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Research Article

Correlation of serum crp levels with disease morbidity and clinical recovery in patients with acute ischemic stroke

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ABSTRACT

Introduction: Stroke remains the second most common cause of death and the leading cause of disability worldwide. Given the large burden of disability following stroke, a need exists to identify clinical biomarkers so that individualized post-ischemic stroke treatment regimens can be developed and aimed at maximizing function and quality of life.
A potential prognostic biomarker of ischemic stroke (IS) is C-reactive protein (CRP), which is currently used for evaluating pathological inflammation and has been extensively studied in relationship to the progression of atherosclerosis.
Methods: A total of 120 randomly selected patients of acute ischemic stroke confirmed by radiological investigations and satisfying inclusion criteria, getting admitted in the department of General Medicine, Government Medical College, Thrissur after getting ethical clearance from IRB was studied. All the participants were subjected to thorough clinical examination and all routine blood investigations including complete blood count, ESR, LFT, RFT, serum electrolytes, Serum CRP, fasting lipid profile and RBS will be obtained. Serum CRP is done by latex slide test. The collected data was entered in excel sheet. Statistical analysis was done using SPSS version 22 trial. Quantitative variables were reported as mean and standard deviation. Qualitative variables were expressed as frequency, proportion, or percentage.
Results: The association of CRP levels at 48 hours showed 60 to 80 years with higher CRP levels, which is statistically significant (p value <0.001). The gender showed females with significantly (p value <0.001) higher CRP levels than males. The duration of hospital stay showed more than or equal to 5 days hospital admission means there is more chance of have higher CRP levels, which is statistically significant (p value <0.0011). The high MRS at admission and at discharge showed a statistically significant (p value <0.001) association with having more CRP score. Similar to MRS NIHSS also showed high CRP levels when the NIHSS was at higher spectrum, and this was statistically significant (p value <0.001). Hence high CRP levels are an indicator for stroke mortality and morbidity.
Conclusion: Our study has shown that CRP level has direct correlation and statistical association with the mortality and morbidity of the patients with ischemic stroke (as evidenced with MRS and NIHSS scores).

INTRODUCTION

Stroke remains the second most common cause of death and the leading cause of disability worldwide.[1] Stroke can be defined as "rapidly developing clinical signs of (at times global) disturbance of cerebral function, lasting more than 24 hours with no apparent cause other than that of vascular origin" this definition includes both ischemic and haemorrhagic aetiologies. Considering the great burden that ischemic stroke exerts, the need to develop more precise estimates of stroke survivors' prognosis remains an important goal. Stroke is the fourth leading cause of death and leading cause of adult disability .Long-term disability is a significant problem among survivors, yet much of the literature has emphasized mortality rates as an outcome measure rather than reduction of morbidity and improved functional status. Studies have shown that nearly 15–30% of stroke survivors are permanently disabled, and 20% of stroke survivors require institutional care 3 months following stroke. Given the large burden of disability following stroke, a need exists to identify clinical biomarkers so that individualized post-ischemic stroke treatment regimens can be developed and aimed at maximizing function and quality of life. Few studies have investigated the relationship between acute biomarkers and functional outcome following stroke.

Ischemic stroke is the most common type of stroke, comprising 87% of all types of stroke[2]. Ischemic stroke causing permanent disability is associated with a remarkable economic and social burden [3]. A decreasing trend in total mortality of ischemic stroke has been observed in many regions[4,5]. The markedly increased number of ischemic stroke survivors may be partly attributed to improvements in in-hospital management.[6] Despite the decline in overall ischemic stroke hospitalizations in the United States, the age-specific acute ischemic stroke

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hospitalization rates increased for patients aged 25 to 64 years[7]. Therefore, early prediction of outcomes after acute ischemic stroke is clinically important for an optimized care. Inflammation plays an important role in the pathophysiology of atherosclerosis and ischemic stroke[8]. Several inflammatory cytokines have been identified as cardiovascular and functional outcome predictors after ischemic stroke[9,10]. Considering the great burden that ischemic stroke exerts, the need to develop more precise estimates of stroke survivors' prognosis remains an important goal.

A potential prognostic biomarker of ischemic stroke (IS) is C-reactive protein (CRP), which is currently used for evaluating pathological inflammation and has been extensively studied in relationship to the progression of atherosclerosis .C-reactive protein (CRP) is a frequently studied inflammatory biomarker that implicated in all stages of ischemic stroke [11]. CRP is an acute phase serum protein is a surrogate for pro-inflammatory interleukin IL-6. It is a member of pentraxin family of proteins and is synthesized by liver, it is also produced by cells in vascular wall such as endothelial cells, smooth muscles and also by adipose tissue. CRP levels in high normal range have been shown to be an underlying systemic inflammation and predictor of future cardiovascular events in prospective cohort studies. Elevated CRP level is independently associated with the excessive risk of ischemic stroke.[12] However, studies on the association of CRP elevation and all-cause mortality risk in patients with acute ischemic stroke have yielded inconsistent results.[13,14] Previous meta-analysis only evaluated the association between CRP elevation and poor functional outcome but not focused on the all-cause mortality outcome in patients with ischemic stroke [15].

Many studies have been done to analyse relationship of CRP with stroke risk factors and stroke severity. But to our knowledge very few studies have been done to investigate the impact of serum CRP levels on clinical outcome after ischemic stroke especially from South India and Kerala. The current study is being considered to study the relation of serum CRP levels with severity and prognosis in case of acute ischemic stroke patients.

AIMS AND OBJECTIVES

1. To study the correlation between serum CRP levels at admission and severity of symptoms in patients with acute ischemic stroke.
2. To study the correlation of serum CRP levels at admission with clinical outcome in patients with acute ischemic stroke.

REVIEW OF LITERATURE

A stroke is a medical condition in which poor blood flow to the brain causes cell death. The main risk factor for stroke is high blood pressure. Other risk factors include high blood cholesterol, tobacco smoking, obesity, diabetes mellitus, a previous TIA, end-stage kidney disease, and atrial fibrillation. An ischemic stroke is typically caused by blockage of a blood vessel, though there are also less common causes. A haemorrhagic stroke is caused by either bleeding directly into the brain or into the space between the brain's membranes. Bleeding may occur due to a ruptured brain aneurysm. Diagnosis is typically based on a physical exam and supported by medical imaging such as a CT scan or MRI scan. A CT scan can rule out bleeding, but may not necessarily rule out ischemia, which early on typically does not show up on a CT scan. Other tests such as an electrocardiogram (ECG) and blood tests are done to determine risk factors and rule out other possible causes.

Low blood sugar may cause similar symptoms. Ischemic stroke can be due to embolic occlusion of large cerebral vessels; source of emboli may be heart, aortic arch, or other arteries such as the internal carotids. Small, deep ischemic lesions are most often related to intrinsic small-vessel disease (lacunar strokes). Low-flow strokes are occasionally seen with severe proximal stenosis and inadequate collaterals challenged by systemic hypotensive episodes. Haemorrhages most frequently result from rupture of aneurysms or small vessels within brain tissue. Variability in stroke recovery is influenced by collateral vessels, blood pressure, and the specific site and mechanism of vessel occlusion; if blood flow is restored prior to significant cell death, the patient may experience only transient symptoms, i.e., a TIA.[16]

Classification of Stroke

Strokes can be classified into two major categories: ischemic and haemorrhagic.[17] Ischemic strokes are caused by interruption of the blood supply to the brain, while haemorrhagic strokes result from the rupture of a blood vessel or an abnormal vascular structure. About 87% of strokes are ischemic, the rest being haemorrhagic. Bleeding can develop inside areas of ischemia, a condition known as "haemorrhagic transformation." It is unknown how many haemorrhagic strokes actually start as ischemic strokes.[18]

Definition

In the 1970s the World Health Organization defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours",[19] although the word "stroke" is centuries old. This definition was supposed to reflect the reversibility of tissue damage and was devised for the purpose, with the time frame of 24 hours being chosen arbitrarily. The 24-hour limit divides stroke from transient ischemic attack, which is a related syndrome of stroke symptoms that resolve completely within 24 hours.[18] With the availability of treatments which can reduce stroke severity when given early, many now prefer alternative terminology, such as brain attack and acute ischemic cerebrovascular syndrome, to reflect the urgency of stroke symptoms and the need to act swiftly.[20]

Stroke is classified into two major types:

- Brain ischemia due to thrombosis, embolism, or systemic hypoperfusion
- Brain haemorrhage due to intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH)

A stroke is the acute neurologic injury that occurs as a result of one of these pathologic processes. Approximately 80 percent of strokes are due to ischemic cerebral infarction and 20 percent to brain haemorrhage.

Brain Ischemia - There are three main subtypes of brain ischemia [21]:

- Thrombosis generally refers to local in situ obstruction of an artery. The obstruction may be due to disease of the arterial wall, such as arteriosclerosis, dissection, or fibromuscular dysplasia; there may or may not be

superimposed thrombosis.

- Embolism refers to particles of debris originating elsewhere that block arterial access to a particular brain region. Since the process is not local (as with thrombosis), local therapy only temporarily solves the problem; further events may occur if the source of embolism is not identified and treated.
- Systemic hypoperfusion is a more general circulatory problem, manifesting itself in the brain and perhaps other organs.

Blood disorders are an uncommon primary cause of stroke. However, increased blood coagulability can result in thrombus formation and subsequent cerebral embolism in the presence of an endothelial lesion located in the heart, aorta, or large arteries that supply the brain.

Transient ischemic attack (TIA) is defined clinically by the temporary nature of the associated neurologic symptoms, which last less than 24 hours by the classic definition. The definition is changing with recognition that transient neurologic symptoms are frequently associated with permanent brain tissue injury. The definition of TIA is discussed in more detail separately.

Thrombosis - Thrombotic strokes are those in which the pathologic process giving rise to thrombus formation in an artery produces a stroke either by reduced blood flow distally (low flow) or by an embolic fragment that breaks off and travels to a more distant vessel (artery-to-artery embolism). Thrombotic strokes can be divided into either large or small vessel disease. These two subtypes of thrombosis are worth distinguishing since the causes, outcomes, and treatments are different.

Large vessel disease - Large vessels include both the extracranial (common and internal carotids, vertebral) and intracranial arterial system (Circle of Willis and proximal branches). Intrinsic lesions in large extracranial and intracranial arteries cause symptoms by reducing blood flow beyond obstructive lesions, and by serving as the source of intra-arterial emboli. At times a combination of mechanisms is operant. Severe stenosis promotes the formation of thrombi which can break off and embolize, and the reduced blood flow caused by the vascular obstruction makes the circulation less competent at washing out and clearing these emboli.

Pathologies affecting large extracranial vessels include:

- Atherosclerosis
- Dissection
- Takayasu arteritis
- Giant cell arteritis
- Fibromuscular dysplasia

Pathologies affecting large intracranial vessels include:

- Atherosclerosis
- Dissection
- Arteritis/vasculitis
- Noninflammatory vasculopathy
- Moyamoya syndrome
- Vasoconstriction

Atherosclerosis is by far the most common cause of in situ local disease within the large extracranial and intracranial arteries that supply the brain. White platelet-fibrin and red erythrocyte-fibrin thrombi are often superimposed upon the atherosclerotic lesions, or they may develop without severe vascular disease in patients with hypercoagulable states. Vasoconstriction (eg, with migraine) is probably the next most common, followed in frequency by arterial dissection (a disorder much more common than previously recognized) and traumatic occlusion. Fibromuscular dysplasia is an uncommon arteriopathy, while arteritis is frequently mentioned in the differential diagnosis, but it is an extremely rare cause of thrombotic stroke. Aortic disease is really a form of proximal extracranial large vessel disease, but it is often considered together with cardioembolic sources because of anatomic proximity.

Identification of the specific focal vascular lesion, including its nature, severity, and localization, is important for treatment since local therapy may be effective (eg, surgery, angioplasty, intraarterial thrombolysis). It should be possible clinically in most patients to determine whether the local vascular disease is within the anterior (carotid) or posterior (vertebrobasilar) circulation and whether the disorder affects large or penetrating arteries.

Delivery of adequate blood through a blocked or partially blocked artery depends upon many factors, including blood pressure, blood viscosity, and collateral flow. Local vascular lesions also may throw off emboli, which can cause transient symptoms. In patients with thrombosis, the neurologic symptoms often fluctuate, remit, or progress in a stuttering fashion

Small vessel disease - Small vessel disease affects the intracerebral arterial system, specifically penetrating arteries that arise from the distal vertebral artery, the basilar artery, the middle cerebral artery stem, and the arteries of the circle of Willis. These arteries thrombose due to:

- Lipohyalinosis (a lipid hyaline build-up distally secondary to hypertension) and fibrinoid degeneration
- Atheroma formation at their origin or in the parent large artery

The most common cause of obstruction of the smaller arteries and arterioles that penetrate at right angles to supply the deeper structures within the brain (eg, basal ganglia, internal capsule, thalamus, pons) is lipohyalinosis (ie, blockage of an artery by medial hypertrophy and lipid admixed with fibrinoid material in the hypertrophied arterial wall). A stroke due to obstruction of these vessels is referred to as a lacunar Lipohyalinosis is most often related to hypertension, but aging may play a role. Microatheromas can also block these small penetrating arteries, as can plaques within the larger arteries that block or extend into the orifices of the branches (called atheromatous branch disease) [22].

Embolism - Embolic strokes are divided into four categories.

- Those with a known source that is cardiac
- Those with a possible cardiac or aortic source based upon transthoracic and/or transesophageal echocardiographic findings
- Those with an arterial source (artery to artery embolism)
- Those with a truly unknown source in which tests for embolic sources are negative

The symptoms depend upon the region of brain rendered

ischemic .[23] The embolus suddenly blocks the recipient site so that the onset of symptoms is abrupt and usually maximal at the start. Unlike thrombosis, multiple sites within different vascular territories may be affected when the source is the heart (eg, left atrial appendage or left ventricular thrombus) or aorta. Treatment will depend upon the source and composition of the embolus.

Cardioembolic strokes usually occur abruptly, although they occasionally present with stuttering, fluctuating symptoms. The symptoms may clear entirely since emboli can migrate and lyse, particularly those composed of thrombus. When this occurs, infarction generally also occurs but is silent; the area of infarction is smaller than the area of ischemia that gave rise to the symptoms. This process is often referred to as a TIA due to embolism, although it is more correctly termed an embolic infarction or stroke in which the symptoms clear within 24 hours.

Cardioembolic strokes can be divided into those with a known source and those with a possible cardiac or ascending aortic source based upon transthoracic and/or transesophageal echocardiographic findings.

High-risk cardiac source - The diagnosis of embolic strokes with a known cardiac source is generally agreed upon by physicians[24,25]; included in this category are those due to:

- Atrial fibrillation and paroxysmal atrial fibrillation
- Rheumatic mitral or aortic valve disease
- Bioprosthetic and mechanical heart valves
- Atrial or ventricular thrombus
- Sick sinus syndrome
- Sustained atrial flutter
- Recent myocardial infarction (within one month)
- Chronic myocardial infarction together with ejection fraction <28 percent
- Symptomatic congestive heart failure with ejection fraction <30 percent
- Dilated cardiomyopathy
- Fibrous nonbacterial endocarditis as found in patients with systemic lupus (ie, Libman-Sacks endocarditis), antiphospholipid syndrome, and cancer (marantic endocarditis)
- Infective endocarditis
- Papillary fibroelastoma
- Left atrial myxoma
- Coronary artery bypass graft (CABG) surgery

Potential cardiac source - Embolic strokes considered to have a potential cardiac) source in which a possible source is detected (usually) by echocardiographic methods [25], including:

- Mitral annular calcification
- Patent foramen ovale
- Atrial septal aneurysm
- Atrial septal aneurysm with patent foramen ovale
- Left ventricular aneurysm without thrombus
- Isolated left atrial smoke on echocardiography (no mitral stenosis or atrial fibrillation)
- Complex atheroma in the ascending aorta or proximal arch

In this group, the association of the cardiac or aortic lesion and the rate of embolism is often uncertain, since some of these lesions do not have a high frequency of embolism and are often incidental findings unrelated to the stroke event [26]. Thus, they are considered potential sources of embolism. A truly unknown source represents embolic strokes in which no clinical evidence of heart disease is present.

Aortic atherosclerosis - In longitudinal population studies with non selected patients, complex aortic atherosclerosis does not appear to be associated with any increased primary ischemic stroke risk. However, most studies evaluating secondary stroke risk have found that complex aortic atherosclerosis is a risk factor for recurrent stroke [27,28].

The range of findings is illustrated by the following studies:

A prospective case-control study examined the frequency and thickness of atherosclerotic plaques in the ascending aorta and proximal arch in 250 patients admitted to the hospital with ischemic stroke and 250 consecutive controls, all over the age of 60 years [29]. Atherosclerotic plaques ≥4 mm in thickness were found in 14 percent of patients compared with 2 percent of controls, and the odds ratio for ischemic stroke among patients with such plaques was 9.1 after adjustment for atherosclerotic risk factors. In addition, aortic atherosclerotic plaques ≥4 mm were much more common in patients with brain infarcts of unknown cause (relative risk 4.7).

Blood disorders - Blood and coagulation disorders are an uncommon primary cause of stroke and TIA, but they should be considered in patients younger than age 45, patients with a history of clotting dysfunction, and in patients with a history of cryptogenic stroke. The blood disorders associated with arterial cerebral infarction include:

- Sickle cell anaemia
- Polycythemia vera
- Essential thrombocytosis
- Heparin induced thrombocytopenia
- Protein C or S deficiency, acquired or congenital
- Prothrombin gene mutation
- Factor V Leiden (resistance to activated protein C)
- Antithrombin III deficiency
- Antiphospholipid syndrome
- Hyperhomocysteinemia

Toast classification - The TOAST classification scheme for ischemic stroke is widely used and has good interobserver agreement .[30] The TOAST system attempts to classify ischemic strokes according to the major pathophysiologic mechanisms that are recognized as the cause of most ischemic strokes. It assigns ischemic strokes to five subtypes based upon clinical features and the results of ancillary studies including brain imaging, neurovascular evaluations, cardiac tests, and laboratory evaluations for a prothrombotic state.
The five TOAST subtypes of ischemic stroke are:

- Large artery atherosclerosis
- Cardioembolism
- Small vessel occlusion
- Stroke of other determined etiology
- Stroke of undetermined etiology

The last subtype, stroke of undetermined etiology, involves cases where the cause of a stroke cannot be determined with any degree of confidence, and by definition includes those with two or more potential causes identified, those with a negative

evaluation, and those with an incomplete evaluation.

SSS-TOAST and CCS classification — Since the original TOAST classification scheme was developed in the early 1990s, advances in stroke evaluation and diagnostic imaging have allowed more frequent identification of potential vascular and cardiac causes of stroke [24]. These advances could cause an increasing proportion of ischemic strokes to be classified as "undetermined" if the strict definition of this category (cases with two or more potential causes) is applied. [31,32]

Brain Hemorrhage - There are two main subtypes of brain haemorrhage:

- Intracerebral hemorrhage (ICH) refers to bleeding directly into the brain parenchyma
- Subarachnoid hemorrhage (SAH) refers to bleeding into the cerebrospinal fluid within the subarachnoid space that surrounds the brain

Intracerebral hemorrhage - Bleeding in ICH is usually derived from arterioles or small arteries. The bleeding is directly into the brain, forming a localized hematoma that spreads along white matter pathways. Accumulation of blood occurs over minutes or hours; the hematoma gradually enlarges by adding blood at its periphery like a snowball rolling downhill. The hematoma continues to grow until the pressure surrounding it increases enough to limit its spread or until the hemorrhage decompresses itself by emptying into the ventricular system or into the cerebrospinal fluid (CSF) on the pial surface of the brain [33,34].

The most common causes of ICH are hypertension, trauma, bleeding diatheses, amyloid angiopathy, illicit drug use (mostly amphetamines and cocaine), and vascular malformations. Less frequent causes include bleeding into tumours, aneurysmal rupture, and vasculitis. The earliest symptoms of ICH relate to dysfunction of the portion of the brain that contains the haemorrhage. The neurologic symptoms usually increase gradually over minutes or a few hours. In contrast to brain embolism and SAH, the neurologic symptoms related to ICH may not begin abruptly and are not maximal at onset. Headache, vomiting, and a decreased level of consciousness develop if the hematoma becomes large enough to increase intracranial pressure or cause shifts in intracranial contents. These symptoms are absent with small haemorrhages; the clinical presentation in this setting is that of a gradually progressing stroke.

ICH destroys brain tissue as it enlarges. The pressure created by blood and surrounding brain edema is life-threatening; large hematomas have a high mortality and morbidity. The goal of treatment is to contain and limit the bleeding. Recurrences are unusual if the causative disorder is controlled (eg, hypertension or bleeding diathesis).

Subarachnoid haemorrhage - The two major causes of SAH are rupture of arterial aneurysms that lie at the base of the brain and bleeding from vascular malformations that lie near the pial surface. Bleeding diatheses, trauma, amyloid angiopathy, and illicit drug use are less common. [35]

Rupture of an aneurysm releases blood directly into the CSF under arterial pressure. The blood spreads quickly within the CSF, rapidly increasing intracranial pressure. Death or deep coma ensues if the bleeding continues. The bleeding usually lasts only a few seconds but rebleeding is very common. With causes of SAH other than aneurysm rupture, the bleeding is less abrupt and may continue over a longer period of time. Symptoms of SAH begin abruptly in contrast to the more gradual onset of ICH. The sudden increase in pressure causes a cessation of activity (eg, loss of memory or focus or knees buckling). Headache is an invariable symptom and is typically instantly severe and widespread; the pain may radiate into the neck or even down the back into the legs. Vomiting occurs soon after onset. There are usually no important focal neurologic signs unless bleeding occurs into the brain and CSF at the same time (meningocerebral haemorrhage). Onset headache is more common than in ICH, and the combination of onset headache and vomiting is infrequent in ischemic stroke [36].

The goal of treatment of SAH is to identify the cause and quickly treat it to prevent rebleeding. The other goal of treatment is to prevent brain damage due to delayed ischemia related to vasoconstriction of intracranial arteries; blood within the CSF induces vasoconstriction, which can be intense and severe. The treatment of SAH is discussed separately.

Acute ischemic stroke

Subtypes are often classified in clinical studies using a system developed by investigators of the TOAST trial, based upon the underlying cause.[37] Under this system, strokes are classified into the following categories:

- Large artery atherosclerosis
- Cardioembolism
- Small vessel occlusion
- Stroke of other, unusual, determined etiology
- Stroke of undetermined etiology

Ischemic strokes are due to a reduction or complete blockage of blood flow.[38] This reduction can be due to decreased systemic perfusion, severe stenosis, or occlusion of a blood vessel. Decreased systemic perfusion can be the result of low blood pressure, heart failure, or loss of blood. Determination of the type of stroke can influence treatment to be used. The main causes of ischemia are thrombosis, embolization, and lacunar infarction from small vessel disease. Ischemic strokes represent about 80 percent of all strokes.

- Thrombosis refers to obstruction of a blood vessel due to a localized occlusive process within a blood vessel.[38] The obstruction may occur acutely or gradually. In many cases, underlying pathology such as atherosclerosis may cause narrowing of the diseased vessel. This may lead to restriction of blood flow gradually, or in some cases, platelets may adhere to the atherosclerotic plaque forming a clot leading to acute occlusion of the vessel. Atherosclerosis usually affects larger extracranial and intracranial vessels. In some cases, acute occlusion of a vessel unaffected by atherosclerosis may occur because of a hypercoagulable state.
- Embolism refers to clot or other material formed elsewhere within the vascular system that travels from the site of formation and lodges in distal vessels causing blockage of those vessel and ischemia. The heart is a common source of this material, although other arteries may also be sources of this embolic material (artery to artery embolism). In the heart, clots may form on valves or chambers. Tumors, venous clots, septic emboli, air, and fat can also embolize and cause stroke. Embolic

strokes tend to be cortical and are more likely to undergo hemorrhagic transformation, probably due to vessel damage caused by the embolus.

- Lacunar infarction occurs as a result of small vessel disease. Smaller penetrating vessels are more commonly affected by chronic hypertension leading to hyperplasia of the tunica media of these vessels and deposition of fibrinoid material leading to lumen narrowing and occlusion.[38] Lacunar strokes can occur anywhere in the brain but are typically seen in subcortical areas. Atheroma can also encroach on the orifices of smaller vessels leading to occlusion and stroke.
- Nonatherosclerotic abnormalities of the cerebral vasculature, whether inherited or acquired, predispose to ischemic stroke at all ages, but particularly in younger adults and children. These can be divided into noninflammatory and inflammatory aetiologies. The following list, though not exhaustive, highlights the major nonatherosclerotic vasculopathies associated with ischemic stroke:
    - Arterial dissection
    - Fibromuscular dysplasia
    - Vasculitis
    - Moyamoya disease
    - Sickle cell disease arteriopathy
    - Focal cerebral arteriopathy of childhood

Decreased systemic perfusion due to systemic hypotension may produce generalized ischemia to the brain.[38] This is most critical in the borderzone (or watershed) areas, which are territories that occupy the boundary region of two adjacent arterial supply zones. The ischemia caused by hypotension may be asymmetric due to preexisting vascular lesions. Areas of the brain commonly affected include the hippocampal pyramidal cells, cerebellar Purkinje cells, and cortical laminar cells discussed below.

Cerebral Autoregulation

Under normal conditions, the rate of cerebral blood flow is primarily determined by the amount of resistance within cerebral blood vessels, which is directly related to their diameter [39]. Dilation of vessels leads to an increased volume of blood in the brain and increased cerebral blood flow, whereas constriction of vessels has the opposite effect. Cerebral blood flow is also determined by variation in the cerebral perfusion pressure.

Cerebral autoregulation is the phenomenon by which cerebral blood flow is maintained at a relatively constant level despite moderate variations in perfusion pressure. The mechanism by which autoregulation occurs is not well understood, and may involve multiple pathways. Evidence suggests that the smooth muscle in cerebral vessels can respond directly to changes in perfusion pressure, contracting when pressure increases and relaxing when pressure drops. Reductions in cerebral blood flow may also lead to dilation of blood vessels through the release of vasoactive substances, although the molecules responsible for this have not been identified. The endothelial release of nitric oxide also appears to play a role in autoregulation.

Maintenance of cerebral blood flow by autoregulation typically occurs within a mean arterial pressure range of 60 to 150 mmHg. The upper and lower limits vary between individuals, however. Outside of this range, the brain is unable to compensate for changes in perfusion pressure, and the cerebral blood flow increases or decreases passively with corresponding changes in pressure, resulting in the risk of ischemia at low pressures and edema at high pressures.

Cerebral autoregulation during stroke - Cerebral autoregulation is impaired during some disease conditions, including ischemic stroke[40]. As cerebral perfusion pressure falls, cerebral blood vessels dilate to increase cerebral blood flow. A decrease in perfusion pressure beyond the ability of the brain to compensate results in a reduction in cerebral blood flow. Initially, the oxygen extraction fraction is increased in order to maintain levels of oxygen delivery to the brain. As the cerebral blood flow continues to fall, other mechanisms come into play.

Inhibition of protein synthesis occurs at flow rates below 50 mL/100 g per minute. At 35 mL/100 g per minute, protein synthesis ceases completely and glucose utilization is transiently increased. At 25 mL/100 g per minute, glucose utilization drops dramatically with the onset of anaerobic glycolysis, resulting in tissue acidosis from the accumulation of lactic acid. Neuronal electrical failure occurs at 16 to 18 mL/100 g per minute, and failure of membrane ion homeostasis occurs at 10 to 12 mL/100 g per minute. This level typically marks the threshold for the development of infarct.

In hypertensive individuals, autoregulation has adapted to occur at higher arterial pressures. Reduction of blood pressure to normal levels could actually exacerbate the derangement to autoregulation that occurs during stroke and lead to a further decrease in cerebral blood flow.

Consequences of Reduction in Blood Flow During Stroke

The human brain is exquisitely sensitive and susceptible to even short durations of ischemia. The brain is responsible for a large part of the body's metabolism and receives about 20 percent of the cardiac output although it is only 2 percent of total body weight. The brain contains little or no energy stores of its own, and therefore relies on the blood for their delivery. Even brief deprivation can lead to death of the affected brain tissue. During stroke, reduction of blood flow to a portion or all of the brain results in a deprivation of glucose and oxygen[41].

Most strokes are caused by focal ischemia, affecting only a portion of the brain, typically involving a single blood vessel and its downstream branches. The region directly surrounding the vessel is the most affected. Within this region, cells in a central core of tissue will be irreversibly damaged and die by necrosis if the duration of ischemia is long enough. At distances farther from the affected vessel, some cells may receive a small amount of oxygen and glucose by diffusion from collateral vessels. These cells do not die immediately, and can recover if blood flow is restored in a timely manner. The central core of tissue destined to die, or containing tissue that is already dead, is called the infarct. The region of potentially salvageable tissue is known as the penumbra.

Mechanisms of ischemic cell injury and death

Brain ischemia initiates a cascade of events that eventually lead to cell death; including depletion of adenosine triphosphate (ATP); changes in ionic concentrations of sodium, potassium, and calcium; increased lactate; acidosis; accumulation of oxygen free radicals; intracellular accumulation of water; and

activation of proteolytic processes.

As a consequence of the electrical failure that occurs during ischemia, the release of the excitatory amino acid glutamate at neuronal synapses is increased [41]. This leads to the activation of glutamate receptors and the opening of ion channels that allow potassium ions to exit the cell and sodium and calcium ions to enter, which has a number of physiologic effects. The primary glutamate receptor subtype involved in ischemic damage is the N-methyl-D-aspartate (NMDA) receptor. In addition, the alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and metabotropic glutamate receptors are thought to play a role. Activation of these receptors leads to membrane depolarization and increased calcium influx.

Numerous cellular signalling pathways respond to calcium levels, and the influx of calcium resulting from glutamate receptor stimulation leads to their activation. These pathways have both beneficial and detrimental effects. The influx of sodium ions is balanced by the influx of water into the cell, leading to oedema. Sodium influx also causes reversal of the normal process of glutamate uptake by astrocyte glutamate transporters, resulting in increased glutamate release.[42] As a result of its increased release and decreased uptake, glutamate accumulates to excessive levels and leads to continuous stimulation. This condition is often referred to as excitotoxicity. Another effect of NMDA receptor activation is the production of nitric oxide [43]. The activity of nitric oxide synthase (NOS) and the total amount of nitric oxide present in the brain are increased following exposure to hypoxia [44].

Nitric oxide is an important signaling molecule within the body and can be beneficial at normal physiologic levels. As an example, endothelial nitric oxide synthase (eNOS) leads to the production of low levels of nitric oxide that cause vasodilation and increase blood flow [45]. However, neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) result in larger amounts of nitric oxide that may lead to brain injury. Nitric oxide is a free radical and reacts directly with cellular components to damage them. Nitric oxide can also react with another free radical, superoxide, to produce the highly reactive peroxynitrite. Peroxynitrite causes single strand breaks in DNA. This results in the activation of DNA repair enzymes, which consume vital energy needed for other processes. DNA damage also may activate the process of apoptosis, leading to cell death.

The production of reactive oxygen species, a normal by product of oxidative metabolism, is also increased during ischemia. Like nitric oxide, they can react with and damage cellular components. Injury to the plasma membrane of a cell can lead to the inability to control ion flux, resulting in mitochondrial failure. Reactive oxygen species, as well as calcium influx and other factors, can also permeabilize the mitochondrial membrane [46]. This leads to metabolic failure as well as the release of initiators of apoptosis and DNA damage. Metabolic failure results in the depletion of cellular ATP levels. ATP is required for nuclear condensation and DNA degradation in the final stages of apoptosis [47]. In the absence of ATP, cell death occurs by necrosis rather than apoptosis. The release of by products from cellular damage and death by necrosis activates components of the inflammatory pathway [48]. The role that inflammation plays during ischemia is mixed, having both positive and negative effects [49]. On the one hand, inflammation results in an increase in blood flow to the ischemic region, which may deliver vital glucose and oxygen to cells. On the other hand, increased blood flow may also deliver more calcium to the area, resulting in increased tissue damage.

Inflammation also results in the migration of activated leukocytes to damaged tissue [50]. Although these leukocytes may remove damaged and necrotic tissue, they also release cytokines to attract additional inflammatory cells. Under severe inflammatory conditions, these cytokines can accumulate to toxic levels.

Necrosis and apoptosis - Cell death following cerebral ischemia or stroke can occur by either necrosis or by apoptosis. The process of necrosis is not well understood. In early stages, cellular chromatin becomes uniformly compacted, the endoplasmic reticulum is dilated, and ribosomes are dispersed [51]. In later stages, swelling of the cell and mitochondria is followed by rupture of the nuclear, organelle, and plasma membranes, leading to the release of cellular material into the surrounding environment. This release of material results in the stimulation of inflammatory processes within the brain.

There are three known pathways by which apoptosis can be initiated[52]:

- Mitochondrial permeabilization
- Death receptor (Fas) pathway
- Endoplasmic reticulum stress

The most well-known pathway involves permeabilization of the mitochondria and release of cytochrome c into the cytoplasm. Activation of membrane-bound Fas, the so called "death receptor," and the accumulation of misfolded proteins at the endoplasmic reticulum during stress, can also lead to apoptosis. These initiators all lead to the activation of caspases that cleave cellular proteins and eventually cause cell death. Caspase-independent mechanisms of apoptosis have also been proposed.

The pattern of cell death after cerebral ischemia, as seen in animal models, depends on the nature of the insult to cerebral tissue.[53] In global cerebral ischemia, such as occurs after cardiac arrest and resuscitation or transient severe systemic hypotension, the entire brain is exposed to ischemia. Formation of infarct is not immediate, but rather occurs after a delay of 12 hours to several days. Cell death is limited to those regions of the brain that are particularly susceptible to ischemic damage, such as the CA1 and CA4 regions of the hippocampus, the striatum, and cortical layers two and five. Cell death in these regions occurs primarily by apoptosis.

In a neuropathology study that compared specimens from 27 patients who had cerebral infarction with specimens from rat brains subjected to experimental transient forebrain ischemia, the patterns of cell death were similar in human and animal brain tissue and included both morphologic and histochemical findings typical of apoptosis.[54] In the human stroke specimens, apoptosis was apparent during the subacute stage, but was not seen in acute or chronic stages.

Levels of ATP in the brain are decreased during stroke due to the lack of glucose and oxygen required for normal cellular metabolism.[55,56] Glucose metabolism is decreased by about 50 percent in both global and focal ischemia models of stroke. As a consequence, ATP levels may fall to 10 percent of normal in global models or 25 percent in the infarct core in focal ischemia models. ATP levels in the penumbra, however, only drop to 50

percent to 70 percent of normal [57].

Loss of brain structural integrity - Cerebral ischemia and infarction leads to loss of the structural integrity of the affected brain tissue and blood vessels. This process of tissue destruction and neurovascular disruption is mediated in part by the release of various proteases, particularly the matrix metalloproteases (MMP) that degrade collagens and laminins in the basal lamina [58]. The loss of vascular integrity leads to a breakdown of the blood-brain-barrier and development of cerebral edema. Catastrophic failure of vascular integrity is postulated to cause hemorrhagic conversion of ischemic infarction by allowing extravasation of blood constituents into the brain parenchyma [59].

Cerebral oedema - Cerebral oedema complicating stroke can cause secondary damage by several mechanisms, including increased intracranial pressure, which may decrease cerebral blood flow, and mass effect causing displacement of brain tissue from one compartment to another (ie, herniation), a process that can be life-threatening. Two types of cerebral edema can occur as a consequence of ischemic stroke.

- Cytotoxic oedema is caused by the failure of ATP-dependent transport of sodium and calcium ions across the cell membrane. The result is accumulation of water and swelling of the cellular elements of the brain, including neurons, glia, and endothelial cells.
- Vasogenic edema is caused by increased permeability or breakdown of the brain vascular endothelial cells that constitute the blood-brain barrier. This allows proteins and other macromolecules to enter the extracellular space, resulting in increased extracellular fluid volume.

C-Reactive Protein (CRP)

CRP, named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumoniae, was the first acute-phase protein to be described and is an exquisitely sensitive systemic marker of inflammation and tissue damage. It is a 23- KDa protein.[60] Other acute-phase proteins include proteinase inhibitors and coagulation, complement, and transport proteins, but the only molecule that displays sensitivity, response speed, and dynamic range comparable to those of CRP is serum amyloid A protein (SAA).

Function*:* CRP is a member of the class of acute phase reactants. It is thought to assist in complement binding to foreign and damaged cells and affect the humoral response to disease. It is believed to play an important role in innate immunity, as an early defence system against infection.

Diagnostic Use: CRP is used mainly as a marker of inflammation. Measuring and charting CRP values can prove useful in determining disease processes or the effectiveness of treatment.

Circulating CRP concentration

In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90th centile is 3.0 mg/l, and the 99th centile is 10 mg/l , but, following an acute-phase stimulus, values may increase from less than 50 µg/l to more than 500 mg/l, that is, 10,000-fold. Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine IL6, although other sites of local CRP synthesis and possibly secretion have been suggested. De novo hepatic synthesis starts very rapidly after a single stimulus, serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological process(es) stimulating CRP production.[61]

Atherosclerosis and inflammation

Chronic systemic, nonvascular inflammation is known to be proatherogenic in general, and acute systemic inflammatory episodes are strongly associated with atherothrombotic events. The increased production of CRP that predicts atherothrombotic events may therefore reflect inflammation elsewhere in the body There is a strong positive association between base-line CRP concentration and BMI, and weight loss lowers the CRP value. Raised baseline CRP values are also associated with many features of the insulin resistance or metabolic syndrome, up to and including frank diabetes mellitus.[62]

C-Reactive Protein in Ischemic Stroke

CRP is a circulating pentraxin that plays a major role in the human innate immune response and provides a stable plasma biomarker for low-grade systemic inflammation. CRP is produced predominantly in the liver as part of the acute-phase response. However, CRP is also expressed in smooth muscle cells within diseased atherosclerotic arteries and has been implicated in multiple aspects of atherogenesis and plaque vulnerability, including the expression of adhesion molecules, the induction of NO, altered complement function, and inhibition of intrinsic fibrinolysis.[63] CRP is considered to be an independent predictor of unfavourable cardiovascular events in patients with atherosclerotic disease. Among patients with stable angina and established coronary artery disease (CAD), plasma levels of hs-CRP have consistently been associated with the risk of recurrent cardiovascular events. Similarly, in the presence of acute coronary ischemia, levels of hs-CRP are predictive of a high risk of vascular events even if troponin levels are not detectable, suggesting that inflammation is associated with plaque vulnerability even in the absence of detectable myocardial necrosis[28]. Despite these data, the most relevant use of hs-CRP remains in the setting of primary prevention. To date, over 2 dozen large-scale prospective studies have shown baseline levels of hs-CRP to independently predict future myocardial infarction, stroke, death from cardiovascular disease, and peripheral arterial disease. Data available through 2002, the Centres for Disease Control and Prevention and the American Heart Association endorsed the use of hs-CRP as an adjunct to global risk prediction, particularly among individuals with intermediate risk.[64]

Several case-control studies with ischemic stroke patients have indicated that recent infections are a possible risk factor for ischemic stroke.[65,66] In particular, there is increasing evidence that inflammatory processes are involved in cerebral ischemia.[67,68] Ischemic brain injury secondary to an arterial occlusion is characterized by acute local inflammation and changes in levels of inflammatory cytokines in body fluids of human patients.[69,70] In addition, several prospective studies have been indicated that elevated levels of inflammation markers, notably C-reactive protein (CRP), are present among individuals at risk for future first-ever myocardial infarction

(MI) or stroke.[71] Elevated CRP also predicts mortality in MI patients and is more reliable predictor of outcome than peak creatine kinase if thrombolytic drugs have been given.[72] Clinical data relating CRP to prognosis after ischemic stroke are sparse; many patients with elevated CRP levels within 72 hours of stroke have an increased risk of death, with an excess of cardiovascular mortality.[73] However, there is no complete information regarding the independent value of this finding or the meaning of CRP determinations carried out at different times after stroke.

Elevated CRP also predicts mortality in MI patients and is a more reliable predictor of outcome than peak creatine kinase concentration if thrombolytic drugs have been given.[4] In a primary care population, CRP concentration correlates with cardiovascular risk indicators.[59] In longitudinal studies of cardiovascular health, baseline CRP has been higher in subjects who develop ischemic heart disease, stroke, or peripheral vascular disease. Inflammation in atherosclerotic plaque is thought to be a significant contributory factor to the plaque rupture that precedes unstable vascular syndromes. These observations suggest that CRP may be a clinically useful risk marker for the development of unstable atherosclerotic disease, as well as a predictor of future cardiovascular morbidity and mortality. We sought an association of CRP concentration with survival after acute stroke and explored whether there was an increased risk of cardiovascular death in patients with elevated CRP.

C-reactive protein (CRP) is an inflammatory biomarker of inflammation and may reflect progression of vascular disease. Conflicting evidence suggests CRP may be a prognostic biomarker of ischemic stroke outcome. Most studies that have examined the relationship between CRP and ischemic stroke outcome have used mortality or subsequent vascular event as the primary outcome measure. Given that nearly half of stroke patients experience moderate to severe functional impairments, using a biomarker like CRP to predict functional recovery rather than mortality may have clinical utility for guiding acute stroke treatments. The primary aim of this study was to systematically and critically review the relationship between CRP and long-term functional outcome in ischemic stroke patients to evaluate the current state of the literature.

Reviewed studies

Keith W. Muir studied on " C-Reactive Protein and Outcome After Ischemic Stroke".[15] This was a subgroup analysis from a prospective observational study based in a University Hospital Acute Stroke Unit serving a population of '260 000. Survival time and cause of death for up to 4 years after the index stroke were determined and related to CRP concentration within 72 hours of stroke and known prognostic variables by a Cox proportional hazards regression model. Ischemic stroke was diagnosed in 228 of 283 consecutive admissions. Median follow-up was 959 days. Geometric mean CRP concentration was 10.1 mg/L. Survival in those with CRP .10.1 mg/L was significantly worse than in those with CRP <10.1 mg/L (P50.00009, log-rank test). Higher CRP concentration was an independent predictor of mortality (hazard ratio, 1.23 per additional natural log unit; 95% CI, 1.13 to 1.35; P50.02), together with age and stroke severity on the National Institutes of Health Stroke Scale. Cardiovascular disease accounted for 76% of deaths in those with CRP ≥10.1 mg/L and 63% of deaths in those with CRP ≥10.1 mg/L. This study Concluded that CRP concentration is an independent predictor of survival after ischemic stroke. These findings are consistent with a role for inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP may predict future cardiovascular mortality.

Bo Yu y *et.al* studied on "C-reactive protein for predicting all-cause mortality in patients with acute ischemic stroke: A meta-analysis".[74] Studies on the association of C-reactive protein (CRP) with all-cause mortality in acute ischemic stroke patients have yielded conflicting results. The objective of this meta-analysis was to evaluate the prognostic value of CRP elevation in predicting all-cause mortality among patients with acute ischemic stroke. They searched the original observational studies that evaluated the association of CRP elevation with all-cause mortality in patients with acute ischemic stroke using. Pooled multivariate-adjusted hazard ratio (HR) with 95% confidence intervals (CI) of all-cause mortality was obtained for the highest versus the lowest CRP level or per unit increment CRP level. A total of 3,604 patients with acute ischemic stroke from eight studies were identified. Acute ischemic stroke patients with the highest CRP level were independently associated with an increased risk of all-cause mortality (HR 2.07; 12 95% CI 1.60–2.68) compared with the lowest CRP category. The pooled HR of all-cause mortality was 2.40 (95% CI 1.10–5.21) for per unit increase in log-transformed CRP. Elevated circulating CRP level is associated with the increased risk of all-cause mortality in acute ischemic stroke patients. This meta-analysis supports the routine use of CRP for the death risk stratification in such patients.

M Di Napoli studied on "C-reactive protein in ischemic stroke: an independent prognostic factor".[75] One hundred ninety-three patients were included in a derivation set (n=128) and a validation set (n=65). Serum CRP was measured, within 24 hours after index ischemic stroke, within 48 to 72 hours, and at hospital discharge. They examined the association between the level of CRP at different stages after stroke and outcome and adjusted for the possible confounding effect using a multivariate Cox proportional hazard model. A cut off point of 1.5 mg/dL for CRP at discharge provided optimum sensitivity and specificity for adverse outcome, based on the receiver operator curves. CRP at admission (hazard ratio [HR] 2.78, 95% CI 1.45 to 5.33; P=0.0021) and discharge (HR 9.42, 95% CI 4.27 to 19.05; P<0.0001) were predictors of the combined end point of new vascular events or death at 1 year. CRP at hospital discharge was the strongest independent marker of adverse outcome (HR 7.42, 95% CI 2.75 to 20.03; P=0.0001). These results were confirmed in the validation set (HR 15.66, 95% CI 3.36 to 72.97; P=0.0005). The study concluded that CRP is a marker of increased 1-year risk in ischemic stroke. CRP at discharge is better related to later outcome and could be of greater utility for risk stratification. These findings are consistent with the hypothesis that elevated CRP may predict future cardiovascular events or death.

Reyna L. VanGilder *et.al* studied on "C-reactive protein and long-term ischemic stroke prognosis." [76] The primary aim of this study was to systematically and critically review the relationship between CRP and long-term functional outcome in ischemic stroke patients to evaluate the current state of the literature. PubMed and MEDLINE databases were searched for original studies which assessed the relationship between acute CRP levels measured within 24 hours of symptom onset and long-term functional outcome. The search yielded articles

published between 1989 and 2012. Included studies used neuroimaging to confirm ischemic stroke diagnosis, high-sensitivity CRP assay, and a functional outcome scale to assess prognosis beyond 30 days after stroke. Study quality was assessed using the REMARK recommendations. Five studies met all inclusion criteria. Results indicate a significant association between elevated baseline high sensitivity CRP and unfavourable long-term functional outcome. Our results emphasize the need for additional research to characterize the relationship between acute inflammatory markers and long-term functional outcome using well-defined diagnostic criteria. Additional studies are warranted to prospectively examine the relationship between high sensitivity CRP measures and long-term outcome. Paolo Calabrò *et.al*.[77] studied on "Role of C-reactive protein in acute myocardial infarction and stroke: possible therapeutic approaches". Myocardial infarction (MI) and stroke are relevant clinical issues in Western Countries for morbidity and mortality. In the last decades, great interest has been paid to the identification of non-traditional risk factors for a better stratification of patients and to recognize those at higher risk, who might particularly benefit from a more aggressive approach. In this field, C-reactive protein (CRP) is the most extensively studied novel marker, since it seems related to several stages of atherogenesis, from its beginning to clinical events (i.e. acute coronary syndromes - ACS). Among its possible pathogenetic role both in coronary artery disease (CAD) and ischemic stroke, several studies have shown that CRP could be used to predict first ever MI and stroke in healthy subjects, as well as outcome in acute settings. Moreover, a decrease of CRP levels can be achieved by several therapies, first of all statins, and this seems to be associated with a better outcome. Then a possible role for CRP to guide treatment of patient with ACS and stroke has been claimed and need to be specifically addressed by large randomized controlled trials.

Sujin Lee *et.al* studied on "Association Between Long-term Functional Outcome and Change in hs-CRP Level in Patients With Acute Ischemic Stroke".[78] They studied 263 patients with acute ischemic stroke and 104 healthy controls (67.5±11.26 and 68.17±11.21 y, respectively). hs-CRP was measured on admission and on the seventh day of hospitalization. The patients were classified into 2 groups on the basis of difference in hs-CRP level from admission to the seventh day of hospitalization (group 1, hs-CRP on admission > the seventh hospital day; group 2, hs-CRP on admission < the seventh hospital day). The correlation between change in hs-CRP level and functional disability using the modified Rankin Scale score (mRS) at 1, 3, 6, and 12 months after stroke onset was analysed. They observed significant differences between initial hs-CRP level in all patients (0.96±2.82 mg/dL) and healthy controls (0.34±0.71 mg/dL, P=0.029). Significant differences in mRS at the 4 different timepoints was not observed between 2 groups (P=0.453, 0.225, 0.229, and 0.396, respectively). The Spearman rank-order correlation coefficients showed that change in hs-CRP level increasingly differed over time and was statistically correlated with mRS (coefficient/P: at 1 mo, 0.139/0.024; at 3 mo, 0.149/0.015; at 6 mo, 0.147/<0.001; and at 12 mo, 0.134/0.03). However, the results were very low correlation coefficients, despite their statistical significance. This study did not clearly show an association between increase in hs-CRP level over time and long-term functional disability.

METHODOLOGY

MATERIALS AND METHODS

Study Setting

All patients who were admitted to Government Medical college, Thrissur with acute ischemic stroke satisfying the inclusion criteria during one year was studied. The consent was taken from the patient or his legally valid immediate relative in the presence of a witness.

Study Design

Prospective observational study.

Inclusion Criteria

All consenting patients with radiologically confirmed acute ischemic stroke who presented within 24 hours of onset of symptoms.

Exclusion Criteria

All patients less than 20 years of age.

Patients with chronic liver disease, chronic kidney disease, thrombophilia, coagulation disorders, malignancies, vasculitis
Patients with previous history of stroke/chronic infarct/ haemorrhagic stroke.
Patients having active infections

Sample Size

A total of 120 randomly selected patients of acute ischemic stroke confirmed by radiological investigations and satisfying inclusion criteria, getting admitted in the department of General Medicine, Government Medical College, Thrissur after getting ethical clearance from IRB was studied.

$$n = \frac{\{z_{1-\frac{\alpha}{2}}\sqrt{P_0(1-P_0)} + z_{1-\beta}\sqrt{P_a(1-P_a)}\}^2}{(P_a - P_0)^2}$$

Po: population proportion =0.3
Pa: sample proportion =0.153
α: significance level = 5
β: power = 1
On applying this equation, required sample size will be = 117 nos.

Study Procedure

After taking informed written consent, all patients satisfying the inclusion criteria admitted in the wards of GMC, Thrissur was enrolled in the study. All the participants were subjected to thorough clinical examination and all routine blood investigations including complete blood count, ESR, LFT, RFT, serum electrolytes, Serum CRP, fasting lipid profile and RBS will be obtained. Serum CRP is done by latex slide test which is simpler, rapid performance and cheaper compared to other tests of CRP For every participant National Institutes of Health Stroke Scale (NIHSS)[79] score at admission, modified Rankin Scale (mRS)[80] at admission and at discharge was taken. The NIHSS at admission, MRS at admission and discharge was calculated and it was seen whether there is any significant difference among the CRP elevated patients

Study Tools

Self-made questionnaire containing questions on socio-demographic details, age, gender, presenting history, general physical examination, laboratory investigations, NIHSS scoring, mRS scores was used.

Study Period

One year (from the date of ethical clearance).

Statistical Analysis

The collected data was entered in excel sheet. Statistical analysis was done using SPSS version 22 trial. Quantitative variables were reported as mean and standard deviation. Qualitative variables were expressed as frequency, proportion, or percentage. Comparison between groups of qualitative data was done using Chi square test and p <0.05 was taken as significant. Quantitative data was analysed using appropriate t test.

Ethical Consideration

Ethical clearance was obtained and consent was obtained before data was collected.

RESULTS

This study is based on patients admitted with acute ischemic stroke satisfying the inclusion criteria.

Gender distribution

Gender distribution showed that males are higher in number i.e 69. (57.5%) and females are less than half of the total patients i.e 51 . (42.5%).

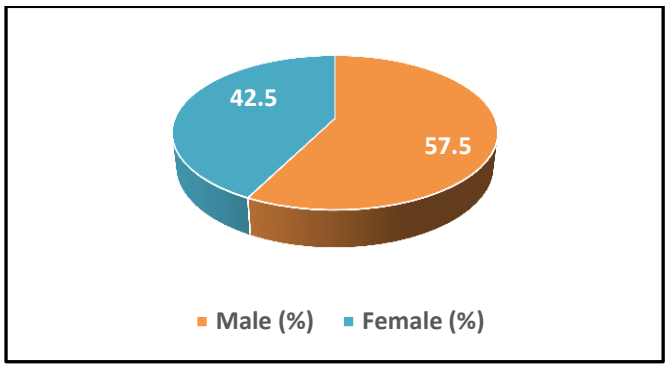

Figure 1 Gender distribution (Male: n=69 nos.; Female: n=51 nos.)

Age and Gender wise distribution

The mean age of the study population is 64.13 ± 8.7 years, in that females are having higher mean age of 66.7 ± 10.4 years when compared to 62.25 ± 6.6 years for males.

Table 1 Age and gender distribution (Male: n=69 nos.; Female: n=51 nos.)

Age groups (years)	Male (n)	(%)	Female (n)	(%)
40 to 59 years	23	33.3	17	33.3
60 to 80 years	43	62.3	29	56.9
> 80 years	3	4.3	5	9.8

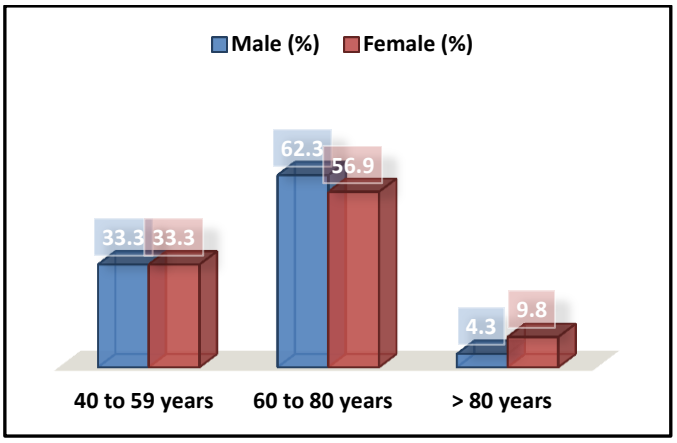

Figure 2 Bar Diagrams showing Age distribution

Majority of them are males and are in the age group 60 to 80 years.

Comorbidities

The Comorbidities showed CAD in 26.7%, CAD with AF in 6.7%, T2DM in 49 patients (40.8%), Hypertension in 77 patients (64.2%) and DLP in 42 patients (35%).

Table 1 Comorbidities

Comorbidities (n=120)	Frequency (n)	Percentage (%)
CAD	32	26.7
CAD with AF	8	6.7
T2DM	49	40.8
Hypertension	77	64.2
DLP	42	35.0

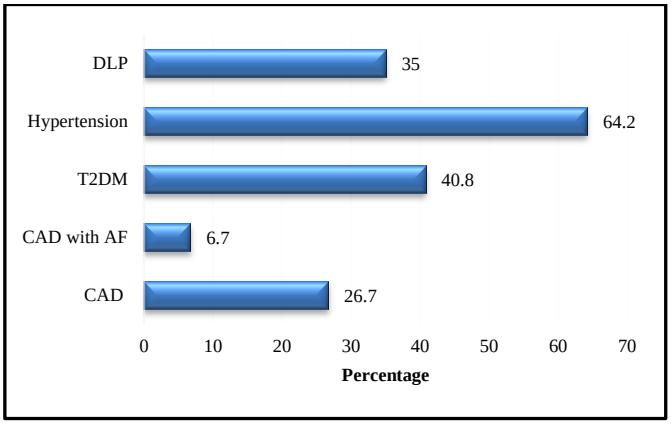

Figure 3 Bar Diagrams showing Age distribution

Addictions

Among the study participants 22.5% are smokers and 12.5% are alcoholic.

Table 3 Addictions

Addictions (n=120)	Frequency (n)	Percentage (%)
Smoking	27	22.5
Alcoholism	15	12.5

Duration of hospital stay

Hospital stay showed majority were admitted more than 5 days (52.5%) and 47.5% were admitted between 2 and 4 days.

Table 2: Duration of hospital stay

Duration of hospital stay (n=120)	Frequency (n)	Percentage (%)
2 to 4 days	57	47.5
≥ 5 days	63	52.5

Modified Rankin Score on admission and on discharge

The MRS at admission showed 0 to 1 with no patients, 2 to 3 with 25 patients (20.8%) and between 4 to 6 score there are more than three forth of the patients (79.2%). At discharge the mean MRS reduced towards normal range with more patients in 0 to 1 range (5%). This difference is statistically significant.

Table 3 MRS on admission and on discharge

MRS on admission (n=120)	Frequency (n)	Percentage (%)
0 to 1	00	00.0
2 to 3	25	20.8
4 to 6	95	79.2
Mean mRS on admission 4.11 ± 0.84		
mRS on discharge (n=120)	Frequency (n)	Percentage (%)
0 to 1	06	05.0
2 to 3	43	35.8
4 to 6	71	59.2
Mean mRS on discharge 3.75 ± 1.2		
T test: p value <0.001		

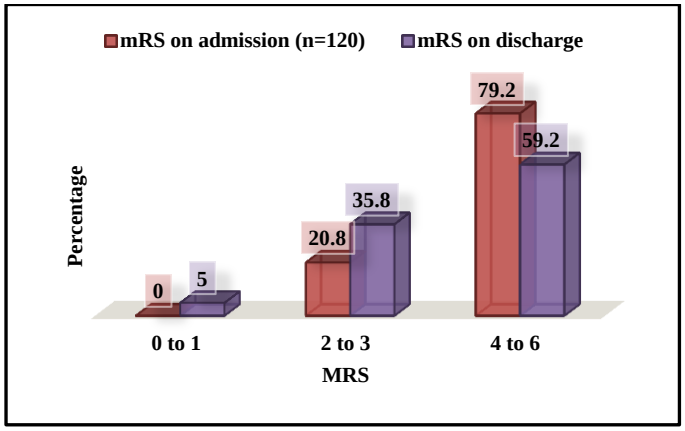

Figure 4 Bar Diagrams showing MRS score admission and at discharge

National institute of Health stroke scale on admission

The NIHSS on admission showed majority of the patients between 5 to 15 (57.5%) followed by 21 to 42 score in 44 patients (36.7%) and lower number in 16 to 20 (5.8%).

Table 4 NIHSS on admission

NIHSS on admission (n=120)	Frequency (n)	Percentage (%)
5 to 15	69	57.5
16 to 20	7	5.8
21 to 42	44	36.7
Mean NIHSS on admission 14.53 ± 7.2		

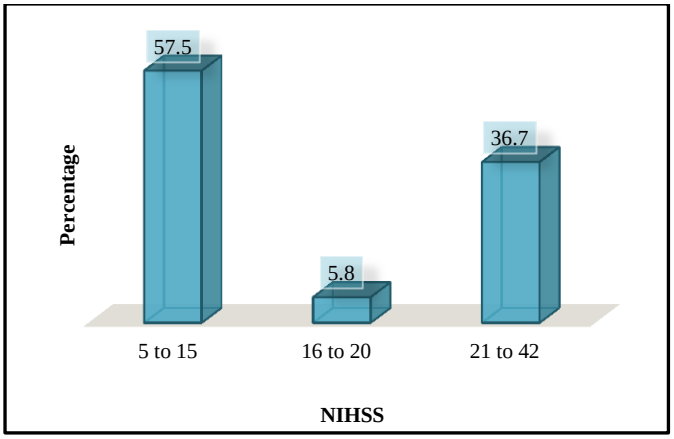

Figure 5 Bar Diagrams showing NIHSS on admission

C-reactive protein at 48 hours

The CRP at 48 hours showed more than half of the patients are having CRP more than 10 mg/dl (54.2%), followed by 29.2% with ≤ 6 mg/dl and 20 patients had 7 to 10 mg/dl (16.7%).

Table 5 CRP at 48 hours

CRP at 48 hours (n=120)	Frequency (n)	Percentage (%)
≤ 6 mg/dl	35	29.2
7 to 10 mg/dl	20	16.7
> 10 mg/dl	65	54.2
Mean CRP at 48 hours: 27.75 ± 2.4 mg/dl		

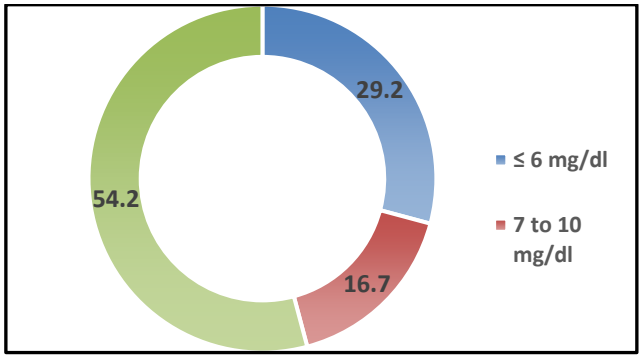

Figure 6 Pie Diagrams showing CRP at 48 hours

CRP and its association with other variables

The association of CRP levels at 48 hours showed 60 to 80 years with higher CRP levels, which is statistically significant (p value <0.001). The gender showed females with significantly (p value <0.001) higher CRP levels than males. The duration of hospital stay showed more than or equal to 5 days hospital admission means there is more chance of have higher CRP levels, which is statistically significant (p value <0.001). The high MRS at admission and at discharge showed a statistically significant (p value <0.001) association with having more CRP score. Similar to MRS NIHSS also showed high CRP levels when the NIHSS was at higher spectrum, and this was statistically significant (p value <0.001). Hence high CRP levels are an indicator for stroke mortality and morbidity. (Table 8)

Table 6 CRP and its association with other variables

	CRP at 48 hours		
Age group in years	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
40 to 59 years	19	0	21
60 to 80 years	16	20	36
> 80 years	0	0	8
Chi-square test value 24.821: d.f 4: p value <0.001			
Gender	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
Male	28	15	26
Female	7	5	39
Chi-square test value 17.903: d.f 2: p value <0.001			
Duration of hospital stay	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
2 to 4 days	22	20	15
≥ 5 days	13	0	50
Chi-square test value 40.963: d.f 2: p value <0.001			
mRS on admission	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
0 to 1	00	00	00
2 to 3	06	12	07
4 to 6	29	08	58
Chi-square test value 22.: d.f 2: p value <0.001			

mRS on discharge	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
0 to 1	6	0	0
2 to 3	24	12	7
4 to 6	5	8	58
Chi-square test value 62.782: d.f 4: p value <0.001			
NIHSS on admission	CRP ≤ 6 mg/dl (n)	CRP 7 to 10 mg/dl (n)	CRP > 10 mg/dl (n)
5 to 15	35	20	14
16 to 20	0	0	7
21 to 42	0	0	44
Chi-square test value 75.050: d.f 4: p value <0.001			

Correlation between CRP and MRS/NIHSS

The Spearman correlation coefficient between the CRP levels and MRS/NIHSS showed significant association. The MRS on admission showed a correlation coefficient of 0.506 (50.6%) with higher CRP levels; the MRS on discharge showed correlation coefficient of 0.557 (55.7%) with higher CRP levels and NIHSS on admission correlation coefficient of 0.661 (66.1%) with higher CRP levels.

Table 7 Correlation between CRP and MRS/NIHSS

Correlation between CRP and MRS/NIHSS	Pearson's Correlation coefficient	p value
Correlation of CRP & MRS on admission	0.506	***< 0.001***
Correlation of CRP & MRS on discharge	0.557	***< 0.001***
Correlation of CRP & NIHSS on admission	0.661	***< 0.001***

DISCUSSION

In our study the association of CRP levels at 48 hours showed 60 to 80 years with higher CRP levels, which is statistically significant. The gender showed females with significantly higher CRP levels than males. The duration of hospital stays showed more than or equal to 5 days hospital admission means there is more chance of having higher CRP levels, which is statistically significant. The high MRS at admission and at discharge showed a statistically significant association with having more CRP score. Similar to MRS, NIHSS also showed high CRP levels when the NIHSS is at higher spectrum, and this is statistically significant. The Spearman correlation coefficient between the CRP levels and MRS/NIHSS showed significant association. The MRS on admission showed a correlation coefficient of 0.506 (50.6%) with higher CRP levels; the MRS on discharge showed correlation coefficient of 0.557 (55.7%) with higher CRP levels and NIHSS on admission correlation coefficient of 0.661 (66.1%) with higher CRP levels.

In our study high CRP levels is an indicator for ischemic stroke mortality and morbidity as associated statistically significant (p value <0.001) with high MRS and NIHSS. The reviewed studies showed similar results with study by Keith *et al*.[15] Survival in those with CRP 10.1 mg/L was significantly worse than in those with CRP <10.1 mg/L (P50.00009, log-rank test). Higher CRP concentration was an independent predictor of mortality (hazard ratio, 1.23 per additional natural log unit; 95% CI, 1.13 to 1.35; P50.02), together with age and stroke severity on the National Institutes of Health Stroke Scale. Cardiovascular disease accounted for 76% of deaths in those with CRP 10.1 mg/L and 63% of deaths in those with CRP 10.1 mg/L. Similarly Bo Yu *yet.al*.[74] Acute ischemic stroke patients with the highest CRP level were independently associated with an increased risk of all-cause mortality (HR 2.07; 12 95% CI 1.60–2.68) compared with the lowest CRP category. The pooled HR of all-cause mortality was 2.40 (95% CI 1.10–5.21) for per unit increase in log-transformed CRP. Elevated circulating CRP level is associated with the increased risk of all-cause mortality in acute ischemic stroke patients. This meta-analysis supports the routine use of CRP for the death risk stratification in such patients. Another study by M Di Napoli *et al*.[75] showed a CRP at admission (hazard ratio [HR] 2.78, 95% CI 1.45 to 5.33; P=0.0021) and discharge (HR 9.42, 95% CI 4.27 to 19.05; P<0.0001) were predictors of the combined end point of new vascular events or death at 1 year. CRP at hospital discharge was the strongest independent marker of adverse outcome (HR 7.42, 95% CI 2.75 to 20.03; P=0.0001). The study concluded that CRP is a marker of increased 1-year risk in ischemic stroke.

Our findings are consistent with the hypothesis that elevated CRP may predict future events or death, which is consistent with the study by Reyna L. VanGilder *et.al*.[76] also showed a significant association between elevated baseline high sensitivity CRP and unfavourable long-term functional outcome. In a similar study by Paolo Calabrò *et.al*.[77] study showed among its possible pathogenetic role both in coronary artery disease (CAD) and ischemic stroke, several studies have shown that CRP could be used to predict first ever MI and stroke in healthy subjects, as well as outcome in acute settings. Sujin Lee *et.al*.[78] showed that the Spearman rank-order correlation coefficients showed that change in hs-CRP level increasingly differed over time and was statistically correlated with mRS (coefficient/P: at 1 mo, 0.139/0.024; at 3 mo, 0.149/0.015; at 6 mo, 0.147/<0.001; and at 12 mo, 0.134/0.03). Similarly, Den Hertog *et al*.[81] studied a multiple logistic regression model was applied to adjust for age, sex, NIHSS score, current cigarette smoking, diabetes mellitus, hypertension, statin use, and stroke subtype. After adjustment for potential confounders, patients with CRP levels ≥7 mg/L had a significantly increased risk of poor outcome (adjusted OR 1.6, 95% CI 1.1–2.4) or death (adjusted OR 1.7, 95% CI 1.0–2.9) at 3 months. Hence, our study has been shown to be similar to the studies reviewed where the CRP level has direct correlation and statistical association with the mortality and morbidity of the patients with ischemic stroke (as evidenced with MRS and NIHSS scores).

CONCLUSION

- Majority of the study population was in the age group of 60 to 80 years
- Most of them were males (57.5%)
- Our study has shown that CRP level has direct correlation and statistical association with the mortality and morbidity of the patients with ischemic stroke (as evidenced with MRS and NIHSS scores).This is statistically significant.

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