CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4553952

Avalable online at: http://www.iajps.com *A Case Study*

EXPOSURE OF SLEEP DISORDERS AND INCIDENCE IN PATIENTS WITH STROKE- A PROSPECTIVE OBSERVATIONAL COHORT STUDY IN A TERTIARY CARE TEACHING HOSPITAL

(Dr) Gayathri Gurram[1], M. Keerthi[1], Y. Sudharani[1], N. Prathyusha[1], Dr. N. V. Sundharachary[2], Dr. K. Nani Babu[3], Dr. Rama Rao Nadendla [4]

Article Received: January 2021 **Accepted:** January 2021 **Published:** February 2021

Abstract:

A stroke is a medical condition in which poor blood flow to the brain results in poor oxygen and nutrition to the brain cells which ultimately leads to death of brain cells. A sleep disorder, or somnipathy, is a medical disorder of the sleep patterns of a person or animal. Some sleep disorders are serious enough to interfere with normal physical, mental, social and emotional functions. The aim of this study is to find the exposure of sleep disorder in patients, those who are newly diagnosed with stroke. The objectives of the study are: To determine the exposure and incidence of sleep disorders in patients with stroke. To assess the type of sleep disorder in patients with stroke. To assess how counselling plays an important role in improving the proper management of diseases. The methodology of the study involves, the subjects who satisfy the study category are taken into study and patient consent form was taken. Subject information was collected using data collection forms and details of the study were secured. Later the standard questionnaires are asked and filled before and after the treatment. The collected data from the subjects with the help of questionnaires are assessed to determine the exposure and incidence of sleep disorders in subjects who are newly diagnosed with stroke (both ischemic and hemorrhagic). Results obtained in our study concludes that Snoring is the most common sleep disorder in patients with stroke followed by Day time sleepiness followed by Sleep talking followed by Sleep apnea followed

by Night terrors followed by Sleep paralysis followed by Bruxism, Restless leg syndrome,

Nightmares and Narcolepsy. However, sleep disorders are self-limiting in the early stages, so by educating bringing awareness about medication usage, lifestyle modification, dietary modifications, and sleep hygiene counseling's and providing patient information leaflets we observed there is a gradual decrease in symptoms.

Keywords: *Stroke, sleep apnea, sleep disorders, bruxisum, night mares, Epworth scale, Berlin questionnaire, Pittsburgh Sleep Quality Scale, Sleep Quality Scale.*

Corresponding author:
Gayathri Gurram,

QR code

Please cite this article in press Gayathri Gurram et al, ***Exposure Of Sleep Disorders And Incidence In Patients With Stroke- A Prospective Observational Cohort Study In A Tertiary Care Teaching Hospital.,*** *Indo Am. J. P. Sci, 2021; 08(02).*

I . INTRODUCTION TO STROKE:

1.1 Definition: A stroke is a medical condition in which poor blood flow to the brain results in poor oxygen and nutrition to the brain cells which ultimately leads to death of brain cells [(1)].

Stroke isalso called as CVA (cerebra vascular accident) [(2)].

There are two main types of stroke:

1.2 Ischemic stroke: This is caused by a blood clot that blocks blood vessels in the brain. 80 % of strokes are ischemic strokes.

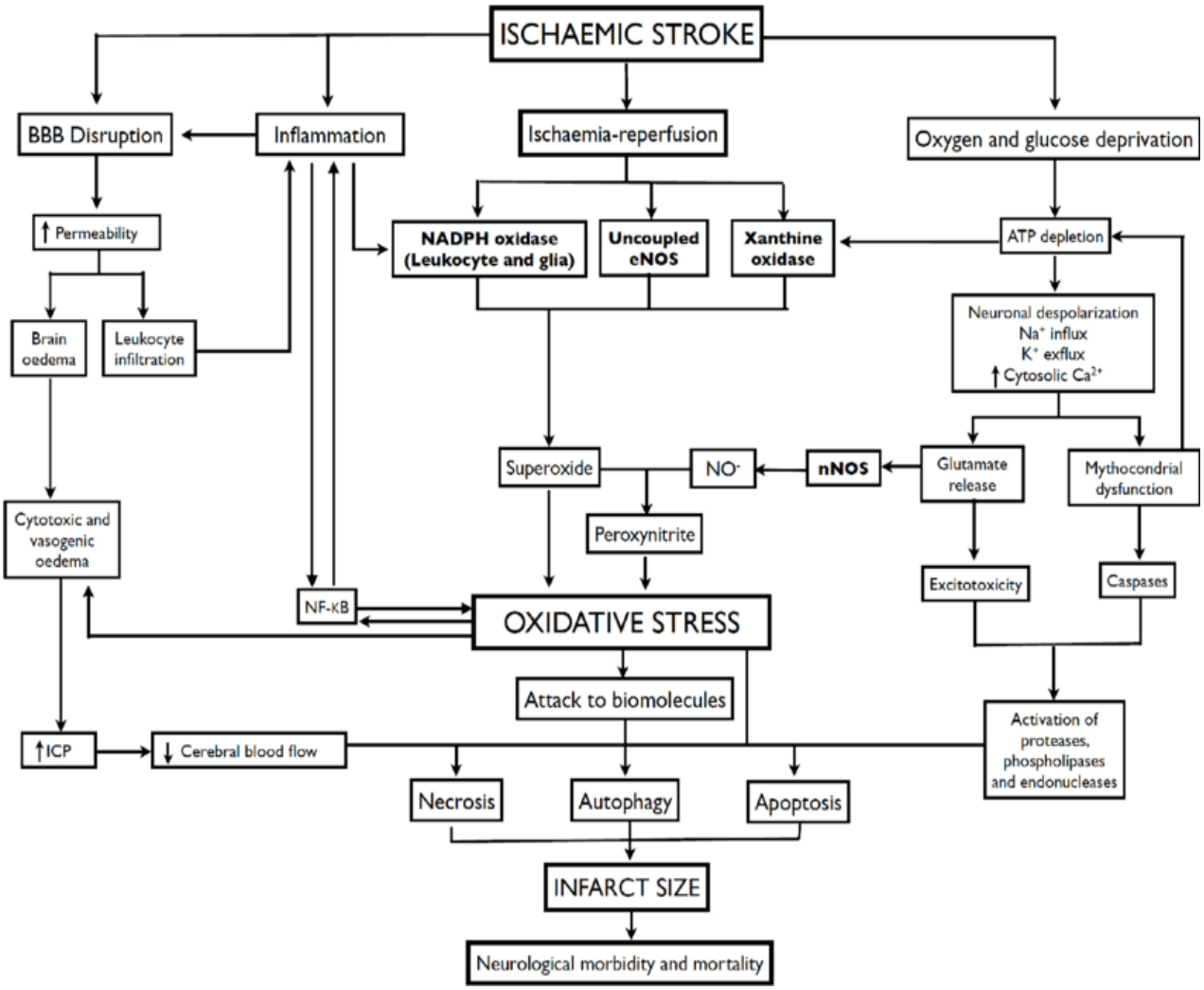


Fig: 1

1.3Hemorrhagic stroke: This is caused due to rupture or break of blood vessels in the brain which ultimately leads to bleeding in the brain called hemorrhagic stroke.

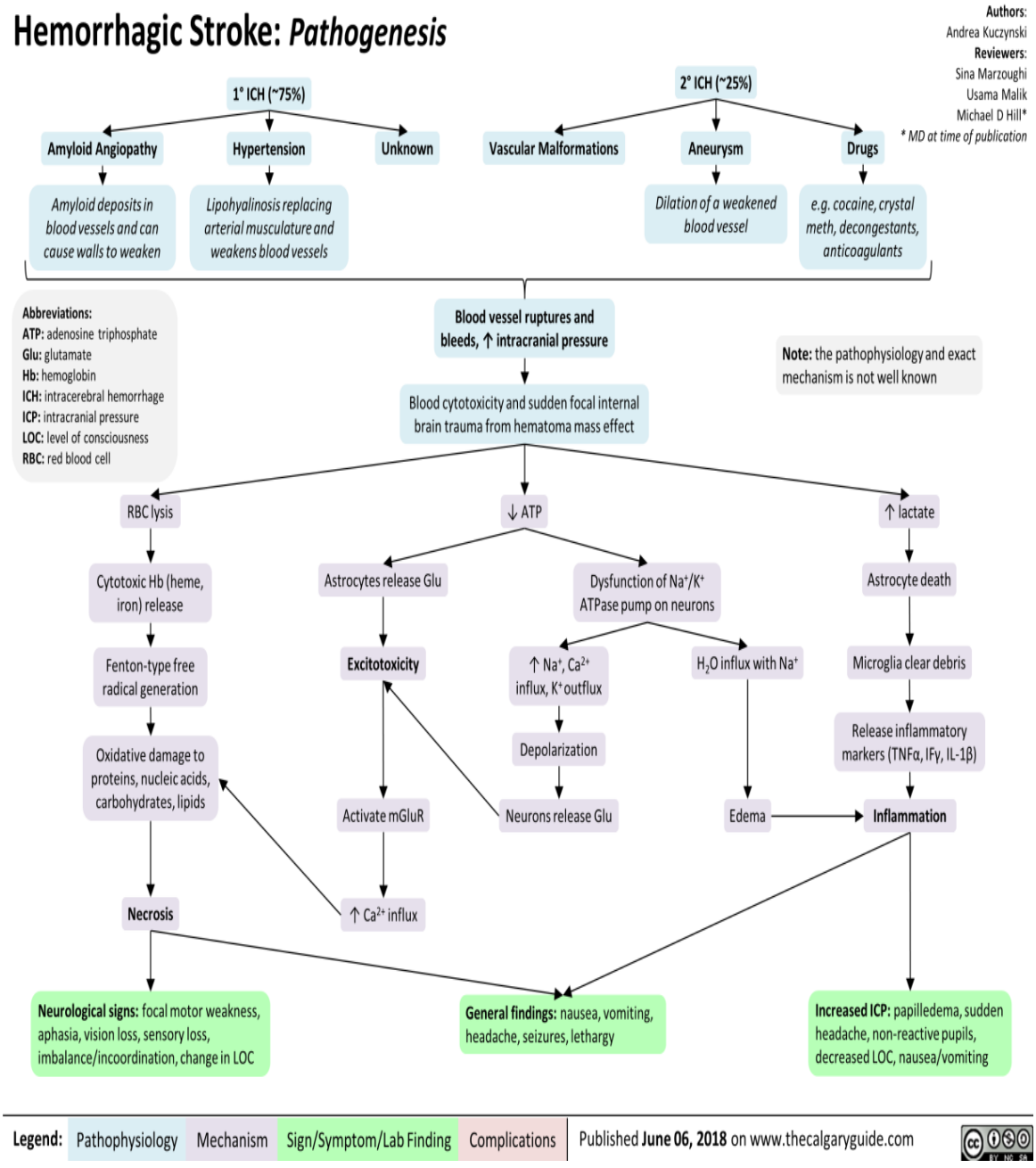


Fig: 2

Both results in parts of the brain not functioning properly [(1)].

1.4 Epidemiology: Stroke is one of the leading causes of death and disability in India. The estimated adjusted prevalence rate of stroke range 84262/1, 00,000 in rural and 334,424/1, 00,000 in urban areas[(3)].

Incidence of stroke in India: - Stroke incidence higher among women and people aged 40 years and older.

Cumulative incidence of stroke ranges from 105 to 152 per 1 lakh population per year.

Crude prevalence of stroke ranges from 44.29 to 559 per 1lakh population in different parts of country these

values were higher than those of high-income countries [4], [5], [6].

Stroke is ranked as second leading cause of death worldwide with an annual mortality rate of about 5.5 million.
Not only does the burden of stroke lies in the highest mortality but also in the high morbidity results in up to 50% of survivors being chronically disabled [7],[8],[9].

According to the current data in 2013 there were almost 25.7 million stroke survivors, 6.5 million stroke deaths, 113million DALYs due to stroke, and 10.3 million new strokes.

The burden of stroke seems to be shifting to the developing world where currently there are 4.85million stroke deaths and 91.4million DALYs annually compared with 1.6million deaths and 21.5million DALYs in high income countries [10].

The estimated prevalence rate of stroke related disability is about 331 per 100000 populations.
In most western European countries, death from stroke declined by 30 to 50% from 1975 to around 2005 and this was most noticeable in countries like Iceland, Italy, Australia, and Germany [7].

Approximately 8 lakh primary or secondary (recurrent) strokes occur each year in US,with majority being primary strokes roughly 6 lakhs. Of these strokes approximately 87% are ischemic infarctions, 10% are primary hemorrhages, and 3% are subarachnoid hemorrhages.

Worldwide estimates indicate that primary hemorrhages constitute a higher percent of all strokes, ranging from 10 % to 25%. Individuals of Asian, African and Latin American origin tend to have a higher frequency of primary hemorrhage than person of European origin [11].

Although primary hemorrhages accounts for 10 to 17% of all strokes in western countries, in Asian it is approximately 25 %[12].

The incidence of stroke rapidly increases with age doubling for each decade after age 55[13].
In 2007, the death rate for stroke was 40.2 per 1lakh for white males and 67.1 per 1lakh for black males, 39.3 for white females and 55.0 for black females [11].

Prevalence of symptomatic cerebral ischemia noted on brain imaging among persons age 55 to 64 years is 11%, and this rises to 22% for those aged at 65 to 69 years, 28% for those aged 75 to 79 years, and 40% for those aged 80-85 years in 43% for those ≥ 85 years of age [11].

1.5 ETIOLOGY: There are multiple factors which causes stroke. Some of common risk factors include

- Diabetes mellitus
- Genetics
- Obesity
- Physical inactivity
- Smoking
- Hypertension
- Hypercholesteremia

In individuals who are previously diagnosed with

- Atrial fibrillation
- Atrial and ventricular ceptal defects
- Valvular diseases
- Chronic rheumatic heart diseases

Originates point for cerebral emboli which larges in preexisting stenosis [16].
Alcohol intake has J shaped relationship with ischemic stroke mild to moderate has lower risk of ischemic stroke whereas chronic alcohol consumption increases risk of ischemic stroke and hemorrhagic stroke.

1.6 PATHOPHYSIOLOGY:
Atherosclerosis is the most common and important underlying pathology which leads to the formation of an atherothrombotic plaque secondary to low-density lipoprotein cholesterol (LDL) build up in the arteries supplying the brain. These plagues may block or decrease the diameter of the neck or intracranial arteries resulting in distal ischemia of the brain. More commonly they may also rupture. Plague rupture leads to exposure of the underlying cholesterol crystals which attract platelets and fibrin. Release of fibrin-platelet rich emboli causes strokes in the distal arterial territories via an artery-to-artery embolic mechanism. The nature of the cardiac source of emboli depends on the underlying cardiac problem. In atrial fibrillation, clots tend to be formed in the left atrium. These are red blood cells rich clots. There may be tumor emboli in

Left atrial myxoma and a bacterial clump from vegetation's when emboli arise during infective endocarditis.

When an arterial blockage occurs, the immediately adjacent neurons lose their supply of oxygen and nutrition. The inability to go through aerobic metabolism and produce ATP causes the $Na+/K^+$ ATPase pumps to fail, leading to an accumulation of sodium inside the cell and potassium outside the cell. The sodium ion accumulation leads to depolarization

and subsequent glutamate release. Glutamate opens NMDA and AMPA receptors and allows for calcium ions to flow into the cells. This continuous calcium flow into the cell leads to continuous neuronal firing and cell death [14].

No significant macroscopically changes are observed in the first 12 hours. Instead cytotoxic edema related to energy production failure with neuronal cellular swelling is observed. This initial infraction can be visualized by diffusion- weighted MRI shows restricted diffusion as a result of neuronal cellular swelling. Vasogenic edema will developed after 6-12 hours after the stroke occurrence. FLAIR sequence and MRI shows best visualization of this phase. Both cytogenic and vasogenic edema causes swelling of infarcted area and increase the intracranial pressure. This is followed by invasion of the phagocytosis which tries to clear the dead cells. This extensive phagocytosis causes softening and liquefaction of the effected brain tissues, with peak liquefaction occurring at 6 months after stroke. Astrocytes forms a dense network of glial fibers mixed with capillaries and connective tissue after several months of stroke. [15], [16].

Hemorrhagic strokes lead to a similar type of cellular dysfunction and concerted events of repair with the addition of blood extravasation and resorption.

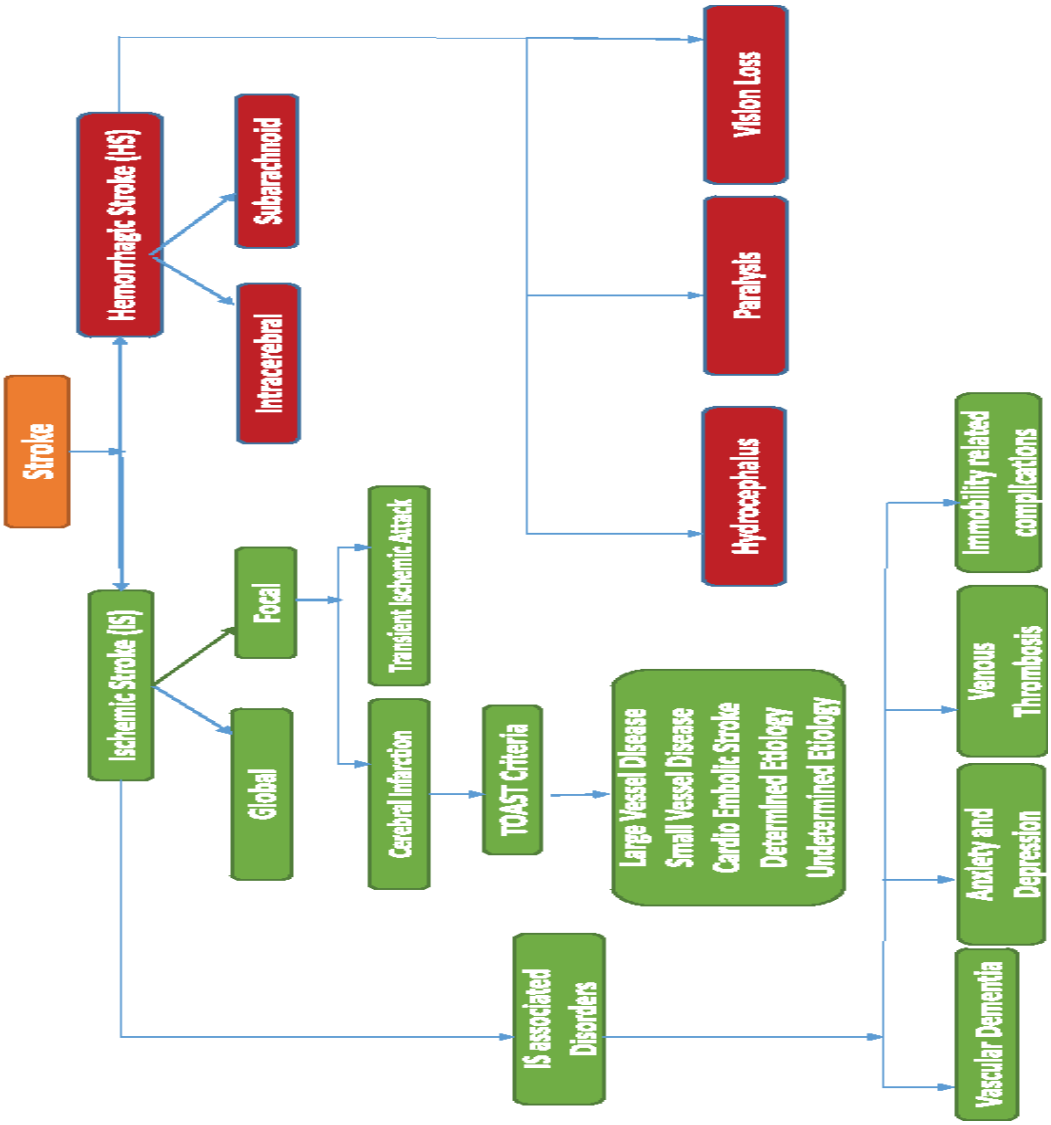


Fig: 3

1.7 SIGNS AND SYMPTOMS OF ISCHEMIC STROKE:[17]

- Sudden numbness
- Weakness of face, arm, leg
- Especially involving one side of the body
- Sudden confusion
- Trouble speaking
- Trouble at understanding
- Loss of vision in one or both eyes

1.8 SIGNS AND SYMPTOMS OF HEMORRHAGIC STROKE: [17]

- Sudden severe headache
- Vision changes
- Loss of balance or coordination
- Becoming unable to move
- Seizures
- Loss of alertness
- Nausea and vomiting
- Inability to look at bright light
- Stiffness or pain in the neck area
- Hand tremors
- Difficulty swallowing
- Frequent fluctuation of heart beat
- Difficulty in breathing

1.9 DIAGNOSIS:[17]

- CT
- MRI
- MRA
- ECG
- EEG
- PHYSICAL EXAMINATION

1.10 INTRODUCTION TO SLEEP DISORDERS

A sleep disorder, or somnipathy, is a medical disorder of the sleep patterns of a person or animal. Some sleep disorders are serious enough to interfere with normal physical, mental, social and emotional functioning. Polysomnography and actigraphy are tests commonly ordered for some sleep disorders.

Disruptions in sleep can be caused by a variety of issues, including teeth grinding (bruxism) and night terrors. When a person suffers from difficulty falling asleep and/or staying asleep with no obvious cause, it is referred to as insomnia. [18]

Sleep disorders are broadly classified into dyssomnias, parasomnias, circadian rhythm sleep disorders involving the timing of sleep, and other disorders including ones caused by medical or psychological conditions.

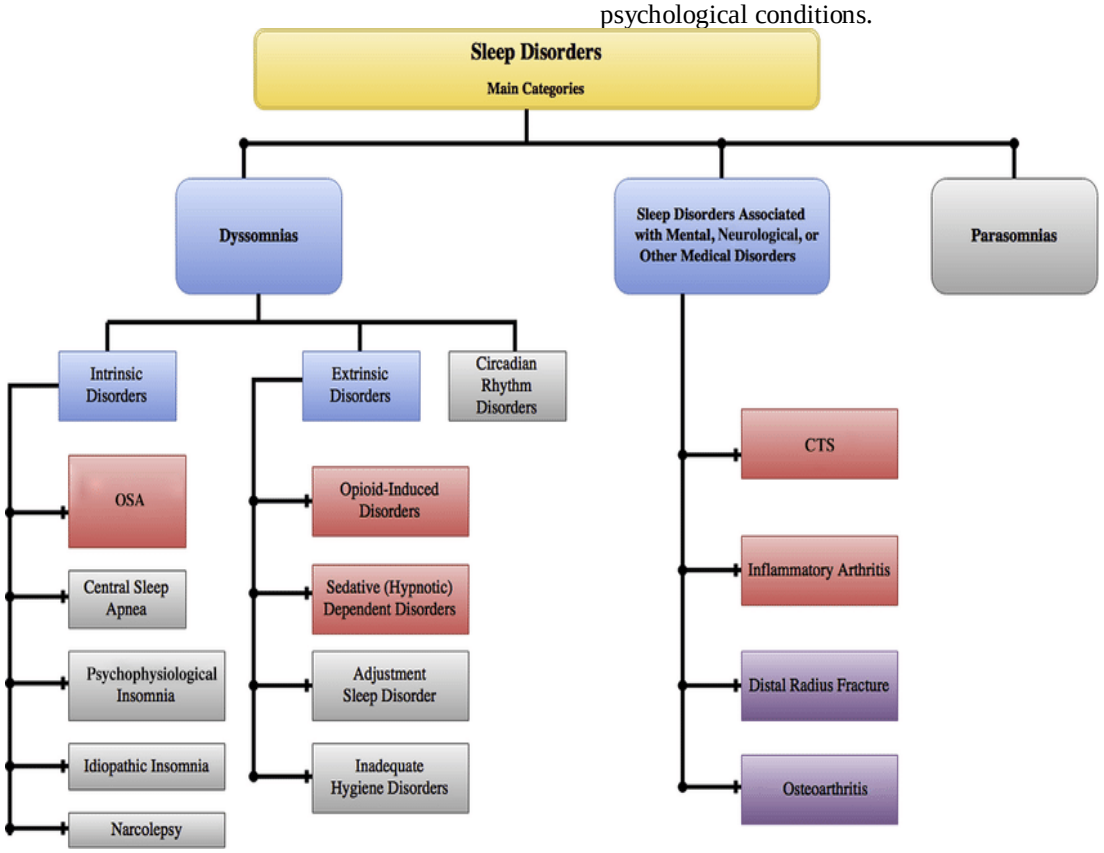


Fig: 4

1.11Dyssomnias :
A broad category of sleep disorders characterized by either hypersomnia or insomnia. The
three major subcategories include intrinsic (i.e. arisin g from within the body), extrinsic (secondary to environmental conditions or various pathologic conditions), and disturbances of circadian rhythm.[19]

1.12Insomnia:
Insomnia may be primary or it may be comorbid with or secondary to another disorder such as a mood disorder (i.e. emotional stress, anxiety, depression) or underlying health condition (i.e., asthma, diabetes, heart disease, pregnancy or neurological conditions).[20]

1.13Primary hypersomnia:
Hypersomnia of central or brain origin.

1.14Narcolepsy:
A chronic neurological disorder (or dyssomnia), which is caused by the brain's inability to control sleep and wakefulness(21)

1.15Idiopathic hypersomnia:
A chronic neurological disease similar to narcolepsy in which there is an increased amount of fatigue and sleep during the day. Patients who suffer from idiopathic hypersomnia cannot obtain a healthy amount of sleep for a regular day of activities. This hinders the patients' ability to perform well, and patients have to deal with this for the rest of their lives.[22]

Fig: 5

Source of data	Sleep variable	Community	TBI	Community	TBI		
Sleep category		$N_{participants}$	$N_{participants}$	*P*	*P*	Z	*prob*
Healthy controls							
Sleep disturbance	Overall	66	85	.32	.56	3.02	.003
Sleep problem	Sleep initiation	77	77	.05	.41	5.33	<.001
	Excessive daytime sleepiness	85	99	.10	.24	2.65	.008
Community samples							
Sleep disturbance	Overall	2187	1706	.41	.50	5.59	<.001
Sleep disorders	Insomnia	1007	581	.10	.29	9.94	<.001
	Hypersomnia	7954	212	.10	.28	8.38	<.001
	Obstructive sleep apnoea	1741	283	.02	.25	15.51	<.001
	Periodic limb movements	18,980	212	.04	.08	2.95	.003
	Narcolepsy	18,980	152	.00b	.04	17.11	<.001
Sleep problem	Snoring	2629	65	.42	.60	3.56	<.001
	Insomnia	6340	1001	.31	.50	11.8	<.001
	Sleep maintenance	24,600	309	.27	.50	8.96	<.001
	Sleep efficiency	1007	119	.27	.49	4.93	<.001
	Sleep initiation	24,600	368	.27	.36	3.80	<.001
	Nightmares	2187	133	.08	.27	7.43	<.001
	Excessive daytime sleepiness	16,583	651	.09	.27	15.27	<.001
	Early morning awakening	24,600	364	.18	.38	9.76	<.001
	Sleep walking	4972	99	.02	.09	4.85	<.001

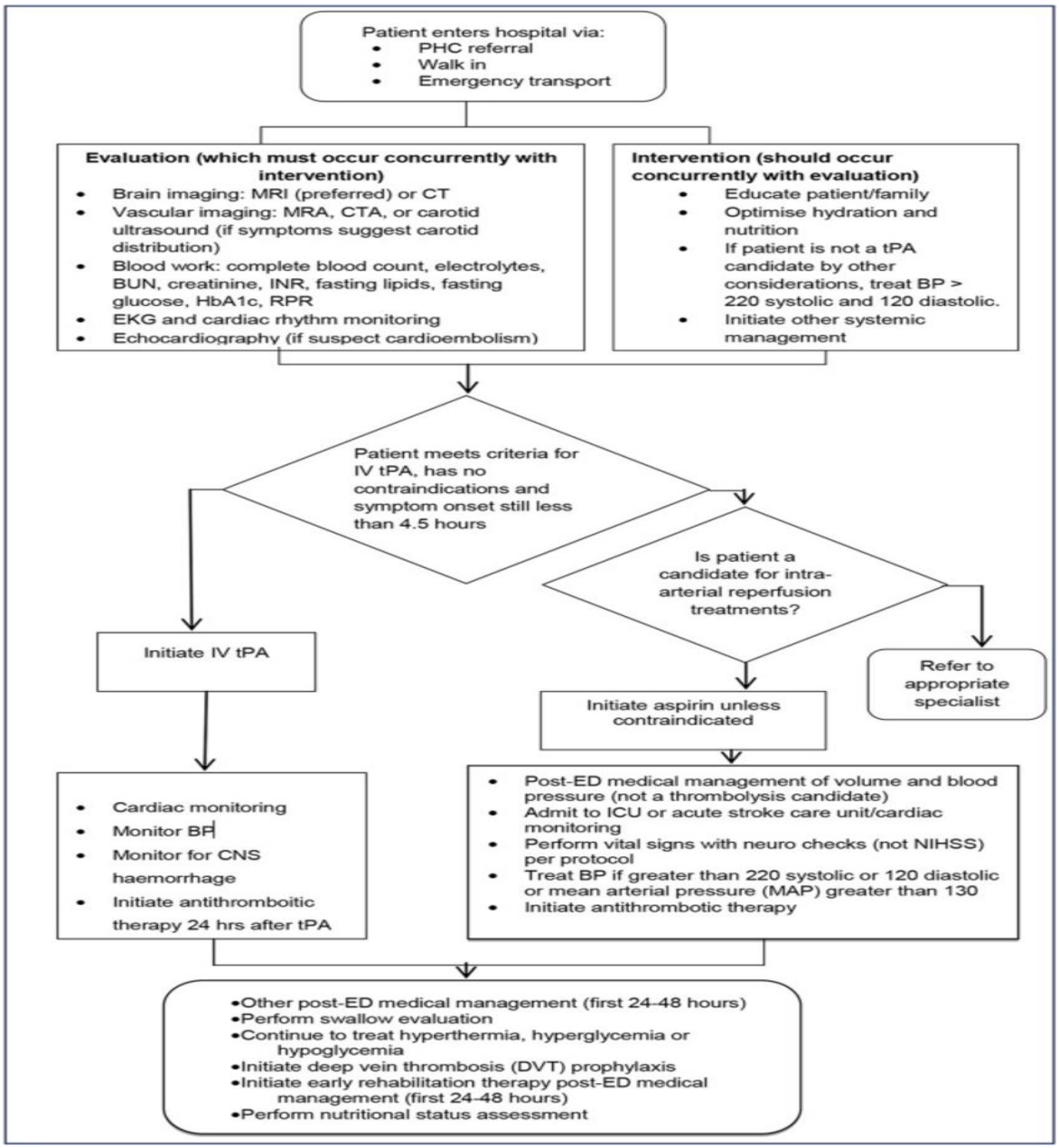
1.16TREATMENT FOR STROKE

When a weakened blood vessel ruptures and spills blood into brain tissue, it's called a hemorrhagic stroke. The treatment goal is to stop the bleeding, but understanding the cause is important.

The most common cause for the rupture is uncontrolled hypertension (high blood pressure). There are two other types of weakened blood vessels that can also cause hemorrhagic stroke: aneurysms (swelling within vessels) and arteriovenous malformations or AVMs (abnormal tangles of blood vessels). Mechanical Treatment

STROKE TREATMENT ALGORITHM

Fig: 6



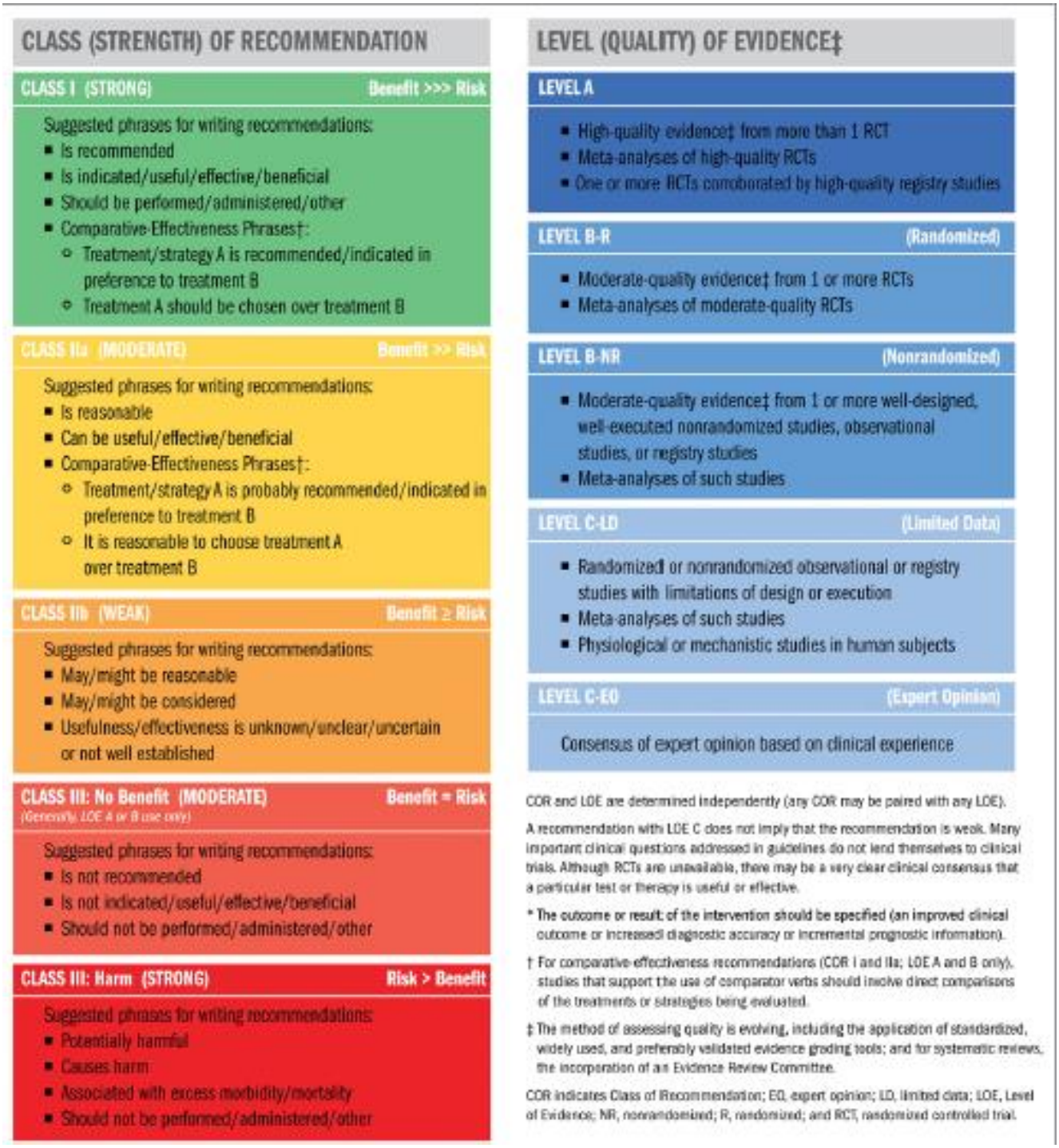

CLASS (STRENGTH) OF RECOMMENDATION
CLASS I (STRONG)
Benefit >>> Risk
Suggested phrases for writing recommendations:
Is recommended
Is indicated/useful/effective/beneficial
Should be performed/administered/other
Comparative-Effectiveness Phrases†:
Treatment/strategy A is recommended/indicated in preference to treatment B
Treatment A should be chosen over treatment B
CLASS IIa (MODERATE)
Benefit >> Risk
Suggested phrases for writing recommendations:
Is reasonable
Can be useful/effective/beneficial
Comparative-Effectiveness Phrases†:
Treatment/strategy A is probably recommended/indicated in preference to treatment B
It is reasonable to choose treatment A over treatment B
CLASS IIb (WEAK)
Benefit ≥ Risk
Suggested phrases for writing recommendations:
May/might be reasonable
May/might be considered
Usefulness/effectiveness is unknown/unclear/uncertain or not well established
CLASS III: No Benefit (MODERATE)
(Generally, LOE A or B use only)
Benefit = Risk
Suggested phrases for writing recommendations:
Is not recommended
Is not indicated/useful/effective/beneficial
Should not be performed/administered/other
CLASS III: Harm (STRONG)
Risk > Benefit
Suggested phrases for writing recommendations:
Potentially harmful
Causes harm
Associated with excess morbidity/mortality
Should not be performed/administered/other
LEVEL (QUALITY) OF EVIDENCE‡
LEVEL A
High-quality evidence‡ from more than 1 RCT
Meta-analyses of high-quality RCTs
One or more RCTs corroborated by high-quality registry studies
LEVEL B-R
(Randomized)
Moderate-quality evidence‡ from 1 or more RCTs
Meta-analyses of moderate-quality RCTs
LEVEL B-NR
(Nonrandomized)
Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
Meta-analyses of such studies
LEVEL C-LD
(Limited Data)
Randomized or nonrandomized observational or registry studies with limitations of design or execution
Meta-analyses of such studies
Physiological or mechanistic studies in human subjects
LEVEL C-EO
(Expert Opinion)
Consensus of expert opinion based on clinical experience
COR and LOE are determined independently (any COR may be paired with any LOE).
A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.
COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Fig: 7

2. LITERATURE REVIEW:

2.1 Zejneba Pasic, Dzevdet Smajlovic, Zikrija Dostovic, Bilijana Kojic, Senada Selmanovic, conducted a prospective study *Incidence and Types of sleep disorders in patients with stroke (2011).* Analysed 200 patients with acute stroke with the help of computerized tomography from a period of 1st August 2007 to 1st June 2008. Of the total 78% were with SD and 42% with very serious level of SD, 20% moderate and 16% medium to severe degree of SD with no statistical difference in frequency of sleep disorder in subjects with ischemic and haemorrhagic stroke. Sleep apnea and snoring are the most common SD. In accordance to Epworth scale sleep apnea and snoring were present in 86%, 49.5% with daytime sleepiness and narcolepsy. This study concludes that SD has a significant incidence in acute phase of stroke and slightly more common in haemorrhagic stroke and right hemisphere stroke.

2.2 H. Klar Yaggi, M.D,M.P.H., John Concato, M.D., M.P.H.,et al conducted a study on *Obstructive Sleep Apnea as a risk factor for Stroke and Death, an observational cohort study(2005).* An observational cohort study conducted among 1022 enrolled patients, 697(68%) had obstructive sleep apnea syndrome. At the baseline the apnea- hypopnea index in subjects with syndrome is 35 in comparison with mean hpopnea index in 2 comparison group. In unadjusted analysis the OSA is in association with stroke and death for any cause with HR= 2.24; 95% CI= 1.30- 3.86; p= 0.004. After adjusting other comorbidities and other factors like alcohol and smoking etc., the OSA is statistically significant with stroke or death with HR= 1.97, 95% CI= 1.12 – 3.48;p= 0.01. This study concludes that OSA increases the risk of stroke or death from any cause, which is independent of other risk factors, include hypertension.

2.3 DaeLim Koo, Hyunwoo Nam, Robert J. Thomas, and Chang- Hoyun conducted a study on *Sleep Disturbances as a Risk Factor for Stroke (2018).* This is a special review article. This review aims on providing ab update information about the effects of altered sleep on stroke development. This study mainly focused on the importance of sleep and managements of sleep pathology to prevent and care of stroke. OSA increases the risk of stroke independently, but lack of therapeutic effectiveness of CPAP for stroke prevention and cardiovascular protection should be caution interpreted. Sleep duration and insomnia with obstructive short sleep duration, sleep related movement disorders (PLMS and RLS) could be risk factor for stroke and mortality. Therefore proper management of sleep disturbance can modify the risk of stroke.

2.4 Douglas M. Wallace, Alberto R. Ramos, and Tatjana Rundek conducted a study on *sleep disorders and stroke (2013).* This is a review article with the purpose to highlight the existing epidemiology, pathophysiology, and treatment of sleep disorders may influence the risk of developing stroke. Sleep disorders are highly prevalent in subjects with stroke and those who are at risk for stroke. Creating awareness of importance of sleep disorders and improving screening for sleep disorders may help in prevention of primary and secondary stroke. This also helps in improving in the stroke outcome.

2.5 Sundeep P.Khot, MD; Lewis B. Morgenstern MD conducted a study on *sleep and stroke (2019).* This is a topical review study which deals with the evaluation of importance of sleep disorders, includes sleep disorder breathing and sleep wake cycle disorder in the development of stroke. This also deals with the identification of impact of treatment to sleep on stroke outcome. This review concludes that Sleep disturbance seems to be both as risk factor for stroke and worsen by the stroke. Management of sleep disturbance may prevent primary and secondary stroke.

2.6 Madihah Hepburn, MD, Pradeep C. Bollu, MD, Brandi French, MD &Pradeep Sahota, MD, preformed a study on *sleep Medicine: stroke and sleep (2018).* A review article that amis to evidence which demonstrates, sleep disorders are intrinsically bounded to ischemic as well as haemorrhagic stroke by elevating the patient risk profile and as a sequel of an acute stroke. Screen of patient about sleep disorder prevents primary and secondary stroke which reduces the morbidity and

Mortality of stroke.

2.7 Mollie Mc Dermott, Devin L. Brown, and Roonald D. Chervin published a review article on *sleep disorder and the risk of stroke (2018).*this review demonstrates the relation between incident stroke and sleep apnea,REM sleep disorder, restless leg syndrome, periodic limb movements of sleep, insomnia, and shift work. Increased risk of ischemic stroke mortality more in women's who sleep more than or equal to 9 hours than in men. Short sleep duration effects in haemorrhagic stroke seen in men in 2016 which is not found in 2009. Duration of sleep and sleep disturbance may lead to increased risk of stroke development. Treatment to the sleep disorder may prevent the

primary and secondary stroke.

2.8 Valham, Fredrik; Mooe, Thomas; Rabben, Terje; Stenlund, Hans'set.al. published an article on *increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10 year follow up(2008).* A total of 392 male and female subjects are included in this study with coronary artery disease and sleep apnea. After 10 year follow up there are 47 subjects with stroke. Sleep apnea associated with increased risk of stroke, with adjusted HR=2.89; 95% CI=1.37-6.09, p= 0.005, independent of other co morbidities and lifestyle. Subjects with apnea-hypopnea index 5-15 and more than 15 are 3.56 times more at risk of stroke with 95% CI= 1.56-8.16, than the patients with no sleep apnea which is independent of confounders like p for trend= 0.011. Finally this study states
that there is an increased risk of stroke in subjects with sleep apnea.

2.9 Robert Munoz, MD Joaquin Duran-Cantolla, MD, PhD Eduardo Martiez- Vila, MD, PhD et.al. study on *sever sleep apnea and risk of ischemic stroke in the elderly(2006).*this is a 6 year longitudinal study in subsamples cohort of 394 with mean age of 77.28 years and 57.1% males in the study. In the follow up 20 ischemic strokes are recorded. After adjustment confounding factoes, the apnea- hypopnea index less or equal to 30 at baseline had increased risk of stroke development with HR= 2.52;95% CI= 1.04- 6.01,p=0.04. However the ultimateresults shows that obstructive sleep apnea hypopnea increases the risk of ischemic stroke in elder patients independent of known confounding factors.

2.10Chaoran Ma, Milena Pavlova, Yesong Liu. Ying Liu, Chunmei Huangfu, Shouling Wu, Xiang GAO, had done a study on *Probable REM sleep behaviour disorder and risk of stroke a prospective study (2017).* Study included 12,003 subjects of mean age54.0 years, free of stroke, cancer, PD, Dementia, and head injury at base line (2012).in a 3 year follow up, 159 participants are diagnose with stroke. Relative to subjects without sleep behaviour disorder at baseline, those with pRBD was associated with 157% high risk of developing stroke. This study finally concludes that presence of pRBD will increase the risk of stroke including both types ischemic and haemorrhagic strokes – with adjusted HR 1.93(95% CI 1.07-3.46) for ischemic stroke and 6.61(95% CI 2.27- 19.27)

2.11Michael Arzt, Terry Young, Laurel Finn, James B. Skatrud, and T. Douglas Bradley made a study *(2005), Association of Sleep-disorder Breathing and the Occurrence of Stroke.* This study is a cross sectional and longitudinal analyses among 1,475 and 1,189 participants took from general population. Cross sectional study and prospective study, states that participants with sleep disorder breathing with an hypopnea index of 20 greater was increased risk of 1st stroke in 4years with unadjusted odds ratio= 4.31; 95% CI= 1.31-14.15;p=0.02. However after adjustment also increases odds ratio. But no longer significant with odds ratio = 3.08; 95%CI= 0.74- 12.81; p= 0.12. This study concludes that relation of moderate to severe sleep disorder breathing and stroke, independent of confounding factors. Also provides the 1st prospective evidence that sleep disorder breathing precedes stroke and development of stroke. However RCT are required to know whether treatment of Sleep disorder breathing will prevent primary and secondary stroke or not.

2.12C-H Chou. J-H Yin, S-Y Chen,C-C Lin, Y-F Sung, C-H Chung, W-C Chien, C-K Tsai, C-LTsai, G-Y Lin, Y-K Lin, J-T Lee conducted study on *The potential impact of sleep-related movement disorders on stroke risk: a population – based longitudinal study(2017).* This study deals with two cohort study with SRMD and without SRMD follow up for occurrence of haemorrhagic and ischemic stroke. Total of 604 subjects are included who are diagnosed with SRMD in 2000- 2005 years, and 2,416 subjects of age and sex matched subjects are included in this study as comparison
Cohort. This study states that subjects with SRMD had a higher risk of developing all cause stroke with adjusted HR= 2.29, 95% CI= 1.42-3.80 subjects with 45 years old and below are at more risk of stroke with HR= 2.29, 95% CI= 3.11-5.62. Then 65 years and below with HR=2.64, 95%CI= 1.12-3.44 and followed by 45 – 64 years with HR= 1.07, 95% CI=1.02-1.71.risk ofhaemorrhagic stroke is greater than ischemic stroke in all age groups. Males are at higher risk of stroke than females who are with SRMD. However SRMD increases the risk of all-cause stroke particularly haemorrhagic rather than ischemic stroke.

Limitations: no clarity about the different severities of SRMD and health information like intensity of tobacco, alcohol consumption, diet and other life style managements influence the risk of stroke or SRMD. In some, stroke outcomes particularly haemorrhagic strokes are small.

2.13Peter Elwood, Melissa Hack, Janet Pickering,

Janie Hughes, John Gallacher studied on *sleep disturbance, stroke and heart disease events: evidence from the Caerphilly cohort (2006).* The objective of this study is to test the hypothesis of sleep disorders are relevant to risk of ischemic stroke and ischemic heart disease events in older men. This is a cohort study in male subjects in south wales, UK. Total subjects 1986 men are included with age between 55 – 69 years. This is a 10 tear follow up study. One third of man reported at least one symptom of sleep disturbance, and one third with daytime sleepiness. Strong association started with sleep apnoea with relative odds = 1.97; 95% CI = 1.96 to 3.09. The association with daytime sleepiness has no significance with stroke. During 10 years follow up 107 men are experienced with ischemic stroke and 213 with ischemic heart disease events. This study concludes that risk of ischemic stroke is increased in men whose sleep is frequently disturbed.

2.14 Capampangan, Dan J. MD; Wellik, Kay E. MLS, AHIP; Parish, James M. MD; Aguilar, Maria I. MD; Synder, Charlene R. Hoffman CNP, NP, Rn; Wingerchuk, Dean MD, MSc, FRCP(C); Demaerschalk, Bart M.MD, MSc, FRCP(C) made a study on *Is Obstructive Sleep Apnea an Independent Risk Factor for Stroke? : A Critical Appraised Topic (2010).* This study aims to determine that is OSA increases the risk of stroke independently of other cardiovascular risk factors. This is a large observational cohort study in which results states that unadjusted OSA analysis is resulted in increased risk of stroke or death from any cause with HR = 2.24;95% CI = 1.30- 3.86; p= 0.004.th adjusted OSA analysis retains a statistical significance association with death or stroke along with HR= 1.94; 95% CI= 1.12-3.48; p= 0.001. In other unadjusted analysis, OSA association in death and stroke with RR = 1.68; 95% CI= 1.10-2.25 and RR= 5.16; 95% CI = 3.72- 6.60. The ultimate conclusion of this study is there is an increased risk of stroke in subjects with OSA independently.

2.15 Qiaofeng Song, Xiaoxue Liu, Wenhua Zhou, et.al. conducted study on *Long Sleep duration and risk of ischemic stroke and haemorrhagic stroke: the Kailuan Prospective Study(2016).* The objective of the study is to determine the relation between the sleep duration and ischemic and haemorrhagic strokes. This is a community based cohort study conducted in 95,023 Chinese subjects who are stroke free at baseline survey. After 7.9 year mean follow up total 3,135 subjects in the study are diagnosed with stroke where 631 are haemorrhagic and 2,504 are with ischemic stroke. The adjusted HR= 1.29 with 95% CI= 1.01-1.64 with 6-8 hours of night sleep in reference group and individuals more than 8 hours. Significant relation between duration of sleep and stroke in elder subjects HR=1.47; 95%CI=1.05-2.07. However women with more than 8 hours of sleep are at higher risk of haemorrhagic stroke with HR= 3.58, 95%CI= 1.28-10.06. The final conclusion of this study is longer duration of sleep also increases the risk of stroke especially in women's longer sleep duration increases risk of haemorrhagic stroke.

2.16 Wenzhen Li, Dongming Wang, Shiyi Cao, et.al.., published an article on *Sleep duration and risk of stroke events and stroke mortality: a systemic review and meta-analysis of prospective cohort study (2016).* They included 11 articles with 16 different results, detecting an approx. J-shaped relationship between sleep duration, stroke mortality and stroke duration. This article states that there is no evidence of curve linear relationship is there between sleep duration and risk of stroke or stroke mortality.7 hours sleep per day comparison, pooled the relative risk of stroke events RR=1.07; 95%CI= 1.02-1.12. Sleep less than 7 hours RR= 1.17; 95%CI= 1.17-1.20, sleep duration 8hours RR= 1.17, 95%CI= 1.13-1.20per one hour increase in duration of sleep. This article finally states that both longer and shorter duration of sleep tends to risk of stroke but longer sleep duration is the marker for stroke mortality.

2.17 Qiao He, Hao Sun, Xiaomei Wu, Peng Zhang, Huixu Dai. Cong Ai, Jingpu Shi published an article on *sleep duration and risk of stroke: a dose- response meta- analysis of prospective cohort studies (2017).* In this article they aimed to conduct a dose response meta- analysis to determine the relation between sleep duration and stroke incidence. The under went through PubMed, Web of sciences and Cochrane Library to find prospective studies based on determining the relationship between sleep duration and non-fatal and/or fatal stroke incidence. Then, they restricted cubic spline functions and piecewise linear and nonlinear dose- response relationship between them. Finally they included 16 prospective studies total of 5, 28,658 subjects with 12,193 stroke events. In 7hrs sleep duration nonlinear dose response meta-analysis showed low risk J-shaped relation between sleep and stroke event. By keeping 7hr sleep as a reference, subjects who have longer sleep duration are at higher risk of stroke rather than the subjects with shorter sleep duration. The risk ratio with 95% CI for 4hrs sleep duration is 1.17(0.99-1.38), and for 6hr sleep duration is 1.10(1.00 – 1.21), 10

hrs.Sleep duration is risk ratio is 1.64 with 95% CI =1.4 – 1.92; ($n_{onlinearity}$<0.001). They also found that subjects with shorter duration of sleep are at lower risk of ischemic stroke. As per piecewise linear trends, 7 hr. sleep as a reference, there is 13% increase of risk of total stroke for every 1 hr. increase in duration of sleep with pooled risk ratio= 1.13; 95% CI= 1.07-1.20 (p<0.001). However, they concluded that nonlinear and piecewise linear dose- response meta-analysis, long sleep duration will increase the risk of stroke incidence.

2.18 Yue Leng, Francesco P Cappuccio, Nick WJ Wainwright, etal. Published an article on *Sleep duration and risk of fatal and non-fatal stroke: a prospective study and meta-analysis (2015).* The objective of the study is to determine the relationship between sleep duration and stroke incidence in British population. This is a prospective study includes 9,692 stroke- free subjects aged within 42-81 years. Subjects reported sleep duration in 1998-2000 and 2002-2004, and all stroke cases are recorded till March 31 2009. They studied Ovid Medline, EMBASE, and Cochrane Library for prospective studies which are published until 2014 may for meta-analysis. By using weighted random effect model estimates pooled effect. After 9.5 years follow up, 365 cases are diagnosed with stroke. After adjustment for all covariates, long sleep duration associated with risk of stroke HR= 1.46with 95% CI= 1.08-1.98. The risk of stroke in shorter sleep subjects is lesser than in subjects with longer sleep with HR= 1.18 95% CI= 0.91-1.53. They concluded that increased sleep duration or prolonged sleep is a marker for risk of stroke.

2.19 Xue Li, Xiuyu Pang, Zhipeng Liu, Qiao Zhang, Changhao, Jianjun Yang, Ying Li published an article on Joint *effect of less than 1 h of daytime napping and seven to 8 h of night sleep on risk of stroke (2018).* This article main aim is to verify the relationship of daytime naps and night sleep on the risk of stroke based on data from a large sample-sized cross-sectional study and cohort study. The study included 7887 subjects, age between 20-74 years. By stratified random sampling. Total 1928 individual subjects included in the cohort study. Then the followed up of 4.94 years and by using Pittsburgh sleep quality index collected sleep information from the subjects. The results of cross-sectional study. HR=1.94 with 95% CI= 1.21-3.13 and in cohort study HR=2.24 with 95% CI= 1.05-4.79 for day time napping moreor equal to 1hr and more or equal to 9hrs of night sleep. No naps in combination with less than 7 hrs. sleep at night the HR= 2.61, 95%CI= 1.17-5.82. For more or equal 1hr naps in combination with less than 7 hrs., 7-8hrs, 8-9 hrs.And more or equal to 9 hrs. of sleep at night HR= 2.16 and 95%CI= 1.03-4.51; HR= 2.36 , 95%CI=1.07-5.20; HR= 2.41, 95%CI=1.11-5.20; HR=3.37,95%CI= 1.05-10.81. They conclude that subject with 7-8hrs of sleep at night with no daytime naps or less than 1hr of day naps are at low risk of stroke. More or equal to 9 hrs.Of night sleep in combination with more or equal to 1 hr. naps at day time and night sleep less than 7 hrs. in combination with less than 1hr day sleep is associated with the risk of stroke.

2.20 Megan E Petrov, George Howard, Michael A Grandner Dawn Kleindorfer, et.al. Published an article on *sleep duration and risk of incident stroke by age, sex, and race: the REGARDS study* (2018). The objective of the study is investigation of association between reported

Sleep duration and incident stroke in US cohort of black and white adults, and evaluate race, age and gender as potential effect modifiers. From 2008 to 2010, total 16,733 black and white adults, aged 45 years and more, without past history of stroke and sleep breathing disorder from the reasons for geographic and racial Differences in Stroke (REGARDS) study, reported their habitual sleep duration (<6hr,6-6.9hrs, 7-8.9,9hr reference sleep). Sample comprised 10.4% where n=1747 <6hr sleep (short sleep) and 6.8% where n=1134 long sleep of more or equal to 9hrs duration. Follow up of 6.1 years, total 460 stroke cases are identified. Among black subjects short sleep duration is significantly related with lower risk of stroke, with HR=0.49; 95%CI=0.28-0.85. Especially black men, HR=0.21; 95%CI=0.07-0.69. Among white men longer duration of sleep are at risk of stroke with HR=1.17; 95%CI=1.06-2.76. Finally, the concluded that black men with shorter duration of sleep will have low risk of stroke and white men with longer duration of sleep are at high risk of stroke.

4. METHODOLOGY:

4.1 Study Place: Department of Neurology, Government General Hospital, Guntur.

4.2. Period of Study: This study is conducted in a period of 6 months i.e., from 25th September 2019 to 24th February 2020.

4.3. Study Design: Prospective observational Cohort study.

4.4. INCLUSION CRITERIA:

- Subjects of both genders are included.
- Subjects of comorbities like diabetes,hypertension, will be included.
- Age with 40 and above are included
- Subjects who are willing to participate are included in the study

4.5 EXCLUSION CRITERIA

- Previous diagnosis of sleep disorder breathing.
- Patient with unstable comorbidities (Cardiac or respiratory failure), ventilator dependence.
- Subjects who do not give their concern for the study.

4.6. STUDY PROCEDURE:

The study will be conducted after obtaining approval from Institutional Ethics Committee and Informed Consent from patients. Then patients will be screened based on inclusion and exclusion criteria. Patients who satisfy inclusion criteria will be included in the study. Afterincluding the subjects into the study the data will be collected in the designed data collection form. Initially the occurrence of stroke will be assessed using the symptoms and imaging techniques. The self-designed and validated questionnaire will be used to assess the type of sleep disorder in patients with stroke which consists of 15 closed ended questions which helps in diagnosis of the type of sleep disorder of patient.

4.7.DATA TOOLS USED:

- Patient data collection form
- Patient information leaflets
- Berlin questionnaire
- Epworth questionnaire
- Sleep quality scale questionnaire
- Pittsburgh sleep quality index
- Swiss Narcolepsy Scale

4.8. STATISTICAL ANALYSIS:

The data was entered in advanced Microsoft excel spread sheet and evaluated. For statistical analysis, SPSS software is used to get accurate results.

5. RESULTS:

Table 1 depicts the information regarding the gender .Majority of the subjects were found to be Males (170) compared to Females (70) which was graphically represented in Figure 8

Table: 1

GENDER	NUMBER OF SUBJECTS (N=240)
MALES	170(70.83%)
FEMALES	70(29.1%)

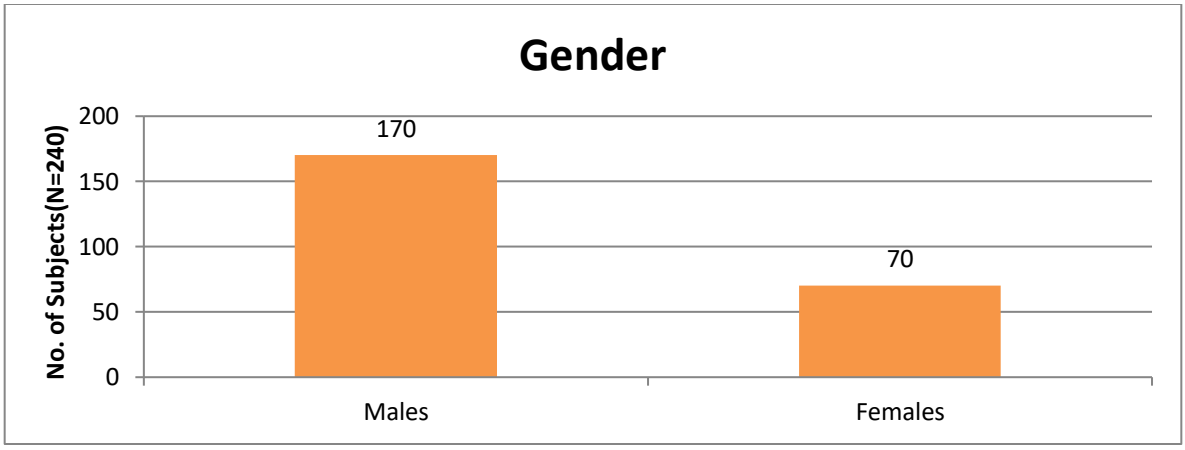


Fig: 8

Table 2: Depicts the association between diabetes mellitus and occurrence of sleep disorders which indicates that there is no significant association of diabetes mellitus in the occurrence of sleep disorders in patients with stroke which is graphically represented in Figure 9

Table 2:

DIABETES MELLITUS	NUMBER OF SUBJECTS (N=240)
YES	111(46.25%)
NO	129(53.75%)

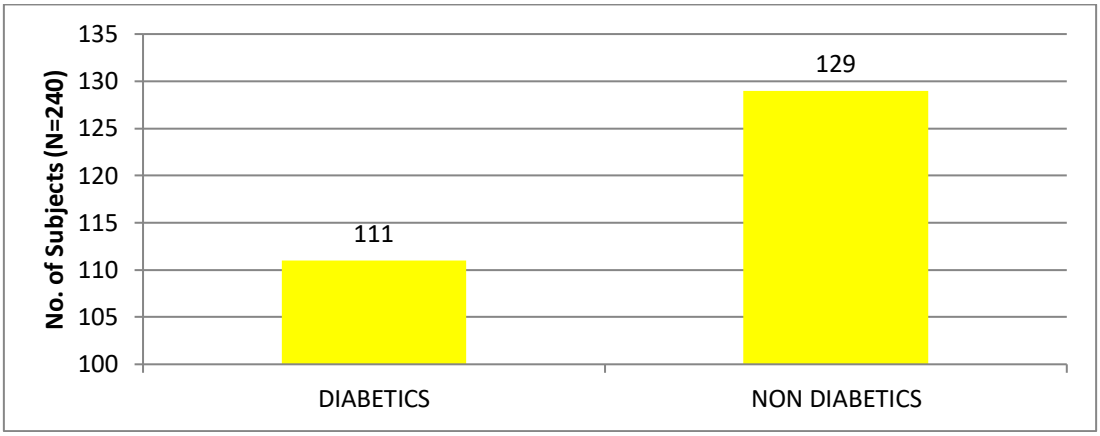


Fig: 9

Table 3: depicts the association between hypertension and occurrence of sleep disorders in patients with stroke. Majority of the subjects were found to be hypertensive (178) which indicates a positive association between hypertension and occurrence of sleep disorders in patients with stroke which is graphically represented in Figure 10.

Table: 3

HYPERTENSION	NUMBER OF SUBJECTS(N=240)
YES	178(74.1%)
NO	62(25.83%)

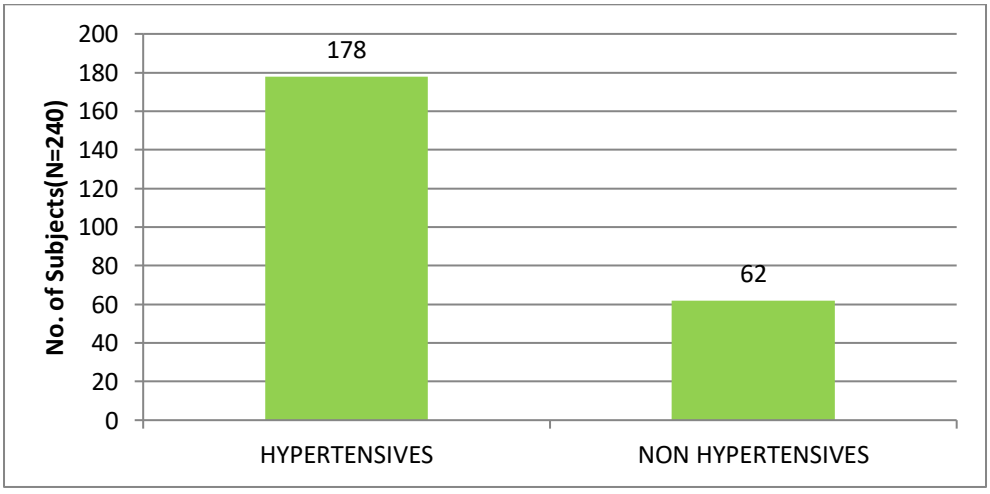


Fig: 10

Table 4: Depicts the association of smoking and occurrence of sleep disorders in patients with stroke. The subjects who are smokers and nonsmokersare equal which indicates that there is no significance of smoking for the occurrence of sleep disorders in patients with stroke which is graphically represented in Figure 11.

Table: 4

SMOKING	NUMBER OF SUBJECTS(N=240)
YES	120(50%)
NO	120(50%)

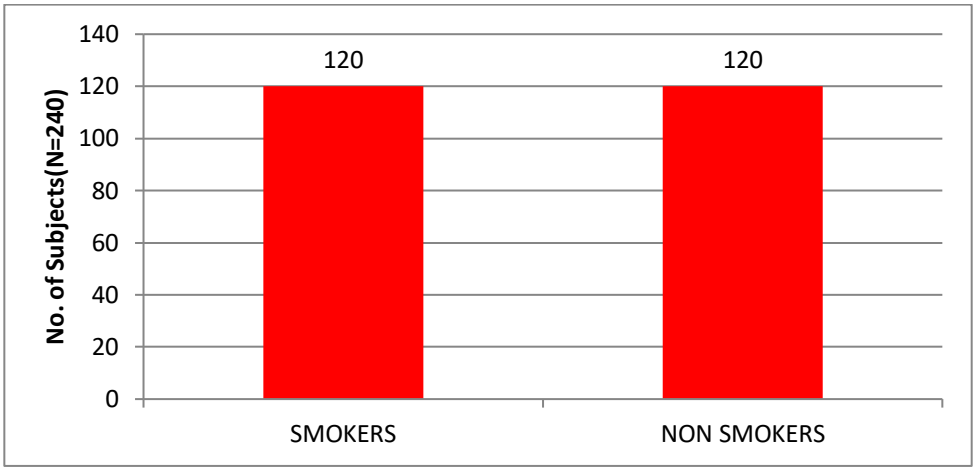


Fig: 11

Table 5: depicts the association of alcohol and occurrence of sleep disorders in patients with stroke. Majority of the subjects were alcoholics (125) which indicates that there is a positive association between alcohol and occurrence of sleep disorder in patients with stroke which is graphically represented in Figure 12

Table: 5

ALCOHOLIC	NUMBER OF SUBJECTS (N=240)
YES	125(52.0%)
NO	115(47.9%)

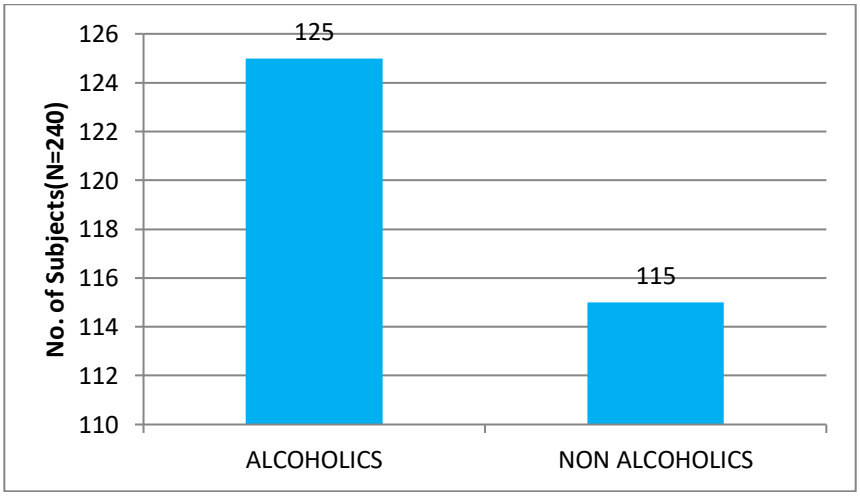


Fig: 12

Table 6: depicts the association of diet and occurrence of sleep disorders in patients with stroke. Majority of the subjects are non-vegetarians (208) which indicates that meat intake can leads to occurrence of sleep disorders in patients with stroke which is graphically represented in Figure 13

Table: 6

VEGETARIANS	NUMBER OF SUBJECTS (N=240)
YES	32(13.3%)
NO	208(86.6%)

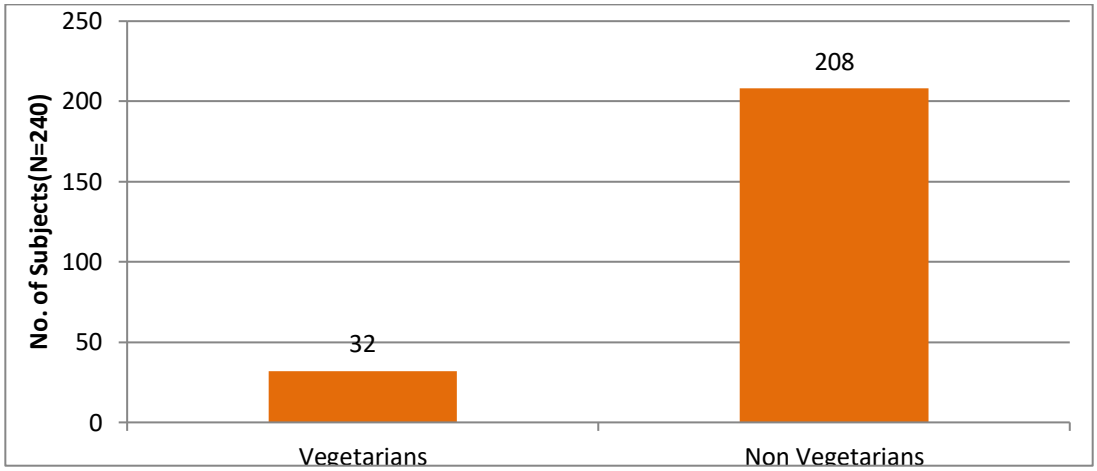


Fig: 13

Table 7 represents the base line and follow up data of sleep quality scale. The score is represented by subdividing In to 0-10, 11-20,21- 30,31-40,41-50,51-60,61-70,71-80,81-84.
Table: 7

SLEEP QUALITY SCALE	Base line	Follow up
0 to 10	3	0
11 to 20	41	22
21 to 30	93	101
31 to 40	40	49
41 to 50	23	26
51 to 60	27	28
61 to 70	13	14
71 to 80	0	0
81 to 84	0	0

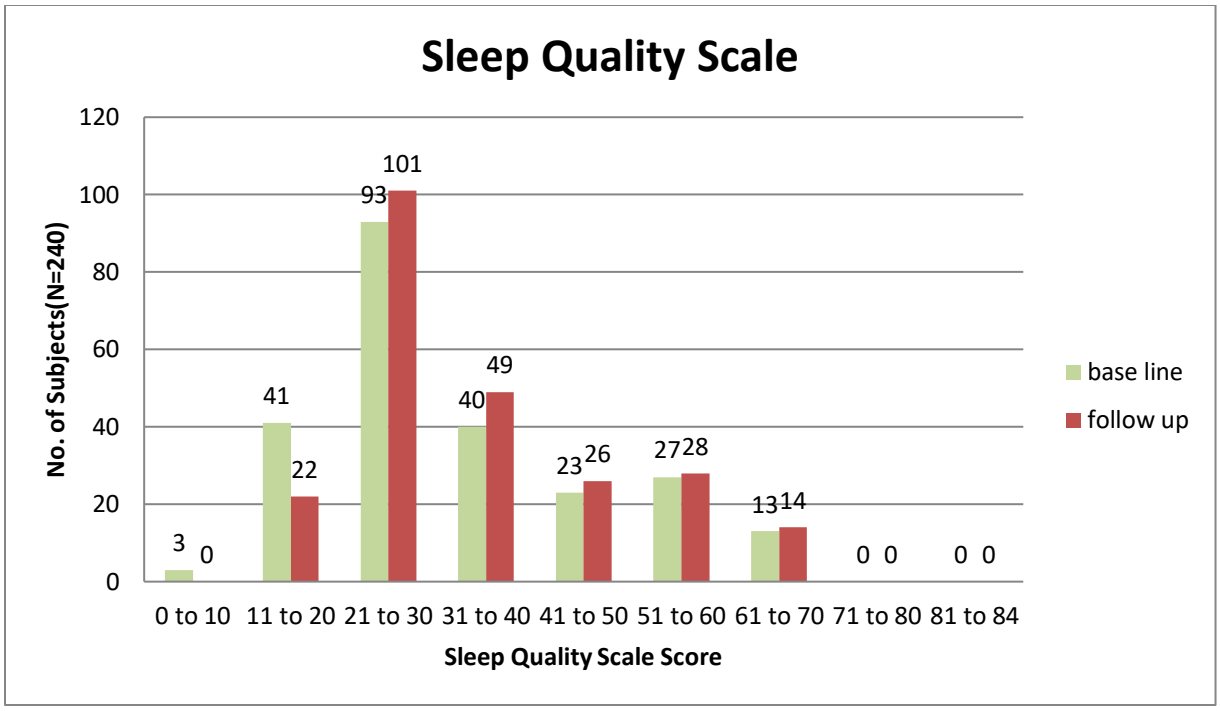


Fig: 14

Table 8 depicts the results of Epworth scale. The scale was subdivided into 0-7, 8-9, 10-15, and 16-24.Majority of the subjects score range is in between 0 to 7, followed by 8 to 9, 10 to15, and 16 to 24.

Table 8:

Epworth scale	Base line	Follow up
0 to 7	220	211
8 to 9	12	22
10 to 15	7	7
16 to 24	1	0

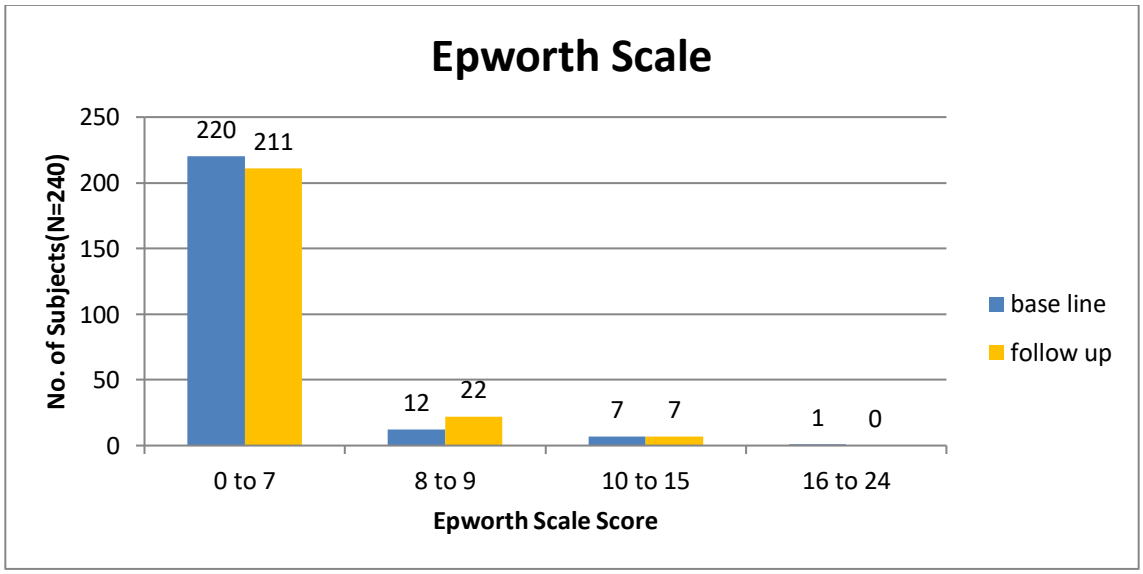


Fig:15

Table 9depicts the result of Pittsburgh scale. This scale was subdivided into 0-5, 6-10, 11-15, 16-21.Majority of the subjects score ranges between 6 to 10 followed by 0 to 5, 11 to 15, and 16 to 21.

Table: 9

Pittsburgh scale	Base line	Follow up
0 to 5	81	84
6 to 10	100	97
11 to 15	45	43
16 to 21	14	16

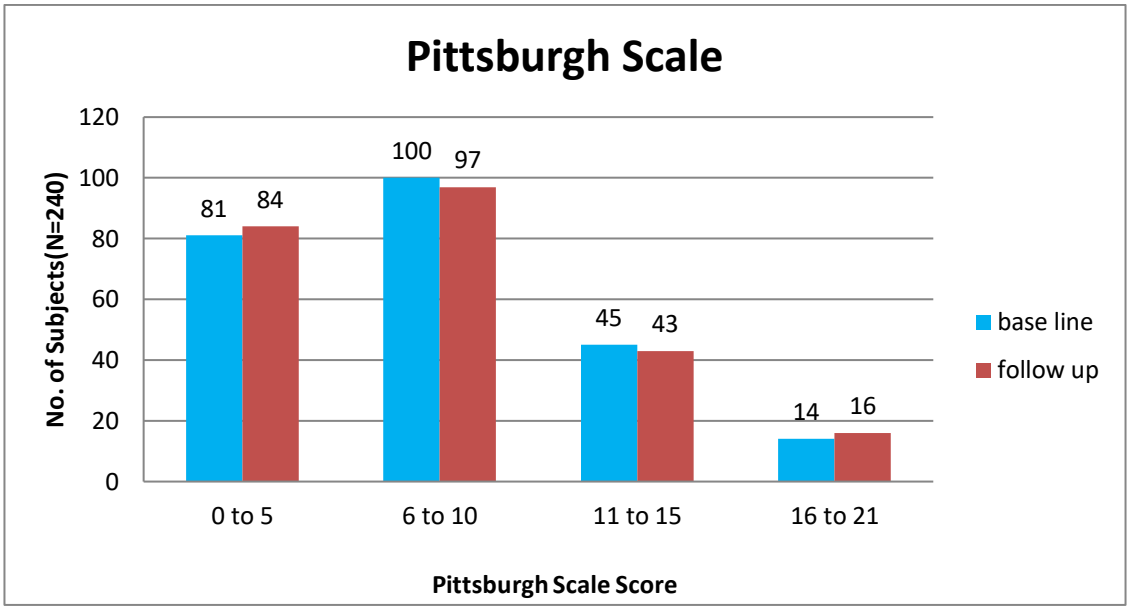


Fig: 16

Table 10depicts the results of berlin scale. Majority of the patients are at low risk.

Table: 10

Berlin scale	Base line	Follow up
High risk	116	102
Low risk	124	138

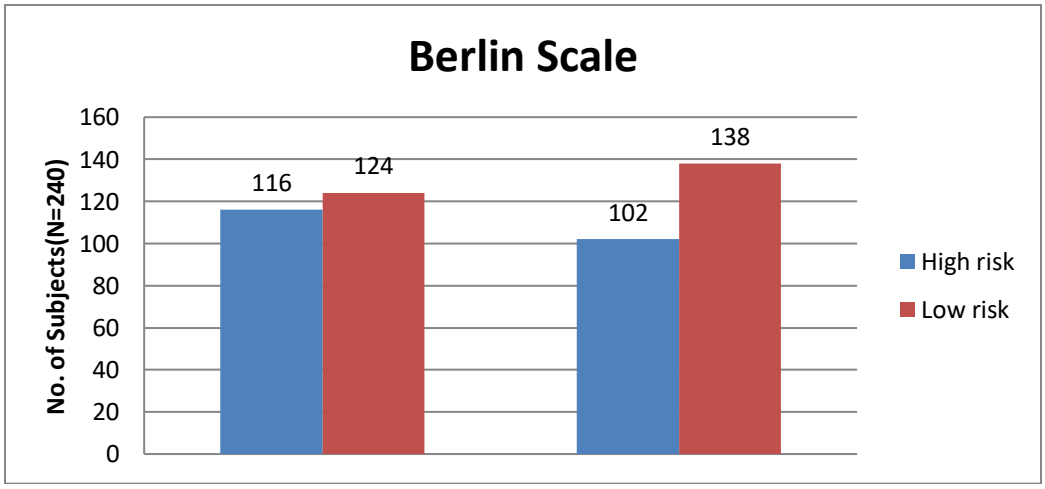


Fig:17

Table 11: Depicts the results of the self-designed and validated questionnaire which consists of 15 closed ended questions. These questions help in identifying the type of sleep disorder of the subject. Majority of the subjects are suffering with Snoring (111) followed by Day time sleepiness (98), followed by Sleep talking (83) followed by sleep apnea (66) followed by Night terrors (9) followed by Restless leg syndrome, Bruxism, Night mares, Narcolepsy.

Table: 11

TYPE OF SLEEP DISORDER	*NUMBER OF SUBJECTS*
DAY TIME SLEEPINESS	98
SLEEP TALKING	83
SLEEP PARALYSIS	5
SLEEP APNEA	66
SNORING	111
REST LESS LEG SYNDROME	1
BRUXISM	1
NIGHT TERRORS	9
NIGHT MARES	1
NARCOLEPSY	1

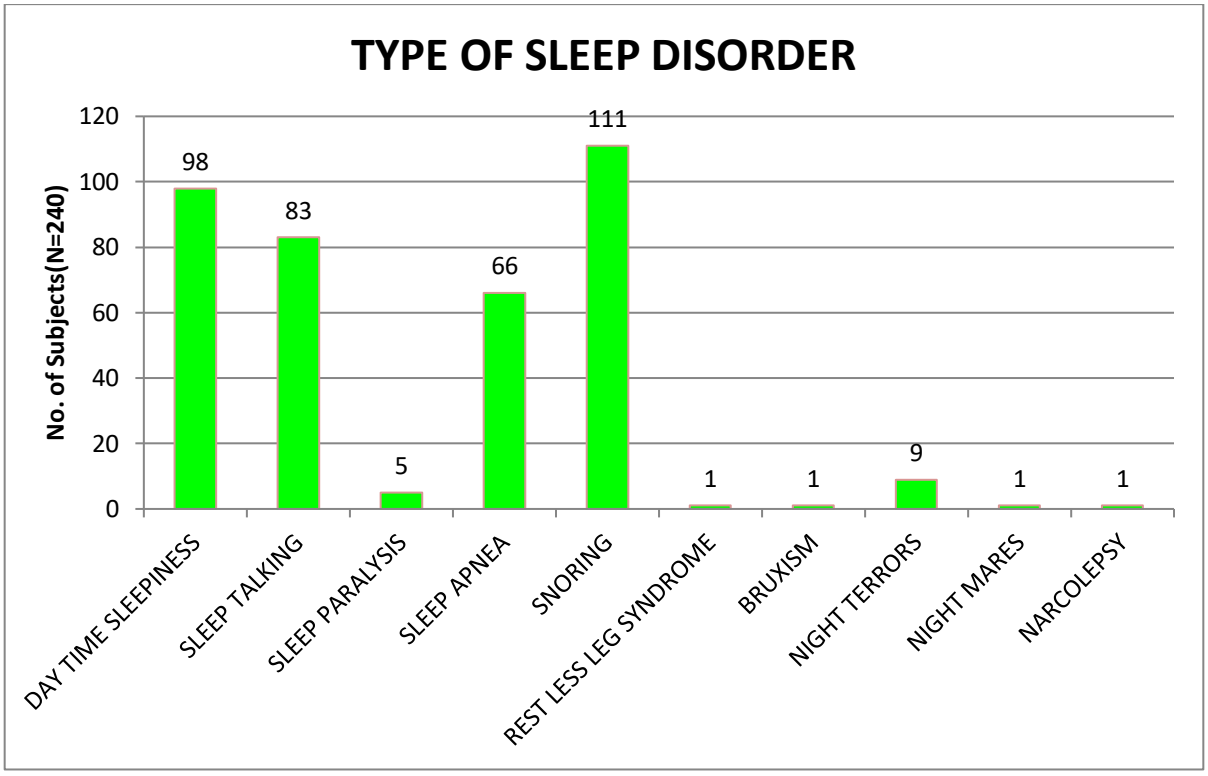


Fig: 18

1. INCIDENCE OF SLEEP DISORDERS

7.1 INCIDENCE OF DAY TIME SLEEPINESS

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 98/240 × 100
= 40.83%

7.2 INCIDENCE OF SLEEP TALKING

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 83/240 × 100
= 34.58%

7.3 INCIDENCE OF SLEEP PARALYSIS

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 5/240 × 100
= 2.0833%

7.4 INCIDENCE OF SLEEP APNEA

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 66/240× 100
= 27.5%

7.5 INCIDENCE OF SNORING

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 111/240 × 100
= 46.25%

7.6 INCIDENCE OF RESTLESS LEG SYNDROME

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

=1/240 × 100
= 0.4166%

7.7 INCIDENCE OF BRUXISM

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 1/240 × 100
= 0.4166%

7.8 INCIDENCE **OF NIGHT TERRORS.**

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 9/240 × 100
= 3.75%

7.9 INCIDENCE OF NIGHT MARES

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 1/240 × 100
= 0.4166%

7.10 INCIDENCE OF NARCOLEPSY

$$\text{Incidence} = \frac{\text{No. of new cases of disease}}{\text{No. of persons in the study population}} \times 100$$

= 1/240 × 100
= 0.4166%

8. DISCUSSION:

A non-experimental prospective observational cohort study was carried out on- "**EXPOSURE OF SLEEP DISORDERS AND INCIDENCE IN PATIENTS WITH STROKE- A PROSPECTIVE OBSERVATIONAL STUDY IN A TERTIARY CARE TEACHING HOSPITAL.**
"240 patients met the inclusion criteria and were included in the study. The data obtained was tabulated and analyzed.

On reviewing the demographic data of the subjects, it was found that majority of the subjects were males compared to females. It was found that Hypertension and Alcoholism have an impact on the occurrence of sleep disorders in patients with stroke. Based on the results obtained our study revealed that majority of the subjects were suffering with Snoring, Day time sleepiness, Sleep talking, Sleep apnea. These findings were in concordance with study done by **Zejneba Pasic, Dzevdet Smajlovic, Zikrija Dostovic, Bilijana Kojic, Senada Selmanovic**, conducted a prospective study *Incidence and Types of sleep disorders in patients with stroke (2011).* Analyzed 200 patients with acute stroke with the help of computerized tomography from a period of 1st August 2007 to 1st June 2008. Of the total 78% were with SD and 42% with very serious level of SD, 20% moderate and 16% medium to severe degree of SD with no statistical difference in frequency of sleep disorder in subjects with ischemic and hemorrhagic stroke. Sleep apnea and snoring are the most common SD. In accordance to Epworth scale sleep apnea and snoring were present in 86%, 49.5% with daytime sleepiness and narcolepsy. This study concludes that SD has a significant incidence in acute phase of stroke and slightly more common in hemorrhagic stroke and right hemisphere stroke.

Our study main objective was to determine the incidence of sleep disorders in patients with stroke.

Incidence of Snoring (46.25%) is more compared to other sleep disorders.
Incidence of Day time sleepiness is 40.83%,
Incidence of sleep talking is 34.58%,
Incidence of sleep paralysis is 2.08%,
Incidence of Night terrors is 3.75%,
Incidence of Sleep apnea is 27.5%,
Incidence of Narcolepsy is 0.4166%,
Incidence of Night mares is 0.4166%,
Incidence of Bruxism is 0.4166%,

Incidence of Rest less leg syndrome is 0.4166%.
Based on the results obtained among the 240 subjects, 186 subjects are suffering with sleep disorders. Of these

25 subjects are suffering with Snoring, Day time sleepiness, Sleep talking and Sleep apnea,
31 are suffering with Snoring and Day time sleepiness,
2 subjects are suffering with Day time sleepiness and Sleep talking,
4 subjects are suffering with Night terrors and sleep talking,
8 subjects are suffering with sleep apnea and Sleep talking,
24 subjects are suffering with Sleep talking, Sleep apnea and Snoring,
1 subject is suffering with day time sleepiness and Narcolepsy,
7 subjects are suffering with Sleep apnea and Snoring,
4 subjects are suffering with Snoring, Sleep apnea and Sleep talking,
13 subjects are suffering with Snoring and Sleep talking.
Our study found that there is no significant association between Diabetes Mellitus and Smoking for the occurrence of sleep disorders in patients with stroke. Our study results reveal that majority of the patients with stroke suffer with sleep disorders.

13. REFERENCES:

1. "What is a stroke?"www.nhlbi.nih.gov/. March 26, 2014. On Feb 18 2015. Retrieved 27 Feb 2015.
2. https://www.healthline.com/health/cerebrovasular-accident#prevention.
3. Https://www.ncbi.nih.gov/pcm/articles/PCM3859004/ accessed on Feb 18 2020. Jeyaraj Durai Pandian and Paulin Sudhan, Stroke Epidemiology and Stroke Care Services in India.
4. Banerjee TK Mukherjee CS, Sarkhel A. Stroke in the urban population of Calcutta- an epidemiological study. Neuroepidemiology 2001; 20:201-7.
5. Das SK, Banerjee TK biswas A, Roy T raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. Stroke 2007; 38: 906-10.
6. Mukhopadhyay A, sundat U, Adwani S, Pandit D. Prevalence of stroke and post-stroke cognitive impairment in the elderly in dharavi, Mumbai. J Assoc physicians India 2012; 60:29-32.
7. A. D. Lopez. C. D. Mathers, M. Ezzati, D. T. Jamison, and C. J. Murray, "Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data," The Lancet, vol. 8, no. 4, pp. 345-354, 2009.
8. C P. Warlow, "epidemiology of stroke", The Lancet, vol. 352, no. 3, pp. 1-4, 1998. View at Google scholar.
9. L. R. Caplan, Caplans Stroke: A Clinical Approach, Woburn, England, 3rd edition, 2000.view at publisher site.
10. A. Moran, M. Forouzanfar,U.Sampson, S. Chugh, V. Feigin, and G.Mensah, "The epidemiology of cardio vascular diseases in sub Saharan Africa " the Global Burden of Diseases, Injuries and Risk Factors 2010 Study", progress in cardiovascular Diseases , vol 56, no. 3, pp. 234- 239 , 2013. View at publisher site, Google scholar.
11. Roger VL, Go AS, Lloyd – Jones DM et al. Heart Diseases and stroke statistics – 2011 update: a report from the American heart association. Circulation 2011; 123: e18 –e209.doi: 10.1161/CIR.0b013e3182009701.
12. Ariesan MJ, Claus, SP Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003; 34: 2060 – 2065. Doi: 10.1161/01.SRT.0000080678.09344.8D. (PUBMED, GOOGLE SCHOLAR).
13. Chong J, Sacco R. Risk factors for stroke, assessing risk, and the mass and high-risk approaches for stroke prevention. In: Gore lick PB, editor. Continuum: Stroke Prevention. Hagerstwon, Maryland: Lippincott Williams and Wilkins; 2005. Pp. 18-34.
14. Xing C, Arai K, Lo EH, Hommel M. Pathophysiological cascades in ischemic stroke. Int J Stroke. 2012 Jul; 7 (5): 378-85.
15. Chung AG, Srye JB, Zbesko JC, Constanotounos E, Hayes M, Figueroa AG, Becktel DA, Anthony Day W, Konhilas JP, McKay BS, Nguyen TV, Doyle KP, Liquefaction of the Brain following Stroke Shares a Similar Molecular and Morphological Profile with Atherosclerosis and Mediates Secondary Neurodegeneration in an Osteopontin- Dependent Mechanism. eNeuro.2018 sep-oct;5(5)
16. Margaritescu O, Mogoanta L, Pirici I, Pirici D, Cernea D, Margaritescu C. Histopathological changes in acute ischemic stroke. Rom J Morphol Embryol. 2009;50(3):327-39.