Risk Factors and Mechanism of Hemorrhagic Transformation of Acute Ischemic Cerebral Infarction

ABSTRACT

A feared complication of ischemic cerebrovascular accident (CVA) is hemorrhagic transformation and it increases the length of hospital admissions, results in poor clinical outcomes and increases mortality. This study aims to identify risk factors of hemorrhagic transformation, discuss the pathogenesis of transformation and prognosis of the condition from original studies conducted within the past 10 years. PubMed and EMBASE are the major databases used. Eight articles met the inclusion criteria and are a mixture of retrospective and prospective studies. The sample size ranges from 32 to 1484 patients. Generally, the mechanism of hemorrhagic transformation identified involves the release of reactive oxygen species and metalloproteinase as a result of cerebral ischemia. Metalloproteinase further causes a breakdown of the extracellular matrix, thereby giving rise to the extravasation of cellular components. Some identified risk factors include: age, use of antithrombotic, the subtype of ischemic stroke, the severity of stroke and hypertension. Prognosis is linked to the type of hemorrhagic infarctions according to the European Cooperative Acute Stroke Study II (ECASS II) with patients with either hemorrhagic infarct type 2 (HI2) and parenchymal hematoma type 2 (PH2) having the worst functional outcome.

Keywords: [Hemorrhagic transformation; Acute ischemic cerebral infarction; Cerebrovascular accident; Risk factors]

1. INTRODUCTION

Acute Ischemic Stroke (AIS) accounts for over 60% of cerebrovascular accidents, which is still a leading cause of mortality in the US and globally [1, 2]. In the US alone, the incidence rate of stroke is 795 000 per year, with an estimated mortality of 1 in every 19 deaths as of 2018 [1]. Although there has been a general decrease in trends for age-standardized rates in the last three decades due to improved quality of care and health, for the most part, its socioeconomic impact cannot be ignored [3, 4].

Hemorrhagic transformation (HT) is one of the interesting phenomena in the series of biochemical events that occur following AIS. It is found in approximately 3-40% of AIS and it is thought to be associated with worsening neurological outcomes [5]. HT is the first sign of hemorrhage immediately after an ischemic event typically occurring within 2 weeks, however, it can be detected radiologically as a hypodense area as early as 5 hours post AIS [6]. “It can be classified according to the European Cooperative Acute Stroke Study II (ECASS II)” [7] , as follows;

1. Hemorrhagic infarction type 1 (HI1) - Petechial hemorrhages at the infarct margins.
2. Hemorrhagic infarct type 2 (HI2) - Petechial hemorrhages throughout the infarct.
3. Parenchymal hematoma type 1 (PH1) - <30% of the infarcted area with slight space occupying effect.

4. Parenchymal hematoma type 2 (PH2) - >30% of infarct zone with significant space occupying effect due to hematoma.

AIS can occur secondary to underlying haematological conditions such as polycythemia vera, sickle cell disease, and essential thrombocythemia. These account for 1.3% of all causes of acute stroke [8]. In addition to current public health measures addressing the modifiable risk factors, improved scoring systems and stroke care, more research is needed for the better understanding of the risk factors and the mechanism of transformation to prevent and improve outcomes. In this review, we will focus on the risk factors for hemorrhagic transformation (HT), mechanism of transformation and its prognosis from original studies conducted within the past 10 years.

2. METHODOLOGY

2.1 Search Strategy

Using specified search terms, EMBASE and PubMed (MEDLINE), we searched two major databases. Search terms used on the Medline database are "Hemorrhagic Transformation Of Cerebrovascular Accident"[Mesh] OR "Hemorrhagic Transformation Of Stroke"[Mesh] And "Risk Factors" [Mesh]. These terms were combined using the Boolean operators (AND, OR). The search terms used for EMBASE are Hemorrhagic transformation and ischemic cerebrovascular disease.

2.2 Study Selection

Studies were selected according to the criteria:

1. Population: Studies focusing on patients with hemorrhagic transformation of ischemic cerebrovascular accidents.

2. Exposure: The risk factors that can result in hemorrhagic transformation in people with ischemic cerebrovascular accidents.

3. Condition or outcome(s) of interest: The primary outcome is to determine the risk factors of hemorrhagic transformation of ischemic cerebrovascular accidents. The secondary outcome is to explore the mechanism of transforming an ischemic cerebrovascular accident into a hemorrhagic cerebrovascular accident.

4. Study design and context: Eligible studies are observational studies and clinical trials.

2.3 Inclusion Criteria:

1. All articles written in English.

2. Articles related to the objectives of the study.

3. Original studies.

4. Articles that met the above criteria and are within the past 10 years (2012-2022).

2.4 Exclusion Criteria:

1. Not original studies (e.g. review, systematic review, and commentary articles)
2. Articles not written in English.
3. Articles not related to the objectives of the study
4. Articles more than 10 years.

2.5 Data Collection and Study Assessment

Four authors (AO, GA, AU, and CC) independently reviewed the abstracts of all the articles identified. Articles adopted were based on the inclusion criteria. The adopted papers were screened, and a spreadsheet was created to include all the proposed articles to be used for this study. All authors were involved in the final selection process.

2.6 Data Synthesis

This was done in a clear and detailed descriptive summary of the studies, including using a summary table. All authors were responsible for reviewing and discussing major identified themes in the study.

3. RESULTS

After applying the inclusion & exclusion criteria, eight articles were eligible to be included in the review (see Table 1). Out of the eight articles reviewed, there were two prospective studies [8,9], five retrospective studies [6,10–13], and one was both a prospective and retrospective study [14]. The studies were carried out in various countries, such as the China [9,11–14], United States [13], United Kingdom [10], Germany [10], Italy [8], and the Republic of Korea [6]. The sample size of the participants ranged from 32 patients to 1484 patients. The studies were conducted on both genders. The eight articles reviewed discussed the risk factors of acute ischemic stroke while four articles described the pathogenesis/mechanism of transformation.

Table 1: Summary of the characteristics of included articles

Author/year	Title	Country	Study design	Study Population/ Sample size	Risk Factors	Pathogenesis/Mechanism of Transformation
1. Hirata Y et al, 2021	Cerebral Microbleeds With Atrial Fibrillation After Ablation Therapy	China	Prospective study	68 patients	Catheter ablation in patients with atrial fibrillation is at higher risk of developing cerebral microbleeds.	NA
2. Kim et al, 2021	Short-term glycemic variability and	Republic of Korea	Retrospective	169 patients were included in	Time-related glycemic variation (GV)	1. Dysglycemia causes an increased damage

	hemorrhagic transformation after successful endovascular thrombectomy		study	the final analysis- 28 patients had a definite atrial fibrillation, 30 patients had probable atrial fibrillation, 111 patients had no atrial fibrillation.	during the first 36 h after successful endovascular recanalization therapy has a stronger correlation with symptomatic intracranial hemorrhage (ICH) and poor functional outcomes compared to any GV parameters. This suggests that maintaining stable glucose may be an important factor in the prevention of ICH after undergoing successful endovascular thrombotomy.	to blood brain barrier (BBB), thereby increasing the risk of HF and aggravates the degree of hemorrhage after reperfusion. 2. Fluctuating glucose has a more deleterious effect on endothelial function and oxidative stress in the brain tissues compared to constantly elevated glucose levels, which gives rise to metabolic dysregulation and secondary brain injury by accelerating microvascular injury.
3. Wei et al, 2021	Development and Validation of a Predictive Model for Spontaneous Hemorrhagic Transformation After Ischemic Stroke	China	Retrospective & Prospective study	Retrospective cohort: 245 patients Prospective cohort 1: 539 patients Prospective cohort 2: 200 patients	1.Age 2. History of diabetes mellitus and atrial fibrillation 3. High NIHSS score 4. Hypertension 5. hypodensity greater than one-third of the middle cerebral artery territory 6. Midline shift 7. hyper dense artery sign	Di 1. BBB disruption is the primary pathophysiology of HT. Reactive oxygen species and matrix metalloproteinases are activated by cerebral ischemia, reperfusion damage, neuroinflammation, and vascular remodeling, which are the typical molecular processes underlying HT. 2. After receiving reperfusion

						treatment, HT might develop according to a few distinct causes. The direct toxicity of alteplase and alteplase-associated coagulopathy may accelerate HT following intravenous thrombolysis.
4. Lin et al, 2021	Fibrinogen Level Combined With Platelet Count for Predicting Hemorrhagic Transformation in Acute Ischemic Stroke Patients Treated With Mechanical Thrombectomy	China	Retrospective study	135 acute ischemic stroke (AIS) patients who had undergone mechanical thrombectomy (MT) And recanalization within 24 hours of symptom onset	Lo1. Lower baseline fibrinogen levels and platelet counts were associated with HT in AIS patients with anterior circulation large-vessel occlusion after MT. 2. The risk of HT after MT can be predicted by a fibrinogen level less than 2.165g/L with a platelet count of less than 171.5 × 109/L.	NA
5. Yuan S et al, 2021	Serum Occludin Level Combined with NIHSS Score Predicts Hemorrhage Transformation in Ischemic Stroke Patients With Reperfusion	China, United States	Retrospective study	76 patients	In this study, it was found that the indicator of BBB damage (serum occludin) and stroke severity (baseline NIHSS score) were independent risk factors of	NA

					HT using multivariate regression analysis	
6. D'Anna L et al, 2021	Extent of white matter lesion is associated with early hemorrhagic transformation in acute ischemic stroke related to atrial fibrillation	United Kingdom, Germany	Retrospective study	441 patients were included in the analysis.	1. Age 2. Presence of large infarct 3. Use of anticoagulants before the stroke 4. Severe neurologic deficit 5. Congestive heart failure 6. Hyperglycemia 7. Renal impairment 8. Low platelet count 9. Elevated systolic blood pressure 10. Use of reperfusion therapies	NA
7. Ruan Y et al, 2021	High fibrinogen-to-albumin ratio is associated with hemorrhagic transformation in acute ischemic stroke patients	China	Retrospective study	256 HT patients and 256 non-HT patients with AIS	High fibrinogen-to-albumin ratio (FAR)	Inflammation has been considered as an important cause of the blood–brain barrier (BBB) disruption, which may directly lead to HT. It suggested that FAR level is positively correlated with HT and high FAR was independently associated with the

						increased risk of HT.
8. Inzitari D et al, 2013	MMP9 Variation After Thrombolysis Is Associated With Hemorrhagic Transformation of Lesion and Death	Italy	Prospective study	327 patients with acute ischemic stroke. (mean age, 68.9±12.1)	Increased level of MMP9. .	Tissue-type plasminogen activator (tPA) may enhance expression and activity of MMPs, particularly matrix metalloproteinase-9 (MMP9). MMP antagonists administered to animals treated with tPA lower the risk of HT and reduce infarct volume.

NA = Not applicable

4. DISCUSSION

4.1 Risk Factors and Mechanisms of Hemorrhagic Transformation

4.1.1 Age

"The majority of studies on age as a risk factor for HT are focused on patients who have had a stroke and have received fibrinolytic therapy" [10,14,15]. "A meta-analysis of 55 studies identified older age as a factor associated with an increased risk of post-alteplase intracerebral hemorrhage" [16]. "The association with age is also consistent with other studies showing that individuals over the age of 80 who receive intravenous tPA may be at increased bleeding risk" [10,14,15,17,18].

4.1.2 Serum Biomarkers

4.1.2.1 Matrix Metalloproteinases: They are zinc-binding proteolytic enzymes which remodel the extracellular matrix [19]. The metalloproteinases 2 and 9 as well as leukocytes are released from the vascular endothelium [8,19]. Cerebral ischemia triggering neuroinflammation and vascular remodeling causes activation of reactive oxygen species and matrix metalloproteinases [8]. The Metalloproteinases attacks fibronectin, collagen type IV and laminin, causing a breakdown of the extracellular matrix and this allows extravasation of plasma and cellular components [8,19].

4.1.2.2 Fibrinogen: It is an important component in the coagulation cascade and thus a biomarker for bleeding [20]. "In conditions of coagulation or fibrinolytic disorders, bleeding is likely to occur. Lin et al discovered that lower baseline fibrinogen levels was associated with an elevated risk of HT after mechanical thrombolysis, they also demonstrated the independent effects of reduced fibrinogen levels on hemorrhagic complications of acute ischemic stroke" [11]. Wang et al described that "fibrinogen less than 1.50g/L was a risk

factor for hemorrhagic transformation after thrombolysis" [21]. Yan et al also found that "early decrease in fibrinogen levels was associated with symptomatic intracranial hemorrhage after reperfusion therapy with thrombolysis, with or without endovascular thrombectomy" [22].

4.1.2.3 Albumin: It has an inverse relationship to the development of early onset neurological complications [12]. Albumin has anti-inflammatory, anti-oxidative and anti-apoptotic properties and is known to predict endothelial dysfunction which is the major mechanism in hemorrhagic transformation [12]. Albuminuria has been seen to be associated with increased risk of HT in patients with acute ischemic stroke [23], as the presence of albuminuria in the first urine sample gotten from patients with acute ischemic stroke has shown to be an independent risk factor for hemorrhagic transformation of cerebral infarction [23]. Rodriguez-Yanez et al demonstrated that "albuminuria increases the risk of hemorrhagic transformation by eightfold and the degree of albuminuria was associated with the severity of hemorrhagic transformation" [23].

4.1.3 Hyperglycemia

Dysglycemia and increased glycemic variability has been linked to increased risk of transformation of ischemic cerebrovascular accidents. This is due to increased inflammation from release of pro-inflammatory cytokines, apoptosis and cytotoxic oedema [6,10] . Hyperglycemia in patients with acute ischemic stroke has been associated with the risk of HT after intravenous treatment with alteplase [24] as well as after intra-arterial treatment with prourokinase [25]. A report from the Canadian Alteplase for Stroke Effectiveness Study (CASES) [26] documented persistent hyperglycemia at baseline and at 24 hour as the strongest predictor of symptomatic intracerebral hemorrhage [27]. The detrimental effects of hyperglycemia in the setting of acute ischemic stroke are thought to be due to a pro-oxidative, pro-inflammatory, and procoagulant state induced by elevated blood glucose [23]. Fluctuating blood glucose is more deleterious than persistently elevated glucose due to metabolic dysregulation and worsening microvascular injury [6].

4.1.4 Antithrombotic (antiplatelets and anticoagulants)

When starting antithrombotic medication after an ischemic stroke, it is critical to identify patients who are at risk for even asymptomatic spontaneous HT. As antithrombotics (either antiplatelets or anticoagulants) might cause silent hemorrhages to expand and lead to neurological deterioration, recording the existence and type of HT on imaging has crucial therapeutic implications for when to start these secondary preventive therapies [28].

4.1.4.1 Antiplatelet agents: In a trial of intra-arterial thrombolysis with prourokinase, aspirin usage was linked to a slight increase in the frequency of HT in patients undergoing thrombolytic treatment [25,29]. "In the National Institute of Neurological Disorders and Stroke NINDS rt-PA trial, the use of antiplatelet medications (mainly aspirin) was not related to an increase in the frequency of symptomatic intracerebral hemorrhages in individuals treated with intravenous alteplase" [30].

According to studies, using aspirin and clopidogrel together before a stroke increases the incidence of symptomatic intracerebral hemorrhage after receiving intravenous alteplase [27,31]. "In the SITS-ISTR (Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register) research, the aspirin–clopidogrel combination was found to have a higher rate of symptomatic intracerebral hemorrhage (13.4%) than either treatment alone" [31].

4.1.4.2 Anticoagulants: **"**The use of oral anticoagulants significantly increased the risk of symptomatic intracerebral hemorrhage in a meta-analysis of clinical trials, which assessed

the efficacy and safety of anticoagulant treatment in acute cardio embolic stroke, whereas the rates of death and disability were similar to those of other antithrombotic treatments" [32] . "Because the use of oral anticoagulants is linked to an increased risk of symptomatic intracerebral hemorrhage, particularly in the presence of large infarcts, the administration of oral anticoagulants after a brain infarction should be delayed for several days [32] in the hopes of promoting the stabilization of the blood-brain barrier and reducing the risk of delayed HT" [32].

4.1.5 Ischemic Stroke Subtypes

According to the TOAST criteria [33], ischemic stroke subtypes were classified as cardioembolic, atherothrombotic, small vessel occlusion, and cryptogenic. Cardioembolic stroke has been associated with the highest frequency of HT among the subtypes of ischemic stroke, with 5% of embolic strokes show hemorrhagic infarction on an early Computerized Tomography, and an additional 10% become hemorrhagic after several days [34]. This tendency for HT is increased when cardioembolism causes substantial arterial occlusion and collateral flow failure. HT is exceptionally rare in cases of small vessel occlusion and lacunar stroke [32] .

4.1.6 Recanalization of Occluded Arteries

"Spontaneous or thrombolysis-induced recanalization of main stem cerebral arteries within a few hours after acute ischemic stroke may lead to a good clinical outcome [35]. However, the beneficial effect obtained by thrombolysis-induced recanalization may be counteracted by an increased risk of hemorrhagic transformation (HT)" [35] . Molina et al., reported that "delayed recanalization occurring 6 hours after symptom onset, independently predicts HT in patients with acute cardioembolic stroke" [35]. "They also reported that transcranial doppler-documented early (<6 hours) recanalization of middle cerebral artery occlusion was associated with the improved functional outcome despite the development of hemorrhagic transformation, whereas late (>6 hours) recanalization was followed by increased rates of symptomatic intracerebral hemorrhage" [35] .

The intra-arterial route of thrombolytic administration is associated with an increased rate of HT compared with the intravenous route, although the predictive factors might be similar (37). Among the factors that increase the risk of HT in intra-arterial thrombolysis are post-procedure evidence of contrast extravasation on CT [37], a higher number of micro-catheter injections (39), and a higher dose of heparin used during the procedure [39].

4.1.7 Stroke Severity

There is a strong relationship between the infarct volume and hemorrhagic transformation. The National Institute of Health Stroke Scale (NIHSS) score has been shown to be a significant predictor unit in assessing the infarct volume [15] and as at such the NIHSS score serves as a rough guide in estimating stroke severity, and in predicting bleeding transformation of acute ischemic stroke [13]. NIHSS score of zero means no stroke symptoms, 1 to 4 means minor stroke, 5 to 15 means moderate stroke, 16 to 20 means moderate or severe stroke, and 21 to 42 means severe stroke [40]. It has been shown that patients with a NIHSS score less than10 had less than 13% rate of HT in comparison with patients who had NIHSS score greater than 15 having more than 50% rate of HT [41]. Findings from Yuan et al showed that stroke severity (baseline NIHSS score) was an independent risk factor of hemorrhagic transformation of acute ischemic stroke [13].

4.1.8 Hypertension

The effect of hypertension on the risk of HT was documented in EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial), a study of intravenous alteplase thrombolysis within 3 to 6 hour of stroke onset [42].

Factors significantly associated with increased risk of HT included a large infarct on diffusion weighted imaging MRI at baseline and elevated systolic blood pressure 24 hours after treatment [42]. High blood pressure has been related to intracranial hemorrhage after rtPA for ischemic stroke in both experimental and clinical settings [43], and an association of baseline systolic blood pressure with PH underscores the importance of thorough management of blood pressure in patients who are given rtPA [14].

4.1.9 Advanced MRI Parameters

MRI is more sensitive than CT for detection of HT after acute ischaemic stroke, [44, 45] especially with inclusion of the gradient echo sequence, which is highly accurate in detection of blood products. Arnould et al, with use of 1·5T MRI, reported high accuracy of the gradient echo sequence for detection of HT after thrombolytic treatment compared with CT and with fluid-attenuated inversion recovery (FLAIR) and spin-echo MRI Sequences [44].

Multiple studies have reported the diagnostic performance of magnetic resonance imaging (MRI) for prediction of hemorrhagic transformation in acute ischemic stroke [46–48]. Conventional MRI using FLAIR sequences, as well as advanced MRI protocols including perfusion-weighted imaging (PWI) (dynamic susceptibility-weighted [T2-weighted (T2-W)]) imaging and dynamic contrast-enhanced [T1-weighted] imaging) and diffusion-weighted imaging (DWI) have shown promising results. In particular, T2-W imaging can sensitively reveal hemorrhagic events of a mild degree in ischemic stroke.

Suh et al discovered that hemorrhagic transformation of ischemic stroke is associated with high permeability, hypoperfusion, low apparent diffusion coefficient (ADC), and FLAIR hyperintensity [49]. They also demonstrated that high blood-brain barrier permeability and low cerebral blood volume (CBV) derived from PWI were associated with hemorrhagic transformation of ischemic stroke. It has been shown that MRI PWI offers several advantages in the prediction of hemorrhagic transformation due to its high contrast-to-noise ratio, ability to capture the entire spectrum of acute ischemic stroke from multiple small foci to the larger vascular territory, and no ionizing radiation [49].

A meta-analysis demonstrated that presence of cerebral microbleeds and high cerebral microbleeds burden on pretreatment MRI were independently associated with symptomatic intracerebral hemorrhage in patients with acute ischemic stroke treated with intravenous thrombolysis [50]. Another study reported that microbleeds on susceptibility-weighted imaging (SWI) showed a significant association with hemorrhagic transformation [51]. Therefore, hemorrhagic transformation is also probably associated with the presence of cerebral microbleed and high cerebral microbleeds burden.

4.1.10 Others

In patients not treated with alteplase, the only independent predictor of HT identified in a prospective study was the detection of focal hypodensity on computed tomography (CT) performed early (within five hours) after symptom onset [44]. The presence of focal hypodensity was associated with subsequent HT in 77% of cases, and its absence predicted the absence of HT in 94% of cases [44]. In the NINDS rt-PA trial using the Alberta Stroke Programme Early CT Scale (ASPECTS) imaging tool, patients with an ASPECTS score of seven or less (showing extensive hypoattenuation of the parenchyma) did not show a

significant increase in symptomatic intracerebral hemorrhage [45]. It should be noted that hemorrhagic transformation of ischemic stroke is almost never seen in acute lacunar stroke. This can be explained from the fact that Lacunar stroke occurs due to occlusion of a small cerebral vessels that supply a small area in the brain [55].

5. PROGNOSIS

Hemorrhagic transformation of CVA has a worse outcome compared to ischemic CVA without it. Some studies have been able to find an association between the subtypes of hemorrhagic transformation and functional outcome. A study conducted by Van Kranendock et al, revealed that more than half of patients(66%) studied with symptomatic intracranial hemorrhages died [46]. An intracranial hemorrhage is considered symptomatic if the patient had clinical deterioration resulting in an increase of less than 4 or more points on National Institute of Health Stroke Scale (NIHSS) [35]. Patients with PH2 and HI2 were said to have the worst functional outcome. Also a large volume infarct has been linked with worse functional outcome [35].

5. CONCLUSION

This study elucidated risk factors associated with hemorrhagic transformation of acute ischemic stroke, and its pathogenesis. We demonstrated that interplay of various factors was involved in the hemorrhagic transformation of ischemic stroke. Although ischemic stroke is known to have a high morbidity, this study has shown that hemorrhagic transformation increases the morbidity and as well as mortality of patients who have ischemic stroke.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Omotola Akinade, Gabriel Alugba, Chidinma Chukwudum, Alexsandra Urhi, Gibson Anugwom designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript and reviewed and made the necessary edits. Adewale Mark Adedoyin, Obiamaka Pamela Okereke, Abimbola Eunice Arisoyin wrote the protocol, managed the analyses of the study and wrote the first draft of the manuscript. Ojali Ruth Unedu, Adeyinka Aladejare, Aduwa Obosakhi, Funmilola Babalola, Ayobami Adesuyi, Favour David, Benedicta Kolajo managed the literature searches, wrote the first and second draft of the manuscript. All authors read and approved the final manuscript.

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