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Full medical support for intracerebral hemorrhage

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ABSTRACT

Objective: This study tested the hypothesis that patients without placement of new do-not-resuscitate (DNR) orders during the first 5 days after intracerebral hemorrhage (ICH) have lower 30-day mortality than predicted by the ICH Score without an increase in severe disability at 90 days.

Methods: This was a prospective, multicenter, observational cohort study at 4 academic medical centers and one community hospital. Adults (18 years or older) with nontraumatic spontaneous ICH, Glasgow Coma Scale score of 12 or less, who did not have preexisting DNR orders were included.

Results: One hundred nine subjects were enrolled. Mean age was 62 years; median Glasgow Coma Scale score was 7, and mean hematoma volume was 39 cm^3. Based on ICH Score prediction, the expected overall 30-day mortality rate was 50%. Observed mortality was substantially lower at 20.2%, absolute average difference 29.8% (95% confidence interval: 21.5%–37.7%). At 90 days, 27.1% had died, 21.5% had a modified Rankin Scale score = 5 (severe disability). A good outcome (modified Rankin Scale score 0–3) was achieved by 29.9% and an additional 21.5% fell into the moderately severe disability range (modified Rankin Scale score = 4).

Conclusions: Avoidance of early DNR orders along with guideline concordant ICH care results in substantially lower mortality than predicted. The observed functional outcomes in this study provide clinicians and families with data to determine the appropriate goals of treatment based on patients' wishes. *Neurology*® 2015;84:1739–1744

GLOSSARY

CI = confidence interval; **DNR** = do not resuscitate; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **mRS** = modified Rankin Scale.

Intracerebral hemorrhage (ICH) is a common, severe form of stroke with 30-day case fatality approaching 50% in population-based series.[1] Predictive models that focus on hematoma volume and level of consciousness are frequently used in the care of patients with ICH.[2–4] None of these models account for the effect of early decisions to limit medical treatment, such as do-not-resuscitate (DNR) orders or withdrawal of medical support, on individual patient outcomes. Recent studies demonstrate that the use of DNR orders early after ICH is heterogeneous and independently influences risk of mortality after ICH.[5–8] The published predictive models are also questioned as a self-fulfilling prophecy since clinicians tend to suggest limitations in medical support for patients with moderate to large hemorrhages.[9] This practice raises the possibility that patients who would survive with intensive medical care are dying because of early treatment limitations. Survival, however, could be at the expense of severe disability.

We performed an observational ICH outcome study at 5 centers whose practice was to offer full care for patients with ICH for at least the first 5 days following symptom onset. The primary hypothesis was that 30-day mortality in these patients would be significantly less than predicted

Supplemental data at Neurology.org

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using a common ICH outcome prediction score. A secondary aim was to provide information on 90-day functional outcome to help families and clinicians in the decision-making process regarding level of treatment intensity after ICH.

If it turns out that the predictive models accurately estimate ICH mortality, then we can be reassured with their use for this purpose. If, as we hypothesize, the models overestimate mortality, then the question remains whether survival occurs at the expense of severe disability. This study spoke to both of these issues, mortality and functional outcome, and provides valuable information for clinicians in discussions with family regarding end-of-life care decisions.

METHODS

We performed a prospective cohort study at 5 hospitals in the United States to determine mortality and functional outcome among patients with ICH meeting entry criteria.

Subjects. All patients with ICH admitted to one of the participating hospitals (San Francisco General Hospital, University of Michigan Hospital [Ann Arbor], Harborview Medical Center [Seattle], Providence Hospital [Spokane], and Detroit Medical Center) were prospectively screened for enrollment by physician investigators and trained coordinators. Inclusion criteria included the following: age 18 years or older; presentation to a study hospital (including transfers) within 24 hours after symptoms onset; nontraumatic ICH from any cause including anticoagulant- and vascular malformation-related hemorrhages; Glasgow Coma Scale (GCS) score ≤12 at the time of admission to the study hospital; and no planned DNR orders or withdrawal of support for the first 5 days of hospitalization. The 5-day time period was chosen after careful deliberation among the investigators and colleagues as a period of time that would likely ensure an initial therapeutic trial of treatment as opposed to a primary plan of early care limitation. Exclusion criteria were as follows: hemorrhage related to brain tumors or hemorrhagic conversion of ischemic stroke; preexisting DNR order or family (surrogate) report that the patient would refuse aggressive treatment for any severe medical illness; and inability to initiate discussion about study participation within the first 5 days of hospitalization. Patients were not withdrawn from the study if they deteriorated or were made DNR after enrollment.

Standard protocol approvals, registrations, and patient consents. This project was approved by all hospital institutional review boards, and written informed consent was obtained from the legally authorized surrogate. If a participant regained decision-making capacity during the course of the study, they were asked to provide oral consent to continue participation.

Study procedures. This was an observational study and no study specific intervention was provided. As part of routine practice, clinicians were encouraged to provide guideline-concordant care.[10] Enrolled subjects' medical records were abstracted for demographic, clinical, and radiographic information.

Outcome measures. Vital status was assessed at 30 and 90 days by medical record review and/or telephone with the patient and/or legally authorized representative. Observed mortality was compared with predicted mortality based on the ICH Score. Development and validation of the ICH Score was previously reported.[3,11] Elements of the ICH Score are as follows: ICH volume (≥30 cm^3 = 1 point); GCS score (3–4 = 2 points, 5–12 = 1 point); intraventricular hemorrhage (yes = 1 point); infratentorial ICH location (yes = 1 point); and age (≥80 years = 1 point). Based on the ICH Score derivation cohort, the predicted mortality at 30 days for each patient was estimated according to the patient's ICH Score: 1 (13%), 2 (26%), 3 (72%), and 4 (97%).[3] The expected mortality for the cohort was calculated as the simple average of the predicted mortality across patients.

Functional outcome was assessed at 30 and 90 days by personnel familiar with assessing the modified Rankin Scale (mRS) by conducting a detailed telephone interview with the patient or family member, as this has been found to be reliable.[12] The prestated goal of the study was to determine the proportion of patients who survived with severe disability, defined as an mRS score of 5 and reflective of being bedridden, incontinent, and requiring assistance for all activities of daily living. Most stroke studies define a good outcome of a modified Rankin Index of 0–2 or 0–3, with an mRS score of 2 reflecting the ability to perform one's affairs without assistance but unable to perform all previous activities. An mRS score of 3 or 4 indicates the need for help to perform activities of daily living; an mRS score of 3 means that the patient is able to walk unassisted by another person. An mRS score of 6 is used for deceased subjects.

Statistical analysis. For the primary analysis, we compared the observed 30-day mortality rate (%) with the average expected mortality for the cohort based on the ICH Score (see above). To estimate a sample size, we used an expected average model-predicted probability of 65% based on the outcome for patients with GCS score ≤12 in the ICH Score development cohort. The required sample size of 105 was approximated with a 1-sample test of proportions with continuity correction assuming 80% power and a robust reduction in mortality of 15%. A significance level of 0.025 was used for the sample size calculations to allow for an interim analysis after the first 61 patients concluded their 30-day follow-up. The sample size for the interim analysis was based on a 20% lower mortality from the expected 65%, 80% power, and a 0.025 significance level.

We constructed a 95% confidence interval (CI) for the difference in observed and predicted mortality using bootstrap methods, since individual patients have different probability of death. A Kaplan–Meier curve was drawn to describe the timing of observed mortality.

Observed mortality for each level of the ICH Score was also computed. We formally compared observed and expected mortality across ICH Scores using a χ^2 goodness-of-fit statistic.[8] For each level of the ICH Score, the expected number of deaths was calculated as the number of patients with the given ICH Score times the predicted probability of death based on the validated ICH mortality model. The expected and observed number of deaths for each ICH Score was used as input for the χ^2 statistic. There was only one patient with ICH Score of 5, and this patient was grouped with those with ICH Score of 4 for this calculation.

The distribution of mRS scores at 30 and 90 days was computed across all patients. Descriptive statistics for all other variables were also computed. All analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

Patients not enrolled because of early DNR orders were compared with enrolled patients on the basis of age, sex, and GCS score using 2-sample Wilcoxon tests (age and GCS) and χ^2 test of proportions (sex). To ensure observed vs expected mortality

differences were not driven by a specific enrolling hospital site, we replicated the primary analysis leaving out one site at a time. We also examined whether observed mortality or the distribution of ICH Scores varied significantly by site.

RESULTS A total of 972 patients were screened for enrollment between December 2009 and August 2013, of whom 555 (57.1%) were excluded because of GCS score >12 and/or preexisting DNR order. Among the remaining 417, 148 (35.5%) were made DNR by family or physician before day 5, and 160 (38.4%) were not enrolled for other reasons. Other reasons for nonenrollment included no family available for consent (51), missed by study team (36), family refusal (33), language barrier (19), transferred more than 24 hours after symptom onset (9), or other (17) (note that numbers do not sum to 160 because of multiple reasons for exclusion in some patients). Of the 417, 109 patients (26.1%) who met study criteria and accepted to participate were included in the study. Table 1 provides the demographic and clinical information for the study participants. The subjects represent a broad range of ICH presentations for those presenting with a GCS score of ≤12. Table e-1 on the *Neurology*® Web site at Neurology.org provides comorbidity data.

Table 1 Demographic and clinical characteristics of the study participants

Characteristic	No. (%) or median (Q1, Q3)
Age, y	62 (52, 73)
Male	52 (48)
Race	
Asian	25 (23)
Black	14 (13)
Native American, Hawaiian, or Pacific Islander	5 (5)
White	64 (59)
Other	2 (2)
Hispanic (any race)	9 (8)
Glasgow Coma Scale score	7 (6, 10)
Coagulopathy (international normalized ratio ≥1.5)	12 (11)
Hemorrhage volume, mL	27.3 (14.6, 57.0)
Hemorrhage location	
Lobar	44 (40)
Deep cerebral	50 (46)
Posterior fossa	15 (14)
Intraventricular hemorrhage	73 (67)
Hydrocephalus	56 (51)
ICH Score	
1	13 (12)
2	43 (39)
3	39 (36)
4	13 (12)
5	1 (1)
Do-not-resuscitate order <5 d	7 (6)
Do-not-resuscitate order ≥5 d	18 (17)
Transitioned to comfort care during hospitalization	17 (15)
Intensive care unit length of stay, d	8 (4, 14)
Other interventions performed	
Induced hypothermia	3 (2.8)
Intraventricular rtPA	3 (2.8)
Brain tissue oxygen monitoring	11 (10)
Hematoma evacuation surgery	26 (24)

Abbreviations: ICH = intracerebral hemorrhage; Q = quartile; rtPA = recombinant tissue plasminogen activator.

Table 2 gives the mortality data at 30 and 90 days. Figure 1 provides the Kaplan–Meier survival curve for participants. Mortality at 30 days was 20.2%, which was overall 29.8% (95% CI: 21.5%–37.7%) less than the ICH Score–predicted mortality. This represents a 60% relative mortality risk reduction compared with predicted. The goodness-of-fit test also indicated that the mortality predictions based on the ICH Score model did not fit the observed data ($p < 0.001$). The ICH Score–predicted mortality compared with observed mortality in participants is provided in figure 2. Of the 109 patients, 41% were transfer patients. Predicted mortality for nontransferred patients was 53%, and 45% for transferred patients; observed mortality was 19.9% and 20.2%, respectively. Both nontransferred (33%, 95% CI: 23%–44%) and transferred (25%, 95% CI: 13%–37.5%) patients had significantly lower than predicted mortality ($p < 0.001$ for both).

Table 2 also provides the functional outcome data. Two patients were lost to follow-up between 30 and 90 days (one left the country with no further contact possible and one requested to not be contacted for future follow-up), leaving 107 participants with 90-day outcome data. At 90 days, 21.5% of the 107 participants had severe disability, were bedridden, incontinent, and required help for all activities of daily living (mRS score 5). A good outcome (mRS score 0–3) was achieved by 29.9% and an additional 21.5% were in the moderately severe disability range (mRS score 4). The presenting ICH scores among those with good outcome (mRS score 0–3) were 1 (16%), 2 (56%), 3 (22%), and 4 (6%).

Comparing nonenrolled with enrolled patients, those nonenrolled patients for whom early DNR orders were written (n = 148) were significantly older (73 vs 62 years, $p < 0.001$) and had a lower presenting GCS score (median 5 vs 7, $p < 0.001$) compared with the 109 enrolled participants. This is a conservative comparison, because it is not known how many of the 148 would have been excluded for other predefined reasons and because additional data on

Table 2 Survival and functional outcome and at 30 and 90 days

Characteristic	30 d	90 d
No. with data	109	107[a]
Modified Rankin Scale score, n (%)		
0	1 (0.9)	1 (0.9)
1	1 (0.9)	3 (2.8)
2	1 (0.9)	6 (5.6)
3	13 (11.9)	22 (20.6)
4	30 (27.5)	23 (21.5)
5	41 (37.6)	23 (21.5)
6 (deceased)	22 (20.2)	29 (27.1)

[a] Two patients were lost to follow-up between 30 and 90 days (one left the country with no further contact possible and one requested to not be contacted for future follow-up).

exclusion criteria were not collected among those with early DNR orders.

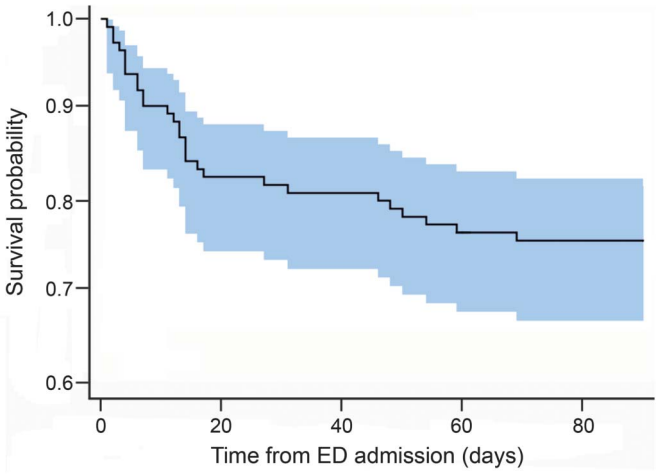
Site effects were examined in sensitivity analyses and there was no effect of enrolling hospital site on mortality or on the difference between observed and predicted mortality. There were no significant differences in mortality or ICH Score by site.

DISCUSSION In this study, we found that patients with ICH (with initial GCS score ≤12) in whom the initial plan was to continue full intensive supportive treatments for at least 5 days had a 30% absolute lower mortality compared with the ICH Score–predicted mortality. At 90 days, approximately 1 in 4 had died, 1 in 5 had severe disability, 1 in 5 had moderately severe disability, and 1 in 3 had good outcome to moderate disability. These numbers allow clinicians to share prognostic estimates following a guideline-concordant, intensive course of medical treatment. Clinicians wishing to apply these data to individual patients should be mindful, however, of the characteristics of the enrolled patients provided in tables 1 and e-1, as our findings may not apply to patients with different clinical and comorbid characteristics. Fundamentally, an accurate estimate of outcome, unbiased by early withdrawal of medical support, is necessary for families to consider the preexisting wishes of the patient, or in the absence of stated wishes, their proxy decision on behalf of the patient.

Previous work suggested that hematoma volume was an especially potent predictor of ICH mortality.[2,4] Since blood is so conspicuous on an acute head CT, clinicians reviewing a CT scan before seeing a patient with ICH may develop preexisting notions regarding survival before examining the patient. The lack of specific treatment for ICH and the failure of therapeutic trials using hemostatic agents[13] and surgery[14] have also led to a nihilistic attitude toward this common disease.[15] Becker et al.[9] challenged the nihilism by demonstrating that better than expected outcomes are possible for patients with severe ICH when treated without early limitations in treatment intensity. When their case vignettes without outcomes were shown to clinicians, the clinicians generally said there was no hope of good outcomes. In a large study of California hospitals, the use of DNR orders within the first 24 hours (early DNR) after ICH was found not only to be a strong predictor of individual patient outcome, but a lower frequency of early DNR use by hospitals was predictive of a higher likelihood of survival of patients with ICH.[6] That is, even patients with ICH who were full code had increased mortality in hospitals that used early ICH DNR orders more frequently, suggesting that early DNR orders were a proxy for overall intensity of care.

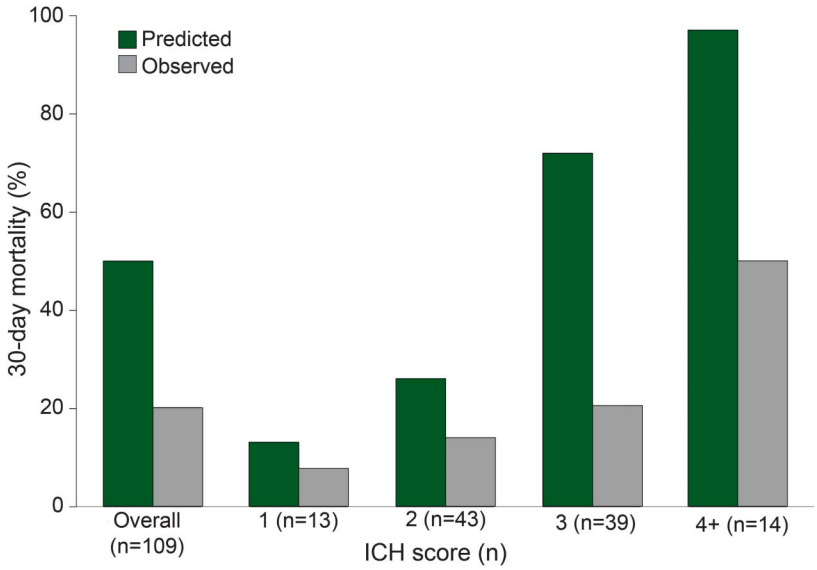
Clinical grading scales such as the ICH Score are often used as part of initial patient assessment, decision-making, and communication. In the current study, each increase in the level of the ICH Score was associated with an increased risk of 30-day mortality, but the actual mortality risk was lower at each ICH Score level than the point estimates from the initial ICH Score publication. This suggests that while clinical grading scales such as the ICH Score may be useful in stratifying patients based on initial severity, caution must be exercised in using specific numeric values as precise outcome estimates for an individual. The ICH Score was based on nontransfer patients and the current study included transferred patients, perhaps more closely resembling real-world practice. In both transferred and nontransferred patients, observed mortality was significantly less than predicted mortality. Furthermore, the ICH Score was developed more than 10 years ago and improvements in

Figure 1 Kaplan–Meier survival curve



Kaplan–Meier survival curve (n = 109) and 95% confidence intervals. Note y-axis starts at 0.6. ED = emergency department.

Figure 2 **Predicted and observed mortality**



Intracerebral hemorrhage (ICH) Score–predicted 30-day mortality compared with observed mortality in study participants based on ICH Score.

neurocritical care may make the instrument less informative in the present day despite its widespread use.

On a positive note, the benefits of neurocritical care for ICH outcome are well documented and advocated,[10,16] including the benefits of acute blood pressure control[17] and recognition that DNR status is a powerful independent predictor of poor outcome,[6,7,18] all of which suggest that a more sustained intensive care approach to ICH treatment may be warranted.

This study has strengths. It prospectively enrolled patients. The sample size was calculated to have enough power only to see a large mortality difference from predicted to ensure a robust result. The study sites and the patients recruited represent a diverse demographic and clinical ICH population. The work also has significant limitations. While centers were chosen because they espoused a full ICH intensive care philosophy, some patients were not included because very early DNR orders were written, raising the concern for selection bias. The conservative post hoc analysis performed suggested that the nonenrolled subjects were older and had lower GCS score, and thus likely had higher ICH scores. Of note, since the primary analysis was linked to the ICH Score, the reported difference in mortality is somewhat protected against selection bias because the expected mortality of the cohort was adjusted for severity and thus representative of observed vs predicted mortality differences at each ICH score of 4 or less. We cannot be sure, however, if within specific ICH Score categories there were variables not captured by the ICH Score that biased our sample by lack of participation. This study could not assess the impact of early DNR avoidance on mortality among the patients with ICH Score of 5, and we acknowledge the possibility that this very severe ICH population may have high mortality regardless of the early DNR order status. Even if our results indicate a "best case scenario," they demonstrate that the ICH Score may greatly overestimate mortality for individual patients who are treated without early care limitations.

The 5-day time period was determined after careful deliberation among the investigators and their local colleagues. However, this time period was arbitrary and may not be long enough to adequately predict prognosis. We chose the ICH Score since it is widely used and validated. However, we cannot be sure that the findings were not specifically a limitation of this grading scale. Outcome assessments were performed by coordinators who were trained to systematically question patients and caregivers for mRS determination. They were not blinded to the study question and this may have resulted in outcomes biased to lower mRS assessments. While we compared ICH Score predicted to observed mortality, we did not study a predictive model for functional outcome.[19] The ICH Score provided a historical control, a weaker study design than the use of a contemporaneous control group. The next study could be a randomized, controlled, behavior change intervention trial.

This study observed a substantially lower mortality among patients treated with full medical support for at least 5 days after ICH compared with that predicted by a validated ICH clinical grading scale that was developed without considering limitations in medical support. There was a potential for good functional outcome among survivors, but a proportion were left severely disabled. These estimates, unbiased by limitations in care, are vital for clinical decision-making in ICH and serve as a model for other acute life-threatening conditions.

AUTHOR CONTRIBUTIONS

L.B. Morgenstern: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, study supervision or coordination. D.B. Zahuranec: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision or coordination. B.N. Sánchez: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, statistical analysis. K.J. Becker: drafting/revising the manuscript for content, including medical writing for content, study concept or design. M. Geraghty: drafting/revising the manuscript for content, including medical writing for content. R. Hughes: drafting/revising the manuscript for content, including medical writing for content, study concept or design, acquisition of data, study supervision or coordination. G. Norris: drafting/revising the manuscript for content, including medical writing for content. J.C. Hemphill III: drafting/revising the manuscript for content, including medical writing for content, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination.

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DISCLOSURE

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