**Study of Clinico radiological Profile and Serum**

**Calcium levels in patients of Haemorrhagic Stroke:**

**Case control study**

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**INTRODUCTION**

**INTRODUCTION**

 Stroke is defined by the World Health Organization as ‘a clinical syndrome which is characterized by the rapidly developing clinical signs of focal disturbance of cerebral function (in case of coma – global) which lasts more than 24 hours or leads to death with no apparent etiology other than vascular origin.1 Globally, the second major cause of mortality and the third most important cause of disability is stroke. One of the major etiologies of dementia and depression among the elderly is stroke as well. With the aging population, there has been a concomitant rise in the number of stroke cases. Moreover, in the developing countries and under-developed countries, young stroke results in premature death and loss of Disability Adjusted Life Years (DALYs). The mortality and morbidity profile of stroke is highly variable across countries due to various ethnicities and geographical factors. 2

 According to the Stroke Atlas by the WHO, each year, 15 million individuals each year are affected by stroke. Of all those who are affected, 5 million have permanent residual disability and another 5 million die. This results in increased economic burden on the affected family and the nation. Stroke among individuals less than 40 years of age is mostly due to elevated blood pressure. The most common modifiable risk factors for stroke are smoking and high blood pressure.

 The incidence of cerebrovascular diseases is more on the decline among developed nations. This is mostly due to better awareness among individuals and control of risk factors such as hypertension and tobacco use. However, globally there is an absolute increase in the number of cases is on the rise due to the increase in proportion of geriatric individuals. The DALYs lost due to stroke is expected to increase from 38 million in 1990 to as high as 61 million DALYs in the year 2020 worldwide3.

 The impact of stroke is especially more severe among the low and middle-income countries such as India. All over the world, 70% of the stroke cases and 87% of mortality due to stroke and loss of DALYs occur in developing countries. Among these nations, there has been a two-fold rise in the incidence of stroke. During the same time period, the incidence of stroke has come down by 42% among the developed countries. Among the developed countries, there has been a reduction in the intracerebral hemorrhagic strokes compared to ischemic strokes. During the same time period, the incidence and proportion of hemorrhagic stroke among the under developed and developing nations have remained the same. The age of onset of stroke is 15 years earlier in developing and under-developed countries. The mortality due to stroke is higher among these countries as well. This implies that stroke among developing nations affects individuals during their most productive years and hence imposes a huge burden on the family economy4.

The increasing incidence of stroke among the developing countries is due to multiple factors. The theory of ‘population change’ is most commonly used to explain the changes in incidence of stroke5. This postulates that developing and under-developed countries are undergoing a major health transition. The improved case finding and advances in health care technologies might have contributed to the apparent increase in the number of cases of stroke. But the increase in cerebrovascular diseases parallels with the rise in the incidence of cardiovascular risk factors. The developing countries are adopting a westernized lifestyle consisting of a diet which has lesser quantities of fruits and vegetables along with increased fat and salt, increased trends of smoking, elevated blood pressure and raised blood sugar levels along with a sedentary life style. With this changing lifestyle factors, there is a concomitant increase in the incidence of cardiovascular and cerebrovascular diseases over the past few decades. This implies that unless stringent measures are implemented for the control of such risk factors, the burden of cerebrovascular diseases will be on the rise6.

 Intracerebral hemorrhagic stroke is increasing in incidence worldwide accounting for 15 million cases each year. There is an increase in hospitalization for hemorrhagic stroke by 18% in the past decade. This is mostly due to the increasing incidence of hypertension, advancing age, poor control of blood pressure, increasing use of anticoagulants and antiplatelet drugs. Despite the advances in medical care, mortality has not declined proportionately for hemorrhagic stroke. Targeted approaches such as control of blood pressure, surgery, early diagnosis and management of hemostasis are the need of the hour for reducing mortality and improving the rehabilitation after stroke.

 Mere reduction in mortality due to stroke is not sufficient. Implementing primary and secondary prevention measures due to stroke among the developed countries has resulted in reduction of deaths. But this resulted in the increase in number of people who are dependent on rehabilitation measures and prolonged hospitalization. With the current statistics of stroke, the proportion of dependent people will increase by 24% within the year 2030. Hence efforts for the management of risk factors such as hypertension are the need of the hour. Among developed countries, 54% of deaths due to stroke are due to hypertension, followed by dyslipidemia (15%) and smoking (12%). In addition, measures at the national level for reduction in consumption of saturated and trans fats along with promotion of regular physical activity are needed as well. 7

 Multiple factors are involved in the prognosis of stroke. One of the most significant prognostic factors is the presence of electrolyte imbalances. There is evidence indicating that the presence of electrolyte imbalances have a negative influence on prognosis after stroke8. Despite growing evidence, there is a paucity of information regarding the epidemiology of electrolyte imbalances among stroke patients in the developing countries. Understanding the electrolyte imbalances occurring in stroke will aid in better patient management and improve the prognosis in cerebrovascular disease, thus reducing the morbidity and mortality. This study seeks to assess the same.

**AIMS & OBJECTIVES**

**AIMS AND OBJECTIVE:**

1. To study the clinical and radiological profile of patients admitted with spontaneous brain haemorrhage.

2. To compare the risk factors for haemorrhagic stroke in cases and controls.

3. To compare ICH score in prognosis of brain haemorrhage at time of discharge.

4. To study association of levels of S. Calcium with the volume of bleed in patients with haemorrhagic stroke.

**AIMS AND OBJECTIVES:**

**REVIEW OF LITERATURE**

**REVIEW OF LITERATURE:**

**Burden of stroke global and India : (Global burden of disease 2017/2013 study findings)**

**Burden of hemorrhagic stroke/ contribution of hemorrhagic stroke Global & India: (Global burden of disease 2017/2013 study findings)**

**Risk factors for hemorrhagic stroke**

**Clinical and radiological profile of hemorrhagic stroke (A brief review and contrast of global and Indian studies can be added either individually for the following factors or overall at the end)**

1. **Demographic (Age & gender distribution)**
2. **Clinical presentation**
3. **Radiological profile (MRI/MR Angiography) : vascular territories involved.**
4. **etiology**
5. **Management & final outcomes of heamorrgic stroke : global & India ( A brief discussion)**

**Role of serum calcium in clotting (A brief note )**

**Association serum calcium levels and hemorrhagic stroke (Quantity of bleeding and outcomes)**

**Relevant global &Indian studies on role of calcium.**

**Lacunae in literature ..**

**Burden of stroke Global:**

 All over the world, cerebrovascular diseases, more commonly termed as stroke are the second leading cause of death next to ischemic heart disease as per the Global Burden of Disease report published in 2017. Stroke contributes to 11.02% of the total deaths worldwide and it is estimated to range from 10.84% to 11.29%. In 2016, stroke contributed to 10.95% of the total deaths and the annual increase is estimated to be about 0.0068%.

 With regards to disability, 6.89% of the total years of life lost (YLLs) are due to stroke worldwide. It also contributes to 2.2% of the total years lived with disability. In respect of quality of life, stroke contributes to 5.29% of the DALYs lost. The annual increase in the incidence of stroke cases is around 0.8%.

There are gender differences in the mortality and morbidity due to stroke. In the year 2017, 10.45% (10.22% to 10.72%) of all the deaths among men were due to stroke. There was an increase of 0.32% from 2016. Among women, the mortality rate was higher at 11.71% (11.47% to 12.05%) of total deaths. Compared to 2016, the mortality declined by 0.33%.

With regards to gender differences in disability due to stroke, 2.26% of the YLDs (years of life lost to disability) among women were due to stroke. Among men, 2.14% of the YLDs were due to stroke. The YLDs have increased by 1.15% and 1.49% among women and men respectively compared to 2016. This YLDs are especially higher among the geriatric age group more than 70 years of age. Among them, 6.3% of YLDs among women and 6.17% of the total YLDs among men were due to stroke.

There are age differences in the mortality and morbidity due to stroke. Among the geriatric age group more than 70 years of age, stroke is estimated to contribute 14.53% of the total causes of death (ranging from 14.29% to 14.92%). There has been an annual decline by 1.24% from 2016. Among women who were more than 70 years of age, the annual mortality due to stroke was high at 14.99%. Among men more than 70 years old, the mortality rate was lesser at 14.04%. The mortality rate increases with increasing age. The mortality rate is highest among those who were 75 to 79 years of age where the mortality rate is 15.37% (15.07% to 15.78%). Among those who are between 80 and 84 years of age the mortality is estimated to be 15.15% (14.85% to 15.56%).

In view of disability adjusted life years, among those over 70 years of age, 12.31% of the DALYs lost among men and 12.48% of the DALYs lost among women are due to stroke. Among all age groups, 5.38% of DALYs lost among men and 5.19% of DALYs lost among women were due to stroke in the year 20179–11.

**Burden of stroke India:**

In contrast to global level, where 11.02% of all deaths were due to stroke, in India, 7.09% (6.63% to 7.47%) of total deaths were due to cerebrovascular diseases according to GBD 2017. In 2013, 6.77% of the total deaths were due to stroke. Hence there has been an increase in incidence compared to previous years. Despite the high mortality, the morbidity due to stroke is lesser. In 2017, 0.64% of the years of life lived with disability were due to stroke. This is much lesser compared to the global estimates. Stroke also causes loss of 3.51% of the total DALYs.

With regards to gender differences in the mortality due to stroke, 6.92% of all the deaths among men and 7.29% of all the deaths among women were due to stroke. The mortality rates are lesser compared to the global averages. Similarly, 0.63% of the YLDs among men and 0.66% of the YLDs among women were due to stroke. Stroke causes loss of 3.63% of the DALYs among men and 3.37% of loss of DALYs among women respectively.

The mortality and morbidity due to stroke are high among those more than 70 years of age. Among them, 8.4% (7.64% to 8.97%) of all-cause deaths is due to stroke. The mortality rate for men more than 70 years of age is 8.41% and women more than 70 years of age is 8.37% respectively.

Among those more than 70 years of age, stroke causes loss of 2.14% of total YLDs. The YLDs for men and women more than 70 years of age is 2.03% and 2.22% respectively. Among all the DALYs lost more than 70 years of age, 7.31% are due to stroke. The DALYs lost among men and women more than 70 years of age are 7.4% and 7.21% respectively.12,13

 Banerjee et al14 (2001) conducted an epidemiological study on stroke among the Urban regions of Kolkata. They surveyed a total of 50,201 individuals. The overall crude prevalence of stroke was estimated to be 147 per 100,000 population. The age-adjusted prevalence of stroke was 334 per 100,000 population and the age adjusted annual incidence was 105 per 100,000 population. Stoke was more common among women compared to men except among those who were 50 to 69 years of age. Hemorrhagic stroke was more common compared to the Western countries. In India, the most important risk factor for cerebrovascular disorders was hypertension.

 Sridharan et al15 (2009) conducted a study on the incidence and risk factors for stroke in India. They collected data from 541 cases of stroke registered over a period of 6 months. Among them, 431 were from urban areas and 110 were from rural areas. The median age for occurrence of stroke was 67 years. The prevalence of young stroke (</=40 years) was only 3.8%. The annual incidence for stroke was 135/1 lakh population. The adjusted annual incidence for rural and urban populations were 138 and 135/1 lakh population respectively. Almost 90% of the stroke patients had modifiable risk factors.

 Pandian and Sudhan16 (2013) conducted a study on the epidemiology of stroke in India. They mention that the adjusted prevalence of cerebrovascular disorders is 334 to 424 per 1 lakh population in rural areas and 84 to 262 per 1 lakh population in urban areas. The incidence rate for stoke was 119 to 145 per 1 lakh population based on the estimate from other studies. The mortality due to stroke is highly variable across regions with the highest mortality of 42% reported from Kolkata.

 Kalkonde et al17 (2015) conducted a study on the burden of stroke in a rural area in India. They mention that of all the deaths occurring over a period of 2 years in the rural community of Gadchiroli, 14.3% of the mortality was due to stroke. The average age for those who died due to cerebrovascular disorders was 67.47±11.8 years. The proportion of women was 48.47%. The crude mortality due to stroke was 121.6 (106.4 to 138.4) The age adjusted mortality rate was 191.9(165.8 to 221.1) per 1 Lakh population. With respect to mortality, 87.3% of mortality due to stroke was at the house and 46.3% was in less than 1 month of symptom onset. Hence the authors mention that stroke is highly prevalent even among the rural communities in India and thus is a significant public health issue.

 Kamalakannan et al18 (2017) conducted a systematic review on the burden of stroke in India. They mention that in the past few decades, the incidence of stroke in India has more than doubled. A total of 78 studies were analyzed after applying the appropriate inclusion and exclusion criteria. They conclude that the crude prevalence of cerebrovascular disorders across India was widely variable, ranging between 44.29 to 559 per 1 lakh populations in the past 20 years. The cumulative incidence of stroke overall was estimated to be between 105 to 152 per 1 lakh population/year in the past 20 years. These estimates were much higher than those in the developed countries19. Hence the authors recommended further studies for assessing the burden of stroke in the Indian-subcontinent for assessing the true burden, mortality and morbidity.

 According to the National Health Profile of India 2018, published by ICMR, the incidence of stroke was estimated to be 0.13%. Tamil Nadu reported the highest number of individuals attending the NCD clinics under the National Program for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). Here almost 12,270,680 individuals have registered out of which 6,563 individuals have been diagnosed to have stroke. Hence, they emphasize the need for implementing primary prevention measures for reducing the increased burden of stroke.

Thus, to summarize, cerebrovascular diseases are the second leading cause of death globally. They also contribute to a significant proportion of mortality and disability both of which are higher among women, especially in the geriatric age group. The incidence has decreased in developed countries. But in developing countries like India, stroke contributes to a lesser proportion of mortality and morbidity compared to the global estimates. The mortality is especially higher among those more than 70 years of age. The incidence and disability due to stroke is on the rise. Hence, further research for developing preventive and therapeutic measures are needed for reducing the burden of stroke.

**Burden of hemorrhagic stroke/ contribution of hemorrhagic stroke Global & India:**

 In a population-based study conducted by Lovelock CE et al20 (2007), changes in the incidence and risk factors for hemorrhagic stroke over time was studied. They mention that among those who were <75 years of age, there was a reduction in the incidence of stroke, but there was a proportionate increase in the number of cases over 75 years, so that the total number of cases remained the same. There was a reduction in the incidence of hypertension associated hemorrhagic stroke. But there was an increase in the incidence of hemorrhagic stroke associated with the use of anti-thrombotic drugs. In the advanced age group >75 years old, amyloid associated hemorrhages were found to cause lobar bleeds. The authors predict that with the increasing proportion of aging population and anti-thrombotic drug usage, the incidence of hemorrhagic stroke is expected to rise in the coming years.

Keep et al21 (2012) mention that hemorrhagic stroke contributes to 10 to 15% of all the strokes occurring in the United States and Europe. In Asia, the proportion is higher accounting for 20% to 30% of all the incident strokes. Unlike ischemic strokes, there has been no decline in the incidence of hemorrhagic strokes worldwide. Furthermore, in addition to symptomatic hemorrhagic strokes, asymptomatic microbleeds also occur at a rate as high as 11.1 to 23.5% among the older age groups22.

An et al23 (2017) conducted a study on the epidemiology of hemorrhagic stroke. They mention that hemorrhagic stroke is a significant disease which results in high mortality rates or severe functional disability. Asian ethnicity, increasing age, male gender are associated with more cases of hemorrhagic stroke. The mortality at the end of 1 month of 40% and 54% at the end of 1 year. Among those who survive the proportion who regain functional independence after stroke is only 12% to 39%. With the increase in the risk of atrial fibrillation among the geriatric population, there is a concomitant increase in the usage of anticoagulant drugs. This has led to an increase in anticoagulant induced intracerebral bleeds. As warfarin is being replaced by anticoagulants which are not antagonists of Vitamin K, management of such hemorrhagic strokes has also become a complicated issue.

In the epidemiological study conducted by Banerjee et al14 (2001), the prevalence of hemorrhagic stroke was 32% and ischemic stroke was higher at 68% of all the stroke cases.

According to the study by Sridharan et al15 (2009) the age adjusted annual incidence of stroke for hemorrhagic stroke was 10.1/100,000 population ranging from 7 to 13.2/100,000. In comparison the annual incidence for ischemic stoke and subarachnoid hemorrhage were 74.8/100,000 population and 4.2/100,000 population respectively. The case fatality rate for stroke was 37.1% for rural population and 24.5% for urban population respectively at the end of 28th day.

One of the highest incidences of hemorrhagic stroke was reported from the Kolkata study by Das et al24 (2007). In their community-based study, 32% had hemorrhagic stroke, which is the highest reported in India, so far.

 Dalal PM et al25 (2008) conducted a survey on stroke incidence in Mumbai. They report that the annual incidence of stroke among males and females was 149/100,000 population and 141/100,000 population respectively. Among those who had storke, 80.2% were ischemic strokes and 17.7% were hemorrhagic strokes.

 In the study conducted by Sridharan et al15 (2009) on analyzing the data from Trivandrum stroke registry, the age adjusted annual incidence for intracerebral hemorrhage and subarachnoid hemorrhage were 10.1 and 4.2 per 100,000 population respectively. On neuroimaging, 11.6% were found to have intracerebral hemorrhages and 4.8% had subarachnoid hemorrhages.

Hence to summarize, the incidence of ischemic stroke is higher compared to the incidence of hemorrhagic stroke both globally and in India. But the incidence of ischemic stroke has declined over time. In developed countries, there has been a decline in the incidence of hypertensive hemorrhagic stroke. However, there has been an increase in incidence of hemorrhagic stroke among elderly due to other factors such as use of anti-thrombotic drugs and cerebral amyloid angiopathy. With the increasing aging population, the incidence is expected to be on the rise. In addition, the mortality and functional disability due to hemorrhagic stroke are high as well, compared to ischemic stroke.

**Demography (Age & Gender distribution):**

 In the systematic review conducted by van Asch et al26 (2010), the incidence of hemorrhagic stroke was estimated to be 24.6 per 100,000 person-years with 95% confidence interval ranging between 19.7 to as high as 30.7 per 100,000 person years. There was no significant difference in the incidence between men and women. Compared to those who were 45 to 54 years of age, those <45 years old had 0.10 times lesser incidence of hemorrhagic stroke. Those who were >85 years of age had 9.6 times increased incidence of hemorrhagic stroke. With regards to ethnicity, the incidence of hemorrhagic stroke was highest among Asians with incidence rate of 51.8 per 100,000 person years. Among the rest, the incidence rate was 24.2 per 100,000 person years for Caucasians, 22.9/100,000 person years for black people and 19.6/100,000 person years for Hispanic ethnicity.

 Kissela et al27 (2012) conducted a study on the association between age and incidence of stroke. They mention that the average age of onset of first stroke episode decreased from 71.2 years in 1993 to as less as 69.2 years in 2005. In 1993, the proportion of hemorrhagic stroke was 43.1% in the 20 to 44-year age group. This increased to 44.1% in 1999 and then decreased to 33.5% in 2005. Among the 45 to 54-year age group, 15.3% of all strokes were hemorrhagic strokes in 1993. This increased to 26.2% in 1999 and then decreased to 23.1% in 2005.

 Hong et al28 (2013) conducted a study on the epidemiology of stroke in Korea. They mention that there is an increase in incidence of hemorrhagic stroke with advancing age. The incidence among 45 to 45 years of age was 14/100,000 person years, which increases to 138/100,000 person years at 65 to 74 years and 350/100,000 person years for 75 to 84-year age group. Among those aged over 85 years highest incidence of 653/100,000 person years is reported. With regards to gender, hemorrhagic stroke was more common among women compared to men. Among those who were more than 85 years of age the incidence among men and women were 3845/100,000 person-years and 3118/100,000 person years respectively. But when stratified by age and gender, the incidence of stroke was higher among men till 65 years of age and after 65 years, women had a higher incidence of hemorrhagic stroke compared to men.

 Gokhale et al29 (2015) conducted a study on the gender differences in hemorrhagic stroke. In their meta-analysis it was found that, the overall incidence of hemorrhagic stroke has consistently been 1.6 times higher among men. Men were also reported to have more frequent deep hemorrhagic strokes in basal ganglia or putamen. In contrast, women were found to have more common lobar hemorrhages. Women also have worse outcomes with increasing age compared to men.

Hence to summarize, the incidence of hemorrhagic stroke increases with advancing age. The incidence is highest among those more than 85 years of age. With respect to ethnicity, Asians have the highest incidence of hemorrhagic stroke compared to Caucasians. Hemorrhagic stroke was higher among women compared to men. Prognosis was also worse among women compared to men.

**Risk factors for hemorrhagic stroke**

 The risk factors for hemorrhagic stroke are classified as: Modifiable and non-modifiable risk factors.

Modifiable risk factors:

* Increased blood pressure/Hypertension
* Substance abuse – Smoking and increased consumption of alcohol/binge drinking
* Low levels of LDL, triglycerides
* Use of anticoagulant drugs, antiplatelet drugs

Non-modifiable risk factors:

* Male gender
* Advancing age
* Asian, African-American origins
* Cerebral microhemorrhages
* Cerebral amyloid angiopathy
* Chronic kidney disease

Hypertension:

 Hypertension is the most significant factors for intracerebral hemorrhage. Hypertension is associated with greater risk for deep ICH compared to lobar ICH30. Among those who are hypertensives, smoking and alcohol consumption are associated with further elevated risk for hemorrhagic stroke31,32.

Thrift AG et al33 (1998) studied the significance of hypertension in the risk of hemorrhagic stroke. They mention that hypertension was associated with twice the odds of hemorrhagic stroke (OR: 1.61 to 1.73). Even among hypertensives, those who stopped their medications had 4.98 times the odds of cerebral hemorrhage. Furthermore, current smoking increased the odds by 6.12 times and <55-year age group were at 7.68 times increased odds of hemorrhagic stroke. Hence the authors emphasize the need for drug compliance among hypertensives.

Low levels of LDL, Triglycerides:

 The relationship between low LDL cholesterol levels and the risk of hemorrhagic stroke is conflicting. A case-control study performed in Australia reported that low cholesterol levels and triglycerides were associated with reduced risk of cerebral hemorrhage34. However, another study reported that low cholesterol and LDL levels were associated with increased risk of mortality due to ICH35.

Anti-coagulant use:

 Usage of anti-coagulants is associated with 2 to 5 times increased odds of hemorrhagic stroke. The risk is more among elderly due to increasing incidence of anticoagulant usage36,37. But the results are conflicting in this as well, since other studies demonstrate that anti-coagulant use and anti-platelet use was not associated with increased risk of intracerebral hemorrhage or subarachnoid hemorrhage in the general population. They mention that chronic low dose antiplatelet therapy with aspirin may be protective against ICH. But studies mention that dual anti-platelet therapy is associated with increased risk of hemorrhagic stroke compared to monotherapy38.

Chronic kidney disease:

 Population based studies indicate that chronic kidney disease is a risk factor for hemorrhagic stroke. The association is independent even after adjusting for other factors. This is explained by the fact that chronic kidney disease indicates the presence of cerebrovascular small vessel abnormalities which is involved in the pathophysiology of intracerebral hemorrhage. In addition, patients with chronic kidney disease have platelet dysfunction which be an additional mechanism for elevated risk for hemorrhagic stroke39,40.

Cerebral microbleeds:

 Cerebral microbleeds are more common in the older age group and men. They are also present in relation with diabetes, hypertension and among smokers. Cerebral microbleeds are an independent risk factor for hemorrhagic stroke and also increases the risk for anti-coagulant/anti-platelet associated intracerebral hemorrhage41–43.

Other potential risk factors:

 Additional risk factors which need exploration are long working duration, jobs involving vigorous physical activity and working in blue collar jobs44. Furthermore, studies have reported that sleeping for more than 8 hours is independently associated with increased risk of hemorrhagic stroke45.

**Relevant studies on the influence of risk factors:**

Giroud et al46 (1995) conducted a study for identifying the risk factors for primary hemorrhagic stroke in France. They mention that the primary risk factors associated with hemorrhagic stroke were hypertension, substance abuse (smoking and alcohol), atherosclerosis in the carotid arteries, history of prior infection in the past week and cardiac arrhythmias. In the acute stage, low serum cholesterol levels, high blood sugar and increased hematocrit were risk factors. After adjusting, only hypertension and low cholesterol levels remained independently associated with the risk of hemorrhagic stroke. Hence the authors suggest that pharmacotherapy with lipid lowering drugs may be associated with increased risk of hemorrhagic stroke.

 The Melbourne Risk Factor Study Group aimed to identify the risk factors for hemorrhagic stroke. They mention that the most significant risk factor for hemorrhagic stroke was hypertension which was doubled the odds for hemorrhagic stroke. Unlike other studies, there was no association between the use of anti-thrombotic drugs and hemorrhagic stroke. Elevated cholesterol levels, moderately overweight BMI and drinking coffee were associated with lowered risk for hemorrhagic stroke34.

Zodpey et al47 (2000) conducted a case-control study on the risk factors for hemorrhagic stroke. They included 166 cases and compared them with controls matched for age and gender. They identified 5 risk factors to be associated with hemorrhagic stroke. Hypertension was associated with 1.9 times odds of hemorrhagic stroke. Total cholesterol levels was associated with 2.3 times odds of hemorrhagic stroke. A history of use of drugs such as anti-thrombotics was associated with 3.4 times odds of hemorrhagic stroke. Alcohol intake was associated with 2.1 times increased odds and a prior history of transient ischemic attack was associated with 8.4 times odds of hemorrhagic stroke. The authors emphasize the need for addressing these preventable risk factors for reducing the incidence of hemorrhagic stroke.

Banerjee et al14 (2001) mention that the most significant risk factor for development of stroke was hypertension. Women with hypertension had 5.04 times the odds of stroke (4.16 to 5.92) compared to normotensives. Men were at a much-increased risk estimated at 21.87 (18.69 to 25.05). Among men, smoking was associated with 2.91 times the odds (1.57 to 4.25) for stroke compared to non-smokers. There was no significant increased risk associated with diabetes among both men and women.

Ariesen et al31 (2003) conducted a systematic review on the risk factors for hemorrhagic stroke. They included 14 case-control and eleven cohort studies. It was found that 10-year increase in age was associated with 1.97 (1.79 to 2.16) times increased odds of hemorrhagic stroke. Male gender was associated with 4.64 (4.02 to 5.4) times increased odds of hemorrhagic stroke. Moderate alcohol consumption and high intake of alcohol were associated with 2.05- and 4.11-times increased odds of hemorrhagic stroke respectively. Current smoking was associated with 1.31 times increased odds of hemorrhagic stroke. Diabetes was associated with 1.3 times increased odds of hemorrhagic stroke. The most significant risk factor overall was hypertension which was associated with 3.68 times (2.52 to 5.38) times increased odds of hemorrhagic stroke.

 Sturgeon et al48 (2007) conducted a prospective study on the risk factors for intracerebral hemorrhage. They enrolled a cohort of 15,792 individuals and followed them up. The incidence of hemorrhagic stroke was 135/263,489 person years. The risk factors were found to be advanced age, African-American origin and hypertension. Increased LDL cholesterol levels and triglycerides were protective against hemorrhagic stroke. Increased systolic BP of more than 160 mm Hg or increased diastolic BP of more than 110 mm Hg was associated with 5.55 times increased risk of hemorrhagic stroke compared to normotensives. Risk factors for ischemic stroke such as smoking, alcohol intake, increased BMI, waist-hip ratio and history of diabetes mellitus were not found to be associated with hemorrhagic stroke.

 The risk factors for stroke was studied in the landmark INTERSTROKE study conducted across 22 countries. Those presenting with acute stroke were included in the study. Thus, 3000 patients were included. Among all the cases, 22% had intracerebral hemorrhagic stroke. The prevalence of hemorrhagic stroke was highest in Africa (34%) and in India the prevalence was 23%. High income countries had the lowest prevalence of hemorrhagic stroke (9%). A history of hypertension was associated with 3.8 times odds (2.96 – 4.78) of hemorrhagic stroke with population attributable risk of 44.5%. When the blood pressure cut-off was lowered to 160/90 mm Hg, hypertension was associated with 9.18 times odds of hemorrhagic stroke. Being a current smoker increased the odds of hemorrhagic stroke by 1.45 times (1.07 to 1.96). Increased waist-hip ratio was associated with 1.65 (1.22 – 2.23) times odds of hemorrhagic stroke. Dietary risk factors accounted for 1.53 times increased odds for hemorrhagic stroke. Regular physical activity was associated with lesser odds of hemorrhagic stroke, but the association was not significant. Alcohol drinks >30/month or binge drinking increased the odds of hemorrhagic stroke by 2.01 times (1.35 to 2.99). Stress was not associated with hemorrhagic stroke after adjusting for other factors. Ratio of ApoB to ApoA1 and cardiac causes were not associated with risk of hemorrhagic stroke49,50. Hence, modifiable risk factors such as hypertension, smoking, alcohol use, increased waist-hip ratio, sedentary life style, imbalanced diet together contribute to 83% of the risk for hypertension. Hence health programs that target these modifiable risk factors are recommended for reducing the global incidence of stroke.

Thus, to sum up, the non-modifiable risk factors for hemorrhagic stroke include, age, Asian ethnicity, cerebral microhemorrhages, cerebral amyloid angiopathy and chronic kidney diseases. Factors such as high blood pressure, low cholesterol levels, use of anticoagulant drugs and substance abuse are modifiable risk factors for hemorrhagic stroke. Factors such as diabetes, high LDL levels which are risk factors for ischemic stroke do not have a significant association with hemorrhagic stroke.

**Clinical presentation:**

 Hemorrhagic stroke usually presents as an acute onset of neurological deficit. There is a rapid worsening of neurological deficits within 30 to 90 minutes. There is also a gradual reduction in the level of consciousness and signs of raised intracranial tension such as headache and projectile vomiting51.

 The presence of contralateral hemiparesis is typical of hemorrhagic stroke since putamen is the common site of involvement along with nearby internal capsule. The following are the stages of progression of hemorrhagic stroke:

* Mild stroke has a sagging of the face to one side over 5 to 30 minutes along with slurring of speech. There is gradual weakness of upper and lower limbs. Ocular deviation to opposite side occurs.
* Paralysis increases in severity and progresses to flaccidity or rigidity.
* As herniation and subsequent compression of brainstem occurs, there is stupor or coma.
* Respiratory irregularities along with fixed dilated pupil on the ipsilateral side occurs along with decerebrate rigidity.

 In case of hemorrhagic stroke involving thalamus, contralateral hemiparesis or hemiplegia may also occur to due to internal capsule involvement. If dominant thalamus is involved, aphasia may occur, but verbal repetition is conserved. In non-dominant thalamic involvement, constructional apraxia may be present. Homonymous visual field defects may occur as well. Skew deviation of eyes to inferior and medial direction, vertical gaze paralysis, ipsilateral Horner’s syndrome, absence of light reaction in pupils and retraction nystagmus are additional features52.

 In hemorrhages involving the pons, the progress is hyperacute where over a few minutes, coma with quadriplegia occurs. Hyperpnea, Decerebrate rigidity, increased blood pressure, hyperhidrosis and pinpoint pupils are diagnostic features. It is associated with high case fatality53,54.

 Hemorrhagic strokes with cerebellar involvement are more slowly evolving. Characteristic features are occipital headache, ataxia, vertigo and vomiting. Contralateral deviation of eyes, ipsilateral palsy of the abducens nerve and conjugate lateral gaze paresis may also be present. In untreated cases, brain stem compression and hydrocephalus can occur leading to mortality55.

 Hemorrhagic stroke can involve the cerebral lobes. When the occipital lobe is involved hemianopia is the main presenting neurological deficit. When the left temporal lobe is involved, aphasia and delirium can occur. Parietal lobe involvement manifests as hemisensory loss. Upper limb weakness occurs in cases of frontal lobe involvement. When hemorrhages involve a large surface area, stupor or coma can occur if the thalamus or the midbrain is compressed due to the hemorrhage. Meningeal signs such as neck stiffness and seizures are rare. On contrast, focal headaches, vomiting and drowsiness are seen among more than 50% of the individuals56.

 Other rare causes of intracerebral hemorrhage include cerebral amyloid angiopathy occurs in the older age groups. There is deposition of amyloid material in the arterial walls along with degeneration of arterioles. This condition can result in both single and repeated episodes of lobar hemorrhages in the geriatric age group. With the increasing proportion of aging population, the incidence of cerebral amyloid angiopathy induced cerebral hemorrhages have increased57.

Thus, to conclude, hemorrhagic stroke manifests as acute onset of neurological deficit which worsens gradually as the hemorrhage expands. Contralateral hemiparesis occurs with thalamic involvement. Occipital lobe involvement causes visual field defects. Coma with quadriplegia occurs in pontine hemorrhage. Cerebellar involvement is characterized by ataxia and gaze palsy. Larger areas of involvement may result in stupor or coma. Herniation of brain stem can occur as well.

**Radiological profile:**

 Hemorrhagic stroke is diagnosed using CT brain without using contrast in the acute stages. CT is also more commonly available and hence is the preferred method. The site of the hemorrhage provides a clue to the etiology of stroke.

Hypertensive etiology hemorrhagic stroke is the result of rupture of small penetrating deep arteries in the brain. Anatomically, sites such as thalamus, pons, basal ganglia and cerebellum are the most frequently affected regions. This is due to the fact that small arteries in these regions are more prone to vascular injury caused due to hypertension.

 Acute intracerebral hemorrhage of hypertensive etiology is characterized by CT imaging as an ‘intra-axial hyperdense hemorrhagic zone’. The classical sites of hemorrhage involve the cerebellum, occipital lobe and basal ganglia. When such hemorrhagic bleeds occur among those less than 50 years of age, alternate etiologies have to be considered such as neoplasms and AV malformations. The initial site of bleed might be variable from less than 1 to 2 cm to massive hematomas which exert mass effect and result in herniation of brain tissue.

Non-contrast CT are also useful in predicting prognosis. According to Broderick et al58 (1993), large volumes of parenchymal hemorrhage are associated with poor prognosis. Other signs of poor prognosis include concomitant intraventricular hemorrhage59 and growth of hematoma found on serial imaging60.

Other differential diagnoses should be considered among those who have no history of hypertension and those who have hemorrhagic strokes involving other areas. Causes in these patients may include neoplasms, AV malformations, cerebral amyloid angiopathy and coagulation disorders.

 For hemorrhagic stroke involving the supratentorial region, CT imaging is the modality of choice for diagnosis of acute focal hemorrhage. However, CT imaging may not be adequate in case of minute hemorrhages involving the pons or medulla since the hemorrhages may be obscured by the bony artifacts obscuring the posterior fossa structures. Initially, 2 weeks after the onset of stroke, sites of hemorrhages may decrease in their x-ray attenuation values till they become iso-dense with the neighboring normal brain tissue. Despite the attenuation, mass effect and edema may persist. In certain instances, an enclosing ring of contrast enhancement begins to appear after a few weeks and lasts for months together61.

Other than plain CT, there is increasing role of CT angiography in the diagnosis during acute stages of hemorrhagic stroke. In cases of hemorrhagic stroke, CT imaging is performed after a delay from the time of performing CT angiography of the intracerebral blood vessels. Contrast extravasation may present as a ‘hyperdense region of accumulation of contrast material inside the hematoma. One or more such areas of enhancement may be found. This appearance is termed as ‘the spot sign’, which is indicative of ongoing bleeding62.

When the spot sign is present, it indicates that there is a greater risk for the expansion of hematoma, reduced probability of favorable prognosis and increased risk of mortality. Performing a lumbar puncture is usually avoided in cases of hemorrhagic stroke since most patients have focal neurologic deficits and raised intracranial tension and thus are prone to cerebral herniation63,64.**TRE**

Unlike ischemic strokes, MRI is not needed for the initial diagnosis of hemorrhagic stroke. MRI and CT angiography can be used when the etiology of hemorrhagic stroke is not certain. This is especially of great utility when the patients are younger in age or the etiology is not hypertensive. In cases of hyperacute ischemic stroke, although MRI is the preferred mode of diagnosis, Computed tomography is required for ruling out hemorrhagic stroke. Hence, Schellinger et al65 aimed to find out the utility of multimodal MRI for assessing hemorrhagic stroke. They performed both CT as well as multimodal MRI among those with hyperacute intracerebral haemorrhage. The size of the intracerebral bleed was compared with both diagnostic modalities. It was found that mMRI identified all cases of intracerebral haemorrhage. Diffusion weighted MRI correlated best with the volume of hematoma. Hence the authors mention that CT is no longer needed for ruling out intracerebral haemorrhage in cases of stroke. **TMEH**

Cerebral amyloid angiopathy is identified in CT scanning as a intra-axial hemorrhagic zone which is hyperdense present in the subcortical region. The presence of microangiopathic changes manifest as bilaterial cerebral hemispheric diffuse hypoattenuation of white matter. But this finding is not always present among those who have cerebral amyloid angiopathy66. MRI is of more use in such cases where amyloid angiopathy presents as multiple small foci of susceptibility blooming in both cerebral hemispheres66,67.

 Hemorrhagic stroke secondary to an ischemic infarct are diagnosed using serial imaging studies using CT or MRI. The extent of hemorrhagic conversion and vasogenic edema post infarct are assessed among those who deteriorate in their neurological status after an episode of ischemic stroke. Among those who have underwent endovascular procedures after stroke, the presence of reperfusion haemorrhage might be hidden by the contrast staining from cerebral angiography. In such instances, dual energy CT is emerging as a novel mode of diagnosis though it is still in the research stage68.

Thus, to summarize, CT imaging without contrast is the basic preferred modality for the diagnosis of hemorrhagic stroke. The location of the hemorrhage provides a clue as to the etiology of hemorrhagic stroke. Hypertensive hemorrhagic stroke usually manifests as an intra-axial hyperdense zone. The presence of spot sign indicates ongoing bleeding and thus poor prognosis. Multimodal MRI is also an upcoming diagnostic modality for hemorrhagic stroke

**Management & Final outcomes of hemorrhagic stroke: Global & India**

Management of airway is an important step during the acute stage of hemorrhagic stroke since the loss of consciousness may increase in severity. In the INTERACT trial, the effect of acute reduction in blood pressure in hemorrhagic stroke is assessed by monitoring functional outcome after stroke. Among the group whose BP was lowered to <140 mm Hg, the mortality rate or 90-day disability rate was 52%. Those whose BP was lowered to <180 mm Hg had a 55.6% rate of mortality or disability. The differences in the mortality were not significant, but those who had acute reduction in BP had improved outcomes. However, this may not be applicable to those in coma or very high systolic BP.

When it is possible to monitor intracranial pressure, the cerebral perfusion should be kept above 60 mm Hg. Beta blockers such as labetolol or esmolol, and intravenous drugs such as nicardipine which do not cause vasodilatation should be used for BP reduction. If the patient is suspected to have hydrocephalus or cerebellar hemorrhage, immediate neurosurgical monitoring is required. On imaging, if herniation is suspected or if the patient is in coma, measures such as osmotic diuresis, intubation and head end elevation are performed. Measures to control the bleeding such as reversal of action of anti-coagulants and surgical decompression of the bleed are also done.

Hemphill JC et al69 (2001) developed a scoring system for assessing the outcomes after intracerebral hemorrhage. They mention that 10 to 15% of all strokes are hemorrhagic strokes and there is no specific mode of management. Unlike ischemic strokes there were no standardized scoring systems for predicting the outcomes after hemorrhagic stroke. They found that Glasgow coma scale, advancing age of more than 80 years, volume of intracerebral bleed, additional presence of intraventricular hemorrhage and origin from the intratentorial regions were the significant factors which predicted the mortality at the end of 30 days. A Glasgow coma scale score of 3 or 4 was assigned 2 points, 5 to 12 was assigned 1 point. One point was assigned if age was more than or equal to 80 years, and one point if the origin of bleed was infratentorial. A large volume bleed of more than 30 ml was assigned 1 point and intraventricular hemorrhage was assigned 1 point. When this scoring was applied in their study, all those who had a score of 0 survived. A score of 5 or above was associated with 100% mortality.

 Van Asch CJ et al26 (2010) conducted a systematic review on outcomes after hemorrhagic stroke over time. They mention that the median case fatality at the end of 30 days was 40.4% ranging from 13.1 to as high as 61%. There was no reduction in case fatality over time. The lowest mortality was found in Japan (16.7%). The independency rates after hemorrhagic stroke ranged between 12% to 39%. They mention that there is a need for data on functional outcomes after hemorrhagic stroke.

The hemorrhagic stroke initially might begin as a small clot and then extend, causing compression of adjacent areas and then brain herniation. Hemorrhagic stroke gradually evolves over 30 to 90 minutes. In hemorrhagic strokes of anticoagulant etiology, the evolution may be as slow as 24 to 48 hours. Phagocytosis of the outer surface of hematoma by macrophages commences as early as 48 hours. By the end of one to six months, glial tissue formation with hemosiderin filled macrophages is formed at the site of hematoma.

 In the study by Hong et al28 (2013), the overall mortality for hemorrhagic stroke at the end of 30 days was 35% which was 35.6% among men and 34.5% among women. When stratified by age and gender, the 30-day mortality was lower for women compared to men till 65 years of age. For those over 65 years, the mortality for women was higher. Among those over 85 years, the case fatality rates for women and men were 77.8% and 50.1% respectively. The crude in-hospital mortality rate for hemorrhagic stroke was 17.5% in 2010.

With regards to functional outcome, 29% only achieved independency with modified Rankin score of 0 to 3. The 90-day mortality rate was 16.9%.

Hence, to summarize, management of airway and reduction in blood pressure are two key measures during the initial phase of hemorrhagic stroke. Specific measures such as reversing the action of anti-coagulants and surgical decompression are needed in specific situations. Mortality and residual functional disability are high after hemorrhagic stroke.

**Role of Calcium in blood clotting:**

 Furie and Furie70 (1988) mentions that calcium in its ionic form plays a crucial role in the coagulation cascade of blood due to the fact that many of the component reactions are either dependent on Ca2+ or require Ca2+ for the interaction between proteins and membrane surfaces.

 Heemskerk et al71 (2012) found that platelets with elevated calcium and phosphatidylserine (PS) control thrombin and fibrin generation. They found that platelets which have adhered to collagen and patches of platelets in a thrombus, activated by thrombin and similar agonists, display with a lengthened high calcium, and expose PS. PS-exposing platelets function as membrane substrate for several clotting factors, with a massive potentiation of thrombin generation as a result. It was observed that population of PS-exposing platelets are typically high in cytoplasmic calcium.

 Palta et al 72(2014) notes that calcium is contained in the dense δ-granules of the platelets. After the adhesion of the platelets to the endothelial collagen which has been exposed due to vascular injury through the von-Willebrand factor and the platelet glycoprotein complex I (GP-Ib) surface receptor, degranulation of the platelets occurs. The released calcium binds to the phospholipids which appear secondary to platelet activation and provides a surface framework for coagulation factor assembly. Calcium is called clotting factor IV. In the extrinsic pathway, TF is exposed by vascular insult and binds with factor VIIa and calcium to precipitate the conversion of factor X to factor Xa. Subsequently the activated factor X along with factor V (its co-factor), tissue phospholipids, platelet phospholipids and calcium forms the prothrombinase complex which changes prothrombin to thrombin. From the anti-coagulant perspective, it is observed that protein S increases the interaction of factor Xa in the presence of calcium and phospholipids. Similarly, protein Z dependent protease inhibitor protease inhibitor/protein Z inhibits factor Xa in a reaction requiring calcium and protein Z.

**Association between Serum Calcium levels and hemorrhagic stroke**

 Altura and Altura73 (1994) note that recent research suggests that alcohol might cause hypertension, stroke and sudden death through its effects on intracellular free magnesium ions (alcohol is known to be the most notorious cause of magnesium-wasting), which in turn modify cellular and subcellular bioenergetics and cause calcium ion overload.

 Altura et al74 (1997) found that among stroke patients (either ischemic or hemorrhagic) admitted in 3 urban hospitals, a significant elevation of ionized calcium and Ca2+/Mg2+ ratio (an indicator of increased vascular tone and cerebro-vasospasm) were detected.

 Appel et al75 (2011) examined the association between levels of serum calcium and albumin-adjusted calcium and stroke outcome in patients with acute stroke. Assessment and follow-up over a period of 1 year was done. It was found that for total calcium, the adjusted hazard ratio (HR) for all-cause mortality over 1 year was 1.83 amongst subjects with low versus normal levels. In the case of adjusted calcium, the adjusted hazard ratio was over 3-fold higher for patients with higher adjusted calcium levels compared to those with normal levels. This finding was present only among women. Each unit rise in total calcium squared was found to be associated with an increase in adjusted HR of all-cause death over 1 year. Every unit increment in adjusted calcium squared was associated with a higher adjusted HR of all-cause mortality over the period of 1 year among only women. The authors concluded that serum calcium levels indicated mortality in acute stroke patients. However, such associations are not linear and increase at both extremes of calcium levels.

 Chowdhury et al76 (2012) conducted a systematic review of prospective cohort studies to study the link between the levels of circulating calcium and risk of cerebrovascular disease. The relative risk in the considered studies that reported on circulating levels of calcium for cerebrovascular disease was 1.40. They concluded that higher circulating calcium levels are associated with an increased cerebrovascular risk.

 Inoue et al77 (2013) investigated the association between admission calcium levels with hematoma volume, stroke severity, and outcomes among patients suffering from acute intracerebral hemorrhage. Based on the serum calcium levels, the total number of patients was divided into quartiles in an increasing manner. The authors found that the median hematoma volumes for each quartiles were 18, 9, 10, and 9 mL respectively. The median National Institute of Health Stroke Scale (NIHSS) scores were 16, 11, 11, and 9 (p=0.010) respectively. Multivariate analysis was conducted. It was noted that the first quartile had larger hematoma volumes and greater NIHSS scores than Q4. They concluded that lower admission serum calcium levels were associated with greater hematoma volumes and higher NIHSS scores among those suffering from acute episodes of intracerebral hemorrhage. The authors opine that lower serum calcium levels may reflect poor liver function. The lowest calcium quartile had a high percentage of liver dysfunction. These findings indicate an alternative mechanism for poor coagulation and therefore larger volume of the hematoma.

 Tagawa et al78 (2014) examined the associations between phosphate, calcium and parathyroid hormone (PTH) levels and stroke, using a longitudinal study. They found that hemorrhagic stroke was associated only with PTH levels.

 Guo et al79 (2015) studied if lower serum calcium levels at admission were associated with hemorrhagic transformation (HT) after thrombolysis. They found that a lower admission calcium level was associated with a higher occurrence of HT within 24 hours after IVT. The possible explanatory mechanisms for this finding are: (1) calcium ion plays a critical role in the conversion of prothrombin to thrombin and (2) activation of extracellular calcium receptors which are located in the perivascular sensory nerves may lead to vasodilator substance release, leading to relaxation of individual arteries. They suggest that serum calcium levels may be used to predict for HT after thrombolysis.

 Liu et al80 (2016) conducted a study to determine the correlation between serum calcium levels, hematoma volume and severity of stroke among patients admitted with acute cerebral hemorrhage and association with prognosis. They found that hematoma volume and National Institute of Health Stroke Scale (NIHSS) scores in the hypocalcemic group were higher than those in the hypercalcemic group. The values were lowest in the normocalcemic group and the differences between the groups were statistically significant. Logistic regression analysis demonstrated that APACHE II score, blood calcium levels on admission and hematoma volume are independent risk factors for stroke survival.

 Morotti et al81 (2016) investigated the association between a low calcium level in serum and extent of bleeding in patients with intracerebral hemorrhage (ICH) using a cohort study design. The extent of bleeding was measured using baseline hematoma volume and risk of bleed expansion. The authors observed that hypo-calcemic patients had an increased median hematoma volume compared to normo-calcemic patients. Lower calcium level was independently associated with higher ICH volume. After adjusting for confounders, an association between higher serum calcium levels and reduced risk of ICH expansion was detected. They concluded that calcium might be a promising therapeutic agent for acute ICH clinical trials.

 You et al82 (2016) aimed to determine the relationship between admission calcium and phosphate levels and short-term and long-term outcomes among patients suffering from acute ICH. The participants were divided into 4 subgroups based on either serum calcium or phosphate levels. Applying univariate analysis, the highest and lowest quartiles were compared, and it was found that raised calcium level was associated with 2.26 and 2.28-fold rise in the odds and 3-month excellent outcomes, respectively. Adjustments for age, sex, and other possible risk factors was done. Patients in the highest quartile had significant better odds of discharge and 3-month excellent outcomes. The respective odds ratios for the above parameters were 3.43 and 5.36. When calcium levels were divided into two groups, the odds ratios of higher calcium were 2.9 and 2.8 for discharge and excellent outcomes at 3 months, respectively. They concluded that only high admission serum calcium levels, and not raised phosphate levels, were associated with excellent outcomes in cases of ICH.

 Morotti et al81 (2017), in their reply to Chen et al83 (2017), admit that the absence of calcium measurements preceding the intracerebral hemorrhage prevented them from analyzing the possibility that hypocalcemia is a result and not a determinant of greater bleeding. Still they claim that the possibility that decreased nutritional support, metabolic stress, or secondary complications could have influenced calcium homeostasis, is low as the serum calcium levels were measured in the immediate acute phase of the disease. The authors repeated multivariable logistic regression for ICH expansion and found that the relationship between hypocalcemia and greater chances for hematoma growth remained high even after adjusting for age and sex (odds for ICH expansion was 4.96).

 Tan et al84 (2018) conducted a case-control study to assess the association between serum calcium and magnesium and hemorrhagic transformation (HT) in stroke overall and stroke subtypes in China among non-thrombolysis patients with serum calcium collected within 24 hours of stroke onset. Multivariate logistic regression analysis was used. It was found that serum calcium was slightly decreased in patients with HT than those without HT. They concluded that serum calcium has no association with HT in patients not undergoing thrombolysis after acute ischemic stroke.

 Mao et al85 (2019) investigated the relationship between admission calcium and outcomes in ICH patients with hypertension. The outcome was measures using initial hematoma volume, hematoma enlargement and functional outcome. They found that lower admission calcium levels were statistically associated with bigger initial hematoma volumes, higher baseline NIHSS and mRSscore (modified Rankin Scale score). There was no association with platelet count, activated partial thromboplastin time and INR on admission. To assess outcomes, 30-days mortality and 6-months mRS scores were used and adjusted for age, gender, time from onset to admission, cigarette smoking, alcohol drinking, history of hypertension, NIHSS score, mRS score and hematoma position. They concluded that lower calcium levels were associated with worse outcomes and may be used as a prognostic factor for acute ICH stroke.

Hence, in conclusion, there is growing evidence that lowered serum calcium levels on admission indicates a large hematoma and poor prognosis in cases of acute hemorrhagic stroke. Higher serum calcium levels are associated with better prognosis. The burden and mortality due to hemorrhagic stroke in developing countries such as India are considerably high. Hence, developing measures to identify high risk patients at the time of admission will enable develop therapeutic measures to reduce mortality and improve prognosis. There is evidence showing that performing serum calcium level measurements at the time of admission will aid in predicting hematoma size and prognosis in hemorrhagic stroke. There are very less studies in India assessing the association between serum calcium levels and hemorrhagic stroke. Hence this study is conducted to determine the association between serum calcium and hemorrhagic stroke.

**MATERIALS & METHODS**

**Study site:** This study was conducted in the Department of …………………. At…………

**Study population:** All diagnosed cases of spontaneous brain hemorrhage by imaging in a tertiary care were considered as cases in study population. The control group patients were randomly selected who matched the case group in terms of age and sex admitted in hospital for some other cause.

**Study design:** The current study was a Case control study

**Sample size: Cases-45, Control 45**

**Sampling method:** All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

**Study duration:** The data collection for the study was done between November 2017 to October 2019 for a period of 2 years. (Please check and specify Dr.Anuj)

**Inclusion Criteria:**

* All patients age group 18 and above.
* Patients of brain haemorrhage diagnosed by imaging.

**Exclusion criteria:**

* Patients of brain haemorrhage who were on anti-coagulant therapy.
* Patients with brain haemorrhage secondary to ischaemic stroke.
* Patients with traumatic brain haemorrhage.
* Patients with subdural hematoma or extradural hematoma or subarachnoid haemorrhage.

**Ethical considerations:** Study was approved by institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

**Data collection tools:** All the relevant parameters were documented in a structured study proforma.

**Methodology:**

In this case-control study, 45 consecutive patients with brain haemorrhage referred to or diagnosed at a tertiary care hospital from 1st November 2017 to 31st October 2019 were evaluated clinically and compared with patients admitted in the hospital for any reason. Informed written consent was obtained from patients prior to enrolment and study procedure will be explained. Information was collected through prepared Performa for each patient. All patients were interviewed as per the Performa and a complete clinical examination was done. Cases of spontaneous brain haemorrhage diagnosed with history, clinical examination and imaging. Patients’ demographic, social, economic and medical details were recorded in the Performa sheet.

**Statistical Methods:**

**OBSERVATIONS AND RESULTS**

**RESULTS:**

**DISCUSSION**

**DISCUSSION**:

**BIBLIOGRAPHY**

**REFERENCES:**

1. WHO MONICA Project Principal Investigators. The world health organization monica project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. Journal of Clinical Epidemiology. 1988 Jan 1;41(2):105–14.

2. Katan M, Luft A. Global Burden of Stroke. Semin Neurol. 2018 Apr;38(2):208–11.

3. WHO. Global burden of stroke - Stroke atlas [Internet]. [cited 2019 Mar 15]. Available from: https://www.who.int/cardiovascular\_diseases/en/cvd\_atlas\_15\_burden\_stroke.pdf?ua=1

4. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. The Lancet Neurology. 2009 Apr 1;8(4):355–69.

5. Omran AR. The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. Milbank Q. 2005 Dec;83(4):731–57.

6. Nadar S, Lip GYH. Secular trends in cardiovascular disease. Journal of Human Hypertension. 2002 Nov 4;16:663–6.

7. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. The Lancet Neurology. 2007 Feb 1;6(2):182–7.

8. Mieke A.H.N. Kembuan, Sekplin A.S. Sekeon. Electrolyte disturbances among acute stroke patients in Manado, Indonesia. 2014;3(1):1–6.

9. GBD 2015 Mortality and causes of death collaborators. Global, regional, and national life expectancy, all-cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053).

10. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1211–59.

11. GBD Compare | IHME Viz Hub [Internet]. [cited 2019 Mar 16]. Available from: http://vizhub.healthdata.org/gbd-compare

12. GBD India Compare [Internet]. Institute for Health Metrics and Evaluation. 2017 [cited 2019 Mar 16]. Available from: http://www.healthdata.org/data-visualization/gbd-india-compare

13. Institute for Health Metrics and Evaluation (IHME). Findings from the Global Burden of Disease Study 2017 [Internet]. 2018 [cited 2018 Mar 16]. Available from: http://www.healthdata.org/sites/default/files/files/policy\_report/2019/GBD\_2017\_Booklet.pdf

14. Banerjee TK, Mukherjee CS, Sarkhel A. Stroke in the urban population of Calcutta--an epidemiological study. Neuroepidemiology. 2001 Aug;20(3):201–7.

15. Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. Stroke. 2009 Apr;40(4):1212–8.

16. Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. J Stroke. 2013 Sep;15(3):128–34.

17. Kalkonde YV, Deshmukh MD, Sahane V, Puthran J, Kakarmath S, Agavane V, et al. Stroke Is the Leading Cause of Death in Rural Gadchiroli, India: A Prospective Community-Based Study. Stroke. 2015 Jul;46(7):1764–8.

18. Kamalakannan S, Gudlavalleti ASV, Gudlavalleti VSM, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. Indian J Med Res. 2017 Aug;146(2):175–85.

19. Bennett DA, Krishnamurthi RV, Barker-Collo S, Forouzanfar MH, Naghavi M, Connor M, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. Glob Heart. 2014 Mar;9(1):107–12.

20. Lovelock CE, Molyneux AJ, Rothwell PM, Oxford Vascular Study. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet Neurol. 2007 Jun;6(6):487–93.

21. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol. 2012 Aug;11(8):720–31.

22. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009 Feb;8(2):165–74.

23. An SJ, Kim TJ, Yoon B-W. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J Stroke. 2017 Jan;19(1):3–10.

24. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. Stroke. 2007 Mar;38(3):906–10.

25. Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, et al. Population-based stroke survey in Mumbai, India: incidence and 28-day case fatality. Neuroepidemiology. 2008;31(4):254–61.

26. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010 Feb;9(2):167–76.

27. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Age at stroke. Neurology. 2012 Oct 23;79(17):1781–7.

28. Hong K-S, Bang OY, Kang D-W, Yu K-H, Bae H-J, Lee JS, et al. Stroke Statistics in Korea: Part I. Epidemiology and Risk Factors: A Report from the Korean Stroke Society and Clinical Research Center for Stroke. J Stroke. 2013 Jan;15(1):2–20.

29. Gokhale Sankalp, Caplan Louis R., James Michael L. Sex Differences in Incidence, Pathophysiology, and Outcome of Primary Intracerebral Hemorrhage. Stroke. 2015 Mar 1;46(3):886–92.

30. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engström G. Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. Stroke. 2007 Oct;38(10):2681–5.

31. Ariesen MJ, Claus SP, Rinkel GJE, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003 Aug;34(8):2060–5.

32. Grønbaek H, Johnsen SP, Jepsen P, Gislum M, Vilstrup H, Tage-Jensen U, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population-based case-control study. BMC Gastroenterol. 2008 May 24;8:16.

33. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Three important subgroups of hypertensive persons at greater risk of intracerebral hemorrhage. Melbourne Risk Factor Study Group. Hypertension. 1998 Jun;31(6):1223–9.

34. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Risk factors for cerebral hemorrhage in the era of well-controlled hypertension. Melbourne Risk Factor Study (MERFS) Group. Stroke. 1996 Nov;27(11):2020–5.

35. Mustanoja S, Strbian D, Putaala J, Meretoja A, Curtze S, Haapaniemi E, et al. Association of prestroke statin use and lipid levels with outcome of intracerebral hemorrhage. Stroke. 2013 Aug;44(8):2330–2.

36. Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, et al. Warfarin use leads to larger intracerebral hematomas. Neurology. 2008 Sep 30;71(14):1084–9.

37. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007 Jan 9;68(2):116–21.

38. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009 May 14;360(20):2066–78.

39. Bos MJ, Koudstaal PJ, Hofman A, Breteler MMB. Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study. Stroke. 2007 Dec;38(12):3127–32.

40. Ovbiagele B, Wing JJ, Menon RS, Burgess RE, Gibbons MC, Sobotka I, et al. Association of chronic kidney disease with cerebral microbleeds in patients with primary intracerebral hemorrhage. Stroke. 2013 Sep;44(9):2409–13.

41. Goos JDC, Henneman WJP, Sluimer JD, Vrenken H, Sluimer IC, Barkhof F, et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology. 2010 Jun 15;74(24):1954–60.

42. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain. 2007 Aug;130(Pt 8):1988–2003.

43. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts. Stroke. 2013 Apr;44(4):995–1001.

44. Kim BJ, Lee S-H, Ryu W-S, Kim CK, Chung J-W, Kim D, et al. Excessive work and risk of haemorrhagic stroke: a nationwide case-control study. Int J Stroke. 2013 Oct;8 Suppl A100:56–61.

45. Kim TJ, Kim CK, Kim Y, Jung S, Jeong H-G, An SJ, et al. Prolonged sleep increases the risk of intracerebral haemorrhage: a nationwide case-control study. Eur J Neurol. 2016;23(6):1036–43.

46. Giroud M, Creisson E, Fayolle H, André N, Becker F, Martin D, et al. Risk Factors for Primary Cerebral Hemorrhage: A Population-Based Study – The Stroke Registry of Dijon. NED. 1995;14(1):20–6.

47. Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. Public Health. 2000 May;114(3):177–82.

48. Sturgeon JD, Folsom AR, Longstreth WT, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007 Oct;38(10):2718–25.

49. O’Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. The Lancet. 2010 Jul 10;376(9735):112–23.

50. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11;364(9438):937–52.

51. Thrift AG, Donnan GA, McNeil JJ. Epidemiology of intracerebral hemorrhage. Epidemiol Rev. 1995;17(2):361–81.

52. Steinke W, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Thalamic Stroke: Presentation and Prognosis of Infarcts and Hemorrhages. Arch Neurol. 1992 Jul 1;49(7):703–10.

53. Schnapper RA. Pontine hemorrhage presenting as ataxic hemiparesis. Stroke. 1982 Aug;13(4):518–9.

54. Nakajima K. Clinicopathological study of pontine hemorrhage. Stroke. 1983;14(4):485–93.

55. Heros RC. Cerebellar hemorrhage and infarction. Stroke. 1982 Jan;13(1):106–9.

56. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous Intracerebral Hemorrhage. New England Journal of Medicine. 2001 May 10;344(19):1450–60.

57. Vonsattel JPG, Myers RH, Hedley‐Whyte ET, Ropper AH, Bird ED, Richardson EP. Cerebral amyloid angiopathy without and with cerebral hemorrhages: A comparative histological study. Annals of Neurology. 1991;30(5):637–49.

58. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993 Jul;24(7):987–93.

59. Steiner T, Diringer MN, Schneider D, Mayer SA, Begtrup K, Broderick J, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. Neurosurgery. 2006 Oct;59(4):767–73; discussion 773-774.

60. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006 Apr 25;66(8):1175–81.

61. Heit JJ, Iv M, Wintermark M. Imaging of Intracranial Hemorrhage. J Stroke. 2017 Jan;19(1):11–27.

62. Kim J, Smith A, Hemphill JC, Smith WS, Lu Y, Dillon WP, et al. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. AJNR Am J Neuroradiol. 2008 Mar;29(3):520–5.

63. Wada Ryan, Aviv Richard I., Fox Allan J., Sahlas Demetrios J., Gladstone David J., Tomlinson George, et al. CT Angiography “Spot Sign” Predicts Hematoma Expansion in Acute Intracerebral Hemorrhage. Stroke. 2007 Apr 1;38(4):1257–62.

64. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. Stroke. 2010 Jan;41(1):54–60.

65. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. Stroke. 1999 Apr;30(4):765–8.

66. Fisher M, French S, Ji P, Kim RC. Cerebral microbleeds in the elderly: a pathological analysis. Stroke. 2010 Dec;41(12):2782–5.

67. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001 Feb 27;56(4):537–9.

68. Gupta R, Phan CM, Leidecker C, Brady TJ, Hirsch JA, Nogueira RG, et al. Evaluation of dual-energy CT for differentiating intracerebral hemorrhage from iodinated contrast material staining. Radiology. 2010 Oct;257(1):205–11.

69. Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001 Apr;32(4):891–7.

70. Furie B, Furie BC. The molecular basis of blood coagulation. Cell. 1988 May 20;53(4):505–18.

71. Heemskerk JWM, Mattheij NJA, Cosemans JMEM. Platelet-based coagulation: different populations, different functions. J Thromb Haemost. 2013 Jan;11(1):2–16.

72. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth. 2014 Sep;58(5):515–23.

73. Altura BM, Altura BT. Role of Magnesium and Calcium in Alcohol-Induced Hypertension and Strokes as Probed by In Vivo Television Microscopy, Digital Image Microscopy, Optical Spectroscopy, 31P-NMR, Spectroscopy and a Unique Magnesium Ion-Selective Electrode. Alcoholism: Clinical and Experimental Research. 1994;18(5):1057–68.

74. Altura BT, Memon ZI, Zhang A, Cheng TP-O, Silverman R, Cracco RQ, et al. Low levels of serum ionized magnesium are found in patients early after stroke which result in rapid elevation in cytosolic free calcium and spasm in cerebral vascular muscle cells. Neuroscience Letters. 1997 Jul 11;230(1):37–40.

75. Appel SA, Molshatzki N, Schwammenthal Y, Merzeliak O, Toashi M, Sela B-A, et al. Serum Calcium Levels and Long-Term Mortality in Patients with Acute Stroke. CED. 2011;31(1):93–9.

76. Chowdhury R, Stevens S, Ward H, Chowdhury S, Sajjad A, Franco OH. Circulating vitamin D, calcium and risk of cerebrovascular disease: a systematic review and meta-analysis. Eur J Epidemiol. 2012 Aug 1;27(8):581–91.

77. Inoue Yasuteru, Miyashita Fumio, Toyoda Kazunori, Minematsu Kazuo. Low Serum Calcium Levels Contribute to Larger Hematoma Volume in Acute Intracerebral Hemorrhage. Stroke. 2013 Jul 1;44(7):2004–6.

78. Tagawa M, Hamano T, Nishi H, Tsuchida K, Hanafusa N, Fukatsu A, et al. Mineral Metabolism Markers Are Associated with Myocardial Infarction and Hemorrhagic Stroke but Not Ischemic Stroke in Hemodialysis Patients: A Longitudinal Study. PLoS ONE. 2014;9(12):e114678.

79. Guo Y, Yan S, Zhang S, Zhang X, Chen Q, Liu K, et al. Lower serum calcium level is associated with hemorrhagic transformation after thrombolysis. Stroke. 2015 May;46(5):1359–61.

80. Liu F, Wang Y, Wang X, Zheng Y, Jin Z, Zhi J. Role of agonistic autoantibodies against type-1 angiotensin II receptor in the pathogenesis of retinopathy in preeclampsia. Scientific Reports. 2016 Jul 6;6:29036.

81. Morotti A, Rosand J, Goldstein JN. Considering Blood Pressure Level in the Association Between Serum Calcium Level and the Size and Expansion in Patients With Intracerebral Hemorrhage—Reply. JAMA Neurol. 2017 Apr 1;74(4):483–4.

82. You S, Han Q, Xu J, Zhong C, Zhang Y, Liu H, et al. Serum Calcium and Phosphate Levels and Short- and Long-Term Outcomes in Acute Intracerebral Hemorrhage Patients. J Stroke Cerebrovasc Dis. 2016 Apr;25(4):914–20.

83. Chen W, Wang L, Chen J. Considering Blood Pressure Level in the Association Between Serum Calcium Level and the Size and Expansion in Patients With Intracerebral Hemorrhage. JAMA Neurol. 2017 Apr 1;74(4):483–483.

84. Tan G, Yuan R, Wei C, Xu M, Liu M. Serum magnesium but not calcium was associated with hemorrhagic transformation in stroke overall and stroke subtypes: a case-control study in China. Neurol Sci. 2018 Aug;39(8):1437–43.

85. Mao J, Jiang W, Liu G, Jiang B. Serum calcium levels at admission is associated with the outcomes in patients with hypertensive intracerebral hemorrhage. British Journal of Neurosurgery. 2019 Feb 18;0(0):1–4.

**ANNEXURES**