



Original Article

Effect of comorbidities on ischemic stroke mortality: An analysis of the National Inpatient Sample (NIS) Database

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ABSTRACT

Background: Stroke risk has been attributed to many pathological and behavioral conditions. Various modifiable and non-modifiable risk factors have been recognized and found consistent throughout epidemiological studies. Herein, we investigate the effect of comorbidities seen with patient's suffering from ischemic stroke and its effect on in-hospital mortality.

Methods: We identified patients >18 year old in the National Inpatient Sample database with diseases of interest utilizing the tenth International Classification of Disease 10 diagnostic codes from the years 2016 to 2018. Interval data were analyzed using one-way ANOVA. *Post hoc* analysis was performed using Bonferroni correction methods. To determine independent predictors of in-hospital mortality, odds ratios were calculated using binary logistic regression for each comorbidity. Descriptive and numerical statistics, imputation, and logistic regression were calculated using SPSS software version 25.

Results: Patients hospitalized with ischemic stroke were found to have the following comorbidities: atrial fibrillation (7.5%), carotid artery stenosis (1.1%), diabetes mellitus type 2 (11.4%), congestive heart failure (CHF) (7.5%), essential hypertension (21.2%), and ischemic heart disease (IHD) (2.3%). In-hospital mortality rates were higher in patients hospitalized with ischemic stroke and concomitant IHD (28.2%, $P < 0.001$). Hospital length of stay was longest in patients with concomitant CHF (5.96 days, $P < 0.001$). Similarly, patients with CHF accrued the greatest in-hospital costs (69,174 USD, $P < 0.001$).

Conclusion: Patients hospitalized from ischemic stroke suffered from the coexistence of other comorbidities. Of the comorbidities studied, IHD was identified as having the most significant impact on in-hospital mortality.

Keywords: Atrial fibrillation, Carotid artery stenosis, Congestive heart failure, Diabetes mellitus, Ischemic heart disease

INTRODUCTION

Stroke is a major cause of death and disability with serious economic and social consequences. Every year more than 795,000 people have a stroke in the United States (US) alone, with 87% of cases attributed to ischemic stroke.^[10] In the US, it was estimated that between 2014 and 2015 the total yearly stroke-related cost was nearly \$46 billion, which included the cost of health care services, missed days of work, and medicines needed to treat stroke.^[10] Projections estimate that by 2030 an additional 3.4 million US adults 18 years of age or older will have had a stroke, a

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20.5% increase in prevalence from 2012. Notably, the highest increase is projected to be in Hispanic males.^[10]

Although stroke mortality has been declining over the past few decades due to the introduction of modern treatments, it still remains the fifth leading cause of death in the US, accounting for an estimated 150,000 deaths/year.^[4,8,10] Moreover, mortality among females is higher accounting for 58% of stroke deaths in 2017 and an estimated 55,000 more females than males dying per year.^[1,10] This could be partly due to a larger number of elderly females than males.^[10] Stroke mortality has also proven geographical distinctions throughout the US, regions recognized as the “stroke belt” and “stroke buckle,” have carried approximately 30% and 40% higher mortality rates, respectively, when compared to the rest of the nation.^[10] Stroke is also considered the third leading cause of disability worldwide and was among the top 18 diseases in the US contributing to years lived with disability in 2010.^[5,8,10] Consequently, it is estimated that more than one-third of stroke survivors become dependent in one or more activities of daily living.^[2]

Stroke risk has been attributed to many pathological and behavioral conditions. Although direct causality is difficult to assign given that most patients suffer from multiple comorbidities at once, various modifiable and non-modifiable risk factors have been recognized and found consistent throughout epidemiological studies.^[1,10] Modifiable risk factors include, but are not limited to hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia, atrial fibrillation (AFIB), sedentary lifestyle, smoking, obesity, peripheral artery disease, carotid artery disease, and alcohol consumption. The non-modifiable risk factors are relatively few and include age, gender, genetics, ethnicity, and race.^[1,10,11] Racial disparities in stroke are well-documented and are it known that the risk of stroke is nearly doubled for African Americans when compared to Caucasians, whom also have a higher mortality associated with stroke.^[10] Although mortality rates have fallen among every race and ethnicity as previously mentioned, there is a notable exception to the Hispanic population in whom death rates attributed to stroke have seen an increase since 2013.^[10]

It is estimated that up to 90% of all strokes are caused by behavioral risk factors, making stroke highly preventable.^[2] In addition, the Heart Disease and Stroke Statistics 2020 Update reported that 29% of the global risk of stroke was attributed to air pollution.^[10]

The National Inpatient Sample (NIS) is a large database that is maintained under the Healthcare Cost and Utilization Project (HCUP), which is both considered the largest collection of longitudinal hospital care data in the US and sponsored by the Agency for Healthcare Research and Quality (AHRQ).^[3] Maintained under the AHRQ since

1988, the NIS is recognized as the largest publicly available all-payer inpatient healthcare database and has been allowing access to a surplus of data for accurate trending on associated analyses over time.^[3,6] The NIS draws data from all states participating in HCUP, which represents approximately 97% of the US population, including individuals both covered and uncovered by Medicare, Medicaid, and private insurance. Ideal for longitudinal analyses, data include clinical and nonclinical elements for each hospitalization as well as hospital characteristics [Table 1]. The NIS was redesigned in 2012, switching from a sample of hospitals to a sample of discharges, therefore prompting current users to utilize revised weights to perform accurate analyses.^[3,6] Furthermore, beginning with data year 2016, the NIS included data with diagnosis and procedure codes reported using the International Classification of Diseases (ICD)-10 Clinical Modification/Procedure Coding System.^[3] Herein, we delineate the use of the NIS database in ischemic stroke patients as we aim to investigate the effect of common comorbidities seen with patient’s suffering from ischemic stroke and its effect on in-hospital mortality.

MATERIALS AND METHODS

Using the NIS database, we identified patients >18 years old with diseases of interest utilizing the tenth ICD-10 diagnostic codes from the years 2016 to 2018. To better account for national estimates, our sample data were weighted using the provided discharge weights from the NIS database. This weighting scale provides a sample of discharges from all hospitals nationally within the HCUP. Patients diagnosed with ischemic stroke were identified using the ICD-10 code

Table 1: List of available data in the NIS database.^[3,6]

Patient demographics	<ul style="list-style-type: none"> • Sex • Age • Race • Location of patient’s residence • Median household income for zip code • Primary and secondary diagnoses† • Disease severity • Comorbidities
Hospitalization characteristics	<ul style="list-style-type: none"> • Emergency department access • Elective versus nonelective admission • Discharge status • Hospital identifiers • Procedures performed† • Length of stay • Mortality
Hospital charges	<ul style="list-style-type: none"> • Primary expected payer • Total charges††

NIS: National inpatient sample, †ICD-10-CM diagnoses, ICD-10-PCS procedures, ††include emergency department charges but exclude professional fees, noncovered charges, and outpatient costs

of interest listed as the first primary diagnosis, indicating a primary diagnosis at hospital discharge. Comorbidities of interest were identified using the subsequent three diagnosis codes following the primary diagnosis code. [Table 2] provides the ICD-10 codes used to identify patients of interest for this analysis. Cases that presented with more than one comorbidity were excluded from this study.

Demographic data in the form of gender, age, and race were collected for analysis from the NIS database. Patient outcomes were evaluated using data from the NIS database including length of stay, total health-care costs billed during hospitalization, and in-hospital mortality. In-hospital mortality is defined as patients dying during hospitalization. Charges accrued during hospital stay did not include professional fees and noncovered charges. If the total charges provided included professional fees, then professional fees were subtracted from the total charge during HCUP processing.

[Table 3] provides missing data encountered during this analysis. Of the six demographic variables provided by the NIS database, five variables were missing data, and zero variables were missing more than 5% of the original data. Imputation of missing data was completed using the mean of nearby values in the original dataset. After, imputation techniques were employed to complete the data set, results of this analysis were calculated. Interval data were analyzed using one-way ANOVA. *Post hoc* analysis was performed using Bonferroni correction methods. To determine independent predictors of in-hospital mortality, odds ratios were calculated using binary logistic regression for each comorbidity. Descriptive

and numerical statistics, imputation, and logistic regression were calculated using SPSS software version 25 (IBM Corp., Armonk, New York, USA). We present continuous variables as mean with standard deviation and odds ratios with the 95% confidence interval. Approval of this study by institutional review board was not required due to its retrospective design with de-classified data.

RESULTS

A total of 1,441,230 hospitalizations were identified with ischemic stroke between 2016 and 2018. 126,215 cases were excluded from this study due to multiple comorbidities reported. 1,315,015 cases were included in this study: about 50.8% female and 49.2% male with a mean age of 69.9 ± 14.4 years. Patients hospitalized with ischemic stroke were found to have the following comorbidities: AFIB (7.5%), carotid artery stenosis (CAS) (1.1%), DM type 2 (DM2) (11.4%), congestive heart failure (CHF) (7.5%), essential HTN (21.2%), and ischemic heart disease (IHD) (2.3%). [Table 4] provides demographic, in-hospital cost, and mortality data for each individual comorbidity of interest found in patients hospitalized with ischemic stroke.

[Table 5] displays the one-way ANOVA and *post hoc* analysis for hospital length of stay, total in-hospital charges, and mortality for the comorbidities studied. In-hospital mortality rates were higher in patients hospitalized with ischemic stroke and concomitant IHD (28.2%, $P < 0.001$). Hospital length of stay was longest in patients with concomitant CHF (5.96 days, $P < 0.001$). Similarly, patients with CHF accrued the greatest in-hospital costs (69,174 USD, $P < 0.001$).

[Table 6] presents odds ratios of mortality from common comorbidities seen with ischemic stroke. Comparing the present comorbidities, concomitant IHD was the strongest independent predictor of mortality in patients with ischemic stroke (OR = 5.16 [5.03–5.31], $P < 0.001$), followed by AFIB (OR = 2.48 [2.428–2.525], $P < 0.001$), and CHF (OR = 1.97 [1.93–2.01], $P < 0.001$). Essential HTN demonstrated the weakest odds ratio but still qualified as a significant independent predictor of mortality in patients with ischemic stroke.

DISCUSSION

Patients suffering from ischemic have variable mortality rates depending on modifiable and non-modifiable risk factors.

Table 2: ICD-10 codes for diseases investigated in this study.

Diagnosis	ICD-10 Code
Ischemic stroke	I63
AFIB	I48
CAS	I652
DM2	E11
CHF	I50
Essential HTN	I10
Chronic IHD	I25

ICD: International classification of diseases, AFIB: Atrial fibrillation, CAS: Carotid artery stenosis, DM2: Diabetes mellitus type 2, CHF: Congestive heart failure, HTN: Hypertension, IHD: Ischemic heart disease

Table 3: Missing data.

		Age in years at admission	Length of stay (cleaned)	Total charges (cleaned)	Indicator of sex	Died during hospitalization	Race (uniform)
N	Valid	1314980	1314945	1304895	1314735	1315015	1271785
	Missing	35	70	10120	280	0	43230
	%	0.002662	0.005323	0.775542	0.021297	0	3.399159

Table 4: Demographic data.

	AFIB (n=98505)	CAS (n=14795)	DM2 (n=149295)	CHF (n=98675)	HTN (n=278420)	IHD (n=30005)
Age*	78.76 (10.5)	69.6 (13.3)	69.0 (12.4)	73.1 (13.7)	67.2 (13.5)	71.8 (12.8)
Gender (Female)	55230	6540	73190	49780	139970	11415
Race						
White	76370 (77.5%)	11125 (75.2%)	87500 (58.6%)	62415 (63.3%)	178885 (64.3%)	22470 (74.9%)
Non white	22135 (22.5%)	3670 (24.8%)	61795 (41.4%)	36260 (36.7%)	99535 (35.7%)	7535 (25.1%)
Length of Stay (Days)*	4.61 (4.14)	4.23 (5.77)	4.66 (5.78)	5.96 (6.53)	3.42 (3.60)	3.89 (3.53)
Total charges (USD)*	54642.2 (53836.0)	58939.8 (61114.3)	53846.5 (56497.0)	69174.0 (81575.2)	44689.3 (42476.6)	49522.7 (48587.8)
Died during hospitalization	15640 (15.9%)	1550 (10.5%)	14025 (9.4%)	12860 (13.0%)	22775 (8.2%)	8475 (28.2%)

*Continuous variables presented as mean (SD), ICD: International classification of diseases, AFIB: Atrial fibrillation, CAS: Carotid artery stenosis, DM2: Diabetes mellitus type 2, CHF: Congestive heart failure, HTN: Hypertension, IHD: Ischemic heart disease

Table 5: One-way ANOVA and *post hoc* analysis results.

	P-value	Post hoc analysis
Hospital length of stay	P<0.001*	Patients found to have congestive heart failure noticed the most significant increase in in-hospital length of stay during hospitalization for ischemic stroke.
Total charges	P<0.001*	Patients found to have congestive heart failure noticed the most significant increase in in-hospital costs during hospitalization for ischemic stroke.
Died during hospitalization	P<0.001*	Patients found to have ischemic heart disease noticed the most significant increase in in-hospital mortality following ischemic stroke.

*Significant P-value

Table 6: Logistic regression analysis results for mortality following ischemic stroke.

Medical comorbidities	Odds ratio	Confidence interval (95%)		P-value
		Upper	Lower	
AFIB	2.476	2.428	2.525	<0.001
CAS	1.535	1.455	1.620	<0.001
DM2	1.360	1.334	1.387	<0.001
CHF	1.966	1.925	2.007	<0.001
HTN	1.169	1.150	1.188	<0.001
IHD	5.164	5.027	5.305	<0.001

AFIB: Atrial fibrillation, CAS: Carotid artery stenosis, DM2: Diabetes mellitus type 2, CHF: Congestive heart failure, HTN: Hypertension, IHD: Ischemic heart disease

These risk factors increase susceptibility to ischemic as well as a variety of pathologic comorbidities that may put patients at

increased risk for stroke mortality. Our results indicated that in individuals with ischemic stroke, mortality is over 5 times higher when concomitant IHD is present, significantly higher than the other comorbidities studied. In addition, we found that in individuals suffering from ischemic stroke, mortality is roughly 1.2 times higher when individuals have pre-existing HTN, the lowest increase in mortality of the comorbidities studied. Despite these findings, however, we found that both the length of stay and total in hospital charges were lowest and second lowest in HTN and IHD, respectively.

The relationship between relatively short length of stay and increased odds of mortality as seen in patients with ischemic stroke suffering from concomitant IHD supports previous research.^[7] Regarding the increased odds of mortality seen in patients suffering from a combination of stroke and IHD, this is because the two conditions share many overlapping, identifiable risk factors. To suffer from either IHD or stroke increases the odds of experiencing another ischemic event significantly. The relationship between these two conditions is bidirectional as each predisposes individuals for the other. Based on our results and previous research, IHD and stroke can be said to behave in a synergistic fashion. Moreover, it is commonly understood that HTN is the leading risk factor for stroke.^[9] However, stroke itself is not a risk factor for HTN. As such it makes sense, based on our results, to understand the increased odds of mortality seen with stroke and preexisting IHD stem from the overlapping risk factors shared by the two conditions and the compounding effect these risk factors have on one another. Contrarily, the unidirectional relationship between HTN and stroke contributes to a relatively lower increase in mortality. Thus, the directionality between two concomitant conditions, such as IHD and stroke or HTN and stroke, must be taken into consideration when determining severity of patients' prognoses.

This study is limited by the inherent nature of retrospective study design and database review. The large sample size of the data collected, however, decreases likelihood of results being produced by confounding variables or chance. The NIS database consists of patient data strictly from US hospitals. Although the sample size is sufficient for interpretation, the outcomes and relationships displayed in our findings may not necessarily apply to other populations. In addition, the database accuracy is relied on heavily when patients are admitted for hospitalization. As such, it is possible that reporting error and misclassification biases existed within databases relying on patient sourcing.

With these factors in mind, it is important to notice that conditions such as AFIB, CAS, DM2, and CHF present in patients experiencing stroke all yielded somewhat similar increase in odds of in-hospital mortality. Further research is needed to evaluate the risk factors shared between these individual conditions and risk factors for ischemic stroke. In addition, the relationships between these risk factors may be further classified (e.g. causal, overlapping, and synergistic).

CONCLUSION

In patients hospitalized from ischemic stroke, the coexistence of other comorbidities – AFIB, CAS, DM2, CHF, HTN, and IHD notably increases the odds of in-hospital mortality. Of the comorbidities studied, IHD made the most significant impact on mortality. Less impactful was AFIB, CHF, CAS, and DM2; the least impactful was HTN. It is possible that the degree of overlap between risk factors of ischemic stroke also plays a large role in the morbidity and mortality. Increased risk factors for ischemia, whether in the context of ischemic stroke or another disease, should be taken into consideration when monitoring and treating patients in the outpatient setting. Further studies evaluating and classifying the relationships between risk factors of various cardiovascular diseases are needed.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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