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Acute Kidney Injury is Associated with Increased Hospital Mortality after Stroke

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Abstract

Background—Acute kidney injury (AKI) is common and associates with poor clinical outcomes. Information about the incidence of AKI and effect on stroke outcomes is limited.

Methods—Data were analyzed from a registry of subjects with ischemic stroke and intracerebral hemorrhage (ICH) hospitalized at a single academic medical center. Admission creatinine was considered to be the baseline. AKI was defined as a creatinine increase of 0.3 mg/dL or a percentage increase of at least 50% from baseline, occurring during hospitalization. Multivariate logistic regression models were created for both stroke types, with hospital mortality as the outcome. Covariates included gender, race, age, admission creatinine, admission NIH Stroke Scale score, performance of contrast-enhanced CT scan of the head and neck, and medical co-morbidities.

Results—There were 528 cases of ischemic stroke with 70 deaths (13%), and 829 cases of ICH with 268 deaths (32%). The mean age was 64 years, with 56% men and 71% whites. AKI complicated 14% of ischemic stroke and 21% of ICH hospitalizations. In multivariate analysis stratified by stroke type, AKI was associated with increased hospital mortality from ischemic stroke (odds ratio (OR) 3.08, 95% confidence interval (CI) [1.49–6.35]) but not ICH (OR 0.82, 95% CI [0.50–1.35]), except for those surviving at least two days (OR 2.11, 95% CI [1.18–3.77]).

Conclusions—AKI occurs frequently after stroke and is associated with increased hospital mortality. Further studies are needed to establish if the association is causal and if measures to prevent AKI would result in decreased mortality.

Introduction

Acute kidney injury (AKI) is defined as an abrupt deterioration in kidney function, manifested by an increase in serum creatinine, a decrease in urine output, or both. Multiple recent studies using national administrative data, electronic health record analysis, as well as hospital chart review all indicate that the prevalence of AKI is high, and may also be

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increasing in hospitalized patients.¹⁻³ In one analysis of Medicare beneficiaries, AKI occurred in 23.8 cases per 1000 hospital discharges, and was increasing at 11% per year.² The incidence is even greater in high acuity states such as sepsis, where AKI has complicated up to 51% of hospitalizations in some studies.⁴

The development of AKI portends a higher risk of in-hospital death, which has been demonstrated in general medical and surgical hospitalizations as well as specific settings such as following acute myocardial infarction and cardiac surgery, and in the intensive care unit.⁵⁻⁸ For instance, in studies involving septic patients, the development of AKI is associated with a two to three-fold higher risk of in-hospital mortality.⁹⁻¹¹ However, data are lacking on the frequency and prognosis of AKI in the setting of stroke, the third leading cause of death in the United States.¹² Moreover, current studies have been limited by lack of an objective measure of stroke severity (such as the NIH stroke scale score), data concerning the frequency of CT angiography performed at admission (which can cause contrast-induced nephropathy), lack of racial and ethnic diversity, and lack of data specifically pertaining to intracerebral hemorrhage (ICH).^{13, 14}

Our goals were to determine the frequency of AKI in patients hospitalized with ischemic stroke or ICH, to characterize the association between AKI and in-hospital mortality, and to determine risk factors for AKI in this setting.

Methods

Study Population

Subjects were selected from a stroke registry maintained at Harborview Medical Center, a tertiary care and teaching hospital of the University of Washington (Seattle, WA). The registry consists of all cases of ischemic stroke, transient ischemic attack, non-traumatic ICH, and non-traumatic subarachnoid hemorrhage admitted to Harborview Medical Center from October 2004 to December 2008. Subjects aged 18 years and older with ischemic stroke or ICH were eligible for inclusion into this study (n=2,029). Subjects were excluded if: 1) they were missing any key covariate data listed below (n=618 missing admission National Institutes of Health Stroke Scale (NIHSS) scores, n=12 missing admission creatinine), or 2) if admission estimated glomerular filtration rate (eGFR)¹⁵ was less than 15 mL/min, in order to exclude those with end stage renal disease (n=42). The Institutional Review Board of the University of Washington approved this study.

Data Collection and Outcomes

All data were collected retrospectively from medical records available from hospital admission to discharge by trained abstractors in the quality improvement program. Medical co-morbidities, including a history of atrial fibrillation, heart failure, diabetes, coronary artery disease, hypertension, hyperlipidemia, stroke or transient ischemic attack (TIA), and smoking within the past year were abstracted based on documentation in the medical record alone, and assigned binary values. Race was categorized as white, African-American, Asian/Pacific Islander, or other/unknown. Stroke subtype was determined based on interpretation of the clinical records, including discharge summaries and ICD-9 codes. Serum creatinine values were measured on admission, and routinely thereafter (typically every day) during the course of hospitalization. NIHSS scores were measured on admission or estimated retrospectively using data from admission physical exams by a validated method.¹⁶ Data were also collected regarding CT angiography of the head and neck performed during hospitalization, if applicable. The primary outcome of this study was all-cause in-hospital mortality.

Estimation of Kidney Function and Definition of AKI

A subject's admission kidney function was considered to be baseline, and was estimated using serum creatinine and the Modification of Diet in Renal Disease (MDRD) formula for eGFR.¹⁵

$$\text{eGFR} = 186.3 \times (\text{creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times (1.21 \text{ if black}) \times (0.742 \text{ if woman})$$

AKI was classified and graded based on severity according to a widely used definition, the Acute Kidney Injury Network (AKIN) criteria.¹⁷ The AKIN criteria has three stages: stage 1) a 50–99% increase in creatinine from baseline or an absolute increase in creatinine of 0.3 mg/dL or greater; stage 2) a 100–199% increase in creatinine from baseline; stage 3) a 200% increase in serum creatinine, or a rise in serum creatinine of 0.5 mg/dL to at least 4.0 mg/dL, or the initiation of renal replacement therapy.¹⁸ Criteria involving urine output were not used in this study as urine output was not routinely recorded in all patients. A subject's highest creatinine during hospitalization was compared to admission creatinine to determine if a subject met criteria for AKI. AKI defined by AKIN stage 1 or greater was used in the models. Data on prevalent or incident renal replacement therapy was not available in this cohort.

Statistical Analysis

Multivariate logistic regression models testing the association between AKI and all-cause in-hospital mortality were constructed. In the overall cohort, there was a significant interaction between stroke type and AKI, thus stratified analyses were performed by stroke type (ICH or ischemic stroke). Potential confounders were included in the models if strong evidence existed in the literature of an association with either outcome or AKI. Differences in covariates based on AKI status and stroke type were tested using χ^2 tests for categorical variables, and two sample t-tests for continuous variables. A two-sided p-value less than or equal to 0.05 was considered significant. Multivariate logistic regression models were also constructed using the entire cohort to determine predictors of AKI, with AKIN stage 1 or greater severity defined as the outcome. All analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the 1,357 subjects in this study stratified by stroke type and AKI are presented in Table 1. For the overall group including both ICH and ischemic stroke, mean age was 64 years (SD 16 years), with 56% men and 71% whites. There were a total of 528 ischemic strokes, and 829 ICHs. Compared to those with ischemic stroke, patients with ICH had a significantly lower prevalence of diabetes, smoking, coronary artery disease, hyperlipidemia, prior stroke, black race, and male gender. ICH subjects also were older, had higher mortality rates and NIHSS scores, slightly lower admission creatinine, and increased frequency of AKI (data not shown; $p < 0.05$ for all comparisons). Overall, AKI was common and developed in 18% of the overall cohort, with significantly higher rates amongst ICH cases as compared to ischemic stroke (21% vs. 14%). Approximately 79% of all AKI was stage 1. Crude frequency and mortality rates for AKI are depicted in Table 2, which also demonstrates that greater severity AKI was associated with greater crude mortality (Cochran-Armitage Trend Test $p < 0.0001$ for ischemic stroke and $p = 0.003$ for ICH).

Table 3 demonstrates several models that were created to test the association between stage 1 or greater AKI and in-hospital mortality, stratified by stroke type. Stages 2 and 3 could not be examined separately because of small numbers. The association between AKI and

mortality after ischemic stroke was robust and only modestly attenuated when additional covariates were added to the model. In the fully-adjusted model, AKI complicating an ischemic stroke hospitalization was associated with a 3.08 greater odds of in-hospital mortality (95% Confidence Interval [CI] 1.49 – 6.35). In the models for ICH, the association between AKI and increased mortality was attenuated in magnitude, and became insignificant once NIHSS score was added (OR 0.82, 95% CI (0.50–1.35)). When the analyses were restricted to those who survived their ICH for at least two days, the odds ratio was 2.11 (95% CI 1.18 – 3.77).

Considering that a significant portion of the original cohort (n=618, 30%) was not included in the analysis because of missing NIHSS data, we performed sensitivity analyses without this variable to include these additional subjects. For ischemic stroke, the relationship between AKI and mortality remained significant (n=956, OR 2.72, 95% CI 1.66 – 4.46), while the relationship in ICH was strengthened and reached statistical significance (n=1019, OR 1.63, OR 1.17 – 2.26). In addition, we compared the baseline characteristics of the group with NIHSS data to the group without using χ^2 tests for categorical variables, and two sample t-tests for continuous variables. The groups were mostly similar except that those with NIHSS data had significantly lower smoking rates (21% vs. 26%), higher mortality rates (25% vs. 18%), older age (64 years vs. 61 years), and more ischemic strokes (69% vs. 39%) (all $P < 0.05$).

We also attempted to determine risk factors for AKI in the setting of either ischemic stroke or ICH (Table 4). In multivariate analysis with AKIN stage 1 or greater as the outcome, higher admission creatinine and NIHSS scores predicted development of AKI, while current smoking appeared to have an inverse relationship with AKI. There was also a trend for ICH predicting AKI, but this did not reach statistical significance (OR 1.37, 95% CI 0.99–1.89, $p=0.057$). Interestingly, there was no association between contrast-enhanced CT scans and AKI in this cohort.

Discussion

In this analysis we found that AKI was a common complication of stroke and that in-hospital death was more than three-fold higher in patients with ischemic stroke who had AKI compared to those who did not. These results for ischemic stroke are in concert with those reported in two other analyses involving stroke and acute kidney injury. In one study of an eastern European population with ischemic and ICH, the incidence of AKI was 14.5%, which carried an unadjusted 30-day mortality rate of 42%, versus 12% for subjects without AKI.¹³ The frequency of AKI was higher (27%) in another European study of subjects hospitalized with ischemic or ICH, with crude mortality higher after one month in those with AKI (21.8% vs. 12.5%), which persisted after 10 years of follow-up.¹⁴

Both of these studies had relatively few ICHs (roughly 15% in each), and analyses were not stratified by stroke type. Our study had a much higher number of ICHs, likely because of the large referral bias and expertise of the medical center in this area. We found no association between AKI and ICH mortality, despite the high rate of AKI in this group. The reasons for this lack of association are unclear. Mortality and NIHSS scores were significantly greater in the ICH group, as expected, and it may be that the relative severity of these strokes overwhelmed any association of mortality with AKI. Indeed, in univariate and some multivariate models, there was an association of AKI with mortality. Mean time to death was also lower in the ICH group, and the high early mortality may have masked AKI development and impact. In a subgroup analysis of subjects with ICH surviving greater than two days, AKI was significantly associated with mortality. Another possibility is that interventions such as hypertonic saline and mannitol are more common in ICH, and may

also cause kidney dysfunction. These interventions could theoretically contribute to the higher rate of AKI seen in ICH, but unclear is how they would dampen the association between AKI and mortality. Unfortunately, these data were not available, and the overall usage is likely to be small.

The frequency of AKI in this study falls along the spectrum described in other studies. In one study of patients admitted to the intensive care unit for a variety of reasons, AKI occurred in 5.7%.¹⁹ In studies specifically examining sepsis in the ICU, incidence has varied between 9–51%.^{4, 10} A recent analysis of patients following myocardial infarction revealed that AKI complicated 19.4% of hospitalizations.⁷ The differences can be explained partly by the setting and severity of illness but can also be explained by the varying definitions used in these studies. In the ischemic stroke cohort, roughly 61% of subjects with AKI had a creatinine increase between 0.3 – 0.5 mg/dL.

This study does not, however, address whether the association between AKI and ischemic stroke mortality is causal. While we attempted to adjust for several risk factors, including stroke severity, that have been shown to contribute to in-hospital mortality, the presence of AKI may still simply reflect a greater burden of illness. For instance, hemodynamic instability, poor nutritional intake leading to dehydration, and myocardial infarction could all cause AKI and lead to higher mortality. On the contrary, AKI is a complicated process characterized by a variety of homeostatic perturbations that could conceivably worsen stroke prognosis independent of other risk factors. For instance, there is evidence to suggest that patients with AKI have increased insulin resistance,²⁰ which could potentially lead to hyperglycemia. Hyperglycemia has been linked to worse outcomes in both ischemic stroke and ICH.^{21, 22} Other physiologic derangements associated with AKI include increased inflammation²³ and oxidative stress,²⁴ which could both hypothetically worsen stroke outcomes. Another mechanistic possibility could involve ischemic stroke subtype, particularly considering that cardioembolic strokes have been associated with higher mortality and perhaps may also be linked with AKI.¹⁴ However, in multivariate analyses cardioembolic subtype did not predict either risk of mortality or risk of AKI. Additionally, rates of other ischemic stroke subtypes were similar amongst subjects with and without AKI, and did not impact multivariate analyses.

This study has a number of strengths. First, this is a large sample size in a population with age, race, and gender diversity, which makes the results more generalizable. Second, serum creatinine values were checked throughout hospitalization and were available for these analyses, and standardized definitions of AKI in conformity with recent expert recommendations were utilized in this cohort. Third, a validated and widely-used measure of stroke severity, the NIHSS, was incorporated into the models. This adjustment has been lacking in some other studies of kidney function and acute stroke. Finally, we had data on which subjects underwent contrast-enhanced CT scans as part of the initial stroke workup, which is a well-known contributor to AKI. Nephrotoxic contrast agents are potentially important confounders given that sicker patients may preferentially undergo a more intense workup, including radiological studies.

This study does have several important limitations. First, it is a retrospective study with data abstracted from medical records. Second, measurements of urine output were not available, which may lead to an underestimation of the number of subjects with AKI. Third, pre-admission creatinine was not available so the true baseline level of kidney function is unknown. The focus of this analysis, however, was on changes in kidney function after hospital admission, where interventions could be attempted to either prevent or treat AKI. Fourth, the study group is taken from a tertiary care center with a large referral base, and thus subjects may be sicker than the average stroke patient, and results may not reflect the

broader US stroke population. Indeed, the in-hospital ischemic stroke mortality rate described here is higher than in other studies.²⁵ However, this finding would tend to bias the association between AKI and stroke mortality towards the null. For instance, in this cohort the majority of strokes were ICH, which is associated with significantly higher mortality than ischemic stroke; and we believe in the case of ICH that the severity of the stroke itself negated any smaller effect that AKI may have. Finally, a significant fraction of the original cohort was not included in the main analysis, primarily because of missing NIHSS data. Analyses including this subset, however, still demonstrated a significant association between AKI and ischemic stroke mortality. Meanwhile the resulting newly significant association in ICH may have been secondary to the greater impact of NIHSS in the ICH models.

In conclusion, we found that AKI is a common problem during stroke hospitalizations and is associated with in-hospital mortality from ischemic stroke, as well as with ICH cases surviving greater than two days. The vast majority of subjects with AKI were AKIN stage 1, highlighting the importance of even minor elevations in creatinine during hospitalization. Further studies are needed to determine if this is a causal relationship, and if interventions designed to aggressively either prevent the development of AKI or treat early manifestations of AKI would result in reduced stroke mortality.

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TABLE 1

Baseline characteristics by stroke type and AKI status

	Ischemic Stroke			Intracerebral Hemorrhage		
	AKI	No AKI	p-value	AKI	No AKI	p-value
N	72	456		171	658	
Demographics						
Male – N (%)	41 (57)	272 (60)	0.664	106 (62)	336 (51)	0.011
White – N (%)	52 (72)	308 (68)	0.428	108 (63)	493 (75)	0.002
Black – N (%)	10 (14)	64 (14)	0.974	19 (11)	38 (6)	0.014
Asian – N (%)	7 (10)	44 (10)	0.984	26 (15)	81 (12)	0.315
Other – N (%)	3 (4)	4 (9)	0.184	18 (11)	46 (7)	0.123
Age – mean years (SD)	66.2 (17.5)	61.1 (15.7)	0.012	63.3 (14.4)	65.1 (16.3)	0.153
Medical History						
Atrial fibrillation – N (%)	18 (25)	78 (17)	0.107	27 (16)	102 (16)	0.926
Heart failure – N (%)	5 (7)	7 (2)	0.004	1 (1)	12 (2)	0.245
Hypertension – N (%)	52 (72)	309 (68)	0.450	117 (68)	419 (64)	0.248
Coronary artery disease – N (%)	22 (31)	100 (22)	0.107	37 (22)	108 (16)	0.109
Hyperlipidemia – N (%)	22 (31)	179 (39)	0.158	33 (19)	136 (21)	0.692
Current smoker – N (%)	12 (17)	139 (30)	0.016	22 (13)	118 (18)	0.115
Diabetes – N (%)	20 (28)	124 (27)	0.918	42 (25)	117 (18)	0.045
Prior TIA – N (%)	5 (7)	32 (7)	0.982	7 (4)	42 (6)	0.258
Prior stroke – N (%)	23 (32)	125 (27)	0.426	21 (12)	123 (19)	0.049
NIHSS score – mean	14.4	10.0	0.006	20.9	15.7	< 0.001
Admission eGFR (mL/min)	68.6	77.0	0.033	79.3	78.4	0.853
Admission creatinine (mg/dL)	1.3	1.1	0.017	1.2	1.0	0.003
Contrast CT – N (%)	29 (52)	237 (40)	0.065	97 (57)	341 (52)	0.253
Stroke Subtype – N (%)						
Embolic	21 (29)	107 (23)	0.294			
Small Vessel	10 (14)	61 (13)	0.906			
Large Vessel	16 (22)	153 (34)	0.056			

	Ischemic Stroke			Intracerebral Hemorrhage		
	AKI	No AKI	p-value	AKI	No AKI	p-value
Cryptogenic	12 (17)	69 (15)	0.737			
Death – N (%)	24 (33)	46 (10)	< 0.001	68 (40)	200 (30)	0.020
Mean time to death (days)	13.6	7.6	0.030	8.1	2.7	< 0.001
Length of stay (days)	17.6	8.4	< 0.001	13.0	8.0	< 0.001

TABLE 2

Frequency of AKI and crude in-hospital mortality by stroke type

	Ischemic Stroke		Intracerebral Hemorrhage	
	Frequency – N (%)	Crude mortality – N (%)	Frequency – N (%)	Crude mortality – N (%)
No AKI	456 (86)	46 (10)	658 (79)	200 (30)
AKI				
Stage 1	57 (10)	19 (33)	135 (16)	48 (36)
Stage 2	7 (1)	2 (29)	24 (3)	14 (58)
Stage 3	8 (2)	3 (38)	12 (1)	6 (50)

TABLE 3

Odds ratios for AKI and in-hospital mortality

	Ischemic Stroke		Intracerebral Hemorrhage	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Model 1	4.46 (2.50–7.94)	<0.001	1.51 (1.07–2.14)	0.020
Model 2	3.88 (2.13–7.06)	<0.001	1.55 (1.09–2.21)	0.016
Model 3	3.36 (1.76–6.42)	<0.001	1.44 (0.99–2.08)	0.053
Model 4	3.08 (1.49–6.35)	0.002	0.82 (0.50–1.35)	0.437
Model 5	-	-	2.11 (1.18–3.77)	0.012

Model 1: AKI only

Model 2: Model 1 + age, gender, race

Model 3: Model 2 + history of atrial fibrillation, heart failure, stroke, TIA, hyperlipidemia, diabetes, current smoking, coronary artery disease, hypertension, CT angiography, admission creatinine

Model 4: Model 3 + NIHSS score

Model 5: Model 4 with subset analysis for length of stay > 2 days

TABLE 4

Predictors of AKI in either ischemic stroke or ICH

Variable	Odds Ratio (95% CI)	P-value
Baseline creatinine (per one mg/dL increase)	1.61 (1.22–2.12)	<0.001
NIHSS score (per 5 point increase)	1.13 (1.07–1.19)	<0.001
Smoking	0.57 (0.38–0.85)	0.006