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Predictive Accuracy of C Reactive Protein in Relation with Adverse Outcome of Ischemic Stroke

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ABSTRACT

Background & Objective: Elevated C Reactive Protein(CRP) is a predictive marker for future cardiovascular events in ischemic stroke patients but the timing of CRP evaluation in relation to the onset of the qualifying event has not been determined. In the backdrop of this knowledge, the current study was taken up with the aim of studying the predictive accruacy of CRP in relation to adverse outcome of patients with acute ischemic stroke.

Methods: The study was carried out in 62 cases of acute ischemic stroke admitted to S.C.B. Medical College & Hospital from Department of Medicine. CRP was determined quantitatively in all the patients of ischemic stroke both at the time of admission & discharge. The CRP value was correlated with infarct size (CT scan), mortality, morbidity (disability i.e Barthel Index (BI), Canadian Neurologic Stroke Scale (CNSS) &vascular events). The end points are death or any new non-fatal vascular events (recurrent stroke, unstable angina, myocardial infarction) recorded during 6months follow up period.

Results: CRP at admission correlated with the occurrence of fatal events only but CRP at discharge correlated with occurrence of both fatal &non-fatal events. On follow up occurrence of events correlated more strongly with CRP at admission. Out of total 14 nonfatal events, maximum was restroke i.e 7(50%) which occurs in high CRP group.BI (degree of disability), both on admission and at 6 months strongly correlated with CRP at discharge (p=0.008 and 0.001 respectively).

Conclusion: The severity of stroke and degree of disability was highest in high CRP group. The. CRP at discharge was a better predictor of future outcome in terms of fatal &non-fatal events than CRP at admission.

Keywords: C Reactive Protein, Inflammation, Ischemic stroke, Prognosis, Stroke outcome

INTRODUCTION

The WHO defined stroke as "rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin" [(1).] Acute ischemic stroke is caused by sudden interruption of cerebral blood flow. The causes of acute ischemic stroke in most patients who have severe symptoms include embolic or thrombotic occlusion (70% to 80% of patients**)** [(2)] Multiple studies reveal that inflammation has a significant role in the pathogenesis of atherosclerotic stroke through mechanisms like increasing the serum levels of cytokines, fibrinogen, clotting factors, and leukocytes by altering the functions of endothelial cells.

Systemic inflammatory response occurs after ischemic events and is responsible for thrombosis progression. Several studies have indicated that higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and interlukin-6 (IL-6) have been associated with worsening ischemic events [(3).] The Framingham study showed that CRP is an important predictor of ischemic stroke and TIA[4]. Also, raised baseline hs-CRP(high sensitive -CRP) levels are independently associated with excessive ischemic stroke risk but exhibit no clear effect on hemorrhagic stroke.[5]

C-Reactive protein:

C-reactive protein was discovered by Tillet and Francis in 1930[(6).] CRP is a systemic inflammatory marker produced in a large amounts by hepatocytes in response to IL-1, IL-6 & TNF factor [7,8]. Rapid induction of CRP, its long half-life (19 hours) and lack of alteration during day and night in comparison with other acute phase reactants has introduced CRP as an important factor for evaluation in inflammatory and infectious diseases. Inflammation is an important feature of atheroma and is associated with activation and proliferation of macrophages, endothelial cells and smooth muscle cells [(9).] As the prototypical member of acute phase proteins, its concentration increases in response to injury, infection or inflammation. Raised CRP also seen in smokers, atherosclerosis, psychological stress, diabetes, obesity and elderly. the serum CRP and ESR are the earliest acute phase reactants to increase during the inflammatory response. Today, however, the best single test of acute inflammation is a serum CRP level that can be readily quantified by nephelometr·[(10)].The median circulating concentrations of C - reactive protein is 0.8 mg/L. Normal range may be as low as 0.07 mg/L and among apparently healthy individuals 90% have less than 3 mg/L[(11)] . The rate of CRP synthesis and secretion increases within hours of an acute injury or the onset of inflammation [(10),] probably under the influence of humoral mediators such as leucocyte endogenous pyrogen[(12)] & PGE. The serum CRP concentration may reach peak levels as much as 300mg/ml within 24-48 hours[13)]. CRP is a confirmed diagnostic marker for the patients with CVA and recent prospective investigations showed that CRP is clinically helpful for predicting the risk of the next cardiovascular diseases[14] .

Multiple studies like Muir et al (1999)[15], Di Napoli et al(2001) [(16)] Ceccarelli et al(2002)[(17)])and Smith et al(2004)[(18)] demonstrated that CRP concentrations are predictive of future cardiovascular events in stroke patients and also CRP values are strongly corelated with stroke severity & disability. Hence elevated CRP is a predictive marker for future cardiovascular events, but the timing of CRP evaluation in relation to the qualifying event remains undetermined. With this backdrop of knowledge, in this study, we intended to evaluate the prognostic significance of CRP as an inflammatory marker in acute cerebral ischemic stroke.

MATERIALS AND METHODS

Aim & Objective

The aim of the present study was to assess the significance of CRP values in prognosis and outcome of patients having acute ischemic stroke.

Study Design

The study was conducted on a total number of 62 patients with clinical and CT Brain diagnosed first ischemic stroke admitted to S.C.B. Medical College &Hospitals, Cuttack, Dept of Medicine from May 2017 to August 2019. The study protocol was approved by institutional Ethical Committee, S.C.B. Medical College, Cuttack.

Inclusion criteria:

All patients of clinical and CT scan brain confirmed first ischemic stroke admitted within 72hrs of symptom onset were included in the study.

Exclusion criteria:

All patients having

- acute infectious disease,
- stable or unstable angina,
- acute myocardial infarction,
- immunological disorders,
- known or suspected neoplastic disorders,
- recent h/o [< 3 months] major trauma,
- surgery,
- burns

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- Osteoarthrosis, costochondritis, rheumatoid arthritis, ankylosing spondylitis,
- renal failure
- hemorrhagic stroke,
- collagen vascular disease.,
- liver disease

Medical history was taken from the patient or his/her relatives if the patient was unconscious or not able to speak. Physical examination was performed by neurology residents. Patients were evaluated for age, sex, diabetes, hyperlipidaemia, ischemic heart diseases, smoking and past history of stroke or hypertension. Routine laboratory tests, brain magnetic resonance imaging (MRI), transthoracic echocardiography (TTE) and carotid Doppler ultrasonography were done in all of the patients.

The patients were assessed at the time of admission and followed up after 1 month, 3rd month & 6th month after discharge.

STUDY PROTOCOL

At admission, Initial stroke severity and disability were assessed by the Canadian Neurological Stroke Scale (CNSS) and Barthel Index, respectively. [19,20]. Besides other routine laboratory investigations, CRP level in patients of acute ischemic stroke was estimated quantitatively at the time of admission and discharge. The patients were followed up at 1 month,3 months and 6 months. During each follow up visit, the disability score was calculated according to Barthel Index(BI).

CRP value was correlated with infarct size (detected by CT scan). The CRP was correlated with mortality and morbidity (disability, vascular events). The patients were regularly followed up over phone every weekly intervals to know about mortality & morbidity.

The end events were death or any new non-fatal vascular events (recurrent stroke, unstable angina, myocardial infarction whichever came first) recorded during the 6 months follow up period.

DEFINITIONS

1.CANADIAN NEUROLOGIC STROKE SCALE[19]

Mentation

- level of consciousness: alert (3), drowsy (1.5)
- orientation: orientated (1), disoriented or non- applicable (0)
- speech: normal (1), expressive deficit(0.5), receptive deficit (0)

Section A1 – no comprehension deficit

Motor weakness

- face: none (0.5), present (0)
- arm proximal: none (1.5), mild (1), significant (0.5), total (0)
- arm distal: none (1.5), mild (1), significant (0.5), total (0)
- leg: none (1.5), mild (1), significant (0.5), total (0)

Section A2 - comprehension deficit

Motor response

- face: symmetrical (0.5), asymmetrical (0)
- arms: equal (1.5), unequal (0)
- legs: equal (1.5), unequal (0)

Section B – patient stuporous or comatose

- use Glasgow Comma Scale

Interpretation

Scores range from 1.5 to 11.5, with a lower score indicating greater stroke severity.

2. BARTHEL INDEX.[20]

FEEDING

0 = unable

5 = needs help cutting, spreading butter, etc., or requires modified diet

10 = independent

BATHING

0 = dependent

5 = independent (or in shower)

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GROOMING

0 = needs to help with personal care

5 = independent face/hair/teeth/shaving (implements provided)

DRESSING

0 = dependent

5 = needs help but can do about half unaided

10 = independent (including buttons, zips, laces, etc.)

BOWELS

0 = incontinent (or needs to be given enemas)

5 = occasional accident

10 = continent

BLADDER

0 = incontinent, or catheterized and unable to manage alone

5 = occasional accident

10 = continent

TOILET USE

0 = dependent

5 = needs some help, but can do something alone

10 = independent (on and off, dressing, wiping)

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance

5 = major help (one or two people, physical), can sit

10 = minor help (verbal or physical) 15 = independent

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards

5 = wheelchair independent, including corners, > 50 yards

15 = independent (but may use any aid; for example, stick) > 50 yards

STAIRS

0 = unable

5 = needs help (verbal, physical, carrying aid)

10 = independent

Interpretation: The BI score is grouped into three standard diagnostic categories according to the standard BI grouping method(16) high disability of ADL (BI score 0 to 40), moderate disability of ADL (BI score 41 to 60), low disability of ADL (BI score 61 to 100).

The patients were divided into three groups based on CRP values i.e Low CRP<5mg/l, Medium =5-33mg/l, and High CRP >33mg/l as done in previous studies.[21] (MD Napoli et al ,2001).

METHODS:

1.*C Reactive Protein Assay*:

All the blood samples were collected from the patients 1st at time of admission and then at discharge and High sensitivity CRP (hs CRP) were measured with an immunoturbidimetry assay on an Architect c16000 chemistry analyzer (Abbott Diagnostics, Abbott Park, USA). The results were expressed in mg/l. Normal reference of CRP was less than 5 mg/L.

2.*CT Scan of brain*

For each patients was done at the time of admission in the Department of Radiodiagnosis, Regional Diagnostic Centre , S.C.B.Medical College, Cuttack. CT scan was used to differentiate between haemorrhagic & ischemic stroke.

STASTICAL ANALYSIS:

The data were analysed using SPSS version 11.0 for statistical analysis. The statistical procedures include proportions, Chi-Square test for association, ANOVA for testing the difference between means and logistic regression for estimating the relative risk.

RESULTS

In our study maximum number of patients were found in age group61-70 years (37%).Incidence among male predominates over female.(Figure-1). Out of all risk factors, hypertension amounts to be the maximum i.e 67.7% cases and incidence was highest at medium value of CRP 5-33 (table-1) followed by dyslipidaemia. Out of all cardiovascular features, left ventricular hypertrophy amounts to be the highest i.e.28% which occurs maximum at high CRP level group i.e >33(Table-2). The severity of stroke, extent of disability and infarct size were all significantly

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higher in the high CRP group.(Table-3). 67% of the patients in the high CRP group suffered adverse events which is statistically significant compared to low and medium CRP group(Figure-2). Out of all the total no of events, maximum occurs in medium CRP level group i.e 35.3%, but the RR is highest in CRP level>33 i.e 6.1. which is significant (Table-4). 66% of patients in the high CRP group suffered fatal &nonfatal events which is statistically significant(Figure-3). A high CRP at discharge is associated with 19.4 times higher risk of adverse events which is statistically significant(Table-5). Out of 14 nonfatal events,4 belonged to high CRP range,8 belonged to medium CRP and 2 belonged to low CRP group(Table-6). Barthel Index at admission and 6 months are both lowest in the high CRP at admission group. These values are statistically significant.(Table-7).Barthel index at admission and 6 months are lowest in the high CRP at discharge group which are highly significant.(Table-8).So BI at admission more strongly corelated with CRP at discharge(P=0.16) than CRP at admission(P=0.008). Also BI at 6 month more strongly corelated with CRP at discharge(p=0.001) than CRP at admission(p=0.01).

DISCUSSION

In our study out of 62 patients in the third to more than seventh decade, maximum number of cases were found in 61-70years (37%) (Figure-1).This is in accordance with studies that state that the commonest age group for ischemic stroke is 60-69years[(22)].(Millikan CH .Mc Dowell, Easton JD,71.Patients more than 60yrs age comprised 51.5%of total cases. This coincides with earlier studies wherein stroke was more common in elderly population[(23)] . In the present study male predominates over female (38(61.2%) in male and 24(38.8%) in female.(Figure-1) which corroborates with [(24)]Haberman ,Rose et a[(19)] .Among the risk factors, (Table-1), the commonest risk factor is hypertension 42(67.7%followed by dyslipidaemia 26(42%) and diabetes in 18(29%). This coincides with study done by Di Napoli et al,2001.&Winbeck et al,2002. For every risk factor, the patients were divided according to CRP level into three groups. On statistical analysis, it was observed that no significant difference between the incidence of risk factor in the three groups of different CRP values. So CRP is an considered as an independent factor and is not influenced by the presence of the aforesaid risk factors as seen in the present study and also in studies conducted earlier[(25)].In our study (Table-2), incidence of atrial fibrillation (6.5%), peripheral arterial disease (9.7%), LVH (45.1%) and carotid stenosis in 5(8%) which was found to be not significantly different among the three group. The severity of stroke was assessed by CNSS score (Table-3) and it was observed that the mean CNSS score was 7 in the low CRP group,6.1 in medium CRP group, and 5.3 in high CRP group. The difference in values are statistically significant (p=0.023)..The mean BI score in the low CRP group is 36.8,medium CRP group is 30.3 and in high CRP group is 30.(p=0.016). The mean infarct size in low CRP group is 1.9cm, in medium CRP group 4.3cm and in high CRP group 6.6(p=0.012). So the severity of stroke, disability and infarct size increases significantly with increase in CRP. Our study corroborates with that of Shoaeb et al 2014,which states that serum CRP level on admission can be used to predict severity and early outcome in ischemic stroke[(26)].. We found that the serum CRP level, measured within 24 h of stroke onset, was significantly correlated with disease severity and outcome in ischemic stroke.

Many investigators have found a wide range of increase in CRP after stroke [27.28].Di Napoli et al. found that CRP concentration increased in the first 24 h following stroke; this increment was associated with the size of the infarction, so mounting CRP levels in the first 24 h were synchronized to poor prognosis[28] . The association between high CRP and a high stroke severity remains unexplained. Atherothrombosis of the cerebral vessels is considered an inflammatory disorder with acute phase reactant proteins produced in the first few hours The degree of inflammation determined by elevated CRP levels has been associated with an increased risk of vascular complications[29]. There is a distinct possibility that elevated CRP is a direct response to the extent of cerebral tissue injury[30].

As an inflammatory marker, it is possible that high CRP is associated with underlying processes that cause more severe strokes. Another link is the activation of coagulation by the elevated CRP levels through the important role of tissue factor expression Previous data showed that activation of coagulation factors in stroke patients increased mortality, and

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fibrinogen has a putative role [31].In the present studyduring the follow up period of 6months, the fatal and non-fatal outcomes were compared with CRP values at admission, (Figure-2). Maximum percentage of events occurred in high CRP groups (66.7%). There was a statistical significance difference in the occurence of events in the 3 groups.(p=0.03).There was statistical significant difference in the occurrence of death among the three groups.(p=0.03), but no significant difference in the frequency of non-fatal events in the 3 groups.(p=0.41).Taking the RR of low CRP as 1, the RR of an event in medium CRP group is 2.7(p=0.17) ,which is not significant and RR of high CRP group is 6.1(p=0.03),which is significant.(Table- 4) .The fatal and non fatal end points were also compared with the CRP values at discharge (Figure-3)) .Out of 23 cases,3 case (10.8%) belonged to low CRP group,12(50%) to medium CRP group and 8(40%) to the high CRP group. The difference in values was highly statistically significant (p=0.007). The highest percentage of death also occurred in high CRP group. There was a significant difference of incidence of deaths in among three CRP groups(p=0.01). also highest percentage of non-fatal events occurred in high CRP group .So there was a significant difference in the incidence of nonfatal events in the 3 groups.(p=0.01). The relative risk (RR)score of the end point was 1 in low CRP group,9.8 in medium CRP group(p=0.002) & 19.4 in high CRP group(p=0.001) which is highly significant.[32](Table-5) Hence CRP at admission corelates with occurrence of fatal events only but CRP at discharge corelates with the occurrence of both fatal &nonfatal events on follow up .Also CRP at discharge correlates more strongly with occurrence of events than CRP at admission.

Hence CRP at hospital discharge (p=0.002&p=0.001) is a stronger predictor of events at 6months than CRP at admission (p=0.17 &p=0.03) **[33].** Table-6 revealed that the commonest adverse event on follow up was restroke followed by unstable angina and myocardial infarction. The ASIST study revealed that among a battery of biomarkers, only hsCRP is a predictor of further cerebrovascular events with an odds ratio of 1.14. The highest number of adverse events were seen in the middle CRP group.[34] In the present study, (table-7&8), the mean BI at admission is more strongly corelated with CRP at discharge((p=0.008) than CRP at admission (p=0.016). Also BI at 6 months is more strongly corelated with CRP at discharge(p=0.001) than CRP at admission, (p=0.01) . The present study also reveals that patients with elevated CRP had a significantly lower follow up BI.[35]The protective effect of CRP apheresis on severity of ischemic stroke is being studied in the CASTRO1 study, the results of which are expected in 2022.[36]

CONCLUSION

Present study showed that CRP, a marker of inflammation rises significantly in patients of ischemic stroke. The degree of rise of CRP indicates the severity of stroke as well as adverse outcomes. CRP at discharge is a better outcome in terms of fatal and nonfatal events than CRP at admission. CRP also correlates with the magnitude of disability.

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TABLES

Table-1**: Distribution of risk factors in relation to level of CRP at admission**

Risk Factors	Total(n=62)	CRP Value(mg/L)			
		<5(n=16)	5-33(n=34)	>33(n=12)	P value
Hypertension	42(67.7)	10(63)	23(68)	9(75)	0.78
Diabetes	18(29)	7(39)	9(27)	3(25)	0.41
Dyslipidaemia	26(42)	5(31)	15(35)	6(18)	0.56
CHD	12(19.3)	2(13)	6(18)	4(33)	0.35
Smoking	11(17.7)	3(19)	5(15)	3(25)	0.71
No risk factors	4(6.5)	1(6)	2(6)	1(6)	0.95

Out of all risk factors, hypertension amounts to be the maximum i.e 67.7% cases and incidence was highest at CRP level 5-33(medium level) followed by dyslipidaemia..

Table-2 **Comparision of Cardiovascular features in relation to CRP value at admission**

Clinical Characteristics	Total (N=62)	CRP Value(mg/l)			P value
		<5	5-33	>33	
Atrial fibrillation	4(6.5)	1(6.3)	3(8.8)	0	0.56
Peripheral arterial disease	6(9.7)	1(6.3)	3(8.8)	2(16.7)	0.63
Left ventricular hypertrophy	28(45.1)	6(37.5)	16(47)	6(50)	0.76
Carotid stenosis	5(8)	1(6.3)	3(8.8)	1(8.4)	0.38

Out of all cardiovascular features, left ventricular hypertrophy amounts to be the highest associated cardiovascular event i.e.45% which occurs maximum at high CRP level group i.e >33.

Table-3.**Comparision of neuroradiological features with CRP at time of admission**

Neuroradiological Features	CRP Value (mg/l)			P value
	<5 (n=16)	5-33 (n=34)	>33 (n=12)	
CNSS(mean)	7	6.1	0	0.023
BARTHELINDEX(mean)	36.8	30.3	2(16.7)	0.016
Infarct size in mm(mean)	2.9	4.3	6(50)	0.012

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The severity of stroke, extent of disability and infarct size were all significantly higher in the high CRP group.

Table-4: **Comparision of CRP at admission and relative risk of end points at 6 months**

CRP(mg/l)	Event	RR	P value
<5	3(18.8%)	1	-
5-33	12(35.3%)	2.7	0.17
>33	8(66%)	6.1	0.03

Out of all the total no of events, maximum occurs in medium CRP level group i.e 35.3%, but the RR is highest in CRP level>33 i.e 6.1. which is significant.

Table-5**: Comparision of CRP at discharge and relative risk of end points at 6 months**

CRP(mg/l)	Event	RR	P value
<5	3(10.8%)	1	-
5-33	12(50%)	9.8	0.002
>33	8(80%)	19.4	0.001

A high CRP at discharge is associated with 19.4 times higher risk of adverse events which is statistically significant.

Table-6: **Distribution of non -fatal events in relation to CRP values**

EVENTS	TOTAL (n=62)	CRP VALUE(mg/l)		
		<5	5-33	>33
Restroke	7	1	4	2
Unstable angina	5	1	3	1
AMI	2	0	1	1
TOTAL	14	2	8	4

Out of 14 nonfatal events,4 belonged to high CRP range,8 belonged to medium CRP and 2 belonged to low CRP group.

Table-7**: Comparison of disability (Barthel Index) with CRP at admission**

BARTHEL INDEX	CRP Value(mg/l)			P value
	<5 n=16	5-33 n=34	>33 n=12	
At Admission (Mean)	36.8	30.3	30	0.016
At 6 months(mean)	72.5	62.6	51.2	0.01

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Barthel Index at admission and 6 months are both lowest in the high CRP at admission group. These values are statistically significant.

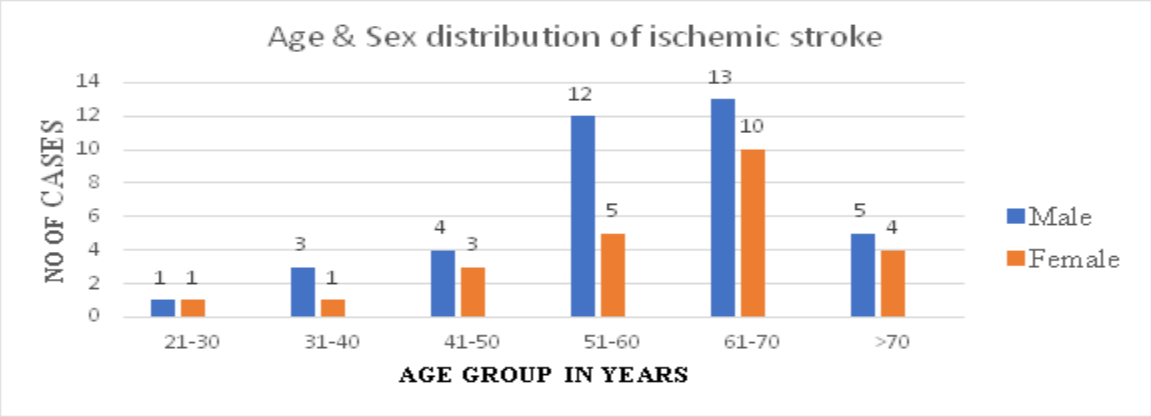
Table-8: **Comparision of disability (Barthel Index) with CRP at discharge**

BARTHEL INDEX	CRP Values(mg/l)			P value
	<5 n=28	5-33 n=24	>33 n=10	
At Admission (Mean)	36.8	27.3	26.5	0.008
At 6 months(mean)	75.4	52.3	41.6	0.001

Barthel index at admission and 6 months are lowest in the high CRP at discharge group which are highly significant.

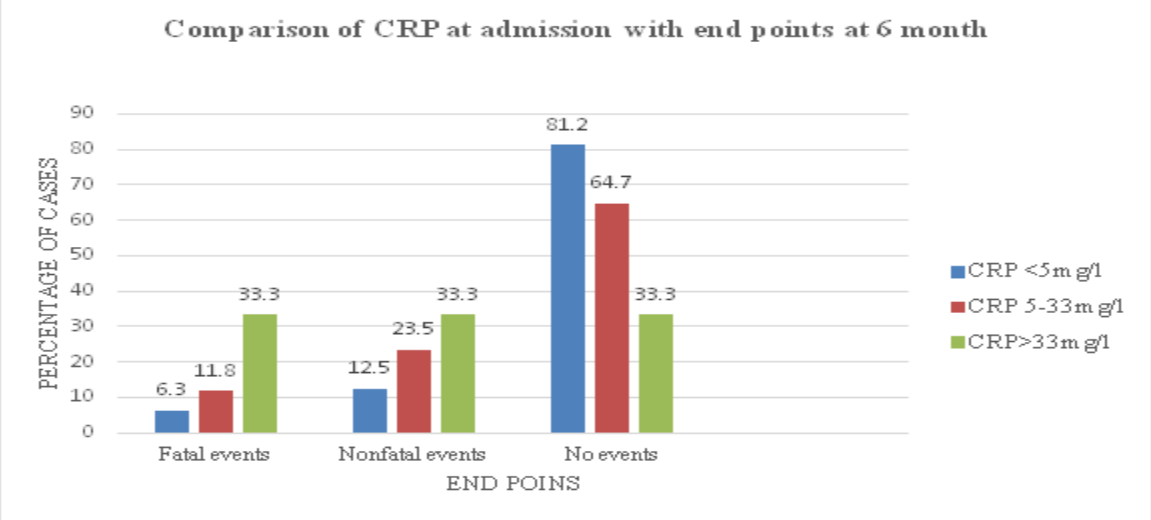
FIGURES

Figure1. Age & Sex distribution of ischemic stroke



Incidence among male is higher as compared to female .Out of all maximum belongs to age group 61-70 years.

Figure 2: Comparison of CRP at admission with end points at 6 month



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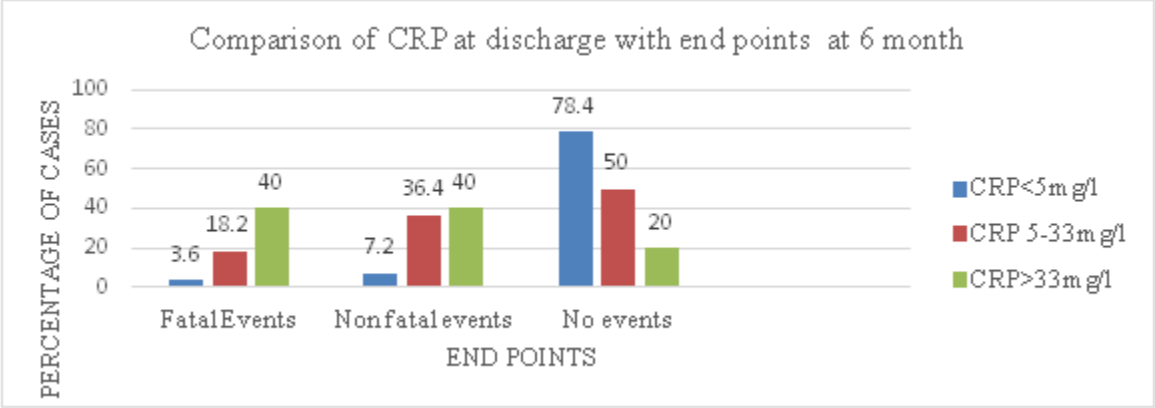
Maximum % of adverse events occurs in patients of high CRP at admission group which is statistically significant compared to low and medium CRP group

Figure 3: Comparison of CRP at discharge with end points at 6 month



Maximum adverse outcome occurred at high CRP at discharge group which was statistically significant.

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