Ten-Year Temporal Trends in Medical Complications After Acute Intracerebral Hemorrhage in the United States

Fadar Oliver Otite, MD, SM; Priyank Khandelwal, MD; Amer M. Malik, MD, MBA; Seemant Chaturvedi, MD; Ralph L. Sacco, MD, MS; Jose G. Romano, MD

Background and Purpose—Data on medical complications after intracerebral hemorrhage (ICH) are sparse. We assessed trends in the prevalence of urinary tract infection, pneumonia, sepsis, deep venous thrombosis (DVT), pulmonary embolism, acute renal failure (ARF), and acute myocardial infarction after ICH in the United States.

Methods—A total of 575 211 adult ICH cases were identified from the 2004 to 2013 Nationwide Inpatient Sample. Weighted complication risks were computed by sex and mechanical ventilation status. Multivariate models were used to evaluate trends in complications and assess their association with in-hospital mortality, cost, and length of stay.

Results—Overall risks of urinary tract infection, pneumonia, sepsis, DVT, pulmonary embolism, ARF, and acute myocardial infarction after ICH were 14.8%, 7.8%, 4.1%, 2.7%, 0.7%, 8.2%, and 2.0%, respectively, but risk differed by sex and mechanical ventilation status. From 2004 to 2013, odds of DVT and ARF increased, whereas odds of pneumonia, sepsis, and mortality declined over time. All complications were associated with >2.5-day increase in length of stay and >$8000 increase in cost. ARF and acute myocardial infarction were associated with increased mortality in all patients; sepsis and pneumonia were associated with increased mortality only in nonmechanical ventilation patients, whereas urinary tract infection and DVT were associated with reduced mortality in all patients.

Conclusions—Despite significant mortality reduction, ARF and DVT risk after ICH have increased, whereas odds of sepsis and pneumonia have declined over the last decade. All complications were associated with increased cost and length of stay, but their associations with mortality were variable, likely due in part to survival bias. Innovative strategies are needed to prevent ICH-associated medical complications. **(*Stroke*. 2017;48:596-603. DOI: 10.1161/STROKEAHA.116.015746.)**

Key Words: cerebral hemorrhage ■ hospital mortality ■ myocardial infarction ■ pneumonia ■ stroke

Intracerebral hemorrhage (ICH) is the most deadly form of stroke[1,2] and accounts for 10% of all strokes in the United States.[3] Up to 50% of stroke-related mortality is attributable to medical complications.[4] Over the last decade, ICH-related mortality in the United States has decreased,[5] but data on the current rates of medical complications after ICH outside of clinical trials are sparse.[4] The aging population and an increase in persons with multiple chronic diseases may have resulted in greater medical complication during hospitalization; however, many of these are potentially preventable, and advances in medical practice and clinical management guidelines[6,7] may have led to decreased frequency. Therefore, the current magnitude and direction of ICH-associated complications are unknown.

The primary aim of this study is to describe current trends in the prevalence of pneumonia, urinary tract infection (UTI), sepsis, deep vein thrombosis (DVT), pulmonary embolism (PE), acute renal failure (ARF), and acute myocardial infarction (AMI) in hospitalized acute ICH patients in the United States from 2004 to 2013. We secondarily evaluated the current association of each complication with other clinical factors, in-hospital mortality, length of stay, and cost.

Methods

Data for this study were obtained from the 2004 to 2013 Nationwide Inpatient Sample (NIS). The NIS is the largest all-payer inpatient care database in the United States and comprises a 20% stratified random sample of all US hospital discharges. Sampling weights provided in the NIS allow for calculation of national estimates. Each individual hospital discharge in the NIS is deidentified so all discharges were considered to be independent. Further details on the NIS design are available at http://www.hcup-us.ahrq.gov.

Study Population

We identified all patients with a primary diagnosis of ICH (n=116 706) by querying the NIS using the International Classification of Disease-Clinical Modification, 9th Revision code 431 (Methods in the online-only Data Supplement).

Definition of Outcomes

All complications were defined using secondary International Classification of Disease, 9th Revision codes or Healthcare Cost and

Received October 13, 2016; final revision received January 22, 2017; accepted January 23, 2017.

From the Department of Neurology, University of Miami Miller School of Medicine, FL.

Presented in part at the International Stroke Conference of the American Heart Association, Houston, TX, February 22–24, 2017.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.015746/-/DC1.

Correspondence to Fadar Oliver Otite, MD, SM, Department of Neurology, University of Miami Miller School of Medicine, C215, 1120 NW 14th St, Miami, FL 33136. E-mail Fadar.otite@jhsmiami.org

Utilization Project (HCUP) constellation of codes corresponding to these diagnoses (Methods in the online-only Data Supplement). In-hospital mortality, home disposition, and length of stay were studied using HCUP variables named DIED, DISPUNIFORM and LOS, respectively.

Covariate Assessment

Comorbidities associated with ICH hospitalization were used to calculate the modified Charlson comorbidity index for all patients. We defined craniotomy/craniectomy, hydrocephalus requiring external ventricular drain or ventriculoperitoneal shunt, and mechanical ventilation (MV) status using International Classification of Disease, 9th Revision or HCUP procedural codes (Methods in the online-only Data Supplement).

Statistical Analysis

Baseline characteristics of participants were summarized using descriptive statistics. We computed the unadjusted national weighted prevalence of each complication and in subgroups categorized by sex. We further stratified some complications by preexisting conditions or interventions expected to influence their occurrence: pneumonia, DVT, and PE risk by MV status and ARF and MI risk by chronic kidney disease (CKD) and coronary artery disease, respectively. We evaluated trends in prevalence of each complication over time by constructing logistic regression model with each complication as the dependent variable and year of discharge as the independent variable, evaluated continuously, with significance of differences in trend over time assessed using the Wald test.

We used a series of nested logistic regression models to evaluate the association of each complication with hospitalization variables and to assess factors that may account for any observed trends in complication risks and control for confounding (Methods in the online-only Data Supplement).

Results

The 116 706 admissions identified in the NIS represent 575 211 ICH hospitalizations in the United States from 2004 to 2013 (Table II in the online-only Data Supplement). About 49.7% of patients were females, and mean age at admission was 68.9 years. The proportion of patients with comorbid hypertension, diabetes mellitus, CKD, and baseline coagulopathy increased over time (Table II in the online-only Data Supplement; P trend <0.001, not displayed). Most patients had low Charlson comorbidity index scores, but the proportion of patients with Charlson comorbidity index score ≥4 increased from 13.3% to 24.7% over time. MV was administered to 26.0% to 29.6%, of patients of which 16.8% to 25.3% occurred in the first 48 hours of admission (Table II in the online-only Data Supplement). Mean length of stay did not change over time, but the proportion of patients transferred to skilled nursing facilities increased from 42.3% in 2004 to 46.9% in 2013 (P<0.001; Table III in the online-only Data Supplement).

Total Medical Complication Risks

Over the study period, 29.3% of all patients and 37.1% of MV patients had at least 1 medical complication during hospitalization (Table 1). The most common complications were UTI (14.8%), ARF (8.2%), and pneumonia (7.8%), but significant disparity existed by sex and prespecified clinical factors: UTI was the most common complication in females (19.8% versus 9.9% in males), whereas ARF was the most common complication in males (10.6% in males versus 5.9% in females). Overall weighted risks of most other complications, including pneumonia (9.1% versus 6.4), sepsis (4.8% versus 3.2%), DVT (3.2% versus 2.1%), and PE (0.9% versus 0.5%), were ≈30% greater in males compared with females (P value for comparison <0.001), but AMI risks did not differ by sex. In analysis stratified by specific clinical factors, we identified >2-fold higher risks of pneumonia and DVT in ventilated compared with nonventilated patients. Moreover, ARF and AMI risks were greater in patients with CKD and coronary artery disease compared with patients with no coronary artery disease and no-CKD, respectively. Among those with DVT, 10.4% had a PE diagnosis, whereas 39.4% of patients with PE had coexisting DVT.

Overall in-hospital mortality was 23.8%, but death risk in MV patients was 59.5%. Notably, 61.6% of in-hospital deaths occurred in the first 3 days of admission, and 82.4% of all deaths occurred within the first week of hospitalization (Table IV in the online-only Data Supplement). Among those that died within the first week of hospitalization, only 16.4% had at least 1 complication compared with the 59.7% complication risk in those that died after 7 days of hospitalization.

Trend Analysis

In-hospital mortality decreased from 27.8% in 2004 to 21.0% in 2013 (relative decline 24.4%; Figure 1), but the proportion of patients with at least 1 complication increased from 26.0% to 31.2% over the same period (relative increase 19.7%; Table 1). The increase in total complication risk was driven mainly by a nearly 3-fold increase in ARF risk (4.4% to 12.2%) over the 10-year period (Figure 2; Table 1). DVT risks also increased by 53.4% (2.0% to 3.2%) but mainly in MV patients, and UTI risks increased over time but only in females (Figures 1 and 2; Table 1). The unadjusted weighted prevalence of pneumonia, sepsis, and PE did not change over time, although PE risks in MV patients increased marginally over time (Figures 1 and 2; Table 1).

Multivariate Association of Each Complication With Clinical Factors

After multivariate analyses including adjusting for MV, odds of pneumonia declined by 4% (odds ratio, 0.96; 95% confidence interval, 0.95–0.97) and sepsis by 3% (odds ratio, 0.97%; 95% confidence interval, 0.96–0.98) for each year (Table 2), whereas odds of ARF increased by 9% (odds ratio, 1.09; 95% confidence interval, 1.08–1.10) per year (Table 2).

Some clinical factors were associated with multiple complications. Compared with whites, blacks had higher odds of UTI, pneumonia, and ARF but lower odds of AMI. Atrial fibrillation, dysphagia, high Charlson comorbidity index score, and Medicaid as opposed to Medicare insurance increased the odds of having ≥4 complications. Surprisingly, MV was associated with decreased odds of UTI but increased odds of all other complications, whereas smoking was associated with reduced odds of all complications except AMI (Table 2). Although odds of sepsis and ARF were greater in teaching hospitals compared with rural hospitals, no consistent significant patterns in multivariate-adjusted odds of complications existed by hospital region or yearly stroke volume (Table 2).

Table 1. Prevalence of Medical Complications After Acute Intracerebral Hemorrhage Hospitalization in the United States From 2004 to 2013

Overall	Overall	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	*P* Value
Any complication												
Total	29.3	26.0	25.1	27.3	28.9	30.9	30.4	31.2	30.9	31.5	31.2	<0.001
Males	28.1	24.1	23.7	26.1	27.6	29.4	29.7	29.9	29.8	30.0	30.1	<0.001
Females	30.6	27.9	26.5	28.5	30.1	32.3	31.1	32.6	32.0	33.2	32.3	<0.001
No MV	27.3	25.2	24.1	25.7	27.1	29.1	28.4	28.5	28.8	28.5	27.8	<0.001
MV	37.1	29.6	30.3	34.1	36.5	37.8	37.6	39.6	37.9	40.4	41.7	<0.001
In-hospital mortality												
Total	23.8	27.8	26.9	24.8	23.6	23.8	23.5	22.8	21.5	22.1	21.0	<0.001
Males	23.4	27.5	26.9	24.9	23.3	22.9	23.4	22.3	22.2	21.4	20.2	<0.001
Females	24.0	28.1	26.9	24.6	24.0	24.7	23.6	23.3	20.7	22.8	21.9	<0.001
No MV	14.3	19.7	18.6	16.0	15.2	14.6	13.9	12.5	10.7	11.0	9.7	<0.001
MV	59.5	66.4	68.0	64.4	60.7	60.1	59.8	56.6	56.6	54.8	54.5	<0.001
Urinary tract infection												
Total	14.8	13.7	13.3	13.9	14.9	15.7	15.0	16.3	15.4	15.4	14.2	<0.001
Males	9.9	9.0	9.5	9.4	10.0	10.5	10.4	10.8	10.4	10.0	8.9	0.193
Females	19.8	18.2	17.1	18.4	19.7	21.1	19.7	22.0	20.3	21.1	20.1	<0.001
Pneumonia												
Total	7.8	7.2	7.5	7.8	8.5	8.5	7.6	7.9	7.6	7.7	7.2	0.573
Males	9.1	8.6	8.3	9.3	9.8	10.3	9.0	9.4	9.0	9.0	8.3	0.763
Females	6.4	5.8	6.7	6.5	7.3	6.7	6.4	6.4	6.2	6.2	5.9	0.325
No MV	5.7	4.2	4.2	4.2	4.5	4.5	3.8	3.6	3.7	3.5	3.2	<0.001
MV	15.7	12.9	13.8	15.5	17.5	16.9	15.6	16.9	15.6	16.4	15.4	0.060
Sepsis												
Total	4.1	3.8	3.7	4.1	4.3	4.8	4.3	4.3	3.9	4.0	4.0	0.631
Males	4.8	4.6	4.3	4.7	5.1	5.4	5.3	4.9	4.8	4.7	4.6	0.792
Females	3.4	3.1	3.0	3.6	3.5	4.1	3.3	3.6	3.1	3.2	3.3	0.833
Deep vein thrombosis												
Total	2.7	2.0	2.2	2.4	2.7	2.8	3.2	2.7	2.6	2.8	3.2	<0.001
Males	3.2	2.4	2.2	3.2	3.3	3.3	3.7	3.2	3.1	3.4	3.8	<0.001
Females	2.1	1.7	2.0	1.7	2.1	2.2	2.6	2.2	2.1	2.3	2.3	0.010
No MV	2.2	2.0	2.0	2.3	2.4	2.5	2.8	2.1	2.1	2.1	2.1	0.977
MV	4.2	2.1	2.6	3.3	4.1	3.7	4.4	4.6	4.4	5.1	6.1	<0.001
Pulmonary embolism												
Total	0.7	0.6	0.5	0.8	0.7	0.7	0.8	0.7	0.7	0.7	0.8	0.054
Males	0.9	0.6	0.5	1.1	1.0	0.9	0.9	0.9	1.1	0.7	0.9	0.145
Females	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.4	0.6	0.7	0.239
No MV	0.7	0.6	0.5	0.9	0.6	0.7	0.7	0.6	0.7	0.6	0.7	0.492
MV	0.8	0.4	0.5	0.5	1.3	0.7	1.2	1.0	0.9	0.9	1.0	0.0129
Acute renal failure												
Total	8.2	4.4	4.8	5.8	7.1	8.6	8.9	9.5	10.2	11.5	12.2	<0.001
Males	10.6	5.4	6.1	7.6	9.5	10.6	11.4	12.2	13.1	14.6	15.2	<0.001
Females	5.9	3.3	3.5	3.9	4.8	6.4	6.4	6.6	7.3	8.2	8.9	<0.001

(*Continued*)

Table 1. Continued

Overall	Overall	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	*P* Value
No chronic renal disease	5.7	3.3	3.6	3.8	4.9	5.7	6.1	6.7	6.9	7.8	8.7	<0.001
Chronic renal disease	30.1	24.5	23.2	24.1	25.2	32.0	30.5	30.5	31.4	35.9	34.9	<0.001
Acute myocardial infarction												
Total	2.0	2.0	1.6	1.9	1.8	1.8	2.4	2.4	1.8	2.0	2.3	0.007
Males	2.0	1.8	1.5	2.1	2.0	1.8	2.5	2.6	1.4	2.0	2.4	0.024
Females	2.0	2.2	1.7	1.7	1.6	1.9	2.3	2.2	2.2	2.0	2.2	0.090
No coronary artery disease	1.6	1.8	1.4	1.5	1.6	1.6	1.8	1.9	1.4	1.5	1.7	0.902
Coronary artery disease	3.5	3.0	2.2	3.5	2.8	3.0	4.6	4.4	3.4	4.0	4.5	<0.001

MV indicates mechanical ventilation.

Multivariate Association of Complications With Length of Stay, Cost, Home Disposition, and In-Hospital Mortality

All complications were associated with increased length of stay and increased cost (Table V in the online-only Data Supplement, multivariate model 1). Sepsis and DVT were associated with the highest mean increase in length of stay (12.9 and 10.5 days, respectively) and cost ($35 755 and $32 336, respectively; Table V in the online-only Data Supplement, multivariate model 1). After mutually adjusting for other medical complications, the associations of each complication with cost and length of stay were attenuated (Table V in the online-only Data Supplement, multivariate model 2). This suggests that some of the increase in cost and length of

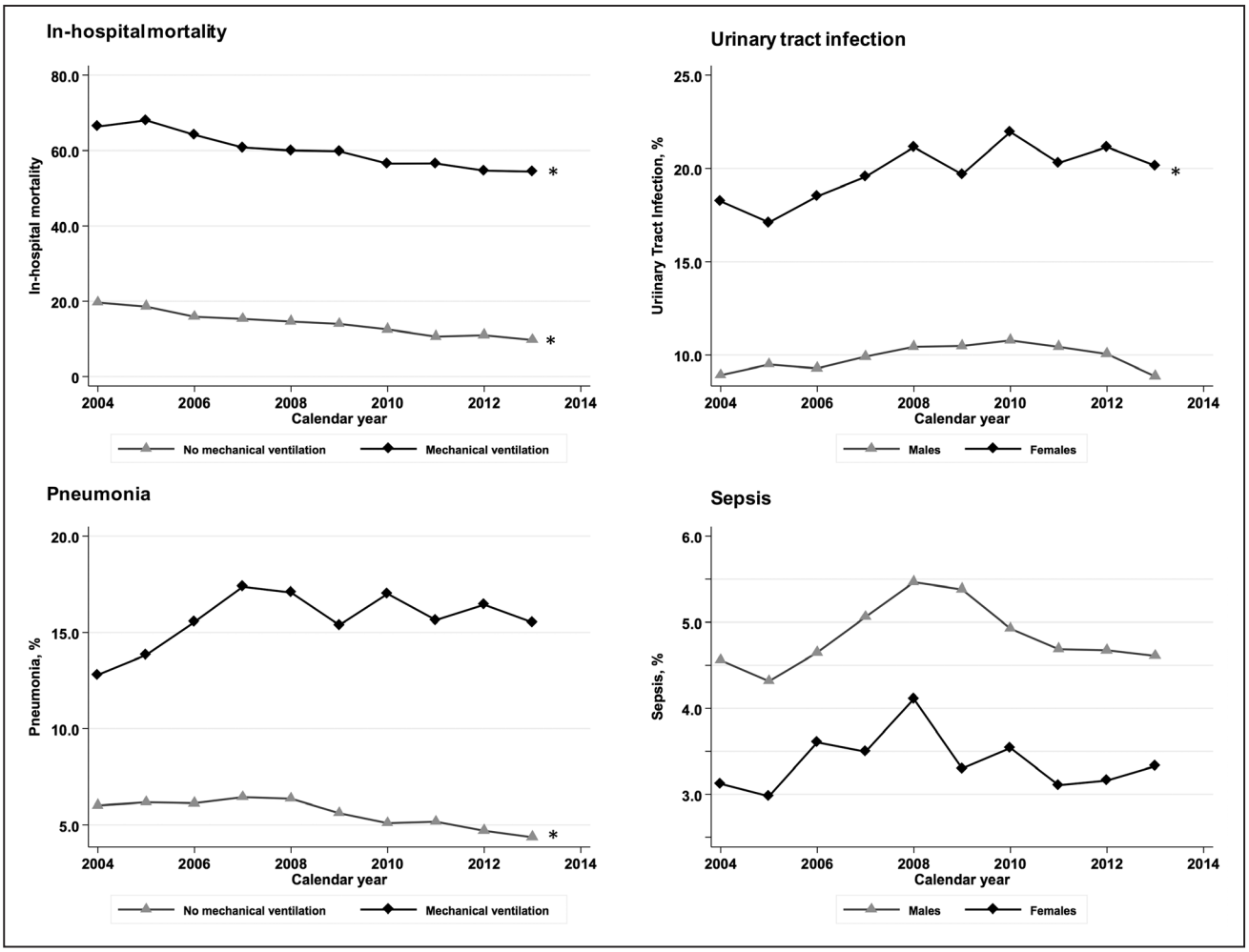

Figure 1. Weighted risk of in-hospital mortality, urinary tract infection, pneumonia, and sepsis after acute intracerebral hemorrhage in the United States according to sex or mechanical ventilation status. *P value for trend <0.05.

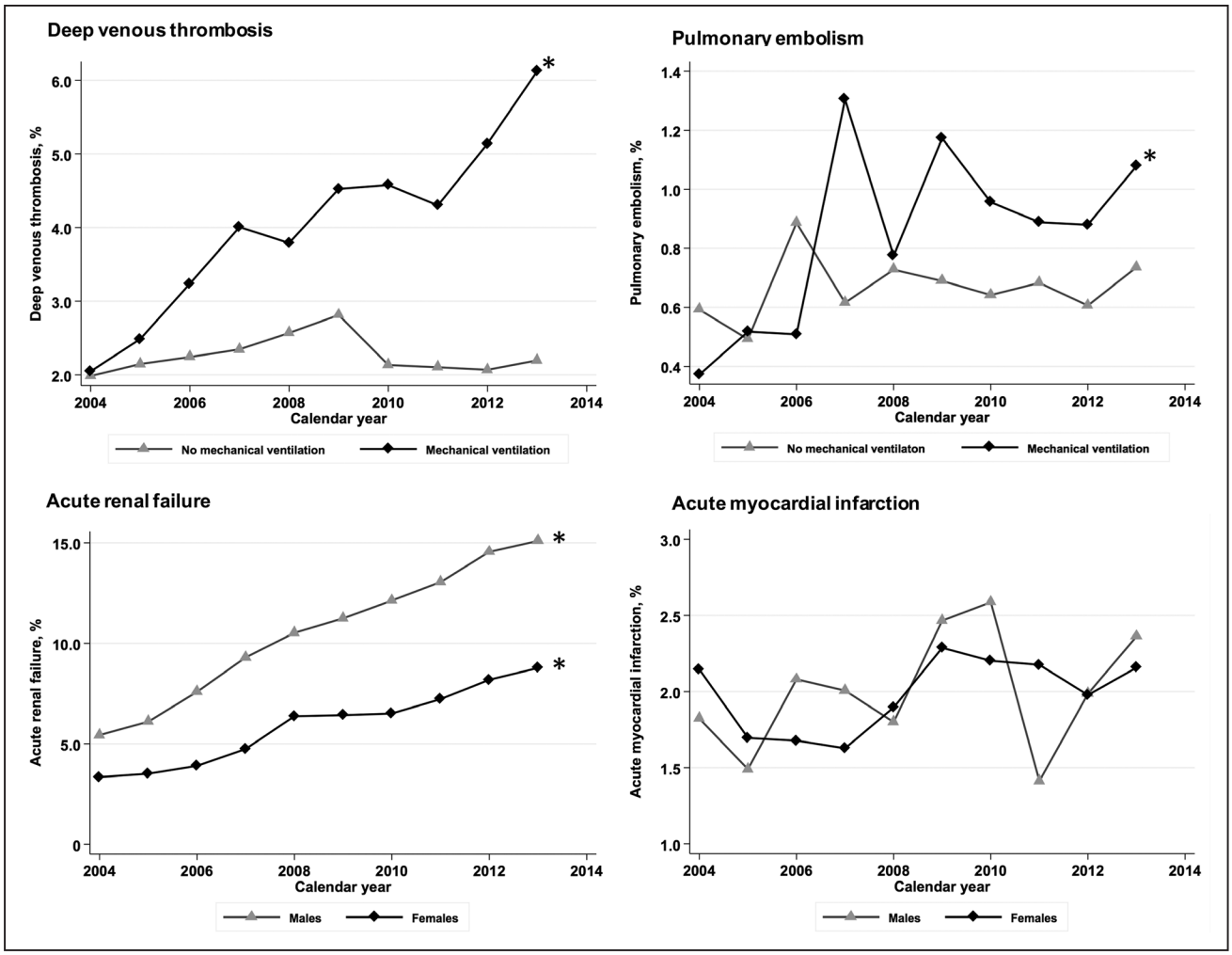

Figure 2. Weighted risk of deep venous thrombosis, pulmonary embolism, acute renal failure, and acute myocardial infarction after acute intracerebral hemorrhage in the United States according to sex or mechanical ventilation status. *P value for trend <0.05.

stay associated with these complications is mediated by their association with other complications.

Similarly, all complications were associated with reduced odds of home disposition, but their associations with in-hospital death were variable. Whereas ARF and AMI were associated with increased odds of mortality, concomitant UTI diagnosis during ICH admission was associated with decreased odds of death.

When evaluating the associations of pneumonia, sepsis, and PE with mortality, we found significant effect modification of their association with mortality by MV, so mortality associations of these complications were stratified by MV status. Pneumonia and sepsis were associated with increased odds of mortality in nonventilated patients but were associated with decreased odds of mortality in ventilated patients (Table V in the online-only Data Supplement).

Discussion

In this contemporary analysis of the NIS, we found that 29% of all ICH admissions in the United States have at least 1 medical complication, and any complication risk increased by ≈20% from 2004 to 2013. This increase was driven mainly by a >2-fold relative increase in proportion of ARF, a >50% increase in unadjusted DVT risk, and marginal increase in UTI prevalence. Whereas AMI risk increased only in patients with coronary artery disease and PE risk increased only in MV patients, pneumonia and sepsis risks declined over time. Overall in-hospital mortality after ICH declined by ≈25% from 27% in 2004 to 21% in 2013, but death risk in MV patients remained >50%. Over 60% of all ICH-associated deaths occurred within the first 3 days of hospitalization and over 80% within 7 days.

The high frequency of MV, high mortality in MV patients, and huge percentage of all deaths that occur within the first few days after ICH are consistent with reports of previous studies.[8–10] These reflect the high proportion of ICH patients who still present with severe or devastating hemorrhage and emphasize the need for innovative severe ICH prevention and management strategies. However, as more patients survive their ICH hospitalization, emphasis is slowly shifting from survival to improving ICH-related morbidity and optimization of functional recovery. Quantification of disparities and trends in complication burden is a crucial step in ameliorating ICH outcome because it highlights aspects of ICH care where marginal progress has been made and accentuates other areas where additional efforts are needed. Complications such as DVT are potential quality measures for ICH hospitalization,

Table 2. Association of Medical Complications During Acute Intracerebral Hemorrhage Hospitalization in the United States From 2004 to 2013 With Clinical and Hospital Factors

	UTI	Pneumonia*	Sepsis*	DVT	PE	ARF†	Acute MI†
Variable	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Y, per unit increase in y	1.00 (1.00–1.01)	0.96 (0.95–0.97)‡	0.97 (0.96–0.98)‡	1.01 (0.99–1.03)	1.01 (0.98–1.04)	1.09 (1.08–1.10)‡	1.01 (0.99–1.02)
Age (y)							
40–59 vs 18–39	1.29 (1.15–1.46)‡	1.13 (1.00–1.29)	1.05 (0.90–1.23)	0.94 (0.78–1.14)	1.08 (0.75–1.54)	1.05 (0.92–1.19)	1.48 (1.06–2.06)§
60–79 vs 18–39	1.47 (1.32–1.67)‡	1.09 (0.95–1.26)	0.85 (0.72–1.00)§	1.05 (0.85–1.28)	1.06 (0.73–1.53)	0.95 (0.84–1.09)	1.56 (1.10–2.21)§
>=80 vs 18–39	1.83 (1.61–2.07)‡	1.11 (0.95–1.31)	0.66 (0.55–0.79)‡	0.64 (0.51–0.81)‡	0.59 (0.39–0.90)§	0.91 (0.79–1.05)	1.47 (1.03–2.10)§
Sex, females vs males	2.25 (2.17–2.34)‖	0.75 (0.71–0.79)‡	0.79 (0.74–0.84)‡	0.77 (0.72–0.84)‡	0.73 (0.63–0.84)‡	0.62 (0.59–0.66)‡	1.06 (0.97–1.16)
Race							
Blacks vs whites	1.07 (1.01–1.14)§	1.07 (0.99–1.15)	1.40 (1.26–1.55)‡	1.23 (1.08–1.40)‖	1.17 (0.97–1.42)	1.66 (1.55–1.78)‡	0.83 (0.71–0.97)§
Hispanics vs whites	1.10 (1.02–1.18)§	1.17 (1.07–1.28)‖	1.24 (1.10–1.41)‖	0.80 (0.68–0.96)§	0.72 (0.53–0.99)§	1.09 (1.00–1.20)	1.04 (0.88–1.22)
Others vs whites	1.04 (0.97–1.12)	1.15 (1.03–1.27)‖	1.16 (1.04–1.30)‖	0.71 (0.60–0.85)‡	0.75 (0.55–1.02)	1.17 (1.07–1.29)‖	1.02 (0.87–1.21)
Income							
$39 000–$47 999 vs <$39 000	1.04 (0.99–1.09)	0.96 (0.90–1.02)	1.01 (0.93–1.10)	1.07 (0.96–1.19)	1.03 (0.85–1.27)	1.00 (0.94–1.07)	0.99 (0.87–1.11)
$48 000–$62 999 vs <$39 000	1.00 (0.94–1.05)	0.88 (0.82–0.95)‖	0.92 (0.83–1.01)	1.11 (0.99–1.26)	0.93 (0.75–1.16)	1.00 (0.93–1.08)	0.93 (0.81–1.07)
≥$63 000 vs <$39 000	0.97 (0.92–1.03)	0.91 (0.83–0.99)§	0.93 (0.84–1.03)	1.16 (1.02–1.33)§	1.02 (0.78–1.24)	0.94 (0.86–1.02)	0.95 (0.83–1.09)
Insurance							
Medicaid vs Medicare	1.26 (1.17–1.36)‡	1.37 (1.26–1.50)‡	1.43 (1.28–1.60)‡	1.34 (1.15–1.56)‡	1.53 (1.17–2.00)‖	1.62 (1.49–1.76)‡	1.13 (0.94–1.36)
Private vs Medicare	0.84 (0.79–0.88)‡	1.02 (0.95–1.09)	0.88 (0.81–0.97)§	1.30 (1.17–1.44)‡	1.25 (1.03–1.54)§	1.11 (1.04–1.19)‖	0.92 (0.81–1.05)
Self-pay vs Medicare	0.85 (0.78–0.93)‡	0.88 (0.78–0.99)§	0.93 (0.81–1.08)	0.91 (0.74–1.11)	1.25 (0.91–1.71)	1.63 (1.47–1.79)‡	1.13 (0.91–1.39)
Other vs Medicare	0.86 (0.76–0.97)§	1.03 (0.89–1.19)	0.94 (0.79–1.11)	1.29 (1.04–1.60)§	1.14 (0.75–1.72)	1.35 (1.18–1.54)‡	1.13 (0.87–1.47)
Hospital region							
Midwest vs Northeast	0.93 (0.86–1.00)	1.11 (0.99–1.24)	0.80 (0.69–0.92)‖	0.94 (0.79–1.13)	0.78 (0.62–0.98)§	0.95 (0.86–1.05)	0.99 (0.83–1.17)
South vs Northeast	1.11 (1.04–1.19)‖	1.08 (0.97–1.20)	0.96 (0.85–1.10)	0.81 (0.68–0.96)	0.77 (0.62–0.96)§	1.09 (0.99–1.19)	0.94 (0.79–1.09)
West vs Northeast	1.05 (0.98–1.12)	1.00 (0.89–1.13)	0.83 (0.72–0.96)§	0.87 (0.72–1.05)	0.91 (0.70–1.17)	0.99 (0.88–1.11)	0.94 (0.79–1.13)
Hospital location/teaching status							
Urban nonteaching vs rural	1.09 (0.99–1.21)	1.11 (0.98–1.26)	1.63 (1.31–2.04)‡	1.27 (0.80–2.00)	0.95 (0.60–1.51)	1.67 (1.42–1.95)‡	1.19 (0.94–1.49)
Urban teaching vs rural	1.25 (1.12–1.39)‡	1.17 (1.02–1.42)§	1.99 (1.58–2.51)‡	1.55 (0.95–2.56)	1.20 (0.74–1.91)	1.92 (1.63–2.27)‡	1.33 (1.05–1.69)
Stroke volume per y							
Middle tertile vs lowest tertile	1.06 (1.00–1.11)	0.93 (0.85–1.00)	0.87 (0.78–0.97)§	1.16 (1.03–1.38)§	1.02 (0.83–1.27)	0.98 (0.90–1.06)	0.81 (0.72–0.93)§
Upper tertile vs lower tertile	1.17 (1.09–1.25)‡	1.00 (0.90–1.11)	0.83 (0.72–0.95)‖	1.44 (1.20–1.73)‡	1.12 (0.87–1.45)	0.90 (0.81–0.99)§	1.02 (0.86–1.20)
Hospital bed size							
Medium vs small	1.02 (0.93–1.11)	0.94 (0.86–1.06)	1.34(1.11–1.62)‖	1.32 (0.97–1.80)	0.79 (0.56–1.11)	1.03 (0.89–1.19)	1.12 (0.90–1.39)
Large vs small	1.05 (0.96–1.14)	0.98 (0.87–1.10)	1.30 (1.08–1.55)‖	1.42 (1.04–1.94)§	1.01 (0.73–1.41)	1.11 (0.97–1.28)	1.15 (0.93–1.42)
Weekend admission	1.00 (0.96–1.04)	1.02 (0.97–1.07)	0.96 (0.90–1.03)	1.00 (0.92–1.09)	0.93 (0.80–1.10)	1.00 (0.95–1.05)	1.04 (0.95–1.14)
Baseline coagulopathy	1.28 (1.20–1.37)‡	1.52 (1.40–1.65)‡	2.18(1.98–2.40)‡	1.90(1.68–2.13)‡	1.58 (1.24–2.00)‡	1.66 (1.53–1.80)‡	1.44 (1.23–1.69)‡
Atrial fibrillation	1.17 (1.12–1.23)‡	1.29 (1.22–1.37)‡	1.19 (1.10–1.29)‡	1.07 (0.96–1.19)	1.15 (0.94–1.40)	1.28 (1.20–1.36)‡	1.04 (0.90–1.14)
Dysphagia	2.17 (2.06–2.28)‡	1.99 (1.86–2.13)‡	1.49 (1.36–1.64)‡	1.73 (1.57–1.1)‡	1.33 (1.09–1.62)‖	1.37 (1.28–1.47)‡	0.94 (0.82–1.09)

(*Continued*)

Table 2. Continued

Variable	UTI OR (95% CI)	Pneumonia* OR (95% CI)	Sepsis* OR (95% CI)	DVT OR (95% CI)	PE OR (95% CI)	ARF† OR (95% CI)	Acute MI OR (95% CI)
Mechanical ventilation	0.74 (0.70–0.78)‡	3.88 (3.19–4.71)‡	1.78 (1.64–1.93)‡	1.31 (1.19–1.44)‡	0.90 (0.75–1.02)	1.51 (1.41–1.61)‡	1.67 (1.50–1.86)‖
Coma	0.75 (0.70–0.80)‡	1.06 (0.98–1.15)	1.05 (0.95–1.17)	0.75 (0.65–0.88)‡	0.76 (0.57–1.01)	1.00 (0.92–1.09)	1.07 (0.92–1.24)
AVM or aneurysm	1.05 (0.93–1.19)	1.36 (1.18–1.57)‡	1.14 (0.94–1.39)	1.57 (1.30–1.90)‡	1.40 (0.96–2.04)	0.74 (0.63–0.88)‖	0.95 (0.70–1.29)
Craniotomy	1.20 (1.01–1.43)§	1.84 (1.58–2.15)‡	1.49 (1.23–1.81)‡	2.16 (1.74–2.69)‡	1.67 (1.09–2.54)§	1.04 (0.84–1.28)	1.21 (0.86–1.71)
EVD/VPS	1.67 (1.55–1.80)‡	2.72 (2.51–2.95)‡	2.22 (2.03–2.43)‡	2.33 (2.09–2.60)‡	2.06 (1.65–2.56)‡	1.49 (1.38–1.61)‡	1.42 (1.22–1.65)‡
Smoking	0.78 (0.73–0.84)‡	0.79 (0.73–0.86)‡	0.58 (0.51–0.65)‡	0.51 (0.44–0.60)‡	0.43 (0.32–0.58)‡	0.83 (0.77–0.90)‡	0.98 (0.84–1.14)
Modified CCI							
CCI=2 vs CCI=1	1.19 (1.13–1.24)‡	1.19 (1.11–1.27)‡	1.16 (1.07–1.28)‖	1.00 (0.88–1.12)	0.93 (0.73–1.17)	1.33 (1.25–1.43)‡	1.03 (0.91–1.17)
CCI=3 vs CCI=1	1.32 (1.25–1.39)‡	1.61 (1.50–1.73)‡	1.54 (1.41–1.69)‡	1.73 (1.55–1.93)‡	1.60 (1.32–1.95)‡	1.50 (1.39–1.62)‡	1.11 (0.97–1.27)
CCI≥4 vs CCI=1	1.33 (1.26–1.40)‡	1.86 (1.73–1.99)‡	1.74 (1.59–1.90)‡	1.90 (1.71–2.11)‡	1.99 (1.62–2.45)‡	1.51 (1.39–1.63)‡	1.13 (0.98–1.31)

Multivariate logistic models adjusted for all factors above with estimates. ARF indicates acute renal failure; AVM, arteriovenous malformation; CCI, Charlson comorbidity index; CI, confidence interval; DVT, deep venous thrombosis; EVD/VPS, hydrocephalus requiring external ventricular drain/ventriculoperitoneal shunt placement; MI, myocardial infarction; OR, odds ratio; PE, pulmonary embolism; and UTI, urinary tract infection.

*Models for pneumonia and sepsis also include interaction term between age and mechanical ventilator use.

†Model for ARF also includes further adjustment for chronic renal failure (OR, 5.32; 95% CI, 4.96–5.72; $P<0.001$) and for acute myocardial infarction further adjusted for coronary artery disease (OR, 1.86; 95% CI, 1.68–2.06), congestive heart failure (OR, 2.63; 95% CI, 2.33–2.96), valvular heart disease (OR, 1.38; 95% CI, 1.18–1.61), all P values <0.001.

‡P value <0.001.

§P value <0.05 but ≤0.01.

‖P value <0.01 but ≤0.001.

but national reference data have hitherto been lacking. This study provides a robust assessment of the current national patterns of important medical complications after ICH with additional information on relevant population subgroups.

A major finding in this study is the exponential increase in ARF. Whereas the proportion of patients with hypertension, diabetes mellitus, and CKD increased over time and may have contributed to some of the observed increase, risks remained significantly high after adjusting for these conditions, suggesting that the additional factors are responsible. Potential explanations include more aggressive lowering of blood pressure in the acute period of ICH to prevent hematoma expansion[4,11] or nephropathy associated with increased use of contrast imaging, but no definite conclusions can be drawn using our retrospective analysis. That aggressive blood pressure control can increase ARF risk was evidenced in the ATACH II trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage II), where adverse renal events occurred in 9.0% of patients in the intensive blood pressure–lowering arm versus 4.0% of patients in the standard-treatment arm.[12] Other prospective studies are needed to assess these and other possible etiologic factors.

ICH patients are at particularly high risk for DVT because of their immobility and altered mental status.[13] Although DVT and PE risks reported in this study are consistent with those in previous studies,[14] rising risks imply that current measures to prevent DVT in ICH patients are far from adequate. Innovative DVT preventive measures are needed particularly in ventilated patients who accounted for all of the observed increase in risks. Current guidelines recommending deferral of subcutaneous anticoagulation for the initial few days may require reappraisal. The observed increase in DVT risk seen in our study may be partly because of increased DVT detection as a result of advancement in imaging technology and improvement in clinical practices, but low frequency of DVT prophylaxis in ICH patients in the United States may also be partly responsible.[15] Ventilated patients represent a subgroup of ICH patients with potentially greater morbidity and disability from their ICH, and there may possibly be a growing reluctance to use DVT prophylaxis in this group of patients.[16] These factors also need to be evaluated prospectively.

The inverse association of DVT and UTI with mortality may reflect early pickup of nonfatal cases of these conditions. Similarly, MV patients are usually monitored closely in an intensive care unit, thus the negative association of sepsis and pneumonia with mortality in ventilated patients may partly be secondary to early diagnosis and aggressive treatment of mild cases. There could also be some survival bias. MV patients are likely to have the most severe ICH and consequently more likely to die quickly from ICH before they develop complications such as DVT, pneumonia, or sepsis. Moreover, the sickest ICH patients on MV are more likely to have withdrawal of clinical care. In such cases where care is withdrawn, mortality is likely greater, and there could be decreased detection and diagnosis of complications.

Disparities in odds of various complications with respect to race and insurance status may be related to differences in timing of withdrawal of care. Compared with whites, black patients in the United States are more likely to have care withdrawn late and therefore more prone to higher detection of complications.[17] Black patients with ICH also have lower white blood cell counts compared with whites and consequently more predisposed to increased risk for infectious complications.[18] These factors also need further evaluation.

This study has limitations. Although we relied on previously validated codes for ICH and for complications, we cannot exclude potential inaccuracies because of coding errors. There is great variability in the accuracy of International Classification of Disease, 9th Revision codes for medical complications and in how clinicians actually diagnose pneumonia,[19] sepsis, and other complications. Our study of trends in complications is based on the implicit assumption that coding practices remained unchanged over time. However, numerous coding guidelines may have led to the improvement in coding over time. We were unable to provide information on the clinical and radiological severity of ICH by virtue of inherent limitations in our database. However, we used ventilator status, hydrocephalus, dysphagia, and coma as surrogate measures of ICH severity and adjusted for comorbid disease status in all multivariate analyses. A significant proportion of medical complications occur subacutely after ICH admission and still contribute to morbidity and mortality, so true prevalence estimates of complications and mortality are likely higher than reported in this analysis. Thirty-day and 90-day outcome measures may provide more accurate information on complication burden. Our finding of excess cost and length of stay associated with all complications should be interpreted with caution because we were unable to show temporal correlation between complications and these outcomes. Reverse causation is also possible. For example, patients surviving and staying longer in the hospital for other reasons not related to a medical complication may be predisposed to a DVT as opposed to a DVT leading to prolonged hospital stay. We were unable to evaluate the impact of withdrawal of care on medical complication burden because this information is unavailable in the NIS.

Despite these limitations, this study represents the most comprehensive assessment to date of medical complications after ICH. Important strengths of our study include better ICH case ascertainment by use of clinically diagnosed hospitalized ICH. The large sample size of our study with national representation and generalizability to all ICH patients in the United States provides a comprehensive evaluation of the risks, associated determinants, outcomes, and importance of medical complications in ICH patients. Medical complications are frequent and pose significant threats to morbidity and mortality for ICH patients, and our findings should trigger increased efforts to prevent them and to lessen their burden.

Acknowledgments

Dr Otite had full access to all of the study data and takes responsibility for the integrity and accuracy of the data analysis. Drs Otite and Romano provided study concept and design. All authors involved in acquisition, analysis, and interpretation of data and revised the article critically for important intellectual content. Dr Otite drafted the article. Dr Otite performed statistical analysis. Drs Malik, Chaturvedi, Sacco, and Romano provided administrative, technical, or material support. Dr Romano supervised the study.

Disclosures

None.

References

1. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol*. 2012;11:101–118. doi: 10.1016/S1474-4422(11)70264-2.
2. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med*. 2001;344:1450–1460. doi: 10.1056/NEJM200105103441907.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.
4. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060. doi: 10.1161/STR.0000000000000069.
5. Ovbiagele B. Nationwide trends in in-hospital mortality among patients with stroke. *Stroke*. 2010;41:1748–1754. doi: 10.1161/STROKEAHA.110.585455.
6. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):7S–47S. doi: 10.1378/chest.1412S3.
7. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA; Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol*. 2010;31:319–326. doi: 10.1086/651091.
8. Gujjar AR, Deibert E, Manno EM, Duff S, Diringer MN. Mechanical ventilation for ischemic stroke and intracerebral hemorrhage: indications, timing, and outcome. *Neurology*. 1998;51:447–451.
9. Staykov D, Wagner I, Volbers B, Hauer EM, Doerfler A, Schwab S, et al. Natural course of perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2011;42:2625–2629. doi: 10.1161/STROKEAHA.111.618611.
10. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987–993.
11. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al; INTERACT Investigators. Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. 2008;7:391–399. doi: 10.1016/S1474-4422(08)70069-3.
12. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. doi: 10.1056/NEJMoa1603460.
13. Koivunen RJ, Haapaniemi E, Satopää J, Niemelä M, Tatlisumak T, Putaala J. Medical acute complications of intracerebral hemorrhage in young adults. *Stroke Res Treat*. 2015;2015:357696. doi: 10.1155/2015/357696.
14. Christensen MC, Dawson J, Vincent C. Risk of thromboembolic complications after intracerebral hemorrhage according to ethnicity. *Adv Ther*. 2008;25:831–841. doi: 10.1007/s12325-008-0092-0.
15. Prabhakaran S, Herbers P, Khoury J, Adeoye O, Khatri P, Ferioli S, et al. Is prophylactic anticoagulation for deep venous thrombosis common practice after intracerebral hemorrhage? *Stroke*. 2015;46:369–375. doi: 10.1161/STROKEAHA.114.008006.
16. Maramattom BV, Weigand S, Reinalda M, Wijdicks EF, Manno EM. Pulmonary complications after intracerebral hemorrhage. *Neurocrit Care*. 2006;5:115–119. doi: 10.1385/NCC:5:2:115.
17. Zurasky JA, Aiyagari V, Zazulia AR, Shackelford A, Diringer MN. Early mortality following spontaneous intracerebral hemorrhage. *Neurology*. 2005;64:725–727. doi: 10.1212/01.WNL.0000152045.56837.58.
18. Lord AS, Langefeld CD, Sekar P, Moomaw CJ, Badjatia N, Vashkevich A, et al. Infection after intracerebral hemorrhage: risk factors and association with outcomes in the ethnic/racial variations of intracerebral hemorrhage study. *Stroke*. 2014;45:3535–3542. doi: 10.1161/STROKEAHA.114.006435.
19. Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke*. 2015;46:1202–1209. doi: 10.1161/STROKEAHA.114.007843.

Ten-Year Temporal Trends in Medical Complications After Acute Intracerebral Hemorrhage in the United States

Fadar Oliver Otite, Priyank Khandelwal, Amer M. Malik, Seemant Chaturvedi, Ralph L. Sacco and Jose G. Romano

Stroke. 2017;48:596-603; originally published online February 22, 2017;
doi: 10.1161/STROKEAHA.116.015746
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIALS

Supplementary Methods

Data for this study was obtained from the 2004-2013 Nationwide Inpatient Sample (NIS). The NIS is maintained as part of the Health Care Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ). It is the largest all-payer inpatient care database in the US and comprises a 20% stratified random sample of all US hospital discharges. Each discharge in the NIS is de-identified so all discharges were considered to be independent. The unit for this analysis was each discharge rather than each individual. Further details on the NIS design are available at http://www.hcup-us.ahrq.gov.

Study Population

From n=78,327,564 hospitalizations contained in the NIS from 2004-2013, we identified all patients with a primary diagnosis of ICH (n=131,730) by querying the database using the International Classification of Disease-Clinical Modification, 9th revision (ICD-9 CM) code 431.[1] This code has a positive predictive value of 79%-97% and a sensitivity of 81%-85% for ICH (supplementary table 1).[2] To ensure only acute ICH cases were captured, we excluded n=6,359 hospitalizations designated as elective admissions. We further excluded n=6,482 hospitalizations with length-of-stay of <24 hours, n=17 patients with missing length-of-stay, n=741 patients with co-existing brain tumor diagnosis, n=781 patients with secondary head trauma diagnosis and n=644 patients <18 years of age leading to a final study population of n=116,706 patients.

Definition of Outcomes

Most complications were identified by searching all secondary diagnoses fields using the HCUP-defined constellation of ICD-9 codes corresponding to these diagnoses and contained in the HCUP Clinical Classification Software (CCS). UTI was identified using CCS code 159, while pneumonia, septicemia, ARF and AMI were identified using codes 122, 2, 157 and 100 respectively. DVT was identified by searching for ICD-9 codes 453.4X, 453.8x, 451.11 451.19, 451.2, 451.9 while PE was identified using codes 415.1X excluding 415.12 for septic pulmonary embolism.

In-hospital mortality, home disposition and length-of-stay were studied using HCUP variables named “DIED”, “DISPUNIFORM” and “LOS” respectively, and cost was calculated by multiplying total hospital charge in the NIS by cost-to-charge ratios provided as an additional file in the NIS. Calculated cost of each hospitalization was adjusted for inflation and expressed in terms of 2015 US dollars using coefficients obtained from the Bureau of Labor and Statistics website: http://www.bls.gov/data/inflation_calculator.htm.

Covariate assessment

Comorbidities associated with ICH hospitalization were identified by AHRQ comorbidity measures available in the NIS. AHRQ comorbidity measures identify different comorbidities using ICD-9-CM diagnoses and the Diagnosis Related Group (DRG) that are likely to have been present prior to hospitalization.[3] The modified Charlson

Comorbidity Index (CCI),[4] a validated weighted comorbid disease severity score composed of 17 comorbid conditions was calculated for all participants and patients were categorized into quartiles according to their CCI scores.

We identified mechanically ventilated patients using ICD-9 procedural codes 967, 967.1 and 967.2. In order to capture patients that were mechanically ventilated before they developed a complication as opposed to those that were intubated secondary to a complication, we defined mechanical ventilation (MV) status as positive only if patients were intubated within 48 hours of admission and as negative otherwise.

Patients with arteriovenous malformations and aneurysms were identified by searching all secondary diagnosis fields for ICD-9 codes 747.81 for intracranial arteriovenous malformation, searching all ICD-9 procedural codes 39.51, 39.52, 39.72, 39.76, 39.79 for clipping, coiling or embolization of aneurysm or arteriovenous malformation ad ICD-9 codes 01.59 for open resection of arteriovenous malformation. Craniotomy/craniectomy was identified using ICD-9 codes 01.23 or 01.24 and hydrocephalus requiring external ventricular drain or ventriculoperitoneal shunt defined using ICD-9 procedural codes 02.2, 02.21 or HCUP CCS procedural code 2 for insertion, replacement or removal of extracranial ventricular shunt.

Information on hospital characteristics including region, teaching status and bed-size were extracted. Total annual AIS admissions of hospitals were counted and hospitals were grouped annually into tertiles based on their yearly stroke volumes.

Statistical analysis

Baseline characteristics of participants were summarized using descriptive statistics. We used weights[5] provided in the NIS to compute the overall unadjusted weighted prevalence of each complication and in subgroups categorized by sex. We further stratified some complications by pre-existing conditions or interventions expected to influence the occurrence of the complications: pneumonia, DVT and PE rates by MV status, ARF rate by chronic renal failure, and myocardial infarction rate by coronary artery disease. We evaluated trends in prevalence of each complication over time by constructing logistic regression model with each complication as the dependent variable and year of discharge as the independent variable, evaluated continuously, with significance of differences in trend over time assessed using the Wald test.

We used a series of nested logistic regression models adjusted for demographic, clinical, and hospital variables to evaluate the association of each complication with hospitalization variables, and to assess factors that may account for any observed trends in complication rates and control for confounding. We used the CCI as a measure of the overall condition of patients in these models including baseline risk of developing in-hospital complications and used MV status, craniotomy/craniectomy and hydrocephalus-requiring EVD placement as surrogate measures for ICH severity.

Similarly, multivariate logistic regression models adjusted for demographic, comorbid conditions, and hospitalization factors were used to evaluate the association of each

complication with mortality and odds of home disposition at discharge (in surviving patients only). We checked for possible effect modification by MV in all models by including interaction terms for MV status and where applicable reported effect estimates stratified by MV status. We assessed the associations of each complication with cost and length-of-stay by fitting generalized linear models with a gamma variance distribution.

Since this was an exploratory analysis with no specific hypothesis, adjustment for multiple testing was not considered necessary.[6, 7] A two-tailed alpha of <0.05 was required for statistical significance. All analyses were performed using Stata 13 (StataCorp, LP, College Station, Texas). We took into account the weighting, clustering and stratification needed in the complex NIS survey design in all analysis by use of Stata's SVY suite of commands with use of the hospital as the primary sampling unit and applying relevant probability sampling weights for robust variance estimation to all models. We assessed all models for collinearity by assessing variation inflation factor diagnostics using Stata's "Collin" command.

Missing variables

Most variables had missing values in <1% of participants except for race and cost data that were missing in 19.1% and 2.7% of participants, respectively. Missing data were imputed to the dominant category for categorical variables and the median for continuous variables.[8] Missing insurance status for those aged ≥65 years was imputed to Medicare. Missing race date was handled using multiple imputation. Missing cost data were handled using re-weighting technique recommended by HCUP[9] and missing hospital variables such as teaching status (0.8%) and number of beds (0.8%) were excluded. Main effect estimates were similar when Stata's MI suite of commands was used to account for all missing variables using multiple imputation.

Reference

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Culebras A, Elkind MS, et al. An updated definition of stroke for the 21st century a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2013;44:2064-2089
2. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiology and drug safety*. 2012;21:100-128
3. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, et al. Trends of hospitalization for atrial fibrillation in the united states, 2000 through 2010: Implications for healthcare planning. *Circulation*. 2014:CIRCULATIONAHA. 114.008201
4. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in icd-9-cm and icd-10 administrative data. *Medical care*. 2005:1130-1139
5. (HCUP). HCaUP. Introduction to the hcup nationwide inpatient sample (nis), 2012. 2015;2016

6. Savitz DA, Olshan AF. Describing data requires no adjustment for multiple comparisons: A reply from savitz and olshan. *American Journal of Epidemiology*. 1998;147:813-814
7. Bender R, Lange S. Adjusting for multiple testing—when and how? *Journal of clinical epidemiology*. 2001;54:343-349
8. Romano JG, Smith EE, Liang L, Gardener H, Camp S, Shuey L, et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: A retrospective analysis of the get with the guidelines–stroke registry. *JAMA neurology*. 2015;72:423-431
9. Yu T-C, Zhou H. Evaluation of techniques for handling missing cost-to-charge ratios in the USA nationwide inpatient sample: A simulation study. *Journal of comparative effectiveness research*. 2015;4:473-483

Supplementary table 1: Reported range of sensitivities and positive predictive values of International Classification of Disease 9 CM codes for intracerebral hemorrhage and complications in published systematic reviews.

Variable	Sensitivity, %	Positive predictive value
Intracerebral hemorrhage[1]	82-85	79-97
Acute myocardial infarction[2]	49-94	49-99
Acute renal failure[3]	15-81	15-96
Sepsis[4]	17-82	6-100
Pneumonia[5]	54-98	57-96
Urinary tract infection[6]	22.2	92.3
Deep venous thrombosis[7]	61-100	31-97
Pulmonary embolism[7]	24-100	24-92

* Single center study, Used only two ICD-9 codes 599.0 and 996.64 to identify UTI patients.

1. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiology and drug safety. 2012;21:100-128

2. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: A systematic review. PLoS one. 2014;9:e92286

3. Vlasschaert ME, Bejaimal SA, Hackam DG, Quinn R, Cuerden MS, Oliver MJ, et al. Validity of administrative database coding for kidney disease: A systematic review. American Journal of Kidney Diseases. 2011;57:29-43

4. Jolley RJ, Sawka KJ, Yergens DW, Quan H, Jetté N, Doig CJ. Validity of administrative data in recording sepsis: A systematic review. Critical Care. 2015;19:1

5. Barber C, Lacaille D, Fortin PR. Systematic review of validation studies of the use of administrative data to identify serious infections. Arthritis care & research. 2013;65:1343-1357

6. Heisler CA, Melton LJ, Weaver AL, Gebhart JB. Determining perioperative complications associated with vaginal hysterectomy: Code classification versus chart review. Journal of the American College of Surgeons. 2009;209:119-122

7. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiology and drug safety. 2012;21:154-162

Supplementary table 2: Baseline characteristics of acute intracerebral hemorrhage patients in the United States from 2004-2013

	Total	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Total number (sampling)	116,706	12,161	11,342	11,835	11,428	11,944	11,391	12,417	11,872	11,074	11,242
Weighted number (national)	575,211	58,901	55,222	57,583	56,534	58,555	57,088	62,661	57,087	55,370	56,210
Age, Years, mean (SE)	68.9 (0.1)	69.1 (0.3)	69.5 (0.3)	68.9 (0.3)	68.9 (0.3)	69.1 (0.3)	69.2 (0.3)	68.6 (0.3)	68.8 (0.4)	68.4 (0.2)	68.3 (0.2)
Age, %											
18-39 years	3.7	3.8	3.5	3.8	3.7	3.5	3.2	3.9	3.8	3.9	3.9
40-59 years	24.6	23.7	23.7	24.9	24.8	24.9	24.3	25.3	25.2	24.8	24.8
60-79 years	41.7	42.8	41.4	40.9	41.3	41.0	42.4	41.4	41.2	42.4	42.4
>=80 years	29.9	29.8	31.4	30.3	30.2	30.6	30.1	29.4	29.8	28.9	28.9
Female, %	49.7	50.9	50.5	50.5	50.6	49.5	49.8	48.8	50.2	48.1	48.0
Race, %											
White	65.1	65.9	69.2	66.7	63.4	66.8	64.6	64.0	63.0	63.1	63.7
Black	17.1	16.8	14.3	15.9	17.2	15.9	16.1	20.0	18.2	18.1	18.0
Hispanic	9.4	9.3	9.0	9.5	10.5	8.7	9.7	8.0	10.1	9.6	9.6
Other	8.5	8.0	7.5	7.8	9.0	8.6	9.6	7.9	8.7	9.2	8.8
Primary payer, %											
Medicare	60.7	61.5	63.4	61.4	60.1	60.0	60.5	58.1	60.4	61.0	60.4
Medicaid	8.9	8.3	7.7	7.9	8.2	8.9	9.0	10.3	10.0	9.8	9.2
Private	20.9	21.9	20.3	21.0	22.0	21.7	21.4	21.4	19.8	19.3	19.7
Self pay	6.5	5.8	5.8	6.6	6.4	6.2	6.4	6.7	6.6	6.8	7.0
Other	3.1	2.6	2.8	3.2	3.2	3.1	2.7	3.6	3.2	3.0	3.7
Median income, %											
$1-$38,999	28.1	28.4	26.7	27.4	28.4	28.0	27.0	29.5	27.6	29.8	28.0
$39,000- $47,999	27.1	28.2	26.2	26.8	26.3	29.4	27.9	26.8	26.2	25.4	27.7
$48,000-$62,999	23.0	22.1	24.1	23.0	22.5	21.3	23.6	22.6	24.5	23.5	23.0
≥$63,000	21.8	21.3	23.1	22.8	22.8	21.3	21.5	21.1	21.6	21.3	21.3
Hospital region, %											
Northeast	19.0	19.3	19.2	20.2	18.9	21.0	19.7	18.1	17.2	18.4	18.12
Midwest	20.5	20.4	23.0	19.9	19.4	20.0	19.7	19.6	22.4	20.9	20.6
South	38.9	40.6	37.5	38.8	38.1	39.7	37.4	40.7	36.5	39.4	39.8
West	21.5	19.7	20.3	21.1	23.7	19.4	23.2	21.5	24.0	21.3	21.6
Location/teaching, %											
Rural	6.0	8.2	7.5	7.0	6.6	5.7	5.5	6.4	4.3	4.3	4.1
Urban nonteaching	33.9	36.2	43.8	33.1	34.7	36.5	33.8	31.5	31.8	29.0	28.4
Urban teaching	60.1	55.5	48.7	60.0	58.7	57.8	60.7	62.2	63.9	66.7	67.4
Hospital bed size*, %											
Small	6.8	7.5	5.9	9.8	8.1	5.3	6.0	6.1	6.9	6.0	5.9
Medium	20.9	21.2	23.4	22.4	21.2	19.6	21.2	17.3	19.4	22.1	22.1
Large	72.3	71.3	70.7	67.8	70.6	75.2	72.8	76.6	73.7	71.9	72.0
Weekend admission	26.9	27.1	27.0	27.0	26.7	26.6	27.2	27.0	26.2	27.3	27.1
Vascular risk factors											

Dyslipidemia	28.3	16.0	19.3	22.4	25.2	27.9	30.9	32.1	35.2	36.8	37.3
Diabetes uncomplicated	22.2	19.1	19.4	20.0	21.8	22.9	23.8	23.0	23.9	23.6	24.6
Complicated diabetes	3.4	2.6	2.8	2.9	3.5	3.4	3.5	3.5	4.2	4.0	3.7
Hypertension	79.5	72.8	74.6	76.2	78.5	79.5	81.2	81.5	82.8	83.8	84.5
Chronic Renal failure	10.5	5.1	6.4	9.6	10.9	10.7	11.5	11.5	13.3	13.2	13.1
Atrial fibrillation	18.1	16.1	17.8	17.5	18.7	17.6	18.9	18.0	18.7	18.7	18.8
Congestive heart failure	10.4	10.2	10.8	10.9	10.7	10.2	10.6	10.3	10.4	10.3	10.0
Valvular disease	5.5	5.1	5.3	5.7	5.7	5.4	5.3	5.5	5,5	5,6	5.9
Coronary artery disease	19.2	17.2	18.4	18.6	18.5	19.4	20.3	18.9	20.4	20.3	20.4
Peripheral vascular disease	4.8	3.8	4.0	4.1	4.8	4.9	5.3	4.3	5.8	5.0	5.8
Drug abuse	3.6	2.8	3.5	3.6	4.0	3.2	3.1	3.9	4.1	3.9	4.3
Tobacco smoking	10.3	7.3	8.4	8.7	8.9	10.0	10.8	11.7	12.2	12.8	12.8
Alcohol abuse	6.2	5.4	5.8	6.0	6.0	6.0	6.2	5.9	6.9	7.1	6.9
Chronic lung disease	12.4	11.9	11.3	12.2	12.9	12.3	12.4	12.3	12.2	13.2	13.1
AIDS	0.2	0.3	0.3	0.2	0.2	0.3	0.2	0.3	0.3	0.2	0.2
Liver disease	2.4	1.9	2.1	2.1	2.2	2.3	2.5	2.1	3.0	3.1	2.9
Coagulopathy	6.3	5.4	5.6	5.1	5.6	5.6	6.3	6.3	7.3	7.7	8.2
Modified Charlson's Comorbidity index, CCI											
CCI=1	39.6	45.5	44.5	43.3	40.6	39.4	38.6	38.6	36.0	35.3	33.9
CCI=2	23.7	25.9	25.2	23.7	23.6	23.6	23.1	22.6	23.1	22.8	23.4
CCI=3	17.2	15.3	16.0	16.8	16.9	17.6	18.3	17.9	17.9	17.6	18.0
CCI≥4	19.5	13.3	14.2	16.3	18.9	19.3	20.1	20.9	23.0	24.3	24.7
Dysphagia	11.5	7.6	8.4	8.3	9.8	11.1	13.0	13.1	14.1	14.6	15.1
Coma	8.6	7.4	7.6	7.2	6.8	7.8	8.6	8.2	9.4	11.3	11.5
Mechanical ventilation	27.7	27.3	26.3	26.0	26.5	27.1	27.9	28.7	28.4	29.6	29.2
Mechanical ventilation within 48hrs	20.9	17.5	16.8	18.0	18.6	20.2	20.8	23.4	23.5	25.3	25.3
AVM/aneurysm†	2.0	1.8	1.7	2.0	2.0	2.0	1.8	2.1	2.3	2.3	2.4
Craniotomy/craniectomy	1.1	1.2	0.8	1.1	1.5	1.0	1.2	1.2	1.1	1.2	1.2
EVD or VP shunt	8.3	7.6	7.1	7.8	8.1	8.4	8.6	9.5	8.4	8.7	8.5

* Number of short-term acute beds in a hospital. See full bed categorization detailed at www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp.

† AVM represents arteriovenous malformation

Supplementary table 3: Disposition of adult intracerebral hemorrhage patients after hospitalization from 2004-2013

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	P-trend
Length of stay, days (SE)	8.4 (0.2)	7.9 (0.2)	8.5 (0.2)	8.5 (0.2)	8.6 (0.2)	8.3 (0.2)	8.5 (0.2)	8.0 (0.2)	8.3 (0.1)	8.0 (0.1)	0.233
Home	19.6	18.9	21.0	20.1	19.1	20.0	20.0	18.9	19.8	19.9	0.943
Home health care	6.3	7.0	7.2	7.6	7.6	6.7	7.5	8.4	8.3	8.3	<0.001
Skilled facility	42.3	43.8	42.8	43.6	44.6	45.7	45.8	47.2	45.9	46.9	<0.001
In-hospital death*	27.8	26.9	24.8	23.6	23.8	23.5	22.8	21.5	22.1	21.0	<0.001
Other†	4.0	3.6	4.3	5.1	5.0	4.1	4.0	4.0	4.0	4.0	0.597

*Includes discharge to hospice, long term care hospital, skilled nursing facility and intermediate care facility

† includes transfer to short term hospital, discharge against medical advice, discharged alive but destination unknown, missing

Supplementary table 4. Proportion of medical complications among all patients that died during ICH hospitalization in the United States from 2004-2013 according to their hospital length-of-stay

	Length of stay <3 days	Length-of-stay <7days*	Length-of-stay >=7days
Died, %	61.6	82.4	17.6
Any complication, %	12.1	16.4	59.7
Urinary tract infection, %	2.8	4.2	W0.1
Pneumonia, %	2.1	3.7	26.8
Sepsis, %	1.3	2.2	18.8
Deep venous thrombosis, %	0.4	0.6	5.7
Pulmonary embolism, %	0.2	0.3	1.8
Acute renal failure, %	5.2	6.8	22.2
Acute myocardial infarction, %	2.2	2.5	5.1

*Includes all patients with length-of-stay <3 days plus patients that died between days 3 and 6 of admission.

Supplementary table 5: Association of medical complications during intracerebral hemorrhage hospitalization with length-of-stay, hospitalization cost, home disposition and in-hospital mortality

Variable	Unadjusted model			Multivariate model 1			Multivariate model 2		
	Estimate	95% CI	P-value	Estimate	95% CI	P-value	Estimate	95% CI	P-value
Length-of-stay, days									
Urinary tract infection	7.22	6.78-7.66	<0.001	4.98	4.71-5.24	<0.001	3.84	3.63-4.06	<0.001
Pneumonia	13.36	12.68-14.03	<0.001	9.65	9.14-10.16	<0.001	7.25	6.87-7.63	<0.001
Sepsis	16.92	15.78-18.06	<0.001	12.85	11.94-13.76	<0.001	9.32	8.52-10.12	<0.001
Deep venous thrombosis	14.52	13.60-15.44	<0.001	10.49	9.65-11.33	<0.001	6.91	6.27-7.55	<0.001
Pulmonary embolism	12.62	10.94-14.29	<0.001	8.75	7.37-10.12	<0.001	3.76	2.81-4.71	<0.001
Acute renal failure	7.86	7.39-8.32	<0.001	4.91	4.58-5.24	<0.001	2.54	2.32-2.76	<0.001
Acute myocardial infarction	4.28	3.50-5.06	<0.001	2.75	2.26-3.23	<0.001	1.13	0.79-1.46	<0.001
Hospitalization cost, $									
Urinary tract infection	16007	14,527-17,487	<0.001	8,629	7998-9,130	<0.001	6,052	5,644-6,460	<0.001
Pneumonia	45,457	43,128-47,786	<0.001	29,103	27,456-30,750	<0.001	22,123	20,743-23,504	<0.001
Sepsis	51,344	48,210-54,478	<0.001	35,755	33,392-38,118	<0.001	25,844	23,857-27,831	<0.001
Deep venous thrombosis	50,518	46,648-54,388	<0.001	32,336	29,570-35,102	<0.001	21,850	19,559-24,141	<0.001
Pulmonary embolism	46,392	39,998-52,787	<0.001	30,095	25,441-34,749	<0.001	14,819	11,112-18,526	<0.001
Acute renal failure	24,662	22,978-26,346	<0.001	13,387	12,387-14,386	<0.001	6,730	6,110-7,350	<0.001
Acute myocardial infarction	15,050	12,271-17,829	<0.001	8,860	7,202-10,519	<0.001	4,065	3,119-5,011	<0.001
Home disposition									
Urinary tract infection	0.41	0.38-0.45	<0.001	0.50	0.47-0.54	<0.001	0.55	0.51-0.59	<0.001
Pneumonia	0.28	0.24-0.32	<0.001	0.45	0.39-0.52	<0.001	0.55	0.48-0.63	<0.001
Sepsis	0.26	(0.23-0.31)	<0.001	0.33	0.28-0.39	<0.001	0.46	0.40-0.53	<0.001
Deep venous thrombosis	0.40	0.34-0.47	<0.001	0.47	0.40-0.56	<0.001	0.60	0.52-0.71	<0.001
PE	0.45	0.35-0.57	<0.001	0.46	0.36-0.60	<0.001	0.66	0.51-0.87	<0.001
Acute renal failure	0.58	0.54-0.63	<0.001	0.67	0.62-0.72	<0.001	0.79	0.74-0.86	<0.001

Acute myocardial infarction	0.40	0.35-0.46	<0.001	0.52	0.44-0.61	<0.001	0.60	0.51-0.71	<0.001
In-hospital mortality									
Urinary tract infection	0.36	0.34-0.38	<0.001	0.35	0.32-0.37	<0.001	0.35	0.33-0.37	<0.001
Pneumonia in no-MV	1.52	1.41-1.65	<0.001	1.26	1.15-1.38	<0.001	1.21	1.11-1.33	<0.001
Pneumonia in MV	0.22	0.20-0.24	<0.001	0.28	0.25-0.30	<0.001	0.33	0.30-0.37	<0.001
Sepsis in no MV	2.01	1.83-2.20	<0.001	1.93	1.73-2.16	<0.001	2.15	1.92-2.41	<0.001
Sepsis in MV	0.37	0.34-0.42	<0.001	0.47	0.41-0.53	<0.001	0.80	0.69-0.92	<0.001
Deep venous thrombosis	0.49	0.44-0.54	<0.001	0.35	0.31-0.41	<0.001	0.39	0.33-0.45	<0.001
Pulmonary embolism in no MV	1.21	0.98-1.52	0.083	1.21	0.94-1.55	0.138	1.36	1.04-1.79	0.024
Pulmonary embolism in MV	0.30	0.22-0.41	<0.001	0.46	0.31-0.66	<0.001	0.89	0.56-1.40	0.612
Acute renal failure	1.22	1.16-1.28	<0.001	1.09	1.02-1.17	0.008	1.23	1.15-1.31	<0.001
Acute myocardial infarction	1.76	1.61-1.91	<0.001	1.49	1.33-1.67	<0.001	1.63	1.43-1.81	<0.001

Abbreviations: MV represents mechanical ventilation

Multivariate Model 1 – adjusted for age, sex, race, year, insurance type, income, hospital region, hospital location/teaching status, hospital bedsize, yearly stroke volume, atrial fibrillation, smoking, mechanical ventilation use, craniotomy/craniectomy, hydrocephalus requiring external ventricular drain or ventriculoperitoneal shunt, arteriovenous malformation/ aneurysm, coma, dysphagia, weekend admission.

Multivariate model 2- mutually adjusted model 1 containing all variables in model 1 + inclusion of all other medical complications.