Pre-Existing Renal Failure Increases In-Hospital Mortality in Patients with Intracerebral Hemorrhage

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Background: To determine the clinical outcome for intracerebral hemorrhage (ICH) patients with pre-existing renal failure in the United States. *Methods:* We analyzed the data from Nationwide Inpatient Sample (2008-2012) for all ICH patients with or without pre-existing renal failure. Patients were identified using the International Classification of Disease, Ninth Revision, Clinical Modification codes. Baseline characteristics, in-hospital complications, and exposure to invasive procedures were compared between groups. Discharge outcomes (mortality, minimal disability, and moderate-to-severe disability) were compared between the two groups, before and after adjusting for the presence of other medical comorbidities, in-hospital complications, and exposure to invasive procedures. *Results:* Of the 328,728 patients with ICH, 36,067 (11.8%) had pre-existing renal failure as a comorbidity. There were higher rates for in-hospital complications like myocardial infarction (3.5% versus 1.9%, $P \leq .0001$), sepsis (5.4% versus 3.0%, $P \leq .0001$), pneumonia (7.1% versus 5.3%, $P \leq .0001$), deep venous thrombosis (1.6% versus 1.2%, $P = .0041$), urinary tract infections (16.9% versus 15.1%, $P = .0101$), and gastrointestinal bleeding (0.4% versus 0.2%, $P \leq .0154$), longer hospital stay (9.4 ± 14.4 versus 7.7 ± 11.4; $P < .0001$), and higher mean hospital charges ($86497.9 ± 131708.1 versus $69583.4 ± 110629.1; $P < .0001$) in patients with pre-existing renal failure . The in-hospital mortality was also higher among patients with pre-existing renal failure as comorbidity in both univariate (26.4% versus 25.3 %, $P = .0010$) and multivariate analysis (odds ratio [OR] = 1.124 [1.042-1.213], $P = .0025$). There was no statistically significant difference for in terms of moderate to severe disability between 2 groups (OR = 1.030 [0.962-1.104], P value: .3953 in multivariate analysis when analysis was limited to alive patients. *Conclusions:* Patients with ICH, who present with pre-existing renal failure, have higher rates of in-hospital mortality but not for disability, the difference remained significant after adjusting for the presence of other medical comorbidities, in-hospital complications or exposure to invasive procedures.

Key Words: Renal failure— In-hospital mortality—Intracerebral hemorrhage—Nationwide Inpatient Sample (NIS)

Introduction

The prevalence of chronic kidney disease in the United States is about 10% among adults.[1] It is already known that patients with intracerebral hemorrhage (ICH) have a higher rate of acute renal failure as a hospital complication[2] and it also results in worse in-hospital outcome including increased mortality.[3] The incidence as well as the impact in clinical outcome of renal failure as a pre-

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existing comorbidity, in patients with ICH has not been studied. We studied the frequency and impact of renal failure as a pre-existing comorbidity on ICH clinical outcome in the United States.

Methods

We analyzed the data from Nationwide Inpatient Sample (2008-2012). A detailed description on National Inpatient Sample data is available at http://www.hcup-us.ahrq.gov.

The database contains information on patients' demographic and clinical characteristics, in-hospital procedures, hospital characteristics, and discharge outcomes. We used the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) primary diagnosis codes 431-432 to identify the patients admitted with ICH. Patients with renal failure were identified using variable "CM_RENLFAIL" from Agency for Health Research and Quality comorbidity data files. We divided ICH patients into 2 groups, with and without renal failure as comorbidity.

Study variables included patient, age, gender, race and/or ethnicity, and comorbidities, ie, hypertension, diabetes mellitus, congestive heart failure, coagulopathy, and alcohol abuse were also obtained from Agency for Health Research and Quality comorbidity data files. We used ICD-9-CM secondary diagnosis codes to identify other comorbidities such as atrial fibrillation (427.30 and 427.31), dyslipidemia (272.0-272.9), and nicotine dependence (305.1).

ICD-9 secondary codes were used to identity patients with ICH-associated complications such as pneumonia (486, 481, 482.8, and 482.3), urinary tract infection (590.0, 590,9), sepsis (995.91, 995.92, 996.64, 038, and 999.3), deep venous thrombosis (451.1, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, and 453.9), pulmonary embolism (415.1), myocardial infarction (410.0-410.9), and gastrointestinal hemorrhage (578) as used previously.[4]

We used ICD-9 procedure codes to determine the ICH patients who were exposed to invasive procedures such as cerebral angiography (88.41) tracheostomy (31.10, 31.21, or 31.29), mechanical ventilation (96.04, 96.70, 96.71, and 96.72), gastrostomy (431.1), and transfusion (99.04).

We determined the length of stay and hospital charges using the variables "length of stay and TOTCHG" from Agency for Health Research and Quality comorbidity data files. In NIS, discharge disposition was categorized as into routine, home healthcare, short-term hospital, against medical advice, and other facilities including intermediate and skilled nursing home or death. We categorized routine discharge, home healthcare, and against medical advice as none to minimal disability, and any other discharge as moderate to severe disability as described previously.[5]

Statistical Analysis

The SAS 9.4 software (SAS Institute, Cary, NC) was used to convert NIS database data into weighted counts to generate national estimates, following Healthcare Cost and Utilization Project recommendations. We performed univariate analysis, chi-square for categorical, and *t* test for continuous variables to identify differences in study variables and outcome end points between ICH patients with and without renal failure as comorbidity.

To assess the effect of renal failure on outcome of ICH patients, 2 logistic regression models were created. Model 1 included all patients, and logistic regression analysis was used to identify the association between renal failure as a pre-existing comorbidity and in-hospital mortality. Model 2 included patients who were discharged alive, and logistic regression analysis was used to identify the association between renal failure as pre-existing comorbidity and odds of moderate-to-severe disability. Logistic regression model was adjusted for age (as a continuous variable), sex (as a categorical variable), comorbidities (as a categorical variables), in-hospital complications (as a categorical variables), and in-hospital exposure to invasive procedures (as categorical variables that were significant ($P \leq .05$) in univariate analysis.

Results

Of 328,728 patients who were admitted for ICH; 36,067 (11.8%) patients had pre-existing renal failure. Patients with pre-existing renal failure were predominantly men (59.6% versus 49.4%, $P < .0001$). The proportions of patients with other comorbid conditions such as hypertension, diabetes mellitus, congestive heart failure, coagulopathy, chronic lung disease, and atrial fibrillation were significantly higher in those with pre-existing renal failure (Table 1). In-hospital complications such as pneumonia, deep venous thrombosis, urinary tract infection, sepsis, myocardial infarction, and gastrointestinal bleeding were also significantly higher in patients with pre-existing renal failure (Table 1). Patients with pre-existing renal failure were more likely to be exposed to invasive procedures such as, blood transfusion, gastrostomy tube placement, and mechanical ventilation. Length of stay (9.4 ± 14.4 days versus 7.7 ± 11.4 days; $P < .0001$) and mean hospital charges \$86497.9 ± 131708.1 versus \$69583.4 ± 110629.1; $P < .0001$) were also significantly higher in ICH patients with pre-existing renal failure (Table 1).

Patients with pre-existing renal failure had higher proportion of moderate to severe disability (48.5% versus 47.2%, $P < .0001$) and in-hospital mortality (26.4% versus 25.3%, $P = .0010$). The in-hospital mortality remained statistically significant after adjusting for age, gender, other medical comorbidities, in-hospital complications, and exposure to invasive procedures; odds ratio, 1.124; confidence interval, 1.042-1.213; $P = .0025$. However, when analysis was limited to alive patients, moderate to severe disability was

Table 1. *Demographic, clinical characteristics, in-hospital events, and outcomes of intracerebral hemorrhage patents with and without renal failure as a pre-exiting comorbidity in the United States (2008−2012)*

	ICH patients without renal failure as pre-exiting comorbidity	ICH patients with renal pre-exiting failure as comorbidity	*P* value
Number of patients	289,995	38,733	
Age (mean years ± SD)	68.6 (±16.0)	68.2 (±15.3)	.115
Women	146,722 (50.6)	15,653 (40.4)	<.0001
Race and/or ethnicity*			
White	169,285 (66.7)	17,758 (51.3)	<.0001
Black	39,512 (15.6)	9641 (27.8)	
Hispanic	22,938 (9.0)	3841 (11.1)	
Other	21,857 (8.6)	3339 (9.6)	
Medical comorbidities			
Hypertension	226,866 (78.2)	36,494 (94.2)	<.0001
Diabetes mellitus	69,872 (24.1)	17,788 (45.9)	<.0001
Congestive heart failure	24,271 (8.4)	9119 (23.5)	<.0001
Coagulopathy	18,106 (6.3)	3560 (9.2)	<.0001
Chronic lung disease	34,905 (12.0)	5742 (14.8)	<.0001
Alcohol abuse	18,502 (6.4)	1664 (4.3)	<.0001
Dyslipidemia	90,634 (31.2)	14,102 (36.4)	<.0001
Atrial Fibrillation	52,000 (17.9)	8099 (20.9)	<.0001
Nicotine dependence	32,888 (11.3)	3529 (9.1)	<.0001
In-hospital events			
Myocardial infarction	5411 (1.9)	1350 (3.5)	<.0001
Sepsis	8872 (3.0)	2081 (5.4)	<.0001
Pneumonia	15,470 (5.3)	2747 (7.1)	<.0001
Deep venous thrombosis	3404 (1.2)	623 (1.6)	0.0041
Pulmonary embolism	2170 (0.7)	227 (0.6)	0.0833
Urinary tract infection	43,887 (15.1)	6577 (16.9)	<.0001
Gastrointestinal bleeding	690 (0.2)	167 (0.4)	.0154
Procedures			
Tracheostomy	1107 (0.4)	136. (0.3)	.6660
Mechanical ventilation	84,883 (29.2)	12,336 (31.8)	<.0001
Gastrostomy	25,007 (8.6)	3809 (9.8)	.0007
Transfusion	10,092 (3.5)	3005 (7.7)	<.0001
Cerebral Angiography	23,793 (8.2)	1792 (4.6)	<.0001
Hospital bed size			
Small	18,762 (6.5)	2597 (6.8)	.5017
Medium	57,466 (20.1)	7899 (20.6)	
Large	209,822 (73.3)	27,676 (72.5)	
Hospital location and/or teaching status			

(*continued on next page*)

Table 1. (*continued*)

	ICH patients without renal failure as pre-exiting comorbidity	ICH patients with renal pre-exiting failure as comorbidity	*P* value
Rural	17,402 (6.1)	1978 (5.2)	.0020
Urban nonteaching	92,399 (32.3)	13,084 (34.3)	
Urban teaching	176,249 (61.6)	23,110 (60.5)	
Hospital charges ($) (mean 95% CL)	69583.4 ± 110629.1	86497.9 ± 131708.1	<.0001
Length of hospital stay (days) (mean 95% CI)	7.7 ± 11.4	9.4 ± 14.4	<.0001
Discharge disposition			
None to minimal disability	78,631 (27.1)	9594 (24.7)	<.0001
Moderate to severe disability	136,977 (47.2)	18796 (48.5)	
In-hospital mortality	73,336 (25.3)	10234 (26.4)	

Abbreviations: ICH, intracerebral hemorrhage.
Symbols used; *Race and/or ethnicity is not uniformly reported in all states.

Table 2. *Unadjusted and adjusted effects of renal failure as a pre-exiting comorbidity on outcomes of patients with intracerebral hemorrhage: Nationwide Inpatient Sample (2008−2012)*

Outcomes	Unadjusted OR (95% CI)	*P* value	Adjusted for age and gender OR (95% CI)	*P* value	Adjusted for age, gender, and potential confounders* OR (95% CI)	*P* value
Analysis comprising all patients						
In-hospital mortality	1.061 (1.005-1.119)	.0314	1.067 (1.011-1.126)	.0191	1.124 (1.042-1.213)	.0025
Analysis comprising alive patients						
None-to-minimal disability	Reference	Reference	Reference	Reference	Reference	Reference
Moderate-to-severe disability	1.125 (1.061-1.192)	<.0001	1.114 (1.050-1.183)	.0004	1.030 (0.962-1.104)	.3953

Abbreviations: CI, confidence interval; OR, odds ratio.
*Race and/or ethnicity, hypertension, diabetes, atrial fibrillation, dyslipidemia, congestive heart failure, chronic lung disease, nicotine dependence, alcohol abuse, in-hospital complications (myocardial infarction, pneumonia, sepsis, urinary tract infections, deep venous thrombosis, and gastrointestinal bleeding) in-hospital stroke related procedures (mechanical ventilation, transfusions, gastrostomy, and cerebral angiography).

not statistically significant between the two groups (odds ratio, 1.030; 95% confidence interval, 0.962-1.104; $P = .3953$).

Discussion

In our study, we found pre-existing renal failure in 11.8% of patients with ICH, and patients with pre-existing renal failure were more likely to have other medical comorbidities, in-hospital complications and were more likely to be exposed to invasive procedures. The in-hospital mortality but not disability was higher among patients with pre-existing renal failure. In our knowledge, this is the only study where national estimates are provided of renal failure in this patient cohort. This is clinically relevant since presence of pre-existing renal failure is not typically taken into account as a prognostic marker for ICH. This may warrant prospective studies to further evaluate this association.

In general, it is already known that cardiovascular disease-related mortality and morbidity is high among patients with all stages of chronic kidney disease.[6]The interaction between different coagulation system components (coagulation cascade, platelets, and vessel wall) is markedly disturbed in patients with renal failure.[7] Platelets dysfunction occurs due to intrinsic platelets abnormalities and impaired vessel wall interaction in uremic environment.[8] Proteinuria in renal failure patients leads to loss of endogenous anticoagulants like antithrombin, protein C, and protein S which leaves the coagulation pathway unchecked, resulting in thrombosis in deep veins and arteries throughout the body.[9] In our study, patients with ICH and renal failure had higher rate of coagulopathy and deep venous thrombosis. In addition, coagulopathy may also worsen ICH, thereby affecting the clinical outcome.

In our study, high rate of in-hospital mortality related to renal failure can be explained by several other reasons. Patients with renal failure had higher rate of other medical comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, chronic lung disease, and congestive heart failure. This high comorbidity burden can lead to more in-hospital complications in these patients, such as pneumonia, deep venous thrombosis, urinary tract infection, sepsis, myocardial infarction, and gastrointestinal bleeding. The higher rates of adverse outcomes may also be related to increased procedure-related complications these patients typically receive during hospitalization. In our analysis, however, the odds of in-hospital mortality of patients with ICH and renal failure remained statistically significant after adjustment with medical comorbidities, in-hospital complications, and exposure to invasive procedures.

Our study was performed using a nationally representative data set that is free of biases introduced by patient demographics and local institutional practices.[3] ICD-9-CM primary diagnosis codes 431-432 for ICH have 85% sensitivity, 96% specificity, and positive predictive value of 89%[11] thereby improving the overall diagnostic certainly for the analysis. Our study was able to categorize disability based on discharge destination. A previous study found that discharge destination strongly correlates with modified Rankin Scale at 3 and 12 months.[10] We acknowledge that payer preference and social situation may also have also affected discharge disposition. However, in our multivariate analysis model with alive patients, we did not find statistically significant association.

Our study is observational, based on NIS dataset and limitations are similar as previously described in analysis of this dataset.[11] We do not know the exact impact of interfacility transfer on ICH admission counts in our dataset. The redundant counting of hospital admissions for ICH patients is unlikely because most transfers occur from the emergency to another hospital, and NIS data do not count emergency department visit before transfer as an event.[3] In addition, an important limitation of NIS dataset is that it lacks several specific and important variables, ie, Glasgow coma scale at presentation, ICH volume at presentation, hematoma progression, location of ICH infratentorial versus supratentorial, intraventricular extension, mass effect on imaging studies that impacts in-hospital mortality and morbidity. Future prospective studies can be conducted in this regard taking into account these specific variables.

Conclusions

Pre-existing renal failure seems to be an important comorbidity in patients with ICH, a prognostication marker of in-hospital mortality. Future prospective studies should be conducted to confirm our findings to further evaluate this association.

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