"STUDY OF SERUM HOMOCYSTEINE LEVELS IN CEREBROVASCULAR ACCIDENT"

By

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Dissertation submitted to BLDE University, Vijayapur

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of

DOCTOR OF MEDICINE

IN

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Under the guidance of

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Affectionately Dedicated to

My Beloved Parents

Mr. Ashok and Mrs. Vidya

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Dr. Nilesh A. Malgar

LIST OF ABBREVIATIONS USED

MTHF	:	Methyltetrahydrofolate
SAM	:	S- Adenosyl- Methionine
CRVO	:	Central Retinal Vein Occlusion
DVT	:	Deep Vein Thrombosis
VISP	:	Vitamin Intervention for Stroke Prevention
WHO	:	World Health Organization
CVA	:	Cerebrovascular Accident
LDL	:	Low Density Lipoprotein
USG	:	Ultra Sonography
SAH	:	S- adenosyl-Homocysteine
TCEP	:	Tris(2Carboxyethyl) Phosphine
NADH	:	NicotinamideAdenine Dinucleotide
HCY	:	Homocysteine
CT	:	Computed Tomography
MRI	:	Magnetic Resonance Imaging
µmol/L	:	Micromol Per Liter

ABSTRACT

Background: Hyperhomocysteinemia is emerging as an important risk factor for cerebrovascular accidents. The present study is performed to evaluate the role of serum homocysteine levels in cerebrovascular accident patients.

Methods: We performed a case control study of patients admitted with focal neurological deficit with cerebrovascular accidents. Serum homocysteine levels were estimated following a thorough history and clinical examination. Other risk factors for stroke were also assessed.

Results: Among the 90 patients of study group the mean serum homocysteine level is 31.47±39.89µmol/L and among the 90 cases of control group the mean serum homocysteine level is 16.62±22.08µmol/L, it indicates that serum homocysteine level is highly significantly raised in cases of stroke compared with control patients.

Conclusion: Hyperhomocysteinemia is an important risk factor for cerebrovascular accidents.

Key words: Hyperhomocysteinemia, Cerebrovascular accidents, Serum homocysteine levels.

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INTRODUCTION

Cerebrovascular accident is an important cause of premature mortality and disability in developing countries like India.[1] In the USA stroke is the third most common cause of mortality and morbidity after cardiovascular disease and cancer.[2] Intracranial atherosclerosis of large vessels is most common cause of cerebrovascular accident in India.[4]

As per WHO study stroke accounted for 5.7 million deaths. Stroke is second leading cause of preventable death and fourth leading cause of lost productivity.[5] Stroke cause approximately 200000 deaths each year in the United state.[5] Stroke was a cause for 6.2 million deaths in 2011.[5] The first community-based study on stroke was carried out in Vellore in South India in 1969-71 and in Rohtak in North India during 1971-74. The age adjusted prevalence rate per 100000 population in south India is 262 and adjusted prevalence rate per 100000 population in North India is 344.[6]

The lifetime risk of stroke after 55 years of age is 1 in 6 for male and 1 in 5 for female.[3] Stroke accounts for 2% of hospital admissions.[2]

A stroke is defined as abrupt onset of neurologic deficit that is attributable to a focal vascular cause.[5] There is a wide range of severity, from recovery in few days through persistent disability, to death.[4]

The diagnosis of stroke (stroke versus non stroke) is still a matter of clinical skill, often without the help of many confirmatory investigations. However this does have the advantage that the diagnosis is independent of

availability and quality of imaging technology, which is most of the time not available in developing country or even universally available in developed country.[4] The definition of stroke in clinical and laboratory studies including brain imaging are used to support the diagnosis.[5]

The highly variable clinical features of stroke is because of complex vascular anatomy of the brain.

After the clinical diagnosis of stroke a brain imaging is needed to determine whether the pathology of stroke is ischemic or hemorrhagic.

There are several causes of neurologic symptoms that mimic stroke, including seizure, intracranial tumour, migraine and metabolic encephalopathy.

A complete cessation of blood supply to brain leads to infarction of brain tissue within 5-10 min. values <16ml/100gm tissue per min. leads infarction within an hour and values <20ml/100gm tissue per min. leads ischemia with no infarction unless prolonged for several hours.[5]

Neurological deficit occurs after few minutes of the cessation of the blood supply because neurons don't have glycogen, due to absence of glycogen there will be rapid energy failure.[5]

Around 85% is ischemic stroke out of this 17% is secondary to atrial fibrillation, 4% is due to carotid disease and 64% is due to other causes. About 15% are hemorrhagic stroke, out of that aneurismal subarachnoid hemorrhage

is 4%, hypertensive intracranial bleed is 7% and others are 4%.[5] Small vessel stroke accounts for 20% of all strokes, large artery and cardiac emboli stroke accounts for 20% and 5% of all strokes.[5] Stroke mortality rises rapidly with age, the burden of cerebrovascular accident begins hugely from geriatric population.[4]

Transient ischemic attack is defined as all neurological manifestations resolve within 24 hours without evidence of brain infarction in brain imaging. Stroke has occurred if the neurologic manifestations last for >24 hours or brain infarction is demonstrated on imaging study.[5]

The brain is highly vascularised organ, its profuse blood supply characterised by a densely branching arterial network. It has a high metabolic activity due in part to the energy requirement of constant neural activity. The cerebral hemisphere supplied by the terminal branches of the carotid and basilar arteries which forms the circle of Willis. There are anastomosis between the various branches over the cortex, and the efficiency of these collateral supplies is often critical in determining the final extent of infarction following major vessel occlusion. Brain takes 15% of the cardiac output and consumes 25% of the total oxygen consumption of the body.[3]

In general the internal carotid artery divides into middle cerebral artery and anterior cerebral artery and supplies parietotemporal lobe and frontal lobe respectively. The vertebral arteries fuses to form basilar artery and basilar artery divides into two posterior cerebral artery which supplies the occipital

lobe and cerebellum. Venous blood from the brain drains into sinuses within the dura matter.[3]

Risk factors of stroke are age, sex, diabetes mellitus, smoking, family history of stroke, dyslipidemia, hypertension and atrial fibrillation but cerebrovascular accident occurs many times in patients without above mentioned risk factors. Therefore there is some chances to have other risk factors. Identification of modifiable risk factor for cerebrovascular accident may lead to more effective prevention of first and recurrent episodes of cerebrovascular disease.

Hyperhomocysteinemia is defined as an elevated plasma homocysteine level (> 13µmol/L) .[106]

Some studies have shown that elevated serum homocysteine is an independent risk factor for stroke.[7,8,9]

Hyperhomocysteinemia associated with Alzheimer's disease[16] and vascular dementia,[14,17] as well as myocardial infarction.[15]

Homocysteine is an intermediate in the synthesis of cysteine from methionine. Homocysteine reacts with collagen to produce reactive free radicals. Homocysteine is also involved in the aggregation of LDL particles, all this leads to increased tendency for atherogenesis.[106]

Hyperhomocysteinemia may cause arterial thromboses as well; this disorder is caused by various mutations in the homocysteine pathways and

responds to different forms of cobalamin depending on the mutation.[5] Mild hyperhomocysteinemia is seen in patients with heterozygous genetic defects for cystathionine β -synthase or methylenetetrahydrofolate reductase gene defects.[19]

Extensive experimental evidence, both *in vitro* and *in vivo*, indicates that homocysteine causes endothelial dysfunction. Homocysteine changes vascular tone by regulating endothelium-dependent vasodilator and constrictor substances, including decreasing nitric oxide bioavailability, increasing contractile prostanoids as well as interfering myoendothelial communication.[7]

Recent study shows in United state, fortification of folate in food has decreased the level of serum homocysteine. Even though evidence for the benefit of lowering homocysteine levels is lacking, Supplementation of folic acid and vitamin B12 has been demonstrated to be efficient in lowering elevated plasma homocysteine levels and in reversing homocysteine-induced impairment of endothelium dependent vasoreactivity.[27]

For healthy middle aged adult individuals, hyperhomocysteinemia is an independent risk factor for endothelial dysfunction.[27] Elevated homocysteine level is common and this is the major prothrombotic factor associated with stroke.[19]

AIM AND OBJECTIVE

To study serum homocysteine levels in cerebrovascular accident as a risk factor for stroke.

REVIEW OF LITERATURE

Atherosclerosis is the leading cause of mortality and disability in developed society. Markedly elevated concentration of homocysteine is associated with atherosclerosis and high risk of atherothrombotic event, including stroke and myocardial infarction.[21,23]

Stroke and transient ischemic attack frequently caused by atherosclerosis of arteries supplying brain.[5] Case control and prospective studies indicate that an elevated plasma homocysteine level is major risk factor for atherosclerotic vascular disease.[12]

Giving a high prevalence of elevated serum homocysteine level in a healthy group of population and the propensity for homocysteine concentration to increase with age, modest effect of homocysteine on cerebrovascular accident risk will have great inference for public health.[21]

PJ Kelly et al study showing clinical and biochemical phenotypes and genetic feature of three unrelated patients with premature stroke and severe Hyperhomocysteinemia because of cystathione β synthase deficiency. Two of the three index cases had not a known diagnosis of homocystinuria and initially presented with embolic retinal and cerebral infarct in middle age group. Mechanism of stroke was carotid arterial thrombosis, cardiac embolism and arterial dissection. Family screening showing another member with clinically concealed homocystinuria and sever elevation in serum homocysteine level.[25]

Dutta et al studied 42 patients of cerebrovascular accident for 1 year. They were noticed that significant hyperhomocysteinemia in patients with cerebral infarction than the patients with hemorrhagic stroke, although homocysteine level did not proved as prognostically remarkable.[1]

Vitamin B12 and folate deficiency along with increased serum homocysteine level is a risk factors in neural tube defect in pregnancy.[4]

Woo et al studied by using high resolution USG that endothelium dependent flow-mediated dilatation and endothelium-independent nitroglycerine induced dilatation of brachial artery in fourteen prospectively defined hyperhomocysteinemic, nonsmoker, healthy subjects of age 53 ± 9 years and fourteen controls with low level of serum homocysteine. Study showed significant lower Endothelial dependent flow and sudden dilatation in hyperhomocysteinemic subjects indicating hyperhomocysteinemia is an independent risk factor for arterial endothelial dysfunction in well nourished middle age adults.[27]

Boysen et al studied on 1039 cerebrovascular accident cases and measured serum level of homocysteine at first visit. On 15 months of follow up duration they found that there is significant hyperhomocysteinemia in 105 cases those who experienced repeated stroke during follow up period than in patients without recurrent stroke. At the index event, serum homocysteine is significantly higher in 909 cases ischemic stroke than in 130 cases of hemorrhagic stroke.[24]

Kristensen et al in a comparative study of 80 consecutive cases of age 18-44 years with ischemic cerebrovascular accident & 41 control subjects observed that moderate increase in serum homocysteine level after methionine loading, had been associated with a high risk for ischemic cerebrovascular accident in young adult.[26]

Allensandro et al in prospective comparative study concluded that increased concentration of serum homocysteine seems to be predisposing condition for ischemic heart disease, where as its role in atherothrombotic heart disease remains a continue matter. Hyperhomocysteinemia causes atherothrombotic changes in intracerebral vessels leading to stroke can't be excluded.[37]

Verhoef et al studied 14,916 cases of 40 to 84 year age with no previous history of transient ischemic attack, ischemic heart disease and cerebrovascular accident, provided blood samples at baseline & are followed for 5 years. By using a case control design, homocysteine in samples from 109 cases who eventually developed ischemic cerebrovascular accident & 427 controls were studied. Result indicated small and no significant correlation between hyperhomocysteinemia & risk of ischemic cerebrovascular accident.[28]

APS Narang et al in their case control study compared the homocysteine level in cases of ischemic cerebrovascular accident with controls. This study included 117 patients of ischemic cerebrovascular accident and 101 controls. The mean homocysteine levels in cases with ischemic stroke were

16.80±6.71 umol/L while in controls it was 12.30±4.68 umol/L, the difference was statistically significant (P<0.01). The increased homocysteine level in patients with ischemic cerebrovascular accident are independent of age and sex & diabetes mellitus. This study concluded that the homocysteine level were higher in hypertensive patients than non-hypertensive subjects.[2]

Osunkalu et al in their cross-sectional study of folic acid and homocysteine level as indicators of stroke done in black Nigerian population. This study showed that increased level of serum homocysteine was a major predictor of cerebrovascular accident. Epidemiologic studies have shown that elevated plasma homocysteine is related to a higher risk of coronary heart disease, stroke and peripheral vascular disease.[20] Other evidence suggests that homocysteine may have an effect on atherosclerosis by damaging the inner lining of arteries promoting blood clots.[2,20] This study also suggests that literature is replete with information on the association between high plasma homocysteine levels and stroke incidence.[20]

The latest study revealed a association between low folic acid and high homocysteine level with cognitive function in Alzheimer's disease and vascular dementia.[42] which is consistent with the idea of secondary increase in serum homocysteine in dementia patient.[41]

Increase in serum homocysteine is emanating risk factor for cerebrovascular accident, possibly because of accelerated atherosclerosis of

cerebral vessels.[60] Cerebrovascular accident and ischemic heart disease are fatal consequences of atherosclerosis.[60]

Observational studies have shown higher level of serum homocysteine in individuals with stroke. Vitamin Intervention for Stroke Prevention (VISP) trial is the only randomized clinical trial that exclusively recruited persons with previous non-disabling cerebral infarction. High dose multivitamin therapy was no better than control in preventing recurrent stroke. However, the control agent contained small doses of vitamins B6, B12, and folic acid, and the reduction in homocysteine levels was less than assumed in the study design.[47]

Ranjeet Kaur et al in their case control study showed that out of 50 cases of cerebrovascular accident 41 patients with cerebral infarct and 9 patients with intracerebral hemorrhage. In stroke patients 32 had raised serum homocysteine level, which was significantly higher than that of control group. This study concluded that hyperhomocysteinemia seems to be a factor for cerebrovascular accident. No significant difference of serum homocysteine present between intracerebral infarct and hemorrhage.[107]

Zolianthanga Zongte et al in their case control study shows that cerebrovascular accident seems to have male preponderance over female and the highest homocysteine level was observed in the age group of 74 years and above. This implies that the level of homocysteine increase as age advances.[8]

There was increasing data that elevated serum homocysteine level contributes to the pathophysiology of ischemic stroke.[45] Homocysteine is

responsible for thrombosis and atherogenesis due to vascular smooth muscle proliferation and coagulation abnormalities and endothelial damage. Elevated level of homocysteine responsible for increased cerebrovascular and cardiovascular disease risk,[55] although there are some studies showing no increased risk[26,57] and there is still controversy as to the strength and validity of association,[59] this discrepancy partially described by methodological disparity between the different studies for instance use of fasting[26,58] and non fasting samples[56,59] differing timing of sampling post stroke[58,60] and different subtypes of stroke studies.[60]

Mc Cully on the ground of natural experiment. He studied the pathological features in an infancy with a rare congenital error of B12 metabolism similar to those in infants with cystathione beta synthase deficiency. He published that increase in serum homocysteine the only metabolic defect shared by these disorders, is the reason of the vascular disorder in these infants. Subsequently observational study and case control study showing that mild to moderate increase in serum homocysteine is responsible for cerebrovascular accident including vascular disease most commonly in persons of young and among persons of old age.[23]

PATHOPHYSIOLOGY OF STROKE

The morphology of cerebral vessels is similar to those in other vascular system, except for absence of external elastic lamina. The cerebral arterial wall formed by three layers the outer adventitia, middle media and inner intima. The intima provides non thrombotic surface for blood flow and formed by smooth endothelial cell, the function of endothelium is inhibition of thrombosis and coagulation.[4]

Development of brain oedema and infiltration of leukocytes will exacerbate the ischemic brain injury. These biochemical changes have been the targets for many agents and strategies aimed at neuroprotection after cerebral infarction

Complete interruption of cerebral blood flow causes suspension of the electrical activity within 12 to 15 seconds, inhibition of synaptic excitability of cortical neurones after 2 to 4 minutes and inhibition of electrical excitability after 4 to 6 minutes. Normal cerebral blood flow at rest in the normal adult brain is approximately 50 to 55ml/ 100gm/ min. There are certain ischemic threshold in experimental focal brain ischemia. when blood flow decreases to 18 ml / 100gm/ min. the brain reaches a threshold for electrical failure. Although the neurons are not functioning normally, they do have the potential for recovery. The second level known as the threshold of membrane failure, occurs when blood flow decreases to 8 ml/ 100gm/ min. Cell death can rapidly

result. These threshold marks the upper and lower blood flow limits of the ischemic penumbra.[5]

The ischemic penumbra or a area of "misery perfusion", is the area of the ischemic brain between these two flow threshold in which there are some neurons that are functionally silent but structurally intact and potentially salvageable.[4]

The pathological characteristic of ischemic stroke depends on the mechanism of stroke, the size of the obstructed artery and the availability of collaterals blood flow. There may be advanced changes of atherosclerosis visible within arteries. The surface of brain within area of infarction appears pale. With ischemia caused by hypotension and hemodynamic changes, the arterial border or water shade zone remains vulnerable. A wedge shaped area of infarction in the area of an arterial territory may result if there is occlusion of main artery in the presence of collateral blood flow. In the absence of an collateral blood flow, the entire territory supplied by an artery may be infarcted. In occlusion of major artery such as internal carotid artery there is multilobar infarction.[4]

The microscopic changes after cerebral infarction are well documented. The observed changes depends on the age of infarction. The changes do not occurs immediately and may be delayed up to 6 hours after the infarction. There is neuronal swelling initially, which is followed by shrinkage, hyperchromasia and pyknosis. Chromatolysis occurs and the nuclei becomes

eccentric. Swelling and fragmentations of astrocytes and endothelial swelling occur. Neutrophils infiltrate appear as early as 4 hours after the ischemia and become abundant by 36 hours. Within 48 hours the microglia proliferates and ingest the product of myelin breakdown and form foamy macrophages. Later there is neovascularity with proliferation of capillaries and increased prominence of the existing capillaries. The elements in the area of necrosis are gradually reabsorbed and a cavity consisting of a glial and fibrovascular elements forms. In a large infarction, there are three distinct zones: an inner area coagulative necrosis, a middle zone of vacuolated neurophil, leukocytic infiltrates, swollen axons and thickened capillaries; and outer marginal zone of hyperplastic astrocyte.[4]

Stroke is multifactorial, identification of these factors and its pathophysiology is helpful in effective management.

RISK FACTORS

- Advanced Age
- Male sex
- Hypertension
- Cigarette smoking
- Dyslipidemia
- Diabetes mellitus
- Increasing plasma fibrinogen

- Raised hematocrite
- Atrial fibrillation
- Physical inactivity
- Hyperhomocysteinemia
- Family history of stroke

Significantly elevated total homocysteine concentration may exist in up to a third of patients with stroke or transient ischemic attack.[64]

PATHOGENESIS OF VASCULAR DISEASE IN HYPERHOMOCYSTEINEMIA

Many researches analyse effects of hyperhomocysteinemia on vascular smooth muscle cell, endothelial cell and connective tissue. The vascular endothelial injury secondary to hyperhomocysteinemia received substantial attention. Numerous studies showed that interaction between hyperhomocysteinemia and plasma lipoprotein, platelet and clotting factors.[26]

Homocysteine shows oxidation effects, due to its reaction with copper and ceruloplasmin, homocysteine forms hydrogen peroxide.[75] Hydrogen peroxide causes lysis of vascular endothelial cells and this reaction is prevented by catalase.[76]

Increase in serum homocysteine level leads to vascular endothelial damage with deficiency of cystathion β synthase.[74] It has been revealed that deoxyribonucleic acid synthesis is inhibited in vascular endothelial cell by increased level of serum homocysteine.[78] Adhesion between endothelial cells and leukocytes increases by hyperhomocysteinemia. Increase in serum homocysteine level causes impairment in generation of nitric oxide by cultured cells.[79]

Serum homocysteine enhances the synthesis of atherogenic oxycholesterol. Hyperhomocysteinemia promotes proliferation of vascular smooth muscle cells and causes atherosclerosis.[81]

Experimental studies shows that increase in diastolic and systolic blood pressure secondary to hyperhomocysteinemia. Patients with diabetes mellitus with hyperhomocysteinemia shows significantly higher mean arterial blood pressure and diastolic blood pressure.[84]

Loscalzo has revealed that elevated serum homocysteine level will causes oxidative stress. This leads to oxidation of low density lipoprotein through generation of superoxide anion radical homocysteine thiloacetone, a product of homocysteine oxidation, which combines with low density lipoprotein to form oxidised low density lipoprotein. It is taken up by the endothelial macrophages to form foam cells, which is early stage of developing atheromatous plaque.[80]

CLINICAL EFFECTS OF HYPERHOMOCYSTEINEMIA

Following are the complications of hyperhomocysteinemia.[84]

1. Acute coronary syndrome
2. Increase in blood pressure
3. Stroke
4. Peripheral arterial disease
5. Mesenteric artery thrombosis
6. CRVO
7. DVT
8. Neural tube defect

TREATMENT OF HYPERHOMOCYSTEINEMIA

Vitamin B12 and B6 along with folic acid decrease the homocysteine level in patients with no vitamin deficient.[85] Folic acid is very effective therapy in hyperhomocysteinemia.[85]

Even though specific therapy for elevated serum homocysteine is best tailored as stated by underling cause, more than 90% of cases respond to vitamin B12 and folic acid therapy within 2-6 week irrespective of cause.[85]

A meta-analysis of homocysteine lowering trial collaboration of different randomized controlled trials, reported that absolute & proportional decrease in homocysteine production by folic acid was greater at higher pre-treatment homocysteine and at lower pre-treatment folate levels. Folate alone

reduces homocysteine level by 25%, addition of vitamin B12 leads to additional 7% reduction, whereas addition of vitamin B6 didn't reduce it significantly.[87]

Subacute combined degeneration of spinal cord in a person with vitamin B12 deficiency is a possible side effect of folic acid therapy.[48] This complication can be prevented by supplementation of folic acid therapy with vitamin B12 at the dosage of 400-1000µgm.[85]

Folate therapy at the dosage of 300-400µgm per day reduces the serum homocysteinemia to lower level. In majority of patients many studies have reported that 0.65 to 10 mg folic acid / day along with vitamin B12 & vitamin B6 decreases serum homocysteine level by 25 to 50%, both in vascular disease and in healthy subjects.[86] Minimum daily effective dose for homocysteine lowering efficacy is about 400µgm.[88,69]

Daily recommended allowance of vitamin B12 is difficult to be met by vegans. Only 1 to 3 % of vitamin B12 is absorbed by simple diffusion. Thus 1500µgm of vitamin B12 should be given. Because 10 to 30 % of older individual may not absorb food bound vitamin B12 completely, the higher dosage of vitamin B12 and food fortified with vitamin B12 is recommended for those persons older than 50 years of age.[88] Dietary intake of vitamin B12, folate and vitamin B6 and riboflavin is low in Indian population as compared to Western population. To increase vitamin B12 intake in population,

consumption of eggs, green leafy vegetables and fruits should be encouraged.[89]

In patients with cystathione beta synthase deficiency high dose upto 500 mg/day of pyridoxine may be required. The dosage of vitamin B6 required to treat mild or moderate hyperhomocysteinemia is much lower i.e. 10 mg/day. High dose pyridoxine can lead to peripheral sensory neuropathy.

ROLE OF SERUM HOMOCYSTEINE IN CEREBROVASCULAR ACCIDENT

Homocysteine is biosynthesized from methionine by the removal of its terminal Cε methyl group. Homocysteine can be recycled into methionine or converted into cysteine with the help of vitamin B12. The formula of homocysteine is HSCH2CH2CH(NH2)CO2H. It is a homologue of the amino acid cysteine, differing by an additional methylene (-CH2-) group.

Serum total homocysteine is, a protein N and S linked homocysteine, homocysteine S-S-Cys disulfide. serum homocysteine used as an important predictive risk factor screening of inborn error of metabolism in newborn, in cardiovascular events, post stroke evaluation and as an additional test for vitamin B12 deficiency.[10]

Homocysteine is a sulfur-containing amino acid. It is produced bydemethylation of the essential amino acid methionine.[24]

Homocysteine is biosynthesised from methionine, it is not directly obtained from diet. First, methionine receives an adenosine group from ATP, a reaction catalyzed by *S*-adenosyl-methionine synthetase, to give S- adenosyl-methionine (SAM). SAM then transfers the methyl group to an acceptor molecule, (i.e., norepinephrine as an acceptor during epinephrine synthesis, DNA methyl transferase as an intermediate acceptor in the process of DNA methylation).The adenosine is then hydrolyzed to yield L-homocysteine.[106]

There is two primary fates of L homocysteine

1. Conversion via tetrahydrofolate back into methionine.

2. Conversion to cystathionine.

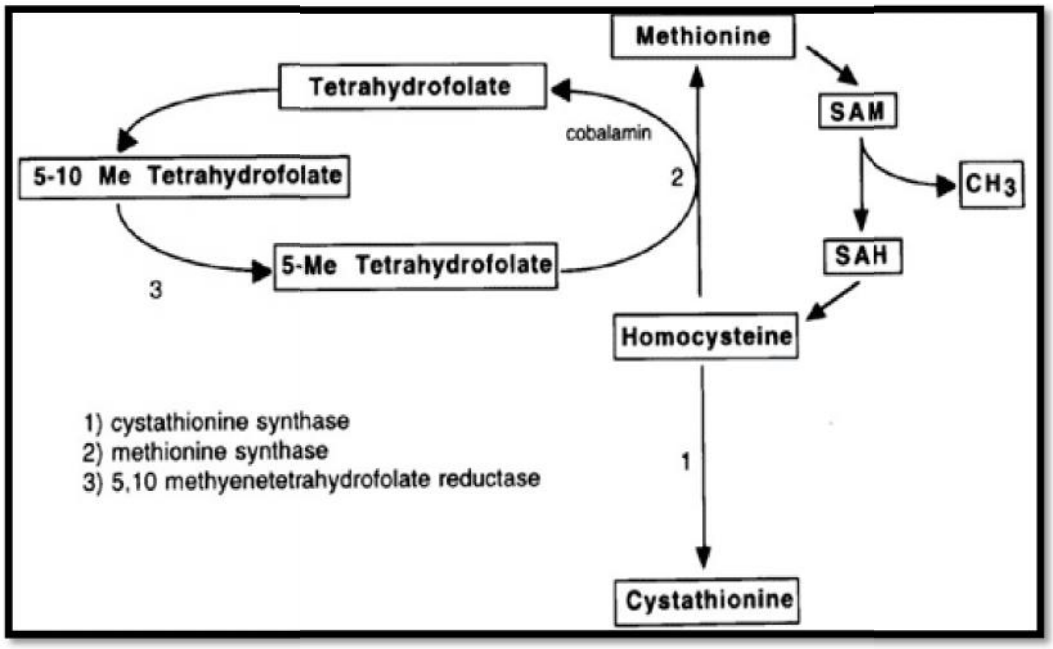

Figure 1: Pathway of metabolism of homocysteine

Homocysteine is metabolized by two pathways:

1. Transulfation pathway-

In transulfation pathway homocysteine combines with serine in the presence of enzyme cystathionine β synthase and gives cystathionine. This metabolic reaction is vitamin B12 dependent. Cystathionine is then converted into cysteine by hydrolysis.[67]

2. Remethylation pathway-

In remethylation, homocysteine needs a methyl group from N-5-methyltetrahydrofolate (MTHF) (this reaction is vitamin B12 dependent) or betaine to form methionine again hence, inherited deficiencies in enzymes necessary for the metabolism of homocysteine can result in increased blood levels of homocysteine, as can deficiencies in required cofactors, folate, vitamin B12, vitamin B6, and betaine. Other factors known to elevate homocysteine are coffee consumption, smoking and renal failure.[24,67]

The leading cause of morbidity and mortality in hyperhomocysteinemia patientsis progressive premature arteriosclerosis and associated thromboembolic complications. Histopathologically there are widespread arterial focal lesions with fibrous intimal plaques and medial fibrosis with fraying and splitting of the internal elastic membranes. Homocysteine or its derivatives are considered to cause these changes.[68]

Elevated serum homocysteine level has associated with vascular disease, including cerebrovascular disease in general, particularly in subjects with significant carotid stenosis.[41]

Under normal physiological state around 10-20% of total homocysteine is present in different oxidized forms such as Homocysteine cystathionine and homocysteine, the homocysteine dimer. Less than 1% of total homocysteine is present in free reduced form.[4,10]

Clarke et al showed that every increase of 2.5 μmol/L in plasma homocysteine can be associated with an increase of stroke risk of about 20%. Moreover plasma homocysteine levels above 20μmol/L are associated with nine fold increase of the myocardial infarction and stroke risk when compared to concentration below 9μmol/L.[10]

MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted to BLDE University's Shri B.M.Patil Medical college and Research Centre, Vijayapur between January 2016 to June 2017.

SAMPLE SIZE:

Statistical Method

The mean difference of homocysteine level in cases and controls as 2.81µmol/L (15.32 ± 6.39 and 12.51 ± 3.34) and common standard deviation 4.8 [107] , at 99 % confidence level and at 90 % power in the study, sample size is 89.

$$n = \underline{(Z\alpha + Z_{\beta})^2} \ \underline{\times 2 \times SD^2}$$

Hence 89 approximately 90 cases and 90 controls of age and sex matched healthy individual included in the study.

Statistical analysis :

Data is presented diagrammatically and as mean ± SD.

Groups are compared using 't' test, chi square test and regression analysis done.

TYPE OF STUDY :

Comparative study

METHOD OF COLLECTION OF DATA:

Information was collected through prepared proforma from each patient. All patients were interviewed as per the prepared proforma and then complete clinical examination was done for all the patients admitted with focal neurological deficit to BLDEU'S Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur.

Principle :

Estimation of serum homocysteine level by Chemiluminescent Immunofluroscent Assay by Instrument Minividas.

Inclusion Criteria for Case Selection:

All the patients admitted to BLDEU'S Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapur with Cerebrovascular accidents diagnosed by clinical examination and confirmed by CT scan and MRI brain.

Exclusion criteria for Case Selection:

All the patients admitted with neurological deficit due to causes other than Cerebrovascular accidents.

ESTIMATION OF HOMOCYSTEINE

METHOD PRINCIPLE : The AMS enzymatic test for the quantitative homocysteine determination based on a series of enzymatic reaction causing a decrease in absorbance value due to NADH oxidation to NAD^+. Homocysteine

concentration in sample is directly propositional to the quantity of NADH converted to NAD^+. The enzymatic reactions are the following:

Total homocysteine ⟶ Free homocysteine

Free homocysteine + S-Adenosyl-methionine $\xrightarrow{\text{s- methyltranseferase}}$ methionine + S- Adenosyl-Homocysteine

S- Adenosyl-Homocysteine $\xrightarrow[\text{Glutamatedehydrogenase}]{\text{SAM Hydrolase + Adenosine deaminase}}$ Inosine + NAD^+

COMPOSITION :

Reagent A:

S-Adenosylmethionine	:	0.1 mmol/L
NADH	:	0.2 mmol/L
TCEP	:	0.5 mmol/L
2-Oxoglutarate	:	5 mmol/L

Reagent B:

Glutamate dehydrogenase	:	10 KU/L
SAH Hydrolase	:	3.0 KU/L
Adenosyne deaminase	:	5.0 KU/L
HCY Methyltranseferase	:	5.0 KU/L

OBSERVATIONS AND RESULTS

Table 1:Age wise distribution of patients

Age(Years)	Study Group N (%)	Control group N (%)
<30	2(2.2)	2(2.2)
30-39	1(1.1)	1(1.1)
40-49	16(17.8)	16(17.8)
50-59	13(14.4)	13(14.4)
60-69	21(23.3)	21(23.3)
70-79	25(27.8)	25(27.8)
80+	12(13.3)	12(13.3)
Total	90(100)	90(100)

According to this study only 1.1 % of patients is of 30-39 years age group and 27.8 % of patients is of 70-79 years age group.

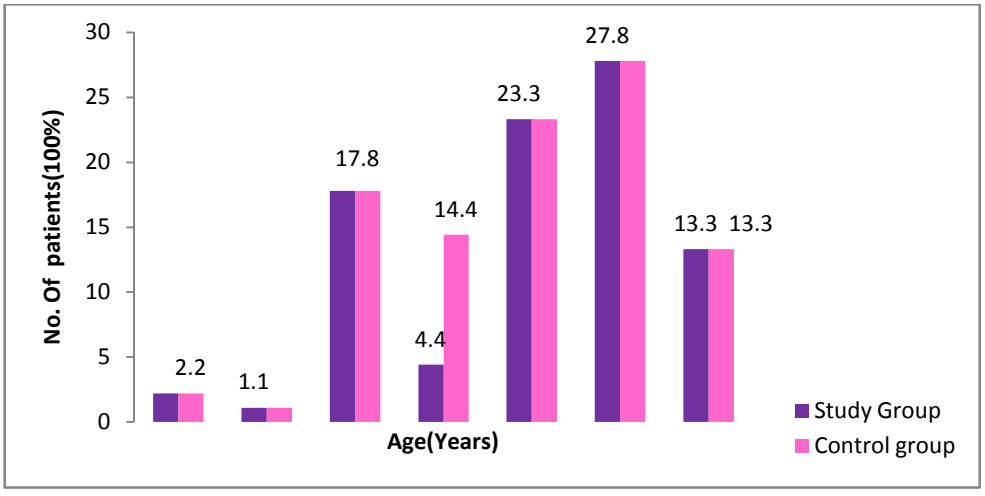

Fig.2 : Age wise distribution of patients

Above graph showing that 27.8 % patients are of 70-79 years age group and only 1.1 % of patients are of 30-39 years age group.

Table 2:Gender wise distribution of patients

Gender	Study Group N (%)	Control group N (%)
Male	60(66.7)	60(66.9)
Female	30(33.3)	30(33.1)
Total	90(100)	90

In this study 66.7 % patients are male and 33.3% patients are female.

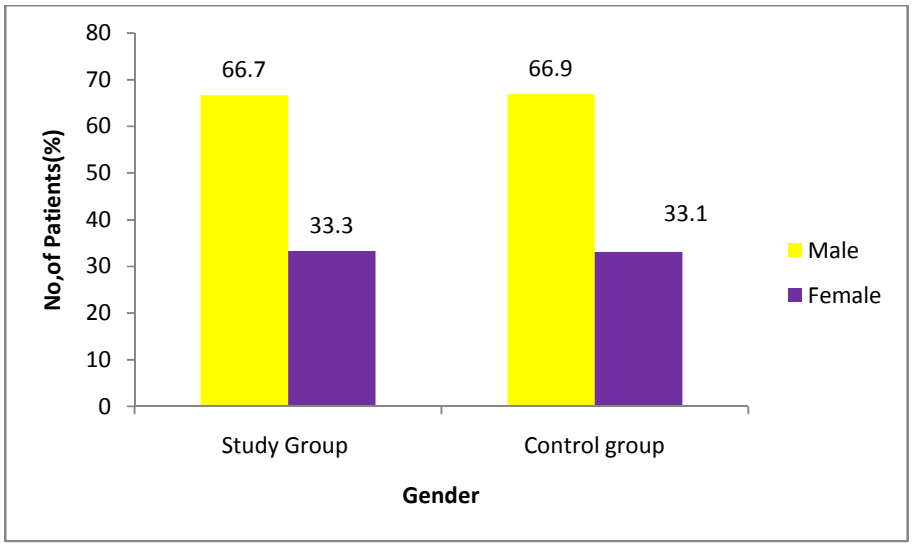

Fig 3 : Gender wise distribution of patients

Above graph showing number of male patients are more than female patients.

Table 3: comparison of serum homocysteine level between study and control group.

Variable	No. of Patients	Study group (µmol/L)	Control group (µmol/L)	Mann whitney U test
Serum homocysteine level	90	31.47±39.89	16.62±22.08	P<0.0001*
Age	90	62.70±14.35	62.63±14.13	P=0.9464 NS
Gender				
Male		60	60	P=1.00 NS
Female		30	30	

In study group the mean serum homocysteine level is 31.47±39.89 µmol/L and in control group 16.62±22.08 µmol/L, it indicates that serum homocysteine level is highly significantly raised in cases of stroke compared with control patients.

Table 4: Distribution of study group patients according to risk factor

Risk factors	Study Group	Percentage
DIABETES MELLITUS		
Yes	19	21.1
No	71	78.9
HYPERTENSION		
Yes	22	24.5
No	68	75.5
SMOKING		
Yes	27	30
No	63	70
DIAGNOSIS		
Infarct	77	85.6
Hemorrhage	13	14.4
Total (CVA)	90	100

Table 4 showing percentage of patients in risk factors.

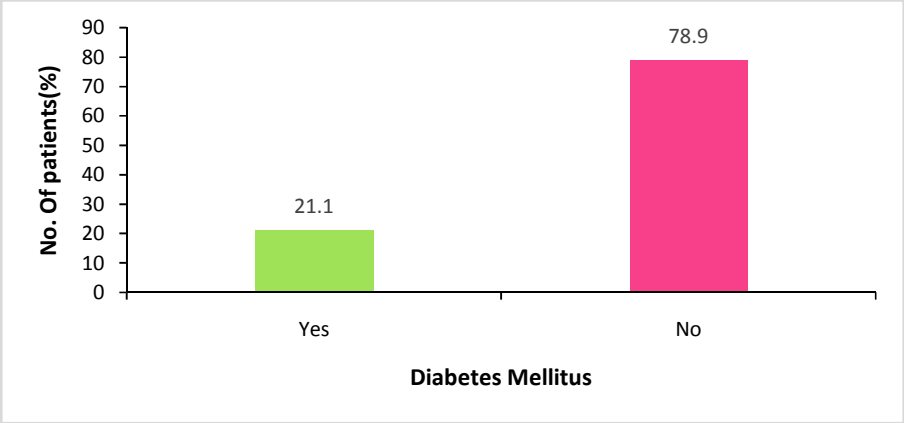

Fig 4: Percentage of patients with diabetes mellitus in study group

Above graph showing, in this study 21.1% patients are Diabetic and 78.9% patients are non diabetic.

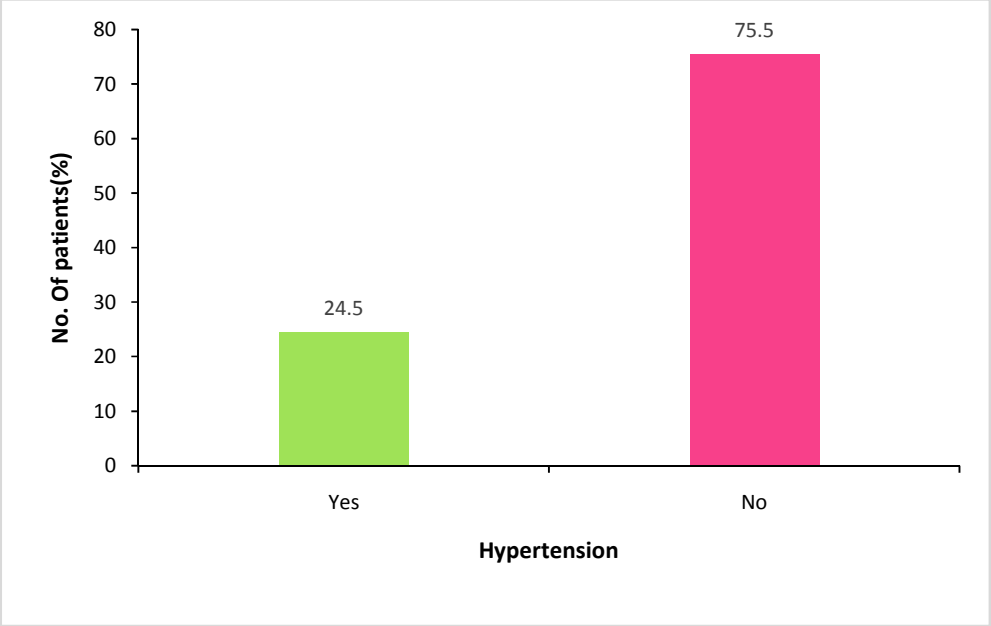

Fig 5: percentage of patients with hypertension in study group

Above graph showing that 24.5 % of patients are hypertensive

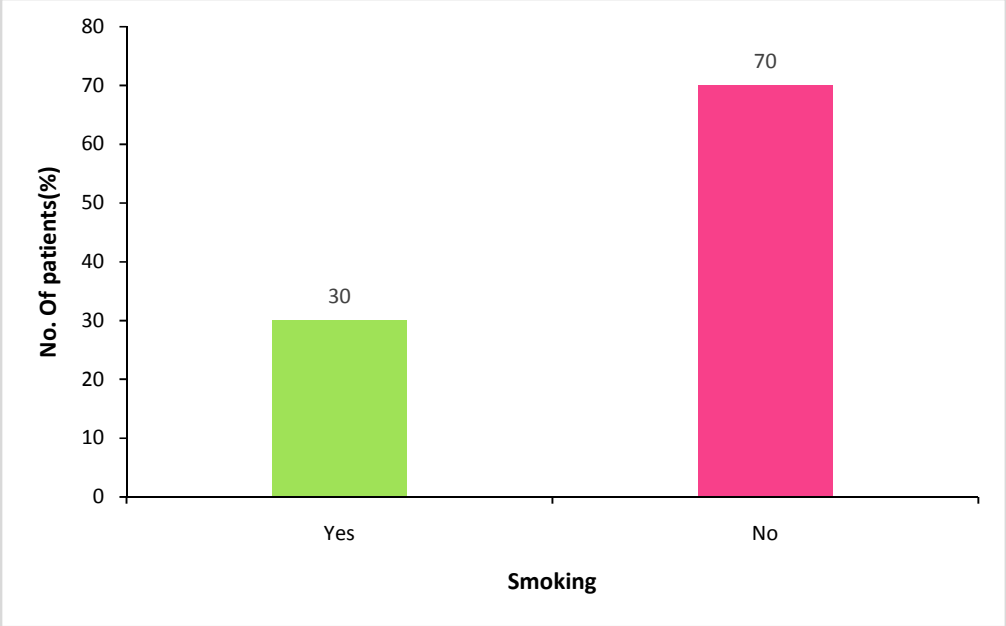

Fig 6: Percentage of patients with smoking in study group

Above graph showing 30% of patients are smoker and 70% are non smoker.

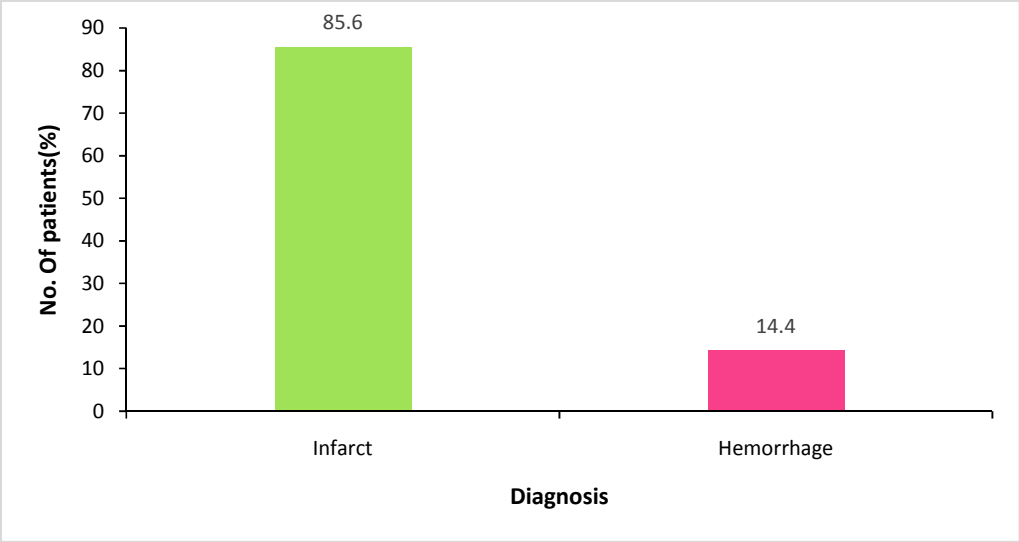

Fig 7: Percentage of patients with Infarct & Hemorrhage in study group

Fig 7 showing that 85.6% patients are with infarct and 14.4% patients are with Hemorrhagic stroke.

Table 5: Descriptive statistics

Variable	Study Group		Control group	
	Range	Mean±SD	Range	Mean±SD
Serum homocysteine (µmol/L)	3-187	31.47±39.893	4-161	16.62±.08
RBS(mg/dl)	29-366	138.44±77.142	62-190	89.73±17.96
creatinine (mg/dl)	0-6	1.10±.704	0-1	0.96±0.207
Sodium(mmol/L)	125-151	137.19±4.454	128-151	136.89±4.4004
Potassium (mmol/L)	3-6	3.97±0.661	3-5	3.78±0.514
Age	22-90	62.70±14.353	25-90	62.63±14.13

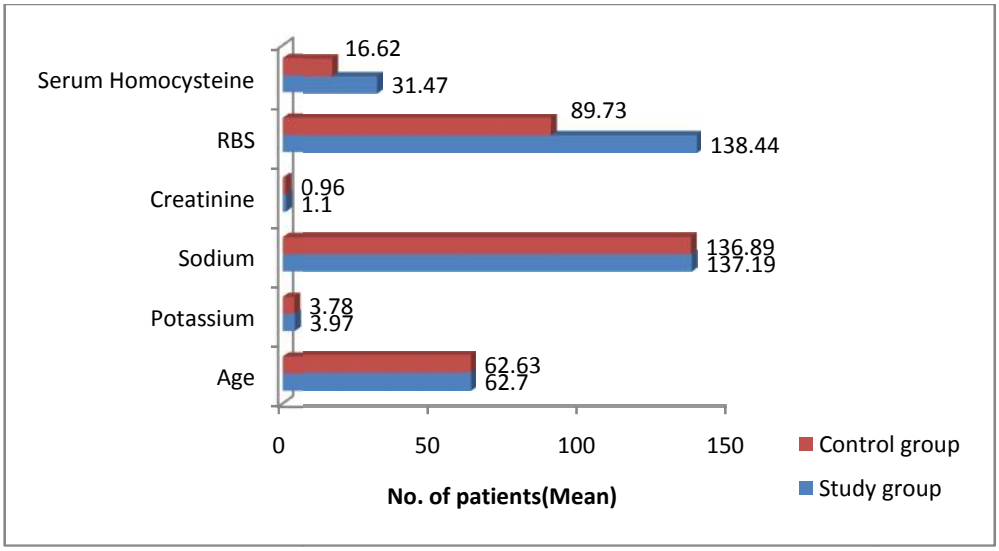

Fig 8: Descriptive statistic

Table 6: Association between the Serum homocysteine level with Age

Age	No. Of Patients	Homocysteine level Mean ±SD (µmol/L)	Mann Whitney U test
<60	32	27.48±35.14	P=0.4281
≥60	58	33.65±42.43	NS

In this study, 32 patients of <60 years of age have mean homocysteine level 27.48±35.14µmol/L and 58 patients of age >60 years have mean homocysteine level 33.65±42.43µmol/L, with P = 0.4281, indicates that association between serum homocysteine level with age is not significant.

Table 7: Association between the Serum homocysteine level with Gender

Gender	No. Of Patients	Homocysteine level Mean ±SD(µmol/L)	Mann Whitney U test
Male	60	29.18±37.47	P=0.4739
Female	30	36.02±44.67	NS

In this study 60 male patients are with mean homocysteine level 29.18±37.47µmol/L and 30 female patient are with mean homocysteine level 36.02±44.67µmol/L, P value is 0.4739, which indicates association between the serum homocysteine level and gender is not significant.

Table 8: Association between the Serum homocysteine level with Diabetes Mellitus.

Diabetes Mellitus	No. Of Patients	Homocysteine level Mean ±SD(µmol/L)	Mann Whtney U test
Yes	19	19.97±33.47	P=0.0078*
No	71	34.53±41.11	

In this study 19 patients with diabetes have mean serum homocysteine level 19.97±33.47µmol/L and 71 patients those who are non diabetic have serum homocysteine level 34.53±41.11µmol/L with P value 0.0078 indicating association between serum homocysteine level and diabetes mellitus is significant.

Table 9: Association between the Serum homocysteine level with Hypertension

Hypertension	No. Of Patients	Homocysteine level Mean ±SD(µmol/L)	Mann Whtney U test
Yes	22	62.21±52.9	P=0.0001*
No	68	21.51±28.75	

In this study 22 patients of hypertension have mean homocysteine level 62.21±52.9µmol/L and 68 patients of non hypertensive patients have mean homocysteine level 21.51±28.75µmol/L with P value 0.0001 which indicates significant correlation between serum homocysteine level and hypertension.

Table 10: Association between the Serum homocysteine level with Smoking habit

Smoking habit	No. Of Patients	Homocysteine level Mean ±SD(µmol/L)	Mann Whtney U test
Yes	27	72.06±53.9	P=0.0001*
No	63	14.06±06.13	

According to above chart mean serum homocysteine level is higher in smokers than non smokers with P value 0.0001, indicates highly significant association between serum homocysteine and smoking.

Table11 : Association between the Serum homocysteine level with Diagnosis

Diagnosis	No. Of Patients	Homocysteine level Mean ±SD(µmol/L)	Mann Whtney U test
Infarct	77	31.38±39.77	P=0.5817
Hemorrhage	13	31.92±42.26	NS

In this study 77 patients of infarct have mean serum homocysteine level 31.38±39.77µmol/L and 13 patients of infarct have mean serum homocysteine level 31.92±42.26µmol/L with P value 0.5817, indicating non significant association.

DISCUSSION

In this case control study we found a strong co-relation of hyperhomocysteinemia with ischemic stroke in both younger and older age group. The result of the present study are consistent with many case control and prospective studies, although few prospective studies failed to establish corelation.[6]

There is no definite threshold level for homocysteine that correlates with the sudden increase in the risk of vascular events. Although the normal range for homocysteine level has been proposed to lie between 5 and 15µmol/L, increased risk of vascular disease within this range is documented by Modi et al.[6]

Many studies have showed that increased homocysteine represents an independent risk factor for coronary, cerebrovascular and peripheral arterial diseases.[21,24,60]

Various risk factors for cerebrovascular accidents like age, sex, food habit, hypertension, diabetes mellitus and lifestyle were studied and analyzed in relation to serum homocysteine levels.

Hyperhomocysteinemia is one of the newly recognized factor that increases the risk of vascular disease.[19] Mechanisms by which hyperhomocysteinemia increases risk of cerebrovascular accidents are not clear, but several possible mechanisms have been proposed.[19]

Hyperhomocysteinemia is associated with premature atherosclerosis. Experimental studies both in vivo and in vitro shows that homocysteine causes endothelial injury and cell detachment. Hence these data suggest that homocysteine might contribute to cerebrovascular disease in patients as an additive risk factor.[68]

Measurement of homocysteine may become the integral part of workup of stroke patients in future.

Comparison of serum homocysteine level between study and control group.

In study group the mean serum homocysteine level is 31.47±39.89µmol/L and in control group 16.62±22.08µmol/L, it indicates that serum homocysteine level is highly significantly raised in cases of stroke compared with control patients. Our findings consistent with Ranjeet K et al.[107]

Clarke R et al,[93] Olsegun et al,[19] Osunkalu et al,[20] Kittner et al,[59] Bruce et al,[64] Perry et al[83] and Zongte et al[8] concluded hyperhomocysteinemia as an independent predictor of stroke risk (both infarct and hemorrhage).

Modi et al,[6] Roudbari et al[7] and Nigel et al[60] concluded that hyperhomocysteinemia as an important risk factor for ischemic stroke.

Verhoef et al in his study said that small but insignificant association between elevated homocysteine and risk of ischemic stroke.[28]

Brattstrom et al findings suggested hyperhomocysteinemia might be a risk factor for atherosclerotic cerebrovascular accidents.[68]

Alfthan et al observed no association between hyperhomocysteinemia and cerebrovascular accidents.[99]

Boushey and colleagues have reported on a meta-analysis of many observational studies relating total homocysteine concentrations to atherosclerotic vascular disease, of which 11 studies addressed the association between homocysteine [45] and risk of stroke[69], 9 case-control studies provided support for the hypothesis that homocysteine is an independent risk factor for stroke while two prospective studies did not support the study.[21]

Comparison of serum homocysteine with age

In this study, 32 patients of <60 years of age have mean homocysteine level 27.48±35.14µmol/L and 58 patients of age >60 years have mean homocysteine level 33.65±42.43µmol/L, with P = 0.4281, indicates that association between serum homocysteine level with age is not significant. However, the difference was statistically not significant (p >0.05). Our findings are consistent with study of Narang et al[2], Modi et al[6] and Nigel et al.[60] However, according to findings of Longo et al[5] and Zongte et al[8] increase inthe serum homocysteine levels were observed with increasing age.

Comparison of serum homocysteine according to sex

In this study 60 male patients are with mean homocysteine level 29.18±37.47µmol/L and 30 female patient are with mean homocysteine level 36.02±44.67µmol/L, P value is 0.4739, which indicates association between the serum homocysteine level and gender is not significant. Our findings are consistent with study of Narang et al,[2] Modi et al,[6] Bogdan et al[10] and Andrew et al.[11]

However Kang et al studies shows that young healthy women have homocysteine levels lower than healthy men. This difference diminishes with ageing. An abrupt increase in serum homocysteine in women after 50 years suggests that sex difference in homocysteine disappears with increasing age.[18]

Comparison of serum homocysteine according to smoking habit

According to above chart mean serum homocysteine level is higher in smokers than non smokers with P value 0.0001, indicates highly significant association between serum homocysteine and smoking. Our results are similar to findings of Modi et al,[6] Nygard et al[63] and Welch et al.[44] However Roudbari et al reported no significant relationship between smoking and serum homocysteine levels.[7] Perry et al found no evidence of an interaction with smoking.[83]

Comparison of serum homocysteine with blood pressure

In this study 22 patients of hypertension have mean homocysteine level 62.21±52.9µmol/L and 68 patients of non hypertensive patients have mean homocysteine level 21.51±28.75µmol/L with P value 0.0001 which indicates significant correlation between serum homocysteine level and hypertension.

Our results are similar to findings of Narang et al,[2] Modi et al,[6] Graham et al,[12] Olusegun et al,[19] Nigel et al,[60] Nygard et al,[63] Perry et al[83] and Manilow et al.[85] However Kittner et al did not find definite evidence of an increased homocysteine in hypertensive patients.[59]

Comparison of serum homocysteine with diabetes mellitus

In this study 19 patients with diabetes have mean serum homocysteine level 19.97±33.47µmol/L and 71 patients those who are non diabetic have serum homocysteine level 34.53±41.11µmol/L with P value 0.0078 indicating association between serum homocysteine level and diabetes mellitus is significant. Our findings are not consistent with study of Narang et al[2] and Modi et al.[6]

Comparison of serum homocysteine level with CT findings

In this study 77 patients of infarct have mean serum homocysteine level 31.38±39.77µmol/L and 13 patients of infarct have mean serum homocysteine level 31.92±42.26µmol/L with P value 0.5817, indicating non significant association.

In this study we have taken 90 cases among that, 19 patients have diabetes mellitus, 27 have hypertension and 22 have smoker. These risk factors are significantly correlating with hyperhomocysteinemia. which is consisting with Ranjeet et al.[107]

In this study 90 cases with risk factors like diabetes mellitus, hypertension and smoking are included and their serum homocysteine level is compared with the 90 controls those are with no risk factors, and it is concluded that serum homocysteine level is increased in patients with risk factors. This is consisting with Ranjeet et al.[107]

SUMMARY AND CONCLUSION

Our study of serum homocysteine levels in cerebrovascular accidents is a case control study. The present study is performed to determine serum homocysteine levels in cerebrovascular accidents. The aim and objective was to study serum homocysteine levels as risk factor for cerebrovascular accident. The study is restricted to patients admitted to Shri B M Patil Medical College, Hospital and Research centre with focal neurological deficit due to cerebrovascular accidents. Neurological deficit due to other causes were excluded.

All the patients were subjected to thorough history, clinical examination and investigations including, CT scan brain and serum homocysteine. Our main observation was that serum homocysteine levels were elevated in cerebrovascular accident patients significantly, both in cases of infarct and hemorrhage. Further serum homocysteine levels were higher in patients with hypertension and smoking. Serum homocysteine did not show any relation with age, sex, diabetes mellitus .

People at risk for cerebrovascular diseases such as hypertension, smoking and diabetes mellitus should be screened for hyperhomocysteinemia.

In conclusion the present study revealed that hyperhomocysteinemia appears to be an important risk factor for cerebrovascular accidents. It is therefore important to use serum homocysteine level as an important tool to

investigate all cases of cerebrovascular accidents and also in those who are at risk of developing stroke.

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ANNEXURES

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

PROFORMA

BLDE'S Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur

"STUDY OF SERUM HOMOCYSTINE LEVEL IN CEREBROVASCULAR ACCIDENT"

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Occupation:

Residence:

Presenting complaints with duration:

History of present complaints:

Past History:

History of hypertension

History of diabetes mellitus

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits

Habits

Family History:

Treatment History :

General Physical Examination

Height :

Weight :

Body Mass Index :

Vitals

PR:

BP:

RR:

Temp:

Head to Toe examination

SYSTEMIC EXAMINATION

Central Nervous System

Respiratory System

Cardiovascular System

Per abdomen

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

URINE ROUTINE:

RBS:

BLOOD UREA:

SERUM CREATININE:

SERUM ELECTROLYTES:

SERUM HOMOCYSTEINE:

CT SCAN BRAIN:

MRI BRAIN:

<u>FINAL DIAGONOSIS</u>

B.L.D.E.U.'s SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____, S/O D/O W/O _____, aged ____ years, ordinarily resident of _____ do hereby state/declare that Dr.Nilesh A. Malgar of Shri. B. M. Patil Mdical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ _____ disease (condition) and this disease/condition mimic following diseases. Further Doctor Nilesh informed me that he/she is conducting dissertation/research titled "Study of serum Homocysteine Level in cerebrovascular accident under the guidance of Dr. S. M. Biradar requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and

also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research /dissertation.

Signature of patient: Signature of doctor:

Witness: 1.

2.

Date:

Place

MASTER CHART

CASE

SR No.	IP No.	NAME	AGE	SEX	SERUM HOMOCYSTEINE (µmol/L)	RBS	CREATININE (mg/dl)	SODIUM(mmol/l)	POTASSIUM (mmol/l)	DIAGNOSIS	DIABETES MELLITUS	HYPERTENSION	SMOKING
1	982	Basavara jNaganur	45	M	18.9	92	0.8	137	3.7	Infarct	NO	NO	NO
2	573	Sattawwa Appu Padagur	40	F	8	112	0.6	137	4.5	Infarct	NO	NO	NO
3	984	Saybanna Bhimasha G	75	M	10.9	170	1	135	4.4	Infarct	NO	NO	YES
4	1154	Barmanna Satirappa	85	M	14	85	0.6	136	3.7	Infarct	NO	NO	YES
5	1363	Gurubasayya Gurayya K	82	M	45.8	127	1.5	137	5.1	Infarct	NO	YES	YES
6	1748	Ramchandra H Joshi	75	M	5	68	0.6	128	4	Infarct	NO	NO	NO
7	1758	Sadashivagouda Patil	60	M	155	66	1.1	128	5.3	Infarct	YES	YES	YES
8	2201	Gangabai H Patil	81	F	11	86	0.7	139	4.7	Infarct	NO	NO	NO
9	2548	Mayyawwa K Arajungi	70	F	9.1	110	0.6	138	4	Infarct	NO	NO	NO
10	3020	Rudrappa Dalwai	75	M	10	150	1	136	4.2	Infarct	NO	NO	NO
11	3939	Gayanappa D Seregond	83	M	47	84	0.9	137	5.2	Infarct	NO	NO	YES
12	4689	Suresh Bindrao Katti	62	M	13	80	0.6	135	2.9	Infarct	NO	NO	NO

13	5853	Mahadevappa S Gundalgiri	60	M	43	82	0.6	132	3.8	Infarct	NO	YES	YES
14	6506	Girimalappa M Dalawai	61	M	14	343	1.1	125	4.7	Infarct	YES	NO	NO
15	6485	Hanamanth S Kumatagi	52	M	12	66	0.8	138	3.2	Infarct	NO	NO	NO
16	7087	Basavaraj N Jogur	63	M	28	171	0.8	130	3.9	Infarct	NO	NO	YES
17	7151	Anil V Huddar	58	M	10	150	0.8	132	4	Infarct	YES	NO	NO
18	7397	Meerabai Mahadikar	70	F	34.9	346	1.9	135	3.9	Hemorrhage	YES	YES	YES
19	7773	Shantabai Kala	68	F	17	121	1.5	142	4.9	Infarct	NO	NO	NO
20	8431	Shivanand C Kori	65	M	27	80	0.7	134	4.2	Infarct	NO	YES	YES
21	9981	Vitthal Chalwadi	60	M	21	113	1.2	138	3.8	Infarct	NO	NO	YES
22	10150	Prakash V Rathod	22	M	22	114	1.1	136	3.5	Infarct	YES	NO	NO
23	10773	Subhash Saibani	55	M	8	97	0.6	135	3.2	Infarct	NO	NO	NO
24	1169	Chanamma Navdagi	80	F	12	349	0.9	136	3.7	Infarct	YES	NO	NO
25	12112	Basamma D Shanknur	48	F	11	110	0.6	137	4.4	Infarct	NO	NO	NO
26	11961	Shivappa P Karugal	63	M	15	187	1	135	4	Infarct	NO	NO	NO
27	12981	Janabai Parankar	70	F	30	80	0.6	140	4.6	Infarct	NO	NO	YES
28	12916	Sadashiv A Hadpad	75	M	9	132	0.9	136	3	Infarct	NO	NO	NO
29	14123	Ravichandra Melinmani	25	M	57	80	0.8	140	3.6	Infarct	NO	NO	YES
30	14291	Mohamed H Algur	70	M	17	29	0.9	144	3.9	Infarct	NO	NO	NO

31	15004	Parshuram H Bajentri	41	M	23	99	0.8	135	3.7	Infarct	NO	NO	YES
32	15681	Sidaraya G Honkande	58	M	12	200	2.8	134	3.4	Infarct	NO	NO	NO
33	16402	Mahesh Hiremath	44	M	13	225	0.6	142	3.7	Infarct	YES	NO	NO
34	16688	Shankar A Danapal	60	M	21	86	6.1	140	3.2	Infarct	NO	NO	NO
35	17339	Gundulal I Maniyar	60	M	5	207	0.8	138	3.2	Infarct	YES	NO	NO
36	17866	Sangappa B Sajjan	86	M	26	113	0.8	135	3.5	Infarct	NO	NO	NO
37	17900	Mahadevi Mathapati	48	F	17	91	0.7	142	4.2	Infarct	NO	NO	NO
38	18123	Shivaraya A Biradar	72	M	22	92	2.6	135	5.3	Infarct	NO	YES	NO
39	18903	Veerendra C Patil	42	M	18	122	0.6	140	3.8	Infarct	NO	NO	NO
40	19497	Gurusiddawwa Rodagi	60	F	64	103	1.1	140	3.6	Infarct	NO	YES	YES
41	20583	Basavaraj T Kembavi	48	M	3	320	0.7	141	4.9	Infarct	YES	NO	NO
42	20861	Amogsidha V Sonnad	52	M	17	96	0.7	141	4.2	Hemorrhage	NO	NO	NO
43	20756	Shankareppa M Chouri	50	M	18	96	0.7	141	4.1	Infarct	NO	NO	NO
44	21240	Arvind Kirasur	48	M	19	120	0.6	137	4.9	Infarct	NO	NO	NO
45	752	Ibrahim M Metri	75	M	4	268	0.8	130	4.4	Infarct	YES	NO	NO
46	817	Laxmibai V Hiremath	53	F	2.8	250	0.6	133	4	Infarct	YES	NO	NO
47	1349	Imamsab T Shekh	75	M	21	120	0.9	135	3.2	Infarct	NO	NO	NO
48	1469	Subhas I Ganganalli	55	M	35	130	0.9	135	3.6	Infarct	NO	YES	YES

49	1571	Rukmawwa B Kadabi	70	F	24	180	1	138	4.4	Infarct	NO	NO	NO
50	1586	Savitri B Talakeri	65	F	34	100	0.6	128	4.2	Infarct	NO	YES	YES
51	7890	Sangamma P Yallawar	75	F	130	183	0.7	130	3.6	Hemorrhage	NO	YES	YES
52	3147	Shivappa Shiramgond	80	M	27	75	0.8	135	4	Infarct	NO	NO	NO
53	3645	Jayanabee Bavimani	45	F	9	120	0.6	131	4	Infarct	NO	NO	NO
54	4067	Mallawwa K Muraman	65	F	24	126	0.6	137	3.5	Hemorrhage	NO	NO	NO
55	4026	Prabhu S Umadi	78	M	181	88	0.6	132	4.3	Infarct	NO	YES	YES
56	4803	Hemalabai Gangu Pawar	85	F	187	60	0.8	132	3.8	Infarct	NO	NO	YES
57	7025	Appa Limbaji Lokande	45	M	127	89	1	136	4.3	Infarct	NO	YES	YES
58	7988	Ashok Shankarappa Petkar	56	M	143	264	0.6	134	4.7	Infarct	NO	NO	YES
59	8733	Mahadevi S Padekanur	70	F	121	90	0.9	146	5.7	Hemorrhage	NO	YES	YES
60	8835	Kashibai Gayakawad	75	F	97	160	0.8	142	3.5	Infarct	NO	NO	YES
61	8949	Mallappa B Bolatotagi	58	M	119	98	3.3	147	4.4	Infarct	NO	YES	YES
62	9614	Kashibai Y Padasalgi	52	F	13	250	0.6	138	5	Infarct	YES	NO	NO
63	9617	Hussainbee P Baganagar	65	M	14	270	0.6	138	5	Infarct	YES	NO	NO
64	10063	Bahubali M Gubachi	30	M	40	85	0.8	136	3.2	Infarct	NO	YES	3NO
65	10352	Manohar R Deshpande	60	M	13	176	1.1	151	3.7	Infarct	NO	NO	NO
66	10356	Dhareppa H Khedagi	72	M	15	366	1.4	143	2.7	Infarct	NO	NO	NO

67	103668	Annapurna M Guddodgi	65	F	13	200	0.9	134	5.4	Infarct	YES	NO	NO
68	10744	Ningappa G Hanamagond	76	F	11	209	0.8	144	3.9	Infarct	YES	NO	NO
69	12729	Sanganabasavaswami S Gobbur	64	M	11.6	250	0.7	135	4.4	Infarct	YES	NO	NO
70	1130	Shakuntala G Hiremath	45	F	14	162	0.6	132	4.2	Infarct	YES	NO	NO
71	12916	Ramappa K Sindhur	72	M	14.3	100	1.2	134	4.1	Infarct	YES	NO	NO
72	25531	Gomalabai D Chavan	80	F	15	78	0.7	139	4.5	Infarct	NO	NO	NO
73	25343	Parvati R Guruswami	60	F	93	116	1.4	138	4.2	Infarct	NO	YES	YES
74	25108	Laxmibai R Godekar	52	F	17.8	105	0.8	143	4.1	Infarct	NO	NO	NO
75	11232	Gourabai B Kurapi	45	F	9	309	0.6	138	4.9	Infarct	NO	NO	NO
76	11513	Gurulingawwa S Warad	77	F	32	90	0.7	135	4.4	Infarct	NO	NO	NO
77	15903	Prema I Chitwadgi	80	F	11	144	0.6	142	4.2	Hemorrhage	NO	YES	NO
78	13734	Shankar R Sarwad	49	M	14	80	0.4	138	3.2	Hemorrhage	NO	NO	NO
79	17204	Chandrakant D Jigajinagi	45	M	16	80	0.4	136	4.2	Infarct	NO	NO	NO
80	17866	Rajakkabai V Sindhe	86	M	26	80	0.6	138	3.2	Infarct	NO	NO	NO
81	17532	Sangappa B Sajjan	70	F	9	280	0.6	140	3.3	Hemorrhage	NO	YES	NO
82	17428	Ramesh S Angadi	51	M	14	90	0.6	142	3.2	Hemorrhage	NO	YES	NO
83	18705	Channappa B Chikgalagali	70	M	10	86	0.4	140	3	Infarct	NO	NO	NO
84	20280	Malkappa D Malgar	70	M	4.1	86	0.6	140	4.2	Hemorrhage	NO	NO	NO

85	27699	Suryakanth S Mali	72	M	11	90	0.4	136	3.1	Hemorrhage	NO	NO	NO
86	26943	Babu N Paki	68	M	38	80	0.8	142	2.8	Infarct	NO	YES	YES
87	21699	Iratappa B Bagewadi	75	M	15	86	0.8	140	3.2	Hemorrhage	NO	YES	NO
88	21476	Bhimaraya S Loni	90	M	10	80	0.4	140	3.2	Hemorrhage	NO	YES	NO
89	29437	Rachappa B Koti	65	M	9	91	1.2	140	4.5	Infarct	NO	NO	NO
90	30271	Yuvraj J Bagade	45	M	19	90	0.6	145	2.9	Infarct	NO	NO	NO

CONTROL

SR No.	IP No.	NAME	AGE	SEX	SERUM HOMOCYSTEINE (µmol/L)	RBS	CREATININE (mg/dl)	SOUDIUM (mmol / l)	POTASSIUM(mmol/l)	DIABETES MELLITUS	HYPERTENSION	SMOKING
1	29827	Shantabai S Benlamath	40	F	18	90	0.6	135	2.8	NO	NO	NO
2	16147	Mahamad M Aigali	45	M	12	76	0.6	138	4	NO	NO	NO
3	2355	Sangappa M Sajjan	75	M	30	110	0.8	132	4.2	NO	NO	NO
4	29737	Parashram B Sagare	85	M	14	80	0.6	135	4	NO	NO	NO
5	26790	Abdulrehman D Jekati	82	M	12	86	0.6	136	4	NO	NO	NO
6	17596	Somesh S Hiremath	75	M	18	89	0.8	140	4.1	NO	NO	NO
7	24308	Sharanappa C Goudappanavar	60	M	9	80	0.6	130	4	NO	NO	NO
8	26971	Laxmi S Bhavikatti	81	F	31	86	0.6	138	4.5	NO	NO	NO
9	14833	Chandawwa S Modi	70	F	15	80	0.6	140	4	NO	NO	NO
10	26815	Prabhugouda S Patil	75	M	12	86	0.6	138	4.2	NO	NO	NO
11	3939	Gayanappa D Seregond	83	M	47	80	0.6	135	3.2	NO	NO	NO

12	29777	Shantawwa G Shirsagi	62	M	10	80	0.4	136	3.1	NO	NO	NO
13	9410	Ashok SiddappaAwati	60	M	11.3	82	0.6	140	3.6	NO	NO	NO
14	14932	Madiwaladevaru S Gadagimath	61	M	15	80	0.6	135	2.9	NO	NO	NO
15	19052	Mallappa V Honnyal	52	M	11	120	0.4	140	3.2	NO	NO	NO
16	14902	Lachu Revu Rathod	63	M	10	62	0.7	135	4.2	NO	NO	NO
17	7988	Ashok Shankarappa Petkar	58	M	14.3	80	0.6	136	4.2	NO	NO	NO
18	7989	Ambavva V Doddamani	70	F	4	80	0.6	135	2.8	NO	NO	NO
19	29412	Danabai Kasanu Jadhav	68	F	10	96	0.6	135	2.9	NO	NO	NO
20	13195	Gurappa Balappa Savalgi	65	M	11.5	70	0.8	138	4.2	NO	NO	NO
21	28312	FatimA lisab Pinjar	60	M	12.6	85	0.6	143	4	NO	NO	NO
22	26396	Malakappa G Sindagi	27	M	12	100	0.8	130	4.2	NO	NO	NO
23	13704	Anusubai B Patil	55	F	55	90	0.6	138	3	NO	NO	NO
24	23769	Kashibai K Awati	80	F	18	90	0.6	140	4	NO	NO	NO
25	26873	Sarubai M Kudali	48	F	10	80	0.4	138	4.2	NO	NO	NO
26	3674	Appasahebgoud Patil	63	M	19.9	80	0.8	141	4.3	NO	NO	NO
27	21134	Gourabai K Rathod	70	F	10.6	90	0.6	140	4.2	NO	NO	NO

28	27394	Chandappa H Gonal	75	M	12	88	0.6	136	4	NO	NO	NO
29	11801	Ravi K Kambale	25	M	12	82	0.6	134	4.2	NO	NO	NO
30	29820	Laxman B Biradar	70	M	11.4	96	0.6	135	2.9	NO	NO	NO
31	25570	Vitthal P Sutagundi	41	M	12	92	0.6	136	3	NO	NO	NO
32	28716	Sahebagoud G Yelagi	58	M	15	82	0.6	146	3.2	NO	NO	NO
33	21043	Bhimanagoud S Patil	44	M	9.3	80	0.6	140	4.2	NO	NO	NO
34	29051	Shankarappa Natikar	60	M	11	68	0.6	128	4	NO	NO	NO
35	28489	Gurunathrao C Salger	60	M	13	89	0.6	140	4.1	NO	NO	NO
36	29257	Irappa S Bagali	86	M	15	90	0.4	140	4	NO	NO	NO
37	26675	Shardabai C Ambiger	48	F	15	86	0.6	136	4	NO	NO	NO
38	15904	BalappaTippannaHirekurbar	72	M	16	80	0.6	136	3.6	NO	NO	NO
39	21136	BabuRamanagoud Patil	42	M	9.6	92	0.8	142	3.1	NO	NO	NO
40	29888	SuvarnaSiddappaAnnappanavar	60	F	13	96	0.6	135	2.9	NO	NO	NO
41	20203	Sharanabasappa S Vanarotti	48	M	10	80	1	135	4	NO	NO	NO
42	29632	Prashanta C Kulakarni	52	M	4	80	0.6	140	3.6	NO	NO	NO
43	233010	Sampapad M Das	50	M	7.5	90	0.6	138	4	NO	NO	NO
44	26675	Ramesh B Gote	48	M	17	89	0.6	140	4.2	NO	NO	NO

45	26820	RamannaBalappa Vandal	75	M	7	90	0.6	141	5	NO	NO	NO
46	13710	Girijadevi D Dembre	53	F	16	80	0.6	140	4.2	NO	NO	NO
47	22847	Mohan T Rathod	75	M	12	89	0.8	140	4.1	NO	NO	NO
48	21755	Revanasidda T Kolhar	55	M	16	143	0.7	140	4.6	NO	NO	NO
49	17415	Shridevi D Kembhavi	70	F	12	84	0.6	140	3.2	NO	NO	NO
50	8415	Mahadevi M Wadeyar	65	F	83	90	0.9	151	2.8	NO	NO	NO
51	16170	Gangawwa S Jamanakatti	75	F	15	86	0.6	140	4	NO	NO	NO
52	14834	Bhimanna V Navi	80	M	11	68	0.6	128	4	NO	NO	NO
53	26227	Anjubai G Pattar	45	F	13.3	80	0.8	130	4.2	NO	NO	NO
54	17907	Dundawwa G Biradar	65	F	5.7	86	0.6	138	4.1	NO	NO	NO
55	27516	Neelakantayya S Hiremath	78	M	13	96	0.8	136	4	NO	NO	NO
56	26754	Shardabi S Pattar	85	F	5	86	0.6	140	4.2	NO	NO	NO
57	10906	Danayya S Math	45	M	9	86	0.6	135	4.2	NO	NO	NO
58	24031	Ravigouda B Patil	56	M	10.3	90	0.6	138	4.2	NO	NO	NO
59	27670	Danamma S Raichur	70	F	13	85	0.6	140	3.5	NO	NO	NO
60	7774	Kasturibai N Policepatil	75	F	3.5	100	0.8	136	3.5	NO	NO	NO

61	7134	Vinayak N Gornal	58	M	161	90	0.6	138	4.2	NO	NO	NO
62	507	Parvati S Avarasang	52	F	4	88	0.7	135	4.4	NO	NO	NO
63	17491	Sidappa B Kalasagond	65	M	18	80	0.9	136	3.2	NO	NO	NO
64	19253	Ramappa S Badagi	30	M	6.7	110	0.9	139	4.6	NO	NO	NO
65	2637	Chandbasha H Managuli	60	M	10	80	0.6	138	4.2	NO	NO	NO
66	27605	Ashok M Kondaguli	72	M	10	70	0.8	138	4.2	NO	NO	NO
67	27517	Sugalabai S Rukumpur	65	F	13	90	0.6	140	4.2	NO	NO	NO
68	16198	Parvati B Madabavi	76	F	13	80	0.6	140	3.5	NO	NO	NO
69	26342	Basangouda H Biradar	64	M	12	98	0.8	136	4.2	NO	NO	NO
70	29973	RenukaIshwar Chawan	45	F	14	96	0.6	135	2.9	NO	NO	NO
71	15214	Shashikant B Savantri	72	M	16.5	80	0.6	140	4.2	NO	NO	NO
72	19188	Parvatewwa R Melli	80	F	9	110	0.8	130	4	NO	NO	NO
73	151	Shivamma S Biradar	60	F	23	114	0.9	136	3.5	NO	NO	NO
74	23688	Indubai Mahadevappa	52	F	6	174	0.6	138	4.2	NO	NO	NO
75	1617	Bhimawwa S Bajantri	45	F	11	88	0.6	128	4	NO	NO	NO
76	19649	Rajkumar A Honakatti	72	M	12	80	0.9	130	2.9	NO	NO	NO
77	28314	Husanbee A Walikar	80	F	11	90	0.8	138	4.2	NO	NO	NO
78	256	Mallappa B Nimbargi	49	M	22	80	0.8	130	4.2	NO	NO	NO

79	21050	Madeva S Gugadaddi	45	M	10.6	90	0.9	135	4	NO	NO	NO
80	9073	Ravi D Chavan	86	M	126	98	0.6	135	2.9	NO	NO	NO
81	20682	Ambawwa V Dodamani	70	F	10	90	0.9	132	3.1	NO	NO	NO
82	17613	Basavaraj M Gajare	51	M	6	82	0.6	128	4	NO	NO	NO
83	26735	Ninganaguda C Chanagond	70	M	10	90	0.6	135	2.9	NO	NO	NO
84	28667	Manoo R Rathod	70	M	12	100	0.6	135	4.6	NO	NO	NO
85	19151	Mitalayya Y Hiremath	66	M	9	86	0.6	140	4	NO	NO	NO
86	21032	Sidram Basappa Indi	68	M	5.3	89	0.6	136	2.9	NO	NO	NO
87	7774	Kasturba N Policepatil	75	M	3.5	80	0.6	135	4.2	NO	NO	NO
88	27664	Shavantrappa M Magimath	90	M	11	80	0.6	140	4.2	NO	NO	NO
89	12909	Ningangouda B Biradar	65	M	12	86	0.8	145	4.2	NO	NO	NO
90	29052	Basavaraj K	45	M	6	190	0.6	135	3.1	NO	NO	NO