a transition from dependent or dead ("poor outcome") to independent ("good outcome") (7).

Measurement of patient outcomes after ICH generally use global, ordinal scores that focus on independence such as the modified Rankin Scale (mRS) (7). The assessment of patients with seizures, however, more often includes health-related quality of life (HRQoL), which is negatively impacted by seizures (8). Sensitive, valid measures of HRQoL have become widely available, such as the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) and Neuroquality of life (QOL) (9–12). PROMIS and Neuro-QOL measures broadly track the mRS while being more granular in patients with ICH (9, 11) and might be more sensitive for detecting a difference in patients who survive. In particular, HRQoL in the domain of mobility closely tracks the mRS (13). We tested the hypothesis that early seizures were associated with lower mobility HRQoL in survivors of ICH.

MATERIALS AND METHODS

Our methods have been described in a previous report (14). In brief, patients with spontaneous ICH were identified at admission to a neurologic ICU. Patients with a structural lesion (e.g., tumor, aneurysm), hemorrhagic conversion of an ischemic stroke, and trauma were excluded. Demographic information, medical history, the ICH Score (a composite of age, hematoma volume, intraventricular hemorrhage, hematoma location, and level of consciousness) (15), imaging data, early seizures, and NCSE were prospectively recorded.

Ethical Approval

The proposal was approved by the Institutional Review Board (IRB). Patients provided consent for data acquisition. If the patient could not be consented due to neurologic injury, a legally authorized representative provided consent. The IRB provided a waiver for decedents and for patients who could not consent due to neurologic injury and for whom no legally authorized representative could be identified (e.g., an "unbefriended" patient).

Identification of Seizures and NCSE

Clinical seizures were prospectively recorded by a board-certified neurologist. Per ICUs protocol, all patients with altered consciousness underwent continuous electroencephalographic monitoring. NCSE was prospectively documented by the presence of a diagnostic electroencephalograph by expert interpretation (S.U.S., S.vH.) as previously described (16, 17). NCSE and seizures were scored separately, that is, a patient could have NCSE discovered on electroencephalograph monitoring without a clinical seizure.

HRQoL Assessment

As previously reported (18, 19), we obtained outcomes with Neuro-QOL, which are validated, standardized tests in specific domains of HRQoL. Neuro-QOL is similar to the NIH PROMIS and was validated with proxy report as part of its development, a necessary condition for obtaining outcomes in patients who may have difficulty communicating (20). We included data from patients from May 2011 to 2018 who survived to posthospitalization follow-up. We analyzed data on mobility HRQoL, as previously reported (12, 13).

We report results on 3 months here because at 1 month, some patients are still in rehabilitation, rendering many questions about independence moot and to avoid potential bias in carrying results forward from 1 month. Results are reported in T Scores normalized to the U.S. general population at 50 ± 10, that is, the average person in the United States will have a score about 50. As previously described, 0.5 SD, 5 points on the T Score, is considered a meaningful difference (21). We also obtained outcomes with the mRS at 3 months as previously described, using a validated questionnaire (22).

Statistical Analysis

Normally distributed data are reported as mean ± SD and were compared between groups with analysis of variance. Nonnormally distributed data are reported as median (quartile 1–quartile 3) and were compared with Mann-Whitney *U* test or Kruskal-Wallis *H* as appropriate. Categorical data (e.g., occurrence of early seizures) are reported as proportions and were compared using a chi-square or Fisher exact test as appropriate. Tests were two sided. Linear models were constructed to estimate T Scores of HRQoL using the lm command with standard software (R Studio v1.1.453, R v3.6; RStudio, Boston, MA [http://www.rstudio.com/]). We included ICH Score as a covariate of overall severity of ICH and hematoma location because they are potential confounders of early seizures and HRQoL (23).

RESULTS

Of 503 patients with ICH, 211 died by 3 months follow-up. Of the 292 survivors, we obtained HRQoL at 3 months in 133 patients. Demographics, stratified by early seizures, are shown in **Table 1**.

There were 12 patients (9%) with early seizures, all of which occurred within 4 days of ICH symptom onset. Other than a lower Glasgow Coma Scale at admission, demographics were similar between patients with and without early seizures (Table 1). In the five patients with NCSE, three of whom also had clinical seizures. NCSE and early seizures were associated (odds ratio, 19.0; 95% CI, 1.9–255.3; $p = 0.004$).

Measures of mobility HRQoL at 3 months were worse in patients with an early seizure (**Fig. 1**). T Scores of mobility HRQoL for patients with seizures were lower than for patients without seizures (30.25 [18.9–39.15] vs 44 [32.75–51.85]; $p = 0.04$). In multivariable models, T Scores of mobility HRQoL were significantly associated with early seizure and ICH Score without additional contribution from lobar hematoma location (**Table 2**). Results were similar for patients with NCSE. Although patients with early seizures had lower T Scores of HRQoL in all domains tested, there were no significant difference in T scores for patients with and without early seizures in the domains of cognitive function (49.5 vs 49.7), social roles and activities (46.3 vs 43.6), or anxiety (48.1 vs 43.9; $p > 0.2$ for all). The mRS was not different between patients with or without seizures ($p = 0.3$) or NCSE ($p = 0.1$).

DISCUSSION

We tested the hypothesis that early seizures were associated with lower HRQoL at 3 months follow-up. We found that early seizures were independently associated with lower T Scores of HRQoL in survivors.

Previous investigations have found no association between early seizures and patient outcomes. Although we found no association between early seizures and the mRS, the usual patient outcome after ICH, we found an association with T Scores of HRQoL. Two potential explanations for the association seem logical. First, T Scores of HRQoL closely track the mRS (10–12); however, they are more statistically sensitive because they are normally distributed numbers rather than categories (24). This suggests that previous investigations may have been underpowered to detect a difference of early seizures on patient outcomes. Second, HRQoL is measured only in survivors. Thus, our results may apply to a subgroup of patients with less severe ICH who survive to follow-up.

Patients with early seizures had a lower Glasgow Coma Scale on presentation. This is not surprising, as seizures are associated with reduced consciousness. This potential imbalance is captured by the ICH Score, which includes the Glasgow Coma Scale, as well as intraventricular hemorrhage, age, infratentorial hematoma location, and hematoma volume (15, 25). We also included lobar hematoma location, as could potentially confound associations with seizures and NCSE, although this did not meaningfully affect the association we found.

Our rate of early seizures is similar to results we previously reported (26). Other groups have reported

TABLE 1.
Demographics of the Cohort

Variables	No Early Seizures ($n = 123$)	Early Seizures ($n = 12$)	p
Age, yr, median (quartile 1–quartile 3)	62 (51–69)	65.5 (62–70.2)	0.1
International normalized ratio, median (quartile 1–quartile 3)	1 (1–1.1)	1 (1.0–1.2)	0.9
Women, *n* (%)	48 (39)	5 (42)	0.9
Race, *n* (%)			
White	85 (69)	7 (58)	0.6
Black	32 (26)	5 (42)	
Other	6 (6)	0	
Intracerebral Hemorrhage Score, *n* (%)			
0	55 (45)	3 (25)	0.3
1	36 (30)	6 (50)	
2	18 (15)	1 (8)	
3	11 (9)	2 (17)	
4	1 (1)	0	
Not determined	2		
Hematoma location, *n* (%)			0.3
Thalamus	24 (21)	0	
Brain stem	7 (6)	0	
Caudate	7 (6)	0	
Cerebellar	9 (8)	3 (25)	
Lentiform nuclei	39 (33)	3 (25)	
Lobar	30 (26)	6 (50)	
Other/not determined	7 (6)	0	
Glasgow Coma Scale at admission, median (quartile 1–quartile 3)	15 (13–15)	10 (7–14)	0.003
Hematoma volume at admission, mL, median (quartile 1–quartile 3)	6 (2–12.2)	6.5 (2–16.7)	0.6
Intraventricular hemorrhage, *n* (%)	43 (36)	3 (25)	0.5
Prophylactic phenytoin, *n* (%)	3 (2)	0	0.9
Prophylactic levetiracetam, *n* (%)	25 (20)	3 (25)	0.7

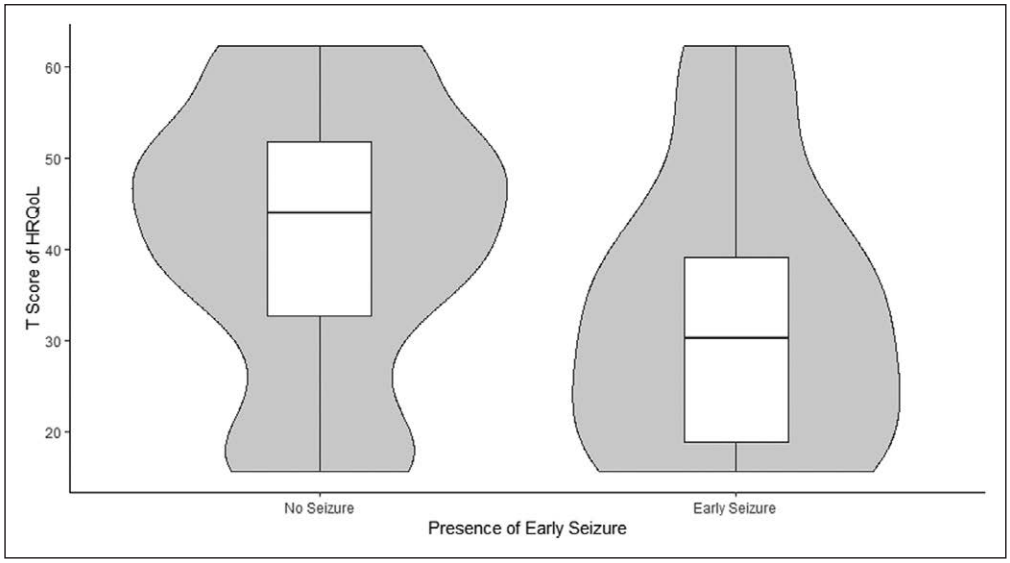

Figure 1. Boxplot and violin plot of T Scores of mobility health-related quality of life (HRQoL), stratified by the occurrence of early seizures.

higher rates of seizures (2). Reasons for different rates of early seizures with similar patient characteristics are speculative; it is possible that cohorts with a higher rate of lobar hematoma would be more likely to have a higher proportion of patients with early seizures. It would be interesting to note if other institutions with a higher prevalence of early seizures find a similar effect on patient outcomes.

We measured HRQoL using Neuro-QOL mobility. We have previously reported that T Scores from this instrument are highly correlated with the mRS in survivors of ICH, with "poor outcome" indicating T Scores of less than 35, indicating that patients with early seizures were likely to be dependent (13). Others have reported that other PROMIS (e.g., general physical function) measures perform similarly to mobility HRQoL (10). The questions used to calculate the T Scores are straightforward and easy to observe (e.g., ability to walk, carry groceries, rise from a chair) for patients who cannot report their own outcomes, although proxy reporting is also sometimes necessary for assessment of the mRS. Other domains of HRQoL were lower in patients with early seizures; however, none were statistically significant. Although a global measure of HRQoL would have been desirable, it was not collected in this cohort. Additionally, many patients did not have HRQoL data. We have previously noted that patients who are neurologically devastated are less likely to be able to provide HRQoL data, underscoring that these results are most likely to apply to patients likely to survive. We only included HRQoL measured at 3 months, a typical time to assess outcomes in clinical trials and for the assessment of the mRS by the Joint Commission. However, it is possible that later assessments of HRQoL would be valuable and provide additional time for patients to recover.

TABLE 2.

Multivariable Model for T Score of Mobility Health-Related Quality of Life at 3 Months After Intracerebral Hemorrhage Onset

	Model With Early Seizure		Model With NCSE	
Variables	**Estimate (95% CI)**	***p***	**Estimate (95% CI)**	***p***
Early seizure	−8.5 (−16.7 to −0.5)	0.03	–	–
NCSE	–	–	−19.3 (−31 to −7.6)	0.001
Intracerebral Hemorrhage Score, per point	−6.2 (−8.5 to −3.9)	< 0.001	−6.4 (−8.6 to −4.2)	< 0.001
Lobar hematoma location	5.1 (−0.1 to 10.5)	0.06	4.8 (−0.3 to 9.9)	0.06

NCSE = nonconvulsive status epilepticus. NCSE and early seizures were not combined in a single model because they are highly correlated—see text for details.

Dashes indicate that a variable was not in that model.

These data do not include a prospective determination of late seizures and later seizure medications, previously defined as seizures occurring more than 1 week after ICH onset (1). Early seizures are a risk factor for late seizures. One would reasonably expect that late seizures would lead to worse HRQoL, although this association could potentially be confounded by early seizures. Unmeasured late seizures would probably strengthen the association we report between early seizures and lower HRQoL.

Prophylactic seizure medications are prescribed to more patients than have a seizure after ICH (27). In this cohort, levetiracetam was most common, as phenytoin prophylaxis was essentially abandoned by the time we began to collect HRQoL at follow-up. It is logical that lobar hematoma location, early seizures, NCSE, late seizures, and seizure medication are correlated. Although there are no evidence-based protocols or guidelines for administering prophylactic seizure medications, clinicians are most likely to do so in patients with a lobar hematoma (28), likely because it is a described risk factor for late seizures (1). Although levetiracetam has been associated with lower HRQoL in cognitive function after ICH (29), to our knowledge, levetiracetam has not been associated with mobility HRQoL. Thus, confounding by prophylactic seizure medication is unlikely to account for the results.

In summary, we found that early seizures were associated with worse HRQoL at follow-up in survivors of ICH. The association of early seizures and worse mobility HRQoL persisted after correction for severity of ICH and lobar hematoma location. Future research should clarify if preventing early seizures is a rational strategy to improve outcomes after ICH.

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