Long-term mortality after intracerebral hemorrhage

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Abstract—Objective: To characterize long-term mortality following intracerebral hemorrhage (ICH) in two large population-based cohorts assembled more than a decade apart. **Methods:** All patients age ≥ 18 hospitalized with nontraumatic ICH in the Greater Cincinnati/Northern Kentucky area were identified during 1988 (Cohort 1) and from May 1998 to July 2001 and August 2002 to April 2003 (Cohort 2). Mortality was tabulated using actuarial methods and compared with a log-rank test. **Results:** There were 183 patients with ICH in Cohort 1 and 1,041 patients in Cohort 2. Patients in Cohort 1 were more likely to be white ($p = 0.024$) and undergo operation for their ICH ($p = 0.002$), whereas patients in Cohort 2 were more commonly on anticoagulants ($p < 0.001$). Among patients in Cohort 1, mortality at 7 days, 1 year, and 10 years was 31, 59, and 82%. Among patients in Cohort 2, mortality at 7 days and 1 year was 34 and 53%. Mortality rates did not differ between cohorts by log-rank test ($p = 0.259$). **Conclusions:** Intracerebral hemorrhage (ICH) mortality did not improve significantly between study periods. Operation for ICH became less frequent, whereas anticoagulant-associated ICH became more common.

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Recent investigations into the surgical and medical management of intracerebral hemorrhage (ICH) prove that large-scale clinical trials for this condition are feasible and provide hope that new treatments may improve patient outcomes.^{1,2} Outside of clinical trials, changes in medical practice and the natural history of disease are ideally documented in population-based studies that capture all disease cases within a defined community. To date, most population-based studies of ICH outcome have been small and racially homogeneous.³ Limited sample size has precluded analysis of some predictors of ICH outcome, such as location of hemorrhage and anticoagulant use in most of these studies.^{3,4} Furthermore, whereas short-term mortality following ICH is known to be high, the pattern of long-term mortality following ICH and recent trends in ICH mortality have not been well documented.³ We present a population-based study of ICH outcome, including long-term mortality data, stratification by location of hemorrhage, and a comparison of two large ICH cohorts assembled more than a decade apart.

Methods. Two ICH cohorts from the five-county Greater Cincinnati/Northern Kentucky area (GCNK) were tracked for this study. Cohort 1 was assembled from January 1988 through December 1988 and has been the subject of previous reports.^{5,6} Cohort 2 was assembled from May 1998 through July 2001 and August 2002 through April 2003 as part of the Genetic and Environmental Risk

Factors for Hemorrhagic Stroke (GERFHS) study, an ongoing population-based study of ICH and subarachnoid hemorrhage in the GCNK region.⁷ The methodology of the GERFHS study has been previously described.^{7,8}

The current study includes all hospitalized cases of ICH that occurred in persons age ≥ 18 within the five GCNK metropolitan counties during the prescribed periods. For both cohorts, cases were identified by retrospective review of primary and secondary International Classification of Diseases-9 (ICD-9) codes. For Cohort 1, ICD-9 codes 430, 431, 432.9, 436, 437.3, and 747.81 were utilized.⁶ For Cohort 2, ICD-9 codes 430 through 432 were utilized through October 1999 and codes 430 through 438.9 thereafter. For Cohort 2, study nurses also maintained active surveillance (“hot pursuit”) at several hospitals that treat most ICH and subarachnoid hemorrhage in the area by reviewing neurosurgery logs and patient rosters several times each week.⁷ In both periods, potential cases were abstracted by study nurses and reviewed in detail by study physicians. Residents of the five-county GCNK region seek care almost exclusively at 1 of the 16 participating metropolitan hospitals.⁶ Patients living within the 50-mile radius required by the GERFHS study but outside of the five counties of interest were excluded by zip code of residence. For the current study, exclusion criteria applied to both cohorts were previous ICH, traumatic ICH, hemorrhagic cerebral infarction, and hemorrhage associated with brain tumor, encephalitis, endarterectomy, and thrombolytic treatment of ischemic stroke. ICHs associated with vascular malformations or anticoagulation were included.

Patient demographics and putative risk factors for ICH were recorded for each cohort by chart review and compared with the χ^2 test, Student t test, or Wilcoxon two-sample test as appropriate. For any case in which ICH location was not unequivocally identified by radiographic reports, radiographic films were reviewed by investigators. Surgical intervention for ICH was defined as hemispherectomy, craniotomy for removal of a hematoma or vascular malformation, or stereotactic drainage of a hematoma. CSF drain-

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Table 1 Comparison of ICH patient demographics, 1988 vs 1998–2003

	1988	1998–2003	<i>p</i> Value
Total cases	183	1,041	
Age, mean (SD); y	70.3 (15.0)	70.0 (15.3)	0.798
Female (%)	104 (56.8)	576 (55.2)	0.689
White (%)	157 (85.8)	817 (78.5)	0.024
Location of ICH (%)			0.605
Deep cerebral	88 (48)	516 (50)	
Lobar	71 (39)	358 (34)	
Cerebellar	14 (8)	102 (10)	
Brainstem	10 (6)	65 (6)	
Admit GCS, mean*	11.0	10.9	0.714
Admit GCS, median*	12.0	14.0	0.004
Hypertensive (%)	126 (68.9)	693 (66.6)	0.545
Diabetic (%)	35 (19.1)	202 (19.4)	0.930
Anticoagulation† (%)	9 (4.9)	190 (18.3)	<0.001
Operation for ICH (%)	33 (18.0)	104 (10.0)	0.002
Intraventricular drain‡ (%)	24 (13.1)	96 (9.2)	0.102

* For 1988, values are available for 182/183 patients. For 1998–2003, values are available for 910/1,041 patients.

† Anticoagulation = warfarin, heparin, or low molecular weight heparin.

‡ Data available for all cases in 1988 and 1,017/1,041 cases in 1998–2003.

ICH = intracerebral hemorrhage; GCS = Glasgow Coma Scale.

age was recorded separately. Hematoma volumes and the presence of intraventricular hemorrhage were not routinely recorded. Survival after ICH was calculated using actuarial methods after querying the 1988 study database, GERFHS study records, the Social Security Death Index, and Ohio and Kentucky death registers. Persons not documented to be deceased were assumed to be alive. Survival curves were compared by log-rank test. To determine if era of hemorrhage (i.e., membership in Cohort 1 or Cohort 2) was an independent predictor of survival after ICH, a Cox regression model for survival among all subjects was created using the variables from table 1 plus era of hemorrhage. Variables with a *p* value of >0.10 were backward eliminated from the model, with era of hemorrhage forced into the final model. Because admission Glasgow Coma Scale (GCS) scores were found to be highly dependent upon hemorrhage location, the model was run with and without GCS score as a variable. The model with GCS score as a variable excluded one patient from Cohort 1 and 131 patients from Cohort 2 because of missing GCS scores. The institutional review board for each participating hospital system approved the GERFHS study.

Results. Cohort 1 included 183 persons. Cohort 2 included 1,041 persons after exclusion of 3 cases because of insufficient information. Patient demographics and putative ICH risk factors are compared by era in table 1. Patients in Cohort 1 were more likely to be white (*p* = 0.024) and undergo operation for their ICH (*p* = 0.002), whereas patients in Cohort 2 were more commonly on anticoagulants (*p* < 0.001), with a greater than threefold increase in the percentage of anticoagulant-associated hemorrhages in the latter group. Mean GCS scores were similar between cohorts, but the median GCS score was higher in Cohort 2 (12 vs 14; *p* = 0.004). The balance of hemorrhage locations

Figure 1. Comparison of intracerebral hemorrhage (ICH) mortality. Cohort 1 = 1988; Cohort 2 = 1998–2003.

was similar between groups (*p* = 0.605). A survival curve comparing cohorts is presented in figure 1. Among patients in Cohort 1, mortality at 7 days, 1 month, 1 year, and 10 years was 31, 48, 59, and 82%. Among patients in Cohort 2, mortality at 7 days, 1 month, and 1 year was 34, 44, and 53. Mortality did not differ between cohorts by log-rank test (*p* = 0.259). Survival stratified by ICH location for all patients is presented in figure 2. Thirty-day and 1-year mortality rates were 44 and 52% for deep cerebral ICH, 46 and 58% for lobar ICH, 60 and 68% for brainstem ICH, and 34 and 45% for cerebellar ICH. Mortality differed by location by log-rank test (*p* = 0.022).

Results reaching a significance level of <0.10 in the Cox regression model of survival among all patients (excluding GCS as a variable) are presented in table 2. Predictors of mortality in this model were increasing age, diabetes, anticoagulation, and brainstem location of hemorrhage. Cerebellar location of ICH and operation for ICH were associated with better survival. There were trends toward better survival for patients from Cohort 2 as compared with Cohort 1 (*p* = 0.13), for deep cerebral location as compared with lobar location (*p* = 0.11), and for African Americans as compared with whites (*p* = 0.101). The relationship between GCS and survival was found to be quadratic rather than linear, and so in the Cox model with GCS, both quadratic and linear terms for GCS were included. In

Figure 2. Survival after intracerebral hemorrhage (ICH) stratified by location.

Table 2 Cox regression model of ICH outcome

	Hazard ratio*	95% CI	p Value
Location of ICH†			
Cerebellar	0.75	0.58–0.98	0.033
Deep cerebral	0.88	0.76–1.03	0.106
Brainstem	1.37	1.02–1.82	0.036
Operation for ICH	0.74	0.58–0.96	0.022
Period of ICH (Cohort 2 vs 1)	0.86	0.71–1.05	0.133
Age‡	1.03	1.02–1.03	<0.001
Diabetes	1.25	1.06–1.49	0.010
Anticoagulation	1.49	1.24–1.79	<0.001

* Hazard ratios of >1 indicate increased risk for death.

† Lobar ICH used as referent.

‡ For each increasing year of age.

ICH = intracerebral hemorrhage.

this model, anticoagulation, increasing age, and diabetes remained predictors of mortality, whereas operation for ICH remained protective. Increasing GCS score was associated with better outcomes ($p = 0.005$), whereas location of ICH became nonsignificant. Era of hemorrhage remained nonsignificant.

Discussion. Our study confirms the high mortality rate following ICH reported in smaller population-based studies. The 1-month case fatality rates of 48% (Cohort 1) and 44% (Cohort 2) are comparable with the 42% rate estimated from other population-based studies.³ Patients with ICH fare worse than those with ischemic stroke, and few are left without disability.^{3,5} After a sharp drop in survival immediately following ICH, a more gradual decline resulted in 10-year survival of only 18% in Cohort 1.

Mortality following ICH did not differ significantly between our cohorts, which were separated by more than a decade. This reflects the lack of proven effective treatments for this condition. Mortality after ICH was reportedly as high as 90% in the pre-CT area.⁹ The lower mortality in our cohorts was likely due to a combination of identification bias in the pre-CT era (with mild hemorrhages misclassified as ischemic infarcts) and improved supportive care.¹⁰ Continuing refinements in neuroimaging and neurointensive care did not translate into a substantial reduction in mortality between 1988 and 1998 through 2003 in our area.

The most striking difference in our cohorts was the variation in risk factor profiles. The groups were similar in patient age and sex as well as the prevalence of hypertension and diabetes. Cohort 1 was more likely to be white, partly reflecting the changing racial balance in our five-county area (84.5% white in 1990 vs 82.4% white in 2000). The median admission GCS score was higher in Cohort 2 than Cohort 1. Although missing data prohibit a definitive conclusion about the cause of this change, it is possi-

ble that more frequent and improved neuroimaging resulted in the proper classification of smaller hemorrhages. A second possibility is that patients in Cohort 2 arrived in the emergency department more quickly than patients in Cohort 1 and had their GCS scores documented before the delayed deterioration sometimes seen with hematoma expansion. Our data were insufficient to allow a detailed comparison of arrival times by period. Another notable difference between cohorts was a 13% absolute increase in the percentage of anticoagulant-associated hemorrhages from 1988 to 1998 through 2003. This increase occurred after the publication of trials demonstrating the efficacy of warfarin for the primary and secondary prevention of ischemic stroke among patients with atrial fibrillation, and it coincides with data showing increased warfarin use in these populations.^{11–14} Patients with anticoagulant-associated ICH had poorer outcomes in our Cox regression model, consistent with previous reports demonstrating greater risk of hematoma expansion and worse survival among anticoagulated ICH patients than those without coagulopathy.^{15,16} Increasing age and diabetes have likewise been associated with worse outcomes.^{17–19} The use of surgery for ICH diminished in our population between 1988 and 2003, in concert with a growing number of negative surgical treatment trials.^{20,21} Whereas surgery showed a protective effect in the Cox model, this may be explained by a selection bias not captured by the available data.

Location of ICH had an effect upon survival that was not adequately described by dichotomizing hemorrhages as supratentorial vs infratentorial or lobar vs deep. Brainstem ICH proved the most lethal subtype, whereas cerebellar ICH had the best prognosis. In these large cohorts, lobar ICH and deep cerebral ICH had similar case fatality rates, contrary to some older reports describing lobar ICH as more often benign.^{22,23} Other studies have shown that lobar hemorrhages have greater average volume than deep cerebral hemorrhages but are less likely to extend into the ventricular system, two counterbalancing influences on prognosis.^{4,24}

The largest previous population-based study of ICH outcome was performed in Izumo City, Japan.⁴ The authors reported on 350 patients ascertained from 1991 to 1998, excluding patients with vascular malformations or coagulopathy. Outcomes in their cohort were remarkably good, with 7- and 30-day mortality rates of 11 and 13%. As in our study, in Izumo City, survival was best after cerebellar ICH and worst after brainstem ICH. Thirty-day case fatality rates in their population were 0% for cerebellar ICH, 11% for lobar ICH, 9 to 14% for different deep cerebral locations, and 53% for brainstem ICH. In a Cox regression analysis of 3-month outcome in their cohort, ICH location was the strongest independent predictor of survival, followed by hematoma volume and admission GCS score. The authors suggest that their low mortality rates may be due to aggres-

sive management (including surgery) and early treatment of patients at hospitals with neurosurgical support. These explanations seem unlikely given the lack of benefit in surgical ICH trials and the fact that most ICH patients in our area are transferred immediately to a tertiary center.^{1,20} Although it is possible that patients with severe hemorrhages have care withdrawn more frequently in Cincinnati than Izumo City, only 30% of survivors in Izumo City were left in a vegetative state or with severe disability. This figure is lower than described in western reports and would not be expected if neurologically devastated patients had life sustained by aggressive, prolonged intervention.⁵

Other possible reasons for the different outcomes were the Japanese exclusion of anticoagulant-associated hemorrhages and differences in admission GCS scores.¹⁵ In Izumo City, 16% of patients presented with a GCS score of 3 to 6 compared with 27% of patients in Cincinnati. Admission GCS score is presumably a reflection of the disease state and the patient's neurologic reserve and is not itself a causal force. In our series, GCS score was highly dependent upon ICH location. When GCS was included in our Cox model, location of ICH became nonsignificant. This may have occurred because we were unable to account for hematoma size and intraventricular hemorrhage, two important factors that may influence GCS score. Because we did not record these values, we cannot determine whether they differed between the populations of Cincinnati and Izumo City.

This study was limited by our inability to control for some of the known variables (hematoma volume, intraventricular hemorrhage) and unknown variables that influence outcome after ICH.¹⁹ Our goal in this setting was to describe survival following ICH in a population-based setting, given existing practice patterns in our large metropolitan area, rather than to develop a comprehensive model or algorithm for survival after ICH as has been previously done.^{19,25}

The fact that survival in our ICH population has not improved significantly in the last 10 to 15 years suggests that changes in practice during that time did not have a major clinical impact. It is possible that improvements in patient care have been counterbalanced by other negative prognostic factors such as the increase in anticoagulant-associated ICH. Alternatively, positive prognostic factors such as smaller hemorrhages detected by more frequent imaging may have improved survival in Cohort 2 (and produced higher median admission GCS scores). The problem of the "self-fulfilling prophecy" in patients with neurologic catastrophes is well recognized (i.e., the perception that survival is impossible, followed by withdrawal of care and death of the patient).²⁶ Patterns of care following ICH may have changed between study periods, with more patients in the current era having care withdrawn. We did not record the prevalence of do-not-resuscitate status or

orders for comfort care, and so we cannot account for this possibility.

This study provides a comprehensive view of long-term mortality following ICH and emphasizes the fundamental challenge of ICH treatment: The majority of ICH deaths occur very shortly after disease onset. Any meaningful reduction in the medical and social burden caused by ICH must therefore arise from primary prevention, very early intervention after hemorrhage, or novel rehabilitation strategies. The survival curves presented will serve as useful baselines for comparison as new therapies for ICH become available.

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Asymptomatic sinovenous thrombosis in a healthy neonate

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Our patient's parents became concerned about a ridge on the back of his skull when he was 2 weeks old. He was otherwise healthy. Head CT demonstrated a normal skull but suggested sinovenous thrombosis; follow-up MRI and venography confirmed this (figure). He showed no signs of dehydration or seizures. His neurologic exam was normal. Prothrombotic evaluation was unremarkable. He was followed conservatively, with repeat imaging and neurologic exams. During the next year, follow-up CT venography revealed gradual resolution of thrombosis. He had normal head growth and development and a normal neurologic exam at 1 year of age.

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Figure. (A) Head CT at 15 days old: enlarged straight sinus. (B) T1-weighted MRI at 17 days old: extensive thrombus in sagittal sinus. (C) CT venography (CTV) at 2 months old: residual thrombus at the torcula and sagittal sinus. (D) CTV at 10 months old: minimal residual thrombus at the torcula.

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