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CLINICAL SEVERITY AND OUTCOME IN ASSOCIATION WITH hsCRP LEVELS IN ACUTE ISCHEMIC STROKE

at

K.A.P.V Government Medical College & A.G.M.Government Hospital, Trichy.

Dissertation submitted for

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CERTIFICATE

This is to certify that the dissertation entitled "**CLINICAL SEVERITY AND OUTCOME IN ASSOCIATION WITH hsCRP LEVELS IN ACUTE ISCHEMIC STROKE**" is the bonafide original work of **Dr. VIGNESH WARAN.P** in partial fulfillment of the requirements of M.D General Medicine [Branch-1] examination of THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY to be held in APRIL 2011.

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DECLARATION

I solemnly declare that the dissertation titled **"CLINICAL SEVERITY AND OUTCOME IN ASSOCIATION WITH hsCRP LEVELS IN ACUTE ISCHEMIC STROKE**" is done by me at K.A.P.VISWANATHAM GOVT MEDICAL COLLEGE, TIRUCHIRAPALLI-1 under the guidance and supervision of **Prof.S.Panneer Selvam ,M.D.** The dissertation is submitted to The Tamil Nadu Dr. M.G.R.Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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CONTENTS

INTRODUCTION

There is growing evidence that C-reactive protein (CRP), a peripheral marker of inflammation, is also a marker of generalized atherosclerosis[1]. This relationship between inflammation and atherosclerosis make CRP a potential marker for prognosis after vascular events and a potential predictor of future vascular events. Acute phase proteins have been implicated to play roles both during acute and chronic inflammatory processes in different diseases including ischemic stroke [2]

The onset of cerebral ischaemia triggers a cascade of pro-inflammatory molecular and cellular events[3]. Clinical studies suggest that the strength of this acute response is important in early and late clinical outcomes, early clinical worsening, and extent of brain damage. Variables that are predictors of adverse stroke outcome include erythrocyte sedimentation rate, **and levels of C-reactive protein (CRP)**, interleukin-6, tumour necrosis factor-α and intercellular adhesion molecule-1. Current data indicate that inflammation serves to fuel atherosclerosis and can act as the link between atherosclerosis and atherothrombosis.[4]

Inflammatory factors play an important role in the pathogenesis of ischemic stroke. Acute phase proteins level such as a fibrinogen, CRP, ferritin increase after acute ischemic stroke. These findings support a possible role of an inflammatory stimulus in the acute ischemic stroke.

The WHO has recently set international reference standard for the use of highly sensitive CRP assays. This has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events.

AIM:

1. To predict the functional outcome of acute ischemic stroke in relation with hsCRP levels after 30 days
2. To assess severity of stroke in association with hsCRP levels
3. To determine its association with other risk factors.

EPIDIMEIOLOGY

Globally, cerebrovascular disease (stroke) is the second leading cause of death. It is a disease that predominantly occurs in mid-age and older adults [5]. WHO estimated that in 2005, stroke accounted for 5.7 million deaths world wide, equivalent to 9.9 % of all deaths. Over 85% of these deaths will have occurred in people living in low and middle income countries and one third will be in people aged less than 70 years

Several population-based surveys on stroke were conducted from different parts of India. During the last decade, the age-adjusted prevalence rate of stroke was between 250-350/100,000 [6]. Recent studies showed that the age-adjusted annual incidence rate was 105/100,000 in the urban community of Kolkata and 262/100,000 in a rural community of Bengal. The ratio of cerebral infarct to hemorrhage was 2.21. Hypertension was the most important risk factor. Stroke represented 1.2% of total deaths in India.

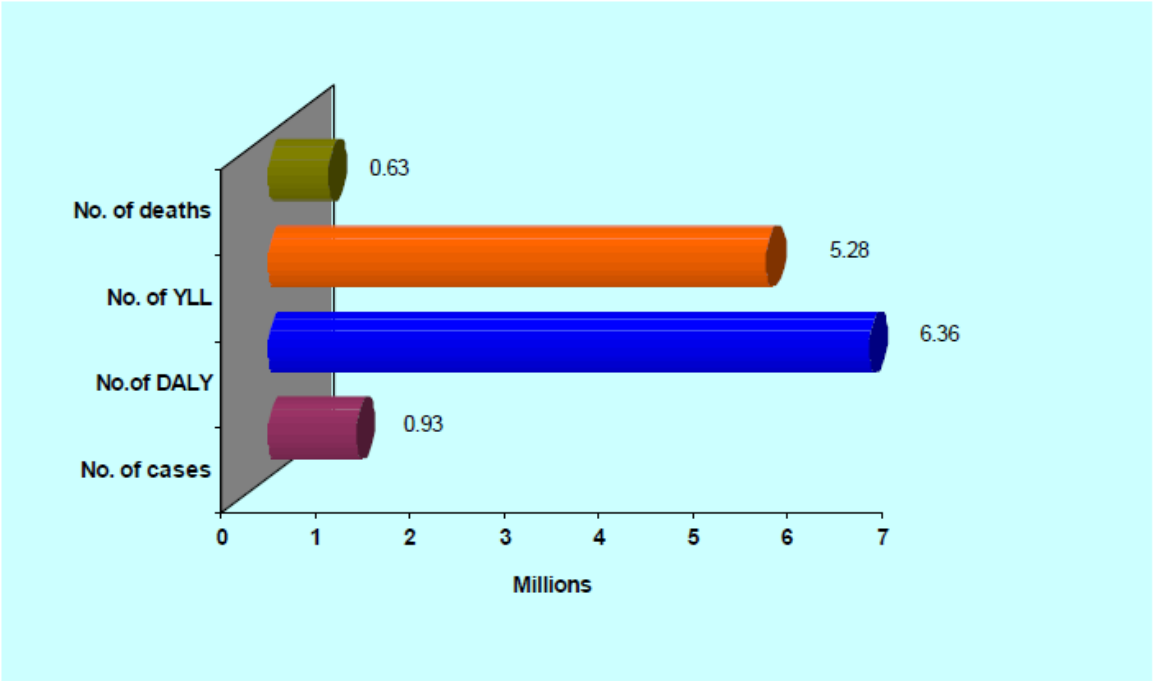
Table 1. The prevalence rates of stroke from various major epidemiological studies in India

Zone	Place	Rural/ urban	Year	Population	Crude prevalence rate per 100,000	Age adjusted prevalence rate per 100,000
North	Rohtak, Haryana[13]	Urban	1971-74	79,046	44	—
	Kuthar Valley, Kashmir[14]	Rural	1986	63,645	143	244*
West	Mumbai, among the Parsis[15]	Urban	1985	14,010	842	424*
	Mumbai [16]	Urban	1997	145,456	220	—
East	Malda, West Bengal[17]	Rural	1989-90	37,286	126	—
	Baruipur, West Bengal[18]	Rural	1992-93	20,842	147	—
	Kolkata [19]	Urban	1998-99	50,291	147	334**
South	Vellore [12]	Rural	1969-71	258,576	57	84#
	Gowribidinur, Karnataka [20]	Rural	1982-84	57,660	52	—
	Bangalore [21]	Rural	1993-95	51,055	165	262#
	Bangalore [21]	Urban	1993-95	51,502	136	

Table 2. The Annual incidence rates of stroke from various epidemiological studies in India

Place	Rural/urban	Year	Population	Annual incidence rate per 100,000	Age adjusted annual incidence rate per 100,000
Vellore [12]	Rural	1969-71	258,576	13	—
Kolkata [19]	Urban	1998-99	50,291	36	105*
Baruipur, West Bengal [22]	Rural	1993-98	20,842	124	262**

BURDEN OF STROKE IN INDIA(2004)



REVIEW OF LITERATURE

World Health Organisation defines the clinical syndrome of "stroke" as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin.[7]

Ischemic stroke is the most common stroke type, representing about 85% of all strokes. Ischemic stroke patients will typically present with the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness.

Focal cerebral ischemia differs fundamentally from global ischemia. In the latter state, if absolute, there is no cerebral blood flow of the entire brain and irreversible destruction of neurons occurs within 4 to 8 min at normal body temperature.

Table 3: Pathologic Classification of Stroke

Pathologic type[8]	Percentage (%)
Cerebral Infraction ▪ Large vessel occlusion ▪ Small vessel occlusion ▪ Cardiac emboli ▪ Hematological disorders	80%
Primary intracerebral hemorrhage ▪ Hypertensive bleeding ▪ Vascular malformations ▪ Bleeding diathesis ▪ Anticoagulants	10%
Non traumatic SAH ▪ Aneurysm ▪ Vascular malformation ▪ Non-aneurysmal SAH	5%
Other causes	5%

CAUSES OF CEREBRAL ISCHEMIA AND INFARCTION

Arterial Wall disorder

• Atherthromboembolism

• Intracranial small vessel disease (lipohyalinosis, microatheroma),

• Trauma

• Dissection

• Fibromuscular dysplasia

• Congenital arterial anomalies

• Moya Moya syndrome

• Embolism from arterial aneurysm

• Inflammatory vascular disease

• Binswanger disease

• Irradiation, infection

• Embolism from the heart

• Hematological disorders

• Miscellaneous:

Pregnancy

OCP

Drug Abuse

Cancer

Migraine

Inflammatory Bowel Disease

Homocystinemia

Fabry's disease

Mitochondrial Cytopathy

Hypercalcemia

Hypoglycemia

Epidermal nevus syndrome

Fat embolism

Thus it is evident that

1) Cerebral infarction accounts for 80% of all strokes.

2) Atherothromboembolism of cerebral arterial supply is the cause in about 50% of the cases of cerebral infarction

RISK FACTORS

Table4: RISK FACTORS [9]

Category	Risk factors
Modifiable	• Elevated blood pressure • Tobacco use • Physical inactivity • Diet (low fruit and vegetable consumption) • Heavy alcohol consumption • Overweight • Diabetes
Environmental	• Passive smoking • Access to medical treatment.
Non-modifiable	• Age • Sex (eg. high age and male sex are in many populations associated with an increased risk). • Family history; genetics

ATHEROSCLEROSIS:

Laboratory and clinical evidence has demonstrated that atherosclerosis is not simply a disease of lipid deposits. Rather, systemic inflammation also plays a pivotal role in atherothrombotic inception and progression. Mononuclear cells, macrophages, and T lymphocytes are prominent in atheromatous plaques in the arterial wall. Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture.[10,11,12]

The development of high sensitivity CRP (hs-CRP) assays has been instrumental in exploration of the role of this acute phase reactant in predicting first cardiovascular and cerebrovascular events.

Accumulating data suggest that arterial tissues can produce CRP, with CRP and complement m-RNA being substantially upregulated in atherosclerotic plaque. Thus CRP may serve as an endogenous activator of complement in atheroma. [13]

PREDICTORS OF STROKE OUTCOME

I) Demographic factors:

1. Age:

Age is one of the major factors that negatively influence the outcome for patients with ischemic stroke [14]. Older patients are less likely to recover than younger patients with similar sized infarcts.

2. Gender:

Some studies have shown male sex associated with poorer outcome whereas other studies have shown no difference. The explanation for this may be hormonal[15]. Estrogen seems to be an important mediator of improved outcome after ischemic brain injury.

3. Race/Ethnicity:

Although it is well understood that the incidence of stroke varies among races and ethnicities, there is no significant difference in the outcome between groups[16].

II) Cerebrovascular risk factors:

1. Previous stroke and atrial fibrillation:

Strokes in patients with previous stroke and atrial fibrillation are usually more severe, more disabling and associated with a higher moratlity.

III) Clinical findings:

1. Level of consciousness and gaze deviation:

Initial level of consciousness is an important predictor with decreased level of consciousness predicting poor outcome[17]. The presence of gaze deviation is associated with poor outcome.

2. Blood Pressure:

Abnormal blood pressure may influence outcome. Clinical studies of blood pressure reduction have shown a decrease in cerebral blood flow to the infarcted area[18]. On the contrary, excessively elevated blood pressure has negative long term effects on blood brain barrier function.

3. Temperature:

For each one degree celsius increase in body temperature, the relative risk of poor outcome rises two fold[19]. This may be due to the increased concentration of excitotoxic neurotransmitters present. Elevated temperature (>37.50C) was an independent predictor of large volume infarct and higher neurological deficit when it occurred in the first 24 hours after first stroke onset.

IV) Laboratory findings:

1. Glycine and glutamate:

High glycine or glutamate levels strongly correlated with large infarct size and severe neurological deficits[20].

2. S-100:

Increased serum levels of S-100 correlate with neurologic outcome.

3. Neuron-specific enolase:

This enzyme has been shown to increase in acute stroke.

4. Serum Glucose:

Hyperglycemia is associated with increased morbidity and mortality[21]. Hyperglycemia seems to produce its detrimental effects by causing a profound cellular acidosis. Clinical studies have shown an association between hyperglycemia and cerebral edema.

Role of Inflammation in Atherosclerosis

Inflammation plays a major role in all phases of atherosclerosis. Stable plaques are characterized by a chronic inflammatory infiltrate, whereas vulnerable and ruptured plaques are characterized by an ‘‘active’’ inflammation involved in the thinning of the fibrous cap, predisposing the plaque to rupture[22.]

SERUM MARKERS CORRELATED WITH PLAQUE INFLAMMATION

Traditional biomarkers for cardiovascular risk include LDL cholesterol and glucose. However, 50% of heart attacks and strokes occur in individuals who have normal LDL cholesterol levels, and 20% of major adverse events occur in patients with no accepted risk factors[23]

PROPOSED BIOMARKERS FALL INTO 9 GENERAL CATEGORIES [24]

1. inflammatory markers
2. markers of plaque erosion,
3.markers of thrombosis
4. lipid-associated markers
5. markers of endothelial dysfunction
6.oxidative stress
7. metabolic markers
8. markers of neovascularisation
9. genetic markers.

Markers of Inflammation

CRP is a circulating pentraxin that plays a major role in the human innate immune response [25] 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[26]. 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 [27].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[29.] Data available through 2002, the Centers 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 [30].

Metabolic Markers

Insulin and glucose are classic metabolic markers of insulin resistance. Recent research has focused on adipokines that may be involved in atherogenesis, including leptin and resistin.[31]

Lipid Markers

Lipid markers, in addition to the classic LDL and highdensity lipoprotein (HDL) cholesterol, include OxLDL cholesterol, small dense LDL cholesterol, lipoprotein (a) [Lp(a)], and lipoprotein-associated phospholipase A2 (Lp-PLA2).[32]

At present, aside from imaging modalities, such as ultrasonography and MRI, and local temperature probes that could help to identify vulnerable plaques, highly sensitive inflammatory circulating markers, such as hs-CRP, cytokines, PAPP-A, and pentraxin 3 are currently the best candidates for diffuse active plaque detection.[33]

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 [34]

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 defense 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 IL-6, although other sites of local CRP synthesis and possibly secretion have been suggested.[35]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.[36]

Structure and phylogeny of CRP

CRP belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins, the other member of which in humans is serum amyloid P component (SAP). The human CRP molecule (M_r 115,135) is composed of five identical nonglycosylated polypeptide subunits (Mr 23,027), each containing 206 amino acid residues. The protomers are noncovalently associated in an annular configuration with cyclic pentameric symmetry.

Ligand binding and biological role of CRP

Human CRP binds with highest affinity to phosphocholine residues, but it also binds to a variety of other autologous and extrinsic ligands, and it aggregates or precipitates the cellular, particulate, or molecular structures bearing these ligands. Autologous ligands include native and modified plasma lipoproteins , damaged cell membranes , a number of different phospholipids and related compounds, small nuclear ribonucleoprotein particles , and apoptotic cells.[37,38,39]

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 [40.] Raised base-line CRP values are also associated with many features of the insulin resistance or metabolic syndrome, up to and including frank diabetes mellitus. Indeed, CRP production predicts the development of type 2 diabetes independently of traditional risk factors [41,42]

Binding of CRP to lipids, especially lecithin (phosphatidyl choline), and to plasma lipoproteins has been known for over 60 years, but the first suggestion of a possible relationship to atherosclerosis came when we demonstrated that aggregated, but not native, nonaggregated, CRP selectively bound only LDL and some VLDL from whole serum. However, native CRP does bind to oxidized LDL and to partly degraded LDL, as found in atheromatous plaques, and then activates complement. This CRP could promote complement activation and thus inflammation in the plaques, and there is experimental evidence supporting a possible role of complement in atherogenesis.[43,44] CRP has also been reported to stimulate tissue factor production by peripheral blood monocytes in vitro and could thereby have important procoagulant effects . Other studies show a variety of effects in cell cultures exposed to CRP, including, for example, increased expression of adhesion molecules, and modulation of NO synthesis.

CRP may have significant proinflammatory effects, and that, by binding to ligands exposed on cells or other autologous structures as a result of infection, inflammation, ischemia, and other pathologies, and triggering complement activation, it may exacerbate tissue damage, leading to more severe disease. The excellent correlation of circulating CRP concentrations with the severity, extent, and progression of many different pathologies, and the prognostic significance of these associations, are consistent with CRP not just being a marker of disease but also contributing to pathogenesis.[45]

HIGH SENSITIVITY CRP (hs-CRP)

In the late 1990s, high sensitivity CRP assays became available, allowing assessment of serum concentrations at the lower end of its distribution. In the subsequent years, hs-CRP levels far beneath the cut-off value, indicative of an immediate-phase response, predicted the risk of cardiovascular, cerebrovascular disease, diabetes mellitus, and cognitive impairment. [46,47]

Normal reference range: 0.02 to 8.0 mg/L

ROLE OF ACUTE PHASE REACTANTS IN ACUTE ISCHEMIC STROKE

Acute phase proteins level such as a fibrinogen, CRP, ferritin increase after acute ischemic stroke. These findings support a possible role of an inflammatory stimulus in the acute ischemic stroke

Fibrinogen:

Fibrinogen is a well known acute phase protein and risk factor for myocardial infarction and stroke. High fibrinogen levels represent an acute phase response in early acute stroke. Fibrinogen is involved in primary

haemostasis, platelet aggregation, and leukocyte-endothelial cell interactions and is the major determinant of whole blood and plasma viscosity.[48]

Ferritin:

It is suggested that high serum ferritin levels within the first day of hospitalization for an acute ischemic stroke are related to poor prognosis.Oxidative metabolism during ischemic stroke together with high iron content in the brain synergise to increase the oxidative damage. High plasma ferritin, as a measurement of iron stores, and high cerebrospinal fluid ferritin have been related to poor outcome in stroke patients.[49]

CRP:

High levels of hs-CRP are associated with adverse cardiovascular and cerebrovascular events. High CRP predicts the risk of carotid stenosis; first stroke and post stroke mortality.

CRP AND ISCHEMIC STROKE

Elevated plasma CRP concentrations are also associated with an increased risk of cerebrovascular events and an increased risk of fatal and nonfatal cardiovascular events in ischemic stroke patients. Determination of plasma CRP concentrations could be used as an adjunct for risk assessment in primary and secondary prevention of cerebrovascular disease and be of

prognostic value. CRP is as an independent predictor of cerebrovascular events in at-risk individuals and ischemic stroke patients.

The 'Bergen stroke study' prospectively studied 498 patients with ischemic stroke who were admitted within 24 hours after the onset of symptoms. CRP and NIH stroke scale (NIHSS) were measured at the time of admission. Short-term functional outcome was measured by modified Rankin scale (mRS) and Barthel ADL index (BI) 7 days after admission. Patients were followed for up to 2.5 years for long-term mortality and future vascular events data. The median CRP at admission was 3 mg/L. High CRP was associated with high NIHSS ($p= 0.01$) and high long-term mortality ($p < 0.0001$). After adjusting for confounding variables, high CRP remained to be associated with high NIHSS ($p = 0.02$) and high long-term mortality ($p =0.002$). High CRP was associated with poor short-term functional outcomes ($mRS > 3$; $BI < 95$). Admission CRP is associated with stroke severity and long-term mortality when measured at least 24 hours after onset. There is a crude association between high CRP and short term functional outcome which is likely secondary to stroke severity. CRP is an independent predictor of long-term mortality after ischemic stroke. Our study in ischemic stroke patients shows that a high CRP at admission is associated with more severe stroke, cardio-embolic etiology, poor functional outcome and high mortality. After adjusting for the effect of confounding factors, high CRP remained to be associated with more severe stroke and high mortality.[2]

FRAMINGHAM STUDY:

To address the baseline CRP level and the risk of subsequent stroke events, the measurement of CRP was done in the Framingham study original cohort who were free of stroke or TIA at the time of their 1980 to 1982 clinical examination and related the baseline CRP plasma generation to the incidence of first stroke or TIA in these subjects during a 12 to 14 years follow up – men with the higher baseline CRP values had twice the risk of ischemic stroke and women with highest CRP level had a 5-fold increase in risk of any vascular event and a 7-fold increase in risk of the comorbid outcome of myocardial infarction or stroke. The data derived from this study demonstrated a graded increase in the incidence of ischemic stroke and TIA with increased levels of CRP.[50]

The Rotterdam study shows that although high CRP is associated with the risk for future stroke, it is not useful for individual stroke prediction

Di Napoli et al concluded that there is insufficient evidence to justify the routine use of CRP for either primary or secondary risk stratification for cerebrovascular disease alone[51]

Another study conducted by Winbeck K [52] and his colleagues investigated the impact of early serial CRP measurements in hyper-acute ischemic stroke on long-term outcome. One hundred twenty-seven consecutive patients without thrombolysis with a first ischemic stroke no more than 12 hours after symptom onset were examined. Serial CRP measurements were done at admission (CRP 1), within 24 hours (CRP 2), and within 48 hours (CRP 3) after symptom onset.

In addition to several cerebrovascular risk factors, the 1-year outcome and the lesion volumes of initial diffusion-weighted images were determined. The CRP level measured within 12 hours after symptom onset of an acute ischemic stroke was not independently related to long-term prognosis. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicted an unfavourable outcome and was associated with an increased incidence of cerebrovascular events.

Ufuk Emry and his colleagues conducted a study to determine the influence of fibrinogen, CRP and other acute phase reactants in acute[53] ischemic stroke in acute period (first 24 to 72 hours). Forty-three patients (23 female, 20 male) who have been diagnosed as acute ischemic stroke, in Neurology department of Ankara Hospital, between June 2001 and December 2001 were included in this study. He concluded that the fibrinogen and CRP have a close relationship as inflammatory markers in the acute phase of ischemic stroke. In this study, which supports the previous ones, it has been found out that CRP levels in the patient were higher than in the control group levels. There was higher CRP level in the patients whose clinical health was poor and had high Stroke Severity Scale.

Another study conducted by Mitchell SV Elkind et al also showed that levels of hs-CRP are higher in stroke patients than in stroke-free subjects.[54] Levels of inflammatory biomarkers associated with atherosclerosis, including hs-CRP, appear to be stable for at least 28 days after first ischemic stroke. This

study also found an association of post-stroke levels of hs-CRP with smoking and stroke severity.

Muir KW et al in his study found that hs-CRP levels above 10.1mg/L when measured within 72 hours of stroke predicted mortality over 4 years102. Others found that the measurement of CRP at 24 or 48 hours, but not at admission, also predicted outcome99. In one study, hs-CRP levels ≥ 15 mg/L at discharge were associated with occurrence of a new vascular event or death at 1 year. hs-CRP levels in the highest quintile measured at least 3 months after a first ischemic stroke or TIA were associated with an increased risk of subsequent stroke or MI in another study

Another study was conducted by Yusuf Tamam et al to show the changes in plasma levels of six APPs (i.e., haptoglobin, ceruloplasmin, hs-CRP, fibrinogen, complement 3 and complement 4 during the first 10 days after acute ischemic stroke. He concluded that the peak levels of APPs were higher in the AIS group than the control group ($p < 0.0001$)1. After stroke, hs-CRP, C3 and fibrinogen reached their highest values on the third day. The plasma levels of hs-CRP correlated positively with other five APPs studied ($p < 0.05$). His findings supported the importance of inflammatory processes after stroke. He suggested that the differences in levels of APPs could be used in predicting the outcome of ischemic stroke patient.

Elevated hs-CRP levels are shown to be strongly associated with the extent of the atherosclerosis in the carotid arteries. The relationship between the

increased serum hs-CRP levels and the atherosclerosis in the carotid arteries was found to be independent from the other known risk factors for the atherosclerosis.

Higher CRP concentration was an independent predictor of mortality together with age and the severity of the stroke on the National Institute of Health Stroke Scale (Muir K. W. *et al.,* 1999). In the same study, it was proposed that the CRP concentration was an independent predictor of the survival after the ischemic stroke which was consistent with the role of the inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP might predict the future cardiovascular mortality Moreover in one study conducted in an elderly population without pre-existing stroke, it has been demonstrated that elevated CRP concentration was an independent risk factor for future ischemic stroke over 10 years of follow-up.

High-sensitivity CRP serum level predicts further intracranial large-artery occlusive disease-related and any major ischemic events in patients with first-ever TIA or stroke with intracranial large-artery occlusive disease. In the study conducted by Arenillas JF, Alvarez-Sabín J, Molina CA 2003,it was shown that Admission inflammatory markers have long-term prognostic implications in patients with acute ischemic neurological events. These findings are relevant in view of the new therapeutic interventions now available for reducing the inflammatory response.Study by anuk in 2002.

CRP formerly considered solely an excellent biomarker of inflammation, is now viewed as a direct contributor in atherosclerosis. Recent evidences have emerged implicating CRP directly in atherogenesis. CRP has been found in human atherosclerotic plaque and CRP has been shown to cause endothelial cell dysfunction[55]

It must be stressed that CRP, because of its analytical and biological properties and the large amount of available data, is the only inflammatory marker accepted for clinical use. hs-CRP not only predicts future cardiovascular events but can also be used to target therapeutic interventions.

Levels of hs-CRP < 1, 1 -3 and >3 mg/L correspond to lower, moderate and higher risk of cardiovascular events at all levels of Framingham Risk Score and at all levels of metabolic syndrome.

Inflammation plays a critical role in the development of vascular disease, and increased levels of the inflammatory biomarkers, lipoprotein-associated phospholipase A_2 (Lp-PLA_2), and high-sensitivity C-reactive protein (hs-CRP) have been shown to be associated with an increased risk for ischemic stroke.[56]

Inflammatory biomarkers, especially hsCRP, may allow improved prediction of the risk of stroke in primary and secondary stroke prevention. Modalities to reduce inflammation are becoming available that may help to modify this risk. Further studies, however, are needed before inflammatory markers become a routine part of the evaluation of stroke patients [57]

MATERIALS AND METHODS

Setting: Medical ward, K.A.P.V.Govt. Medical College,

AGM. Govt. Hospital, Trichy

Study design:

Prospective hospital based study.

Period of study:

January 2010 to Oct 2010

Inclusion criteria:

1. All patients who presented within 48 hours of onset of stroke and who gave informed consent to participate in the study were included.

EXCLUSION CRITERIA:

1. Hemorrhagic stroke
2. Age > 70 yrs
3. NSAID INTAKE
4. Connective tissue disorder/arthritis
5. Recurrent stroke
6. Active infections
7. Ischaemic heart disease/ Coronary heart disease

Study method:

A total of 50 patients who presented with acute ischemic stroke were enrolled into the study. That the stroke was an ischemic one was confirmed by CT scan. As soon as the patients were admitted within 48 hours of onset of stroke, serum samples were taken for hs-CRP estimation. Serum hs-CRP levels were also estimated in fifty normal patients (without any evidence of acute infection, neoplasm, rheumatic heart disease, collagen vascular disease, hypertension, DM, IHD) and was found to be within normal limits. Standard guidelines for the treatment of acute ischemic stroke were followed. None of the patients received any thrombolytic treatment.

CRP and NIH stroke scale (NIHSS) were measured at the time of admission. Short-term functional outcome was measured by modified Rankin scale (mRS) and 30 days after admission.

The NIH stroke score (NIHSS) was assessed at the time of admission. The NIHSS was categorized as 0–7, 8– 14

Patients with score of 0,1and 2 were included in the good outcome and patients with score of 3,4,5 and 6 were included in the poor outcome category.

Definitions followed in the Study:

1.Stroke

Stroke (as defined by WHO) was defined as rapidly developing clinical signs of focal or global (for patients in coma) neurological deficit lasting more than 24 hours or leading to death with no apparent cause other than vascular origin.

2. hs-CRP:

Cut off value for hs-CRP for assessing the prognosis of stroke in this study was taken as ≥ 10.1 mg/L and the serum hs-CRP level was correlated with the functional recovery of patients after 30 days using the MRS. This was based on a study by **The 'Bergen stroke study'**

3.modified Rankin scale (mRS)

The mRS was utilized to assess the functional outcome and residual neurological deficit.

The scale runs from 0-6, running from perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.
- **Score 0,1,2– good outcome**
- **Score of 3,4,5 and 6 -poor outcome**

Risk factors were defined according to protocol

1.Hypertension (HTN)

Hypertension (HTN) was defined as treatment with antihypertensive drugs before stroke onset or introduction of antihypertensive drugs before discharge.

2.Diabetes mellitus

Diabetes mellitus (DM) was defined as treatment with glucose lowering medications or diet prior to stroke onset, or a fasting serum glucose >126 mg/dl during hospital stay.

3. Smoking

Smoking was defined as the use of at least one cigarette per day prior to stroke onset.

MEASUREMENT OF hs-CRP

`The Quantia CRP-US (from Tulip Diagnostics Pvt. Ltd) was used for the measurement of hs-CRP. Quantia CRP is a turbidimetric immunoassay for ultrasensitive determination of CRP in human serum and is based on the principle of agglutination reaction . The test specimen is mixed with quantia CRP US latex reagent and activation buffer and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured at wavelength between 505-578 nm. The increase in turbidity corresponds to the concentration of CRP in the test specimen.

Test procedure:

400 microlitre of quantia CRP US activation buffer (R1) was pipette out and added to 100 microlitre of Quantia CRP US latex reagent (R2) in the measuring cuvette. It was mixed well and incubated for 5 minutes.5 microlitre of test specimen was added and mixed gently. Absorbance (A1) was read exactly at 10 seconds and absorbance (A2) was read again at the end of exactly 4 minutes. ΔA (A2-A1) for test specimen was calculated.ΔA gives the CRP concentration (‘C’) of the test specimen.The CRP concentration C was

multiplied with the dilution factor (F) of the test specimen for obtaining the concentration of CRP in the test specimen.

Concentration of CRP in the test specimen in mg/dl=C x F,

(where F is the dilution factor of the test specimen)

The quantia CRP US reagent has been designed to measure CRP concentrations in the range of 0.015-1.0 mg/dl and is linear within the measuring range.

Statistical Analysis:

The statistical methods used for analysis were

1. Chi- Square test
2. Sensitivity/Specificity test.

All the analysis was done using Windows-based SPSS statistical package (Version 11.5).

RESULTS AND ANALYSIS

Total number of subjects included in the study = 50

Number of males =29(58%)

Number of females =21(42%)

Table 5: Age of individuals

	Number of Cases	**Mean**	**SD**	**Std. Error Mean**	**Minimum age**	**Maximum age**
Age	50	55.56	8.389	1.186	40	69

Mean age of individuals studied =55.56±8.389

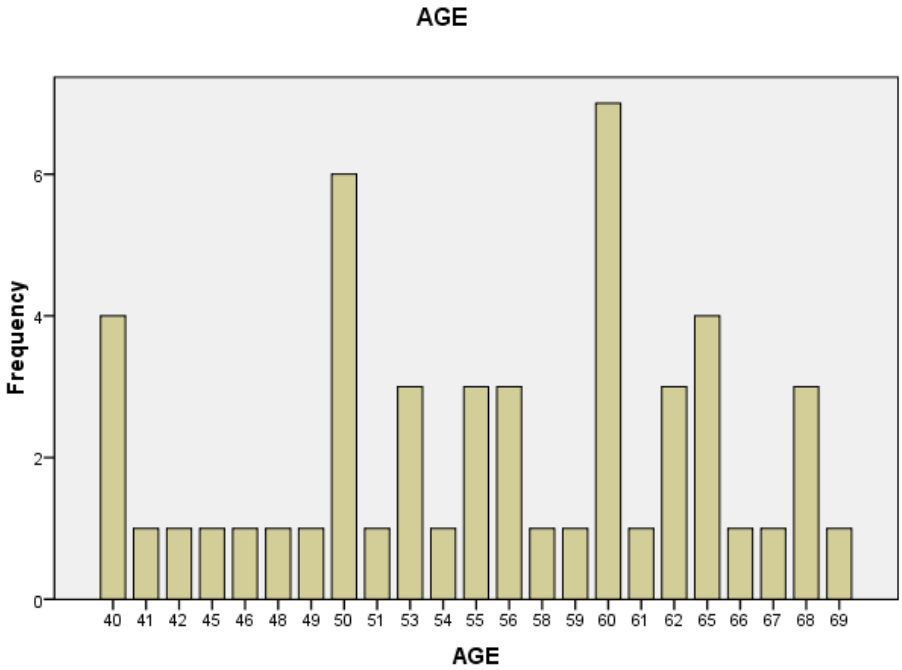


Table 6: Time of sample collection

	Number of Cases	**Mean**	**SD**	**Std. Error Mean**	**Minimum Time**	**Maximum time**
Time of collection(hrs)	50	21.48	10.61	1.5	6	42

Mean time of sample collection =21.48±10.61

Mean time collected within 24 hrs in our study

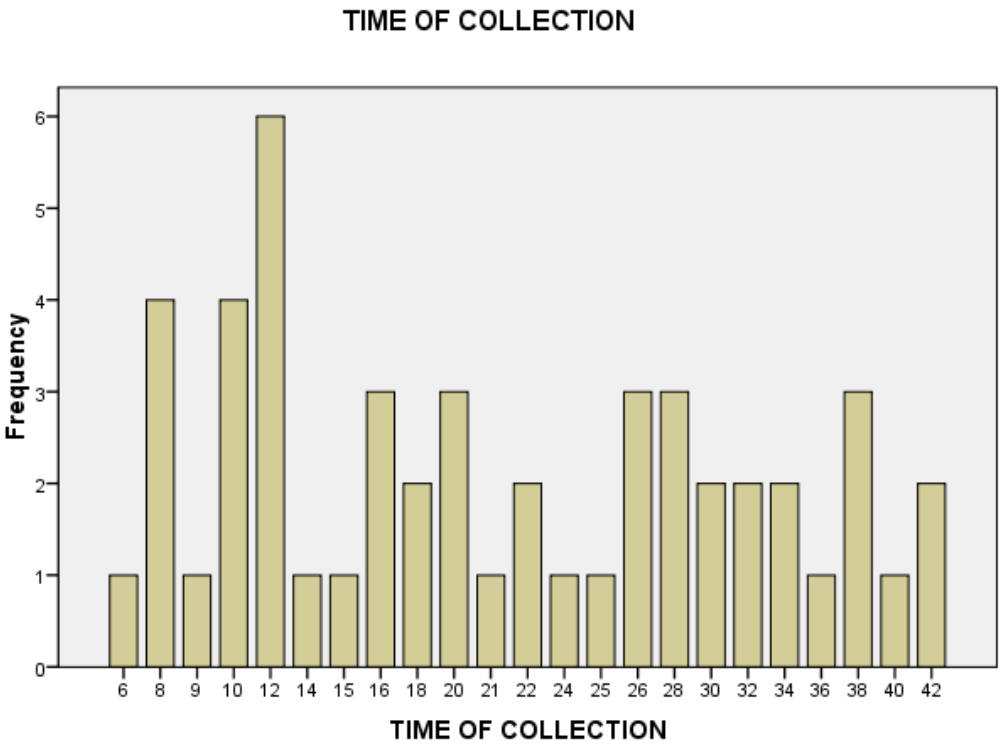


Table 7: CRP and S. Cholesterol levels

Sl.no	Marker	No.Of.Cases	Mean	SD	Std Error Mean	95% Confidence Interval Of Difference	
						lower	upper
1.	Sr.chol	50	205.78	35.05	4.96	196.50	226.70
2.	hsCRP	50	30.06	21.25	3.005	26.45	34.56

Mean serum cholesterol level in these patients was 205.78 mg/dL

Mean hs-CRP level was 30.06 mg/L

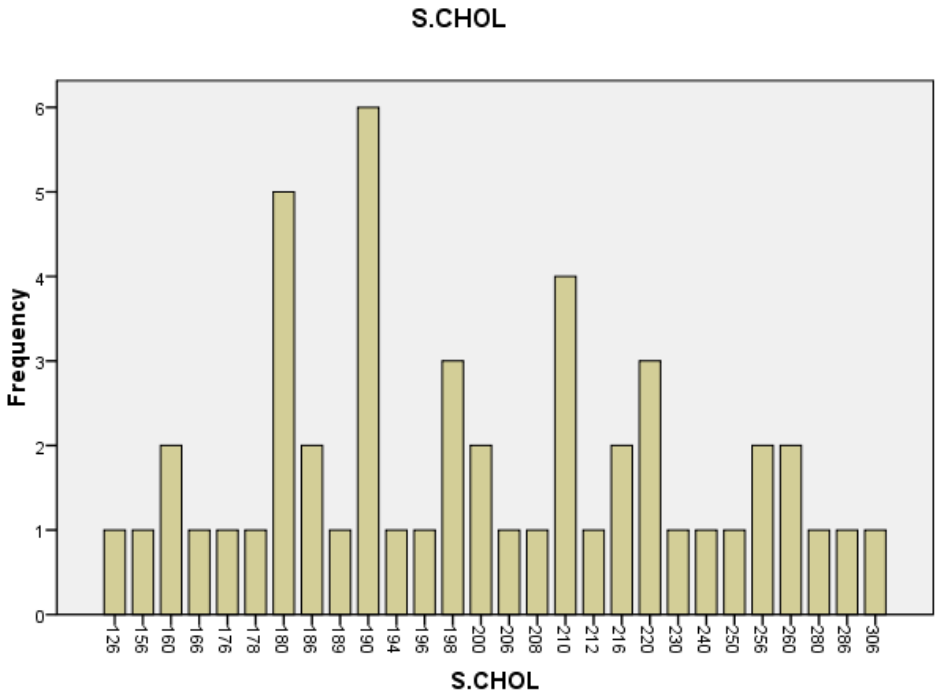


Table 8: hs-CRP vs Age group

Age group (YRS)	**hsCRP mg/l**		**TOTAL**
	<10.1	>10.1	
40-50	7(14%)	9(18%)	16(32%)
51-60	3(6%)	17(34%)	20(40%)
61-70	4(8%)	10(20%)	14(28%)
TOTAL	14(28%)	36(72%)	50(100%)

Table 9: hs-CRP Vs Sex

SEX	**hsCRP mg/l**		**TOTAL**
	<10	>10	
MALE	11(22%)	18(36%)	29(58%)
FEMALE	3(6%)	18(36%)	21(42%)
TOTAL	14(28%)	36(72%)	50(100%)

hsCRP showed no significant relation with gender and age group.

Table 10: hs-CRP Vs Smokers

		CRP GRP		
		0 <10	1 >10	Total
SMOKER	0(NO)	5(10%)	19(38%)	24(48%)
	1(YES)	8(16%)	18(36%)	26(52%)
	Total	13(26%)	37(74%)	50(100%)

P=0.424 NOT SIGNIFICANT

Smoker and non-smoker from our study found to be at equal risk.

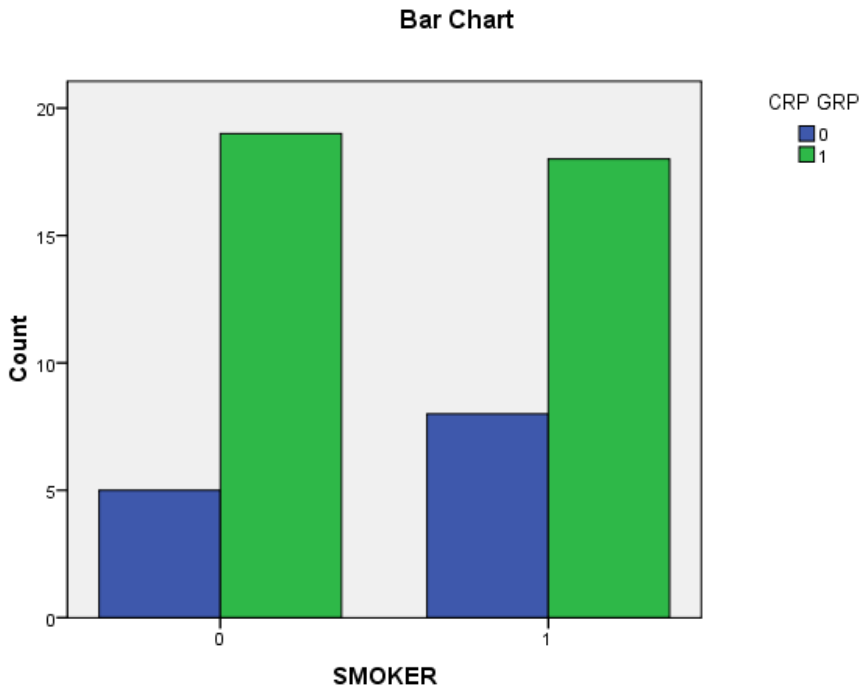


Table 11: hs-CRP Vs Alcoholics

		CRP GRP		
		0 <10.1	1 >10.1	Total
ALCOHOL	0(NO)	5(10%)	25(50%)	30(60%)
	1(YES)	8(16%)	12(24%)	20(40%)
	Total	13(26%)	37(74%)	50(100%)

P=0.065 NOT SIGNIFICANT

Alcoholics not associated with elevated hsCRP levels.

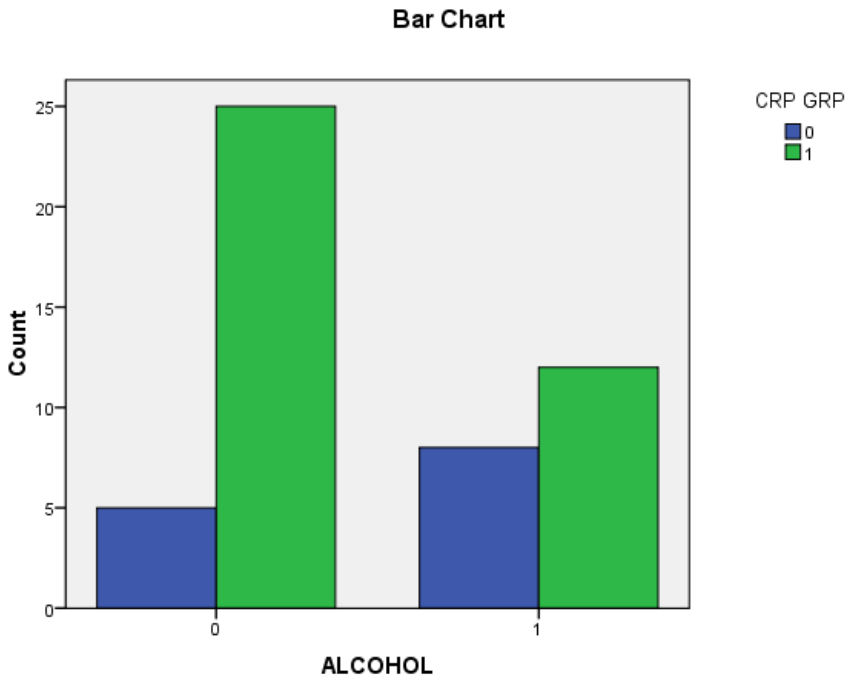


Table 12: hs-CRP Vs Hypertension

		CRP GRP		
		0 <10.1	1 >10.1	Total
HT	0(NO)	7(14%)	19(38%)	26(52%)
	1(YES)	6(12%)	18(36%)	24(48%)
	Total	13(26%)	37(74%)	50(100%)

P=0.877 NOT SIGNIFICANT

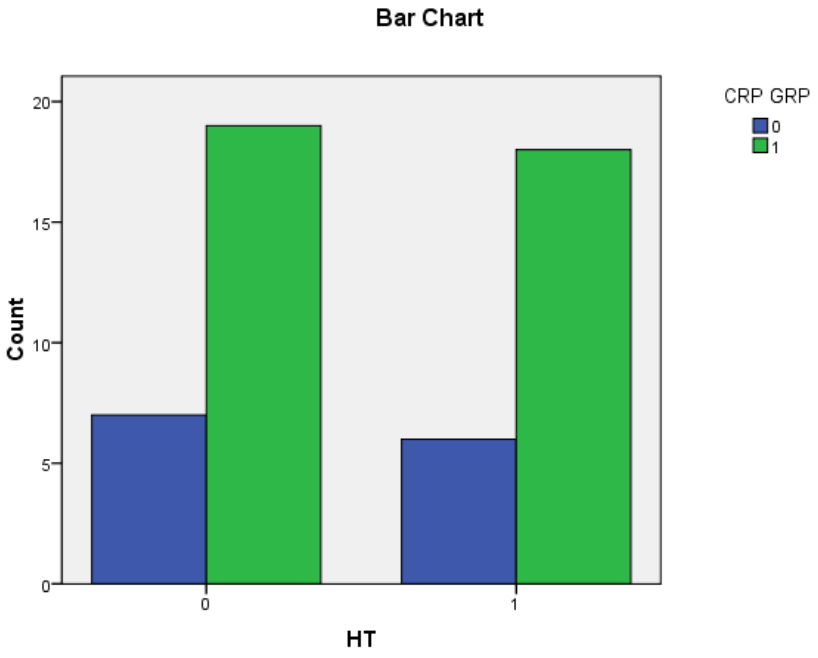


Table 13: hs-CRP Vs Diabetics

		CRP GRP		
		0 <10.1	1 >10.1	Total
DM	0(N0)	9(18%)	17(34%)	26(52%)
	1(YES)	4(8%)	20(40%)	24(48%)
	Total	13(26%)	37(74%)	50(100%)

P=0.148 NOT SIGNIFICANT

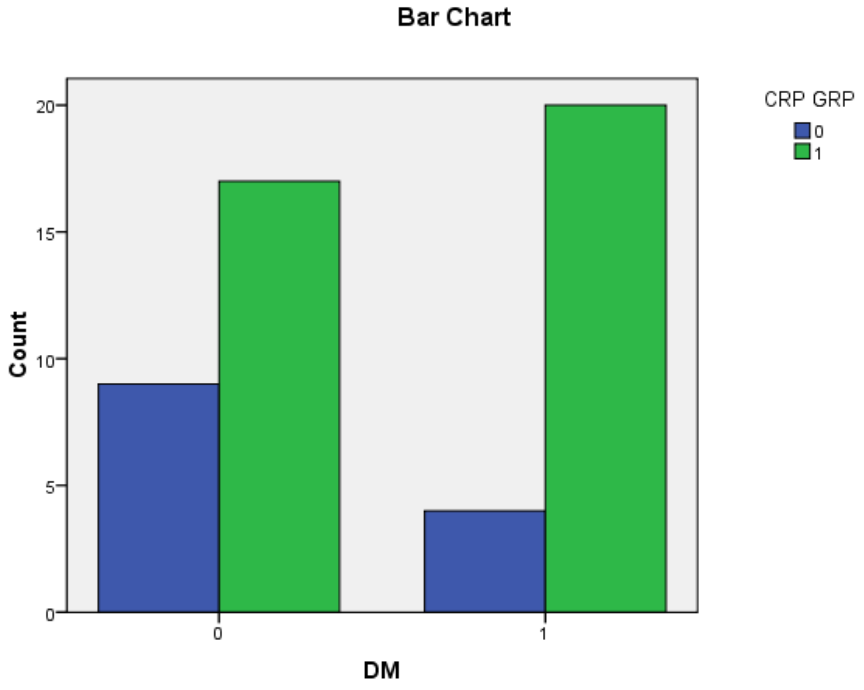


Table 14: hs-CRP Vs mRS Group

		MRS GRP		
		0	1	Total
CRP GRP	0(<10.1)	13(26%)	0	13(30%)
	1(>10.1)	4(8%)	33(66%)	37(70%)
	Total	17(34%)	33(66%)	50(100%)

P= 0.002 SIGNIFICANT

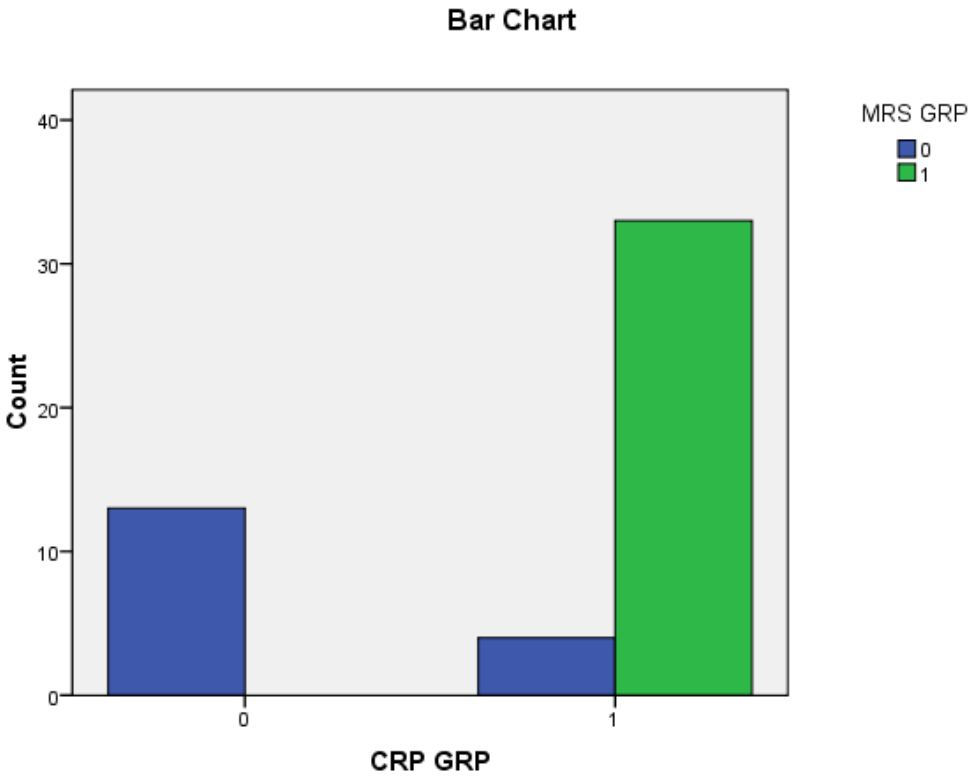
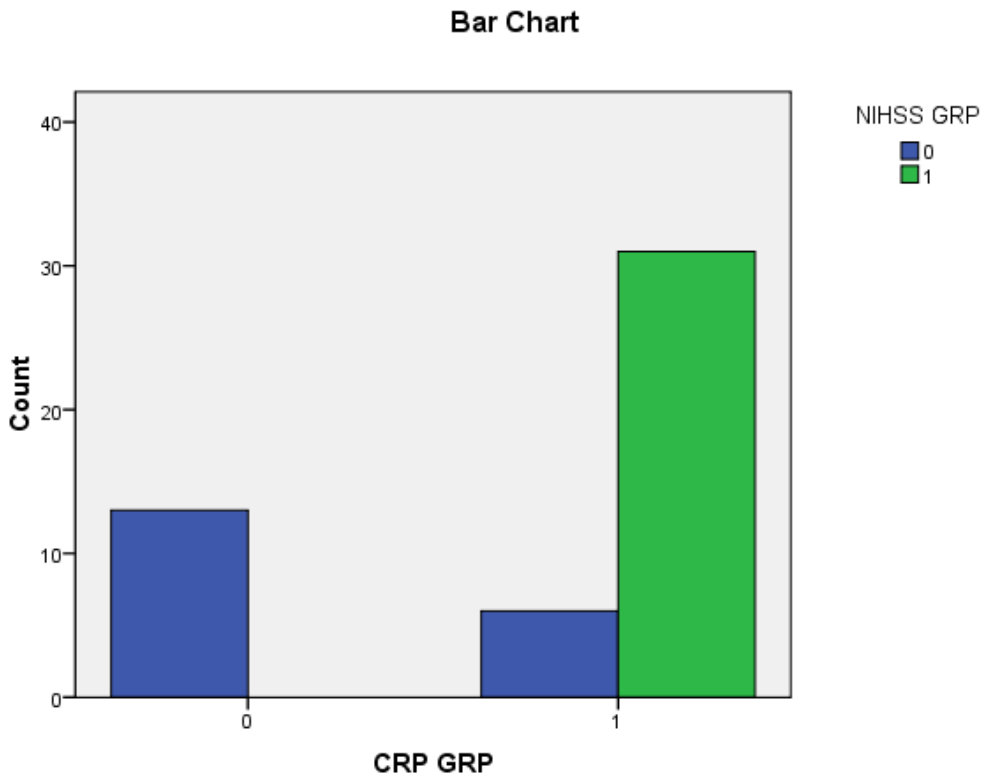


Table 15: hs-CRP Vs NIHSS Group

		NIHSS GRP		
		0	1	Total
CRP GRP	0	13(26%)	0	13(26%)
	1	6(12%)	31(62%)	37(74%)
	Total	19(38%)	31(62%)	50(100%)

P= 0.001 SIGNIFICANT



DISCUSSION

The correlation between hs-CRP levels measured within 48 hours of onset of stroke to that of the functional outcome of the patient at the end of 30 days (using mRS) was carried out.

Out of the 50 cases enrolled in the study, 37 cases (74%) had CRP values > 10.1 mg/L and 13 cases (26%) had CRP < 10.1 mg/L.

Out of the 37 cases with CRP > 10.1 mg/L 33 cases(66%) associated with poor outcome 4 cases (8%) associated with favourable outcome.

On the other hand, of the remaining 13 cases with CRP < 10.1 mg/L,none had poor outcome all 13 (26%) had favourable outcome.

Out of the 50 patients, 1 died who had very high hs-CRP levels. Thus patients with CRP levels < 10.1 mg/L had a relatively favourable outcome (mRS score of 0,1, 2) when compared to patients with levels > 10.1 mg/L (mRS score of 3,4,5and 6).

So, in our study, the correlation between hs-CRP levels within 48 hours of onset of ischemic stroke and the prognosis of the cases at the end of 30 days was statistically significant, the p value for hs-CRP being 0.001

This is consistent with the various studies conducted using hs-CRP as a prognostic indicator of acute ischemic stroke.

Table 16: Studies conducted using hs-CRP as a prognostic indicator

SL.NO	STUDY	YEAR
1	The 'Bergen stroke study'	2009
2	Mitchell S V Elkind et al	2006
3	Ufuk Emre et al	2007
4	Di Napoli et al	2005
5	Winbeck K et al	2002

The major difference between our study and those of other studies mentioned above was that our study involved only hs-CRP levels and not other acute phase reactants like fibrinogens. Also, in our study we assessed the outcome of patients with acute ischemic stroke at the end of four weeks and not at the end of one year. Also, we measured the CRP levels only within 48 after the onset of ischemic stroke and not at the end of four weeks or at the time of

discharge. This was because of the cost involved in the measurement of hs-CRP. The other reason, why our study did not have significant correlation with age, sex, DM, IHD was that our study sample size was very small.

Out of the 37 cases with CRP > 10.1 mg/L 31 cases (62%) had admission NIHSS >7 and 6 cases(12%) had NIHSS <7. On the other hand, of the remaining 13 cases with CRP < 10.1 none had admission NIHSS>7.

Diabetes had no statistical significance with hs-CRP in our study. This is in contrast to many of the previous studies. This may be because of the small sample size and also because of the fact that our study included only acute ischemic stroke patients; it was not done exclusively on diabetic subjects.

In our study, total serum cholesterol did not have statistically significant correlation with hs-CRP levels. This is in contrast to a study conducted by So Yeon Ryu et al in 2005. A limitation of our study was that only total serum cholesterol was estimated and not the complete lipid profile.

In our study, smoking and alcohol had no statistical significance with hs-CRP levels. Also age and sex had no statistical significance with hs-CRP levels.

As CRP was found to be an independent risk indicator of further cardiovascular and neurovascular events as shown by the subset of Framingham study, routine CRP screening of susceptible population like chronic smokers and sibilings and first degree relatives of patients with IHD and stroke may prove a valuable indicator for predicting future atherothrombotic events and then it can be assessed as a routine indicator for aspirin prophylaxis. Thus CRP measurements may be helpful in grading patients into high risk and low risk category for predicting future cardiovascular and neurovascular events.

CONCLUSION

Patients with **elevated hs-CRP had a poorer outcome** when compared to patients with lower levels of CRP, 30 days after the onset of ischemic stroke.

Patients with elevated hs-CRP had a poor admission NIH stroke score>7.

• hs-CRP levels showed no significant correlation in patients with high blood pressure.

• hs-CRP levels had no significant correlation with age or gender.

• hs-CRP did not show a statistically significant correlation with smoking or cholesterol intake.

- There was no statistically significant correlation between hs-CRP levels and those with diabetes.
- hs-CRP is 100% sensitive and 86.14% specific as a prognostic tool in acute ischemic stroke. hs-CRP has a diagnostic accuracy of 94% in patients with acute ischemic stroke.

SL.NO	NAME	AGE	SEX	TIME OF COLLECTION	SMOKER	ALCOHOL	HT	DM	CHOLESTROL	hsCRP	CRP GRP	MRS	MRS GRP	NIHSS	NIHSS GRP
1	PASUPARAJ	65	1	16	0	0	1	0	180	24.8	1	3	1	2	0
2	KALIMUTHAN	50	1	20	1	0	0	0	220	11.1	1	4	1	11	1
3	NAZEER AHMED	50	1	12	1	1	1	0	216	58.6	1	5	1	11	1
4	DHARMALINGAM	62	1	26	1	1	0	0	160	9.1	0	3	1	3	0
5	SELVAMARY	53	2	10	0	0	1	1	220	74.2	1	4	1	12	1
6	MUNIYAMMAL	58	2	42	0	0	1	1	306	42.33	1	3	1	9	1
7	SUBRAMANI	60	1	36	1	1	0	1	178	5.6	0	1	0	3	0
8	ANNADURAI	40	1	22	1	1	0	0	260	49.4	1	3	1	9	1
9	ANNAKILI	53	2	28	0	0	0	1	250	53.6	1	3	1	12	1
10	LAKSHMI	54	2	8	0	0	1	0	160	8.16	0	1	0	4	0
11	PERIYASAMY	60	1	10	1	1	1	0	190	17.7	1	3	1	8	1
12	RAMAN	50	1	30	1	1	1	0	196	6	0	1	0	3	0
13	KARUPPAN	50	1	18	1	1	0	0	198	25.2	1	4	1	9	1
14	XAVIER	45	1	26	0	1	1	0	126	3.4	0	1	0	2	0
15	FATHIMA	60	2	32	0	0	0	1	286	20.8	1	3	1	10	1
16	MARIYAMMAL	55	2	15	0	0	1	1	256	58.2	1	4	1	9	1
17	PODUM PONNU	53	2	10	0	0	0	0	180	5.6	0	1	0	4	0
18	VEERAMANI	51	1	22	1	1	1	1	189	83	1	5	1	13	1
19	MADALAIMUTHU	55	1	16	1	1	0	0	280	71.09	1	6	1	14	1
20	CHINNASAMY	60	1	38	0	0	0	1	190	13.4	1	2	0	4	0
21	UMA	67	2	9	0	0	1	0	230	25.2	1	4	1	10	1
22	KALYANI	68	2	24	0	0	0	1	216	48.1	1	4	1	9	1
23	ABDUL HAMEED	66	1	40	0	0	1	1	208	10	0	3	1	4	0
24	RAJKUMAR	40	1	16	1	1	0	0	198	7.1	0	1	0	3	0
25	KANDASAMY	68	1	20	1	1	1	1	198	26.2	1	3	1	8	1
26	SEKAR	46	1	25	1	1	0	0	190	35.6	1	2	0	5	0

27	CHINATHAMBI	65	1	32	1	0	0	1	220	35.4	1	3	1	9	1
28	AROKYAMARY	60	2	18	0	0	1	1	240	50.1	1	4	1	12	1
29	SANGEETHA	50	2	30	0	0	1	0	200	40.6	1	3	1	10	1
30	MEENAMBAL	62	2	42	1	0	1	1	260	62.3	1	4	1	12	1
31	MAHALINGAM	65	1	34	1	0	1	0	210	35.1	1	3	1	10	1
32	RAJASEKARAN	48	1	8	1	1	0	1	190	37.1	1	3	1	9	1
33	LEELA	50	2	12	0	0	0	1	210	4.2	0	1	0	4	0
34	BALAKRISHNAN	60	1	38	1	0	1	1	190	39.43	1	3	1	11	1
35	NALLU	41	1	26	1	1	0	0	180	8.3	0	1	0	8	1
36	SUBRAMANI	40	1	6	1	1	0	0	206	6.7	0	1	0	2	0
37	RAJALINGAM	62	1	14	1	0	1	1	156	2.88	0	1	0	5	0
38	CHELLAM	68	2	28	0	0	0	0	256	25.2	1	3	1	6	0
39	LEELAVATHY	61	2	34	0	0	1	0	180	26.1	1	1	0	3	0
40	SUNDARI	59	2	20	0	0	0	1	210	25.2	1	3	1	9	1
41	THANGAMANI	56	1	38	1	1	0	0	180	26.96	1	1	0	4	0
42	CHINNAYAN	65	1	8	1	1	1	0	186	4.9	0	1	0	3	0
43	KARUTHAVANAM	56	2	12	0	0	1	0	186	11.68	1	3	1	10	1
44	RASU	60	1	21	1	1	1	1	190	19.9	1	4	1	13	1
45	THOMAS	40	1	28	1	1	0	0	176	70.6	1	4	1	11	1
46	MANICKAM	56	1	12	1	0	0	1	200	31.8	1	3	1	9	1
47	THILAGAVATHY	69	2	12	0	0	0	1	212	41.6	1	3	1	8	1
48	MEENAKSHI	42	2	8	0	0	1	0	166	25.2	1	3	1	11	1
49	AMBIGA	49	2	10	0	0	0	1	194	33.2	1	3	1	10	1
50	SELVI	55	2	12	0	0	0	1	210	45.1	1	4	1	13	1

CLINICAL SEVERITY AND OUTCOME IN ASSOCIATION WITH hsCRP LEVELS IN ACUTE ISCHEMIC STROKE

PROFORMA

NAME: I.P.NO:

AGE:

SEX:

OCCUPATION: ADDRESS:

PRESENTATION:

PAST H/O:

DM- YES/NO ARTHRITIS- YES/NO

HT- YES/NO NSAID INTAKE- YES/NO

CAD- YES/NO TIA/CVA – YES/NO

PERSONAL H/O:

SMOKING- YES/NO

ALCOHOL- YES/NO

CLINICAL EXAMINATION:

GENERAL EXAMINATION:

VITALS: PR- /MIN BP- MM HG

CVS:

RS:

ABDOMEN:

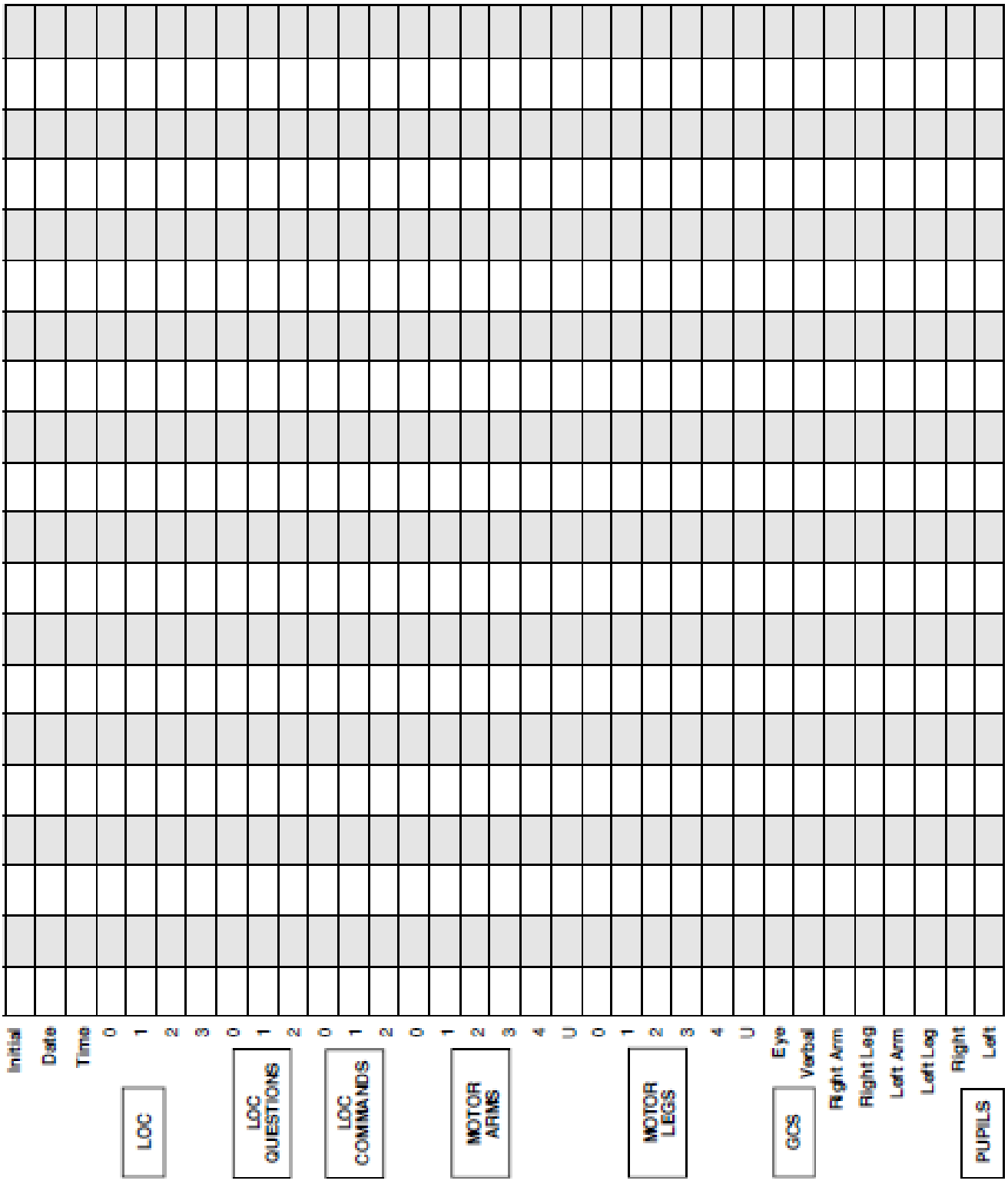
CNS:

INVESTIGATIONS:

S.NO	INVESTIGATION	REPORT
1.	COMPLETE HEMOGRAM	HB- TC- DC- ESR-
2.	BLOOD SUGAR	
3.	BLOOD UREA	
4.	SERUM CREATININE	
5.	SERUM CHOLESTROL	
6.	SERUM ELECTROLYTES	
7.	**hsCRP**	
8.	ECG	
9.	URINE ROUTINE	
10.	CT BRAIN	

OUTCOME AFTER 30 DAYS (MODIFIED RANKIN SCORE):

ABBREVIATED NIH STROKE SCALE



ABBREVIATIONS

APP - Acute phase protein

BP - Blood pressure

CAHD - Coronary artery heart disease

CHD - Coronary heart disease

CI - Confidence Interval

CRP-US - C-Reactive Protein ultra sensitive

DM - Diabetes mellitus

hs-CRP - High sensitivity C-Reactive Protein

HT - Hypertension

IHD - Ischemic heart disease

IL - Interleukin

mRS –modified Rankin Scale

NIHSS-National Institute of Health Stroke score

mg/L - Milligram/litre

MI - Myocardial infarction

m-RNA - Messenger – RNA

OCP - Oral contraceptive pill

SAA - Serum amyloid A

SAP- Serum amyloid P

SAH - Subarachnoid haemorrhage

SD - Standard deviation

TIA - Transient ischemic attack

LDL-Low Density Lipoprotein

VLDL- Very low Density Lipoprotein

Lp(a)- Lipoprotein a

DALY- Disability Adjusted Life Years

hsCRP Grp- High sensitivity C-Reactive Protein group

mRS Grp–modified Rankin Scale group

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