Predictors for Hemorrhagic Transformation among Patients with Ischemic Stroke Admitted in a Tertiary Hospital in the Philippines from July 2018-July 2019

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ABSTRACT

Background. Among the multiple scoring systems for hemorrhagic transformation, only few of these address spontaneous hemorrhagic transformation after an ischemic stroke, with most done with Western population data.

Objectives. This study aims to identify the predictors for hemorrhagic transformation among patients with ischemic stroke admitted in a tertiary hospital in Cebu City, Philippines.

Methods. This is a retrospective cohort study of patients with ischemic stroke admitted in a tertiary hospital in Cebu City. Patients' baseline characteristics, clinical, and radiologic data were collected. Chi square test and t-test were used to determine which variables were significantly different between patients with and without hemorrhagic transformation. Odds ratio (OR) and 95% confidence interval (CI) were determined to measure the association between the different variables and hemorrhagic transformation.

Results. A total of 500 ischemic stroke patients were included in the study. There were 28 (6%) ischemic stroke patients with Hemorrhagic Transformation. The mean age of these patients is 66.93 ± 12.42 years, 48.8% male, 10.8% had atrial fibrillation, and 2.4% had myocardial infarction. Controlling for the effect of confounders, white blood cell count (OR 1.11; 95% CI 1.03-1.19), myocardial infarction (OR 5.25; 95% CI 1.13-24.34), and presence of brain edema (OR 2.86; 95% CI 1.05-7.80) were significant predictors of hemorrhagic transformation.

Conclusion. White blood cell count, presence of brain edema, and myocardial infarction were significantly associated with hemorrhagic transformation among ischemic stroke patients.

Keywords: ischemic stroke, hemorrhagic transformation, predictors, Philippines

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INTRODUCTION

Cerebrovascular disease is divided into two major categories: 1) hemorrhagic stroke which results from the rupture of a cerebral blood vessel; 2) ischemic stroke which results from the occlusion of a cerebral blood vessel.[1] The goal of treatment for ischemic stroke is to restore blood flow to the ischemic area with thrombolytic therapy. The cerebral vasculature becomes more friable due to ischemia which leads to a high rate of hemorrhagic transformation (HT) following infarction and thrombolysis. HT after different types of thrombolytic therapy is frequently reported; however, it is important to note that HT also occurs as part of the evolution of a cerebral infarct.[2] There are a few prognostic scores for identifying patients with high risk of HT that have

been proposed to apply in the clinical setting. These include the HAT (Hemorrhage After Thrombolysis) score, SEDAN (baseline blood Sugar, Early infarct signs, hyperdense cerebral artery signs, Age, NIH Stroke Scale) score, GRASPS (Glucose, Race, Age, Sex, systolic blood Pressure, stroke Severity) score, SPAN 100 (Safe Implementation of Treatments in Stroke score and Stroke Prognostication using Age and NIH Stroke Scale 100), and the HeRS (Hemorrhagic Risk Stratification) score. These models were developed based on a Western population and found that age, NIHSS score, blood glucose or diabetes, demographic characteristics (race, gender, weight), hypertension, or systolic blood pressure, platelet count, previous antiplatelet medication, onset to treatment time and early CT signs, were predictors of HT.[3] The HeRS score, in particular, which is a valid predictor for HT, included a retrospective cohort of ischemic stroke patients. The scoring system used univariate analysis for each predictor of interest. Covariates that were significant in univariate analysis or thought likely to be clinically significant (either as primary predictors or confounders) were evaluated using multivariable regression. The HeRS score identified age, infarct volume, and EGFR as predictors for HT.[4] In a Chinese-based population, risk factors for HT included age, NIHSS score, systolic or diastolic blood pressure, serum glucose level, previous antiplatelet treatment, atrial fibrillation, and previous stroke history.[3]

There are multiple scoring systems that predict systemic hemorrhage in patients taking anticoagulants; however, few addresses HT after an ischemic stroke, and these are mostly based on a Western Population.[5]

The objective of this study is to identify predictors for HT in the local setting, which may be different from that of the Western population. Specifically, the objectives are:

1. To determine the predictors for HT among ischemic stroke patients admitted in a tertiary hospital in Cebu City from July 2018 to July 2019.
2. To determine the percentage of HT in patients with ischemic stroke.
3. To determine and compare the following variables between those with HT and those without among ischemic stroke patients:
   A. Demographic data
   B. Clinical Data
   C. Radiologic data

Review of Related Literature

In the Philippines, stroke is the second leading cause of death. Ischemic stroke comprises 70% of all stroke cases.[6] Hemorrhagic transformation, which refers to a spectrum of ischemia-related brain hemorrhage, is a frequent complication of ischemic stroke. HT may occur spontaneously as part of the natural history of ischemic stroke or secondary to thrombolytic therapy. It may be asymptomatic or symptomatic causing significant morbidity and death. The incidence of spontaneous HT ranges from 38% to 71% in autopsy studies and from 13% to 43 % in CT scan, whereas the incidence of symptomatic HT is from 0.6% to 20%.[7] HT may also be classified as to the timing of occurrence. Early HT occurs within the first 18 to 24 hours of stroke onset and delayed HT occurs after 18 to 24 hours of stroke onset. HT can be divided into hemorrhagic infarction (HI) and parenchymal hematoma (PH). On CT scan, HI is seen as a heterogeneous hyper-density occupying a portion of an ischemic infarct zone, while PH is seen as a homogeneous dense hematoma with mass effect.[7] The relationship between clinical outcome and radiographic hemorrhage has been consistent with PH. Hemorrhagic infarction were not associated with worsened outcomes. Healthcare providers should weigh the risk of worsening ischemia against the risk for hematoma expansion. Careful consideration should be given to the risk and benefit of starting antithrombotic therapy after hemorrhagic transformation.[8]

The blood brain barrier is formed by endothelial cells and the tight junctions in between them.[9] After the onset of cerebral ischemia, levels of ATP decrease, disrupting the activity of the Na^+-K^+ ATPase pump present in the blood brain barrier. A series of cellular and metabolic imbalances occur which subsequently leads to a disruption of the blood brain barrier. Due to its disruption and the impairment of the autoregulatory capacity of the cerebral vasculature, once ischemic tissue is re-perfused, there is extravasation of the blood.[10] An improved understanding of the predictors of HT is essential to reduce its impact on patients with ischemic stroke. There have been studies conducted to identify them; however, they were mostly done in the Western setting.

Age has been identified as an independent risk factor for HT in patients with cerebral embolism.[11]

Hypertension was a significant risk factor for post-alteplase intracranial hemorrhage. Elevated systolic blood pressure measured 24 hours after thrombolysis significantly increased risk for HT.[11]

Hyperglycemia in patients with acute ischemic stroke is the strongest predictor for symptomatic intracerebral hemorrhage, death, and poor outcome after 90 days in patients treated with intravenous alteplase. Hyperglycemia induces a pro-oxidative, pro-inflammatory, and procoagulant state.[11] Hyperglycemia aggravates hypoxia and malnutrition of the artery wall resulting in a blood vessel that is more prone to degeneration and necrosis.[7]

Glomerular Filtration Rate (GFR), measuring overall kidney function, is a predictor for HT. Renal dysfunction increases platelet dysfunction and induces abnormal platelet-vessel wall interaction. Impaired kidney function also increases the risk for hemorrhagic microangiopathy which may eventually lead to cerebral hemorrhage.[12]

Atrial fibrillation is associated with higher volumes of more severe baseline hypoperfusion leading to greater infarct growth, more frequent severe HT, and worse stroke outcomes.[7] Among the different types of ischemic stroke, cardioembolic stroke has been linked to the highest frequency for HT.[11]

The National Health Institute Stroke Score is a powerful predictor of larger infarcts and HT, and is composed of: 1) level of consciousness, 2) ability to answer question, 3) best gaze, 4) vision, 5) facial palsy, 6) motor function of both arms and legs, 7) limb ataxia, 8) sensory deficits, 9) best language, 10) dysarthria, 11) extinction and inattention.[7]

Cholesterol plays a major role in maintaining the integrity of small vessels. Low cholesterol levels may reduce the blood vessel's ability to resist rupture and thus increasing risk for HT, independent of thrombolytic therapy.[13]

The decreased overall number of platelets available for activation and aggregation increases the risk of HT.[7]

In a study by Marsh et al., having a large stroke with coexisting medical illness may be the greatest predictor of HT. Leukocytosis may indicate an upregulated inflammatory state in the setting of ischemia or a coexisting medical disorder.[5]

Higher INR and APTT values were associated with a more intense degree of anticoagulation. This was more likely to result in hemorrhage that was more severe. However, in a study by Marsh et al., there was no association between increased INR and HT.[5]

An elevated globulin level is a risk factor for HT in patients receiving thrombolytic therapy because of an elevated level of inflammatory cytokines and positive acute phase reactants synthesized by the liver.[7]

Albuminuria is a marker of chronic endothelial damage and is thus an independent predictor of HT.[7]

Patients with massive cerebral infarction leads to cerebral edema. Edematous brain tissue compresses peripheral vasculature and causes increasing permeability of the vessel walls. This subsequently increases the chance of HT after reperfusion and once cerebral edema resolves.[7]

HT often occurs in the gray matter due to the presence of collateral circulation, which tends to worsen reperfusion injury. Gray matter infarction is also associated with large artery occlusion and massive cerebral edema, which causes ischemic injury to the surrounding blood vessels. In contrast, white matter infarction is usually of the lacunar type.[7] In addition, ischemic stroke located in the posterior circulation was associated with a lower risk of spontaneous HT, compared to anterior circulation stroke. This may be due to the smaller size of infarction in the posterior area.[14]

The use of antiplatelet therapy 24 hours after thrombolysis is contraindicated since this is associated with a significantly increased risk for symptomatic ICH. However, antiplatelet therapy prior to thrombolysis should not be a consideration against thrombolysis. Despite the increased frequency of symptomatic ICH in patients who received antiplatelet therapy prior to thrombolysis, this was also associated with a more favorable outcome after thrombolysis. This may be due to improved rates of arterial recanalization with prior antiplatelet therapy.[11] Thrombolytic treatment under dual antiplatelet therapy, Aspirin and Clopidogrel, increases the risk of HT. In a study by Lieshke et al., in the absence of Recombinant Tissue Plasminogen Activator (rt-PA), dual antiplatelet therapy increased HT non-significantly; however, with rt-PA administration, dual antiplatelet therapy results in significant hemorrhage.[15]

The use of oral anticoagulants, especially in the presence of a large cardioembolic stroke, significantly increased the risk of symptomatic intracerebral hemorrhage. Thus, starting anticoagulation after an acute ischemic stroke should be delayed for several days, when the blood-brain barrier permeability is more stable.[11]

The incidence of HT depends on the thrombolytic agent used, the route of administration, and the time window allowed for initiation of therapy. Intravenous rt-PA is the most effective treatment for acute ischemic stroke; however, approximately 6% of all stroke cases treated with intravenous rt-PA, experience a hemorrhagic conversion.[7] Data on the different thrombolytics show that the rate of HT is associated with the dose of the thrombolytic rather than the type of thrombolytic. The intra-arterial route of administration of thrombolytics was associated with a higher rate of HT compared to the intravenous route. This may be attributed to the higher drug concentration in the area of the occluded vessels when given via the intra-arterial route. Delayed recanalization of MCA (> 6 hours) was associated with an increased risk of parenchymal hemorrhage. This suggests that the prolonged state of arterial occlusion could lead to more severe vascular endothelial damage and lower tolerability for reperfusion.[11]

METHODS

Study design

This is a retrospective cohort study of records of adult patients admitted at a tertiary hospital in Cebu City from July 2018 to July 2019, who were diagnosed with ischemic stroke and had HT based on CT scan or MRI of the brain findings.

Study population

The study population included records of all patients admitted at a tertiary hospital in Cebu City, diagnosed with ischemic stroke using imaging modalities and subsequently had HT during the same admission.

Inclusion Criteria

This study included the following:

1. Patients >18 years old admitted at a tertiary hospital in Cebu City from July 2018- July 2019.
2. Patients with a diagnosis of ischemic stroke during admission and had brain imaging done.

Exclusion Criteria

Patients who initially presented with hemorrhagic stroke or transient ischemic attack were excluded from this study.

Sample Size

A retrospective study done last 2018 by Ong, in a tertiary hospital in Cebu City, showed that out of 2546 patients with ischemic stroke admitted from 2013 to 2016, 90 (3.53%) had HT. Of these, 48 of the 90 patients (53.33%) had atrial fibrillation. The odds ratio of 5.14 HT in patients with atrial fibrillation was calculated. It was estimated that a sample size of at least 496 patients with ischemic stroke, with at least 87 of whom are diagnosed to have atrial fibrillation, will be enough to test the hypothesis at 80% power with a two-sided confidence interval of 95%.[16]

Data Collection

The study was implemented upon approval of the protocol by the Hospital Institutional Review Board and the Office of the Medical Director.

The monthly census of the hospital's Internal Medicine Department was reviewed. Patients with a final diagnosis of Cerebrovascular Disease Infarct with and without HT were included in the study. Patients with a diagnosis of hemorrhagic stroke or transient ischemic stroke were excluded from this study. Through review of the patient's medical records, laboratory results, and brain imaging results, the following data were gathered: age, blood pressure, weight, height, presenting signs and symptoms, initial capillary blood glucose, HbA1c, CBC, INR, APTT, creatinine, sulfonylurea use, cholesterol, presence of atrial fibrillation and myocardial infarction, antithrombotic therapy (loading dose, dual anti-platelet therapy, timing of antithrombotic therapy), initial brain CT or MRI reading, transcranial doppler, carotid doppler, and MRA. The HT noted on brain imaging was categorized as hemorrhagic infarction or parenchymal hematoma.

Data Analysis

Descriptive analysis of the distribution of patients with HT and predictors of HT of ischemic stroke were determined. Mean and standard deviation were used to describe the continuous variables while frequency and percentage were used to describe the categorical variables. Chi square test and t-test were used to determine which characteristics or variables were significantly different when comparing patients with and without HT. A p-value of less than 0.05 was used to determine if the variables had a significant difference between those with HT and those without HT. Multiple logistic regression analysis was used to control for confounders. Odds ratio and 95% confidence interval were used to determine the association between the significant variables with that of HT.

Ethical Considerations

The protocol was submitted to the Ethics Review Board for review and approval. All the information gathered remained confidential and were used exclusively for this research.

RESULTS

There were 500 ischemic stroke patients admitted in a tertiary hospital in Cebu City from July 2018 to July 2019 that were included in the study. There were 28 ischemic stroke patients (6%) with HT. Table 1 shows the demographic and clinical characteristics of the ischemic stroke patients admitted. The mean age was 63.46 ± 13.12 years and ranges from 20 to 99 years old. There were 48.8% males and 99.2% were Filipinos.

Table 2 shows the baseline characteristics of patients diagnosed with ischemic stroke. The baseline characteristics were not statistically different between patients diagnosed with ischemic stroke with and without HT with p-value of not less than 0.05.

Table 3 shows the clinical predictors of HT in patients diagnosed with ischemic stroke. Using t-test and chi square test, there was a significant difference between ischemic stroke patients with and without HT when it comes to leukocytosis, atrial fibrillation, and myocardial infarction with a p-value of less than 0.05.

Table 4 shows the radiologic predictors of HT in patients diagnosed with ischemic stroke. Comparing patients diagnosed with ischemic stroke with and without HT, the presence of brain edema, lacunar infarct, and cardioembolic infarct, were different between the two groups, with p-value of less than 0.05.

Table 5 shows the multiple logistic regression analysis of clinical and radiologic predictors of HTs among ischemic stroke patients. Controlling for the effect of confounders, white blood cell count, myocardial infarction, and presence of edema were significant predictors of HT. Patients with ischemic stroke and myocardial infarction were five times more likely to develop HT. Patients diagnosed with ischemic and had brain edema on imaging studies were three times more likely to develop HT. Ischemic patients with lacunar infarct are less likely to develop HT - OR of 0.18 (95% CI 0.04-0.82).

Of the 28 patients with HT, 15 patients had hemorrhagic infarction and 13 patients had parenchymal hematoma.

DISCUSSION

This study included data retrieved from records of patients admitted at a tertiary hospital in Cebu City from July 2018 to July 2019 and included several variables which could predict the incidence of HT.

In our cohort of patients with ischemic stroke, 28 patients or 6% of ischemic stroke patients, showed evidence of HT.

Clinical Predictors of Hemorrhagic Transformation

Based on our study of ischemic stroke patients, the presence of brain edema, elevated white blood cell count, and myocardial infarction were significant predictors of

Table 1. Demographic and Clinical Characteristics of Patients Diagnosed with Ischemic Stroke with and without Hemorrhagic Transformation

Characteristics	No. / Mean	% / SD
***Age** (years)*	63.46	13.32
Sex		
Female	256	51.2
Male	244	48.8
Ethnicity		
American	2	0.4
Filipino	496	99.2
German	2	0.4
***Weight** (kg)*	64.71	12.58
***BMI** (kg/m^2)*	25.01	4.18
HbA1c[a]	6.68	1.80
High	210	42.0
Low	9	1.8
Normal	190	38.0
Prior Statin Use	148	29.7
Atrial Fibrillation	54	10.8
Myocardial Infarction	12	2.4
Initial Capillary Blood Glucose[a]	147.74	66.95
Sulfonylurea Use	0.18	0.38
INR[a]	1.14	1.82
APTT[a]	28.86	4.38
WBC	9.95	5.05
Hematocrit	39.98	5.96
Platelet Count	249.11	90.95
Creatinine	1.33	1.28
EGFR	67.24	25.00
Total Cholesterol[a]	182.61	52.05
LDL Cholesterol[a]	114.42	46.18
Dual Antiplatelet	119	23.9

[a] *Data may not be available for all patients*

Table 2. Baseline Characteristics of Patients Diagnosed with Ischemic Stroke with and without Hemorrhagic Transformation

Baseline Characteristics	No Hemorrhagic Transformation (n=472)		Hemorrhagic Transformation (n=28)		p-value
	No. / Mean	(%) / SD	No. / Mean	(%) / SD	
***Age** (years)*	63.26	13.36	66.93	12.42	0.157
Sex					0.300
Female	239	93.4%	17	6.6%	
Male	233	95.5%	11	4.5%	
Ethnicity					0.887
Caucasian	2	100.0%	0	0.0%	
Filipino	468	94.4%	28	5.6%	
German	2	100.0%	0	0.0%	
BMI	25.00	4.17	25.22	4.53	0.791

Table 3. Clinical Predictors of Hemorrhagic Transformation in Patients Diagnosed with Ischemic Stroke

Clinical Data	No Hemorrhagic Transformation		Hemorrhagic Transformation		p-value
	No. / Mean	(%) / SD	No. / Mean	(%) / SD	
Systolic Blood Pressure	146.64	31.285	138.85	27.628	0.207
Diastolic Blood Pressure	85.41	16.054	84.04	12.802	0.663
WBC	9.68	3.79	14.50	14.02	0.001
Hematocrit	40.00	5.89	39.71	7.14	0.808
Platelet Count	250.11	90.04	232.54	105.50	0.321
EGFR	67.18	25.42	68.21	17.12	0.831
Total Cholesterol	183.41	52.18	169.91	49.35	0.228
LDL Cholesterol	114.98	45.99	105.09	49.51	0.330
Atrial Fibrillation	43	79.6%	11	20.4%	0.001
Sulfonylurea Use	85	95.5%	4	4.5%	0.617
Prior Statin Use	140	94.6%	8	5.4%	0.891
Pre-admission Antithrombotic	145	92.9%	11	7.1%	0.346
Myocardial Infarction	9	75.0%	3	25.0%	0.003
HbA1c	6.71	1.812	6.22	1.476	0.202
HbA1c					0.217
Normal	175	92.1%	15	7.9%	
Low	8	88.9%	1	11.1%	
High	203	96.7%	7	3.3%	

HT. This study differed from previous studies and scoring systems, because it showed that leukocytosis and myocardial infarction were predictors for HT.

Cerebral Edema

In this study, the presence of brain edema is a significant predictor of HT with a p-value of 0.003. Patients with significant brain edema were three times more likely to develop HT. These results are similar to the study done by Zhang et al., wherein edematous brain tissue compresses peripheral vasculature and increases vessel wall permeability, subsequently increasing rates of HT.[7] A limitation of this study is that the size of infarction is not routinely measured and encoded in the official brain CT scan reports.

Area of Infarction

Based on our study, patients with lacunar infarct are less likely to develop HT. Our results are similar to the study of Zhang et al., in which white matter infarction, usually of the lacunar type are less likely to be associated with HT.[7]

Leukocytosis

Leukocytosis with a mean WBC count of 14.5 X 10^3/ uL, was significantly associated with HT, as shown on this

Table 4. Radiologic Predictors of Hemorrhagic Transformation in Patients Diagnosed with Ischemic Stroke

Radiologic Data	No Hemorrhagic Transformation		Hemorrhagic Transformation		p-value
	No. / Mean	(%) / SD	No. / Mean	(%) / SD	
Lesion Side					0.101
Both	139	97.2%	4	2.8%	
Left	125	90.6%	13	9.4%	
Right	139	94.6%	8	5.4%	
Presence of Brain Edema	39	84.8%	7	15.2%	0.003
Lacunar Infarct *(presence of lacunar infarct on CT scan)*	171	98.8%	2	1.2%	0.002
Atherothrombotic Stroke *(Presence of significant stenosis based on TCD or MRA)*	113	92.6%	9	7.4%	0.171
Cardioembolic Stroke *(AF or other embolic sources)*	54	83.1%	11	16.9%	0.001

Table 5. Multiple Logistic Regression Analysis of Clinical and Radiologic Predictors of Hemorrhagic Transformations among Ischemic Patients

	OR	95% CI	p-value
WBC	1.11	1.03 - 1.19	0.005
Atrial Fibrillation	4.54	0.83 - 24.77	0.080
Lacunar Infarct	0.18	0.04 - 0.82	0.027
Cardioembolic Stroke	1.29	0.23 - 7.08	0.770
Myocardial Infarction	5.25	1.13 - 24.34	0.034
Presence of Brain Edema	2.86	1.05 - 7.80	0.040

study. In a study done by Jickling et al., ischemic stroke elicits a robust activation of the immune system, with leukocytes adhering to the vascular endothelial cells within 30 minutes of stroke onset. Leukocyte adhesion and migration across the cerebral vasculature and increases blood brain barrier permeability.[8]

Myocardial Infarction

In our study, patients with myocardial infarction were five times more likely to develop HT after ischemic stroke. This association may be related to the treatment of myocardial infarction, which usually requires dual antiplatelet and anticoagulant therapy. In a study by Marsh et al, having a large stroke with coexisting medical illness may be the greatest predictor of HT.[5] After myocardial infarction, a pro-inflammatory response is noted, including an increase in leukocytes and activation of reactive oxygen species. In a study by Jickling et al., an increase in ROS production can disrupt the neurovascular unit through damage of endothelial cells, pericytes, smooth muscle cells, and astrocytes, leading to an increase in blood brain barrier permeability.[8]

CONCLUSION

The predictive value of cerebral edema, elevated white blood cell count, and myocardial infarction needs to be considered in the context of clinical management of patients with acute ischemic stroke. Therefore, in patients with massive cerebral edema, it is very important to perform cranial CT scan or MRI regularly, regardless of whether the clinical symptoms worsen or improve. In addition, it is important to monitor for leukocytosis and symptoms of myocardial infarction during the patient's admission. When the patient has cerebral edema, leukocytosis, or myocardial infarction, it is necessary to choose the treatment plan carefully, especially with respect to thrombolytic therapy.

Statement of Authorship

SMSI contributed in the acquisition and analysis of data, and drafting and revising of manuscript. MTAC contributed in the conceptualization of work and final approval of the version to be published.

Author Disclosure

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