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Essential hypertension and cognitive function in elderly

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ABSTRACT

Essential Hypertension is considered as an important independent risk factor for decline cognitive function leading to dementia and stroke. We assess cognitive function of essential hypertension over 60 years of age and its association with various socio-demographic in Indian setting. This cross-sectional study includes 62 hypertensives (stage 1 and 2) as cases and 21 normotensives and 41 prehypertensives as comparison group. Cases and comparison group were age and sex matched. Data was collected through interview and investigations. Cognitive function was measured by minimental status examination scale.

In hypertensives, total mean MMSE score as well as the score for orientation, attention-calculation, immediate recall and language (except registration) was significantly less compared to normotensives (p<0.001) and prehypertensives (p<0.001). Similar trend was observed for hypertensives with age, gender, education, smoking and alcohol (p<0.001). The overall MMSE scores in prehypertensives and normotensives were almost similar. SBP, DBP and age shows independently statistically significant inverse relationship with cognitive function. Measuring the cognitive function in essential hypertensive patients may have important health implication, as cognitive function along with WML are considered as a prognostic factor for stroke and early marker of brain damage

Keywords: *Essential Hypertension, Systolic blood pressure, Diastolic blood pressure, Cognition*

INTRODUCTION

Hypertension is an Iceberg disease. Globally, hypertension ranks third risk factor for poor health resulting in 13% of total deaths, whereas in developing countries, hypertension ranks eighth among risk factor for poor health.[1] The prevalence of hypertension in adults in India is showing an increasing trends, i.e. from 0.25 in 1960 to 7.08 in 1995.2,3,4 A very high prevalence of 72% was reported by a Hypertension Study Group5 in Maharashtra, India in persons over 60 years of age.

It is well known that hypertension, especially long standing undetected or uncontrolled hypertension is a risk factor for cerebrovascular disease. Even in apparently healthy persons hypertension causes partial and complete small vessel occlusion resulting in silent white matter lesions (WML) with associated cognitive impairment, progressing to dementia and subsequently stroke.[10,11] Studies have documented the negative effects of hypertension on specific cognitive functions. [6,7,8,9] Framingham heart study[8]provided the first clear evidence of relationship between hypertension and cognition in aging population.

Earlier studies have demonstrated that the long duration and/or uncontrolled hypertension is of an important consideration because it is believed to be a more powerful predictor of poor cognitive outcome,

particularly in older adults than high blood pressure assessed at one point in time.[6-11] However very few studies have examined cognitive function across all stages of blood pressure levels as per the JNC VII classification(i.e. normotensives, prehypertensives and stage 1 and 2 hypertensives). Furthermore, South East Asian people are even at most risk of these diseases, probably because of higher fat deposit at lower BMI, when compared to their western counterpart and most of the studies on cognitive function and hypertensivewere conducted among persons over 60 years of age.

Giving the increasing prevalence of hypertension at relatively younger age in Indian population and its effect on cognition which subsequently leads to dementia, we conducted this study to assess the cognitive function of patients of essential hypertension over 60 years of age and its association with various socio-demographic and clinical correlates in Indian setting.

MATERIAL AND METHODS

A cross-sectional study was conducted in tertiary care teaching hospital in Central India. Participants comprises of study group (cases) and comparison group. JNC VII classification was used to classify blood pressure level. Cases included persons over 60 years of age, either sex, diagnosed as having raised blood pressure (hypertension stage 1 and stage 2 as per the JNC VII criteria) and may or may not on antihypertensive treatment. Comparison group consists of persons over 60 years of age, matched with cases for age and sex and does not have hypertension (either normotensives or prehypertensives). Persons with secondary hypertension, known case of diabetes mellitus were excluded. The study protocol was approved by the Institutional Ethical Committee.

The study includes 124 participants (62 cases and 62 comparisons). Sample size of was calculated at 5% significance level (α), with precision of 20% and considering prevalence of impaired cognition in hypertensives and normotensives to be 40% and 18% respectively.

Data was collected using pre-designed structured interview schedule. The interview schedule was pilot tested and final schedule included question on socio demographic information, presenting complaints and history, clinical examinations and investigations like blood sugar, urine examination, renal function test, ECG, serum electrolytes, lipid profile, fundus examination, USG – KUB, carotid doppler and minimental status examination scale (MMSE) for cognitive function. Persons over 60 years of age attending tertiary care center were subjected to blood pressure measurement. Those with essential hypertension, were included in the study as cases after informed consent. Complete socio-demographic information, presenting complaints were recorded. Participants were examined and later on subjected to necessary investigations. Persons who were normotensives at the initial blood pressure examination were considered for comparison group and the same steps were followed for them.

PROCEDURES AND DEFINITIONS

Blood pressure measurement: Blood pressure was measured by mercury sphygmomanometer. The individuals were made comfortable and seated for at least for five minutes before measurement. Pressures at which sound appeared and muffled or disappeared were taken as a systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively. The measurement was made with individual in sitting position. Two readings were taken half an hour apart and the average of two was taken as a final reading. [12] As per the JNC VII[13]blood pressure was classified as normal (SBP<120 and DBP<80 mm of Hg), pre-hypertensive (SBP = 120-139 and DBP = 80-89 mm of Hg), Stage I hypertension (SBP = 140-159 and DBP = 90 - 99 mm of Hg), stage II hypertension (SBP >160 and DBP >100 of Hg).

Body weight, height and Body MassIndex (BMI) were measured as per the procedure specified in WHO Technical Report Series (1995) No 854[13]. Smokers were classified as current smokers, past smokers, and nonsmokers. Past smokers were those who quit smoking for at least 1 year at the time of Study. Current-smokers were defined as those who are currently smoking any number or any form of tobacco. Alcohol intake was categorized as regular

intake (almost daily), irregular (social) drinker, or never.

Cognitive functions were measured by the Faolstein Mini-Mental State Examination (MMSE) scale. It evaluates orientation, memory, calculation, attention, language, and praxis, for a maximum score of 30.[8,14,15,]

Continuous-wave Doppler examination of the extracranial cerebral arteries and duplex scanning of the extracranial carotid arteries were performed in all subjects. Diabetes mellitus was defined as presence of either random plasma glucose levels more than 200 mg/dl or fasting plasma glucose levels more than 126 mg/dl, or a history of diabetes mellitus requiring treatment. Lipid profile was done to diagnose dyslipidaemia (increase in total cholesterol, LDL, VLDL, triglycerides, or decrease in HDL). Urine albumin was tested using dipstick method on spot sample. To rule out any renal disease, kidney function test and KUB USG was done. The participants were excluded from the study if he/she had an evidence of target organ damage. Infection control guidelines were strictly adhered to while investigations. The results of the investigations were explained to the participants, and were referred for appropriate treatment, if indicated.

Data analysis: The main outcome variable was Cognitive Function. The initial null hypothesis was that the cognitive function remains unaffected with increasing level of blood pressure regardless of age and other socio-demographic predictors. The mean values and standard deviations (SD),or proportions of selected socio-demographic attributes were computed. Mean differences in cognitive function by hypertension status, systolic and diastolic pressure were examined using appropriate statistical test of significance – t test or analysis of Variance. To test the independent effect of predictors on cognitive function across all stages of blood pressure, multiple linear regression analysis was done.

RESULTS

The study includes 124 participants, 62 cases (hypertensives) and equal number of comparison group (normotensives and prehypertensives). The age range was 60 to 80 years and majority belongs to 60 to 69 years (39.5%). Average age in hypertensives was 69.48 (SD 8.63) and that in comparison group was 68 (SD 8.54) years. The cases and comparison were age (T= $p>0.05$) and sex matched (chi square = 3.49, $p>0.05$). The overall mean BMI in study participant was 24.61 (SD 2.48). (**Table 1**) Of the 62 participants from comparison group, 21 (33.87%) were normotensives, 41 (66.13%) were pre-hypertensive as per the JNC VII criteria and among hypertensives 29 (46.77%) were stage 1 and 33 (53.23%) stage 2 hypertensives. Mean systolic and mean diastolic blood pressure of the study participants across various stages of blood pressure were within the range specified in the JNC VII classification of blood pressure. (**Table2**)

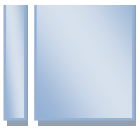

Table 1 Participants socio-demographic characteristics in cases (hypertensives) and comparison (normotensives and Prehypertensives)

Participants characteristics		Cases*	Comparison*	Total	P Value
		No (%)	**No** (%)	**No** (%)	
Sex	Male	48 (77.4)	53 (85.5)	101 (81.5)	$X^2 = 3.39$ p>0.05
	Female	14 (22.6)	6 (14.5)	23 (18.5)	
Age group (years)	60-69	24 (38.7)	25 (40.3)	49 (39.5)	$X^2 = 0.34$ P=0.84
	70 – 75	22 (35.5)	23 (37.1)	45 (36.3)	
	76 – 80	16 (25.8)	14 (22.6)	30 (24.2)	
Education	Illiterate	13 (20.9)	13 (20.9)	26 (20.9)	--
	Till Secondary	4 (6.5)	4 (6.5)	8 (6.5)	
	Higher sec.	7 (11.3)	7 (11.3)	14 (11.3)	
	Above	38 (61.3)	38 (61.3)	76 (61.3)	
Smoking	Never smoker	16 (25.8)	11 (17.7)	27 (21.8)	$X^2 = 1.23$ P=0.541
	Past smoker	36 (58.1)	39 (62.9)	75 (60.5)	
	Current smoker	10 (16.1)	12 (19.4)	22 (17.7)	
Alcohol	Non Alcoholic	25 (40.3)	19 (30.6)	44 (35.5)	$X^2 = 1.35$ P=0.50
	Occasional	35 (56.5)	40 (64.5)	75 (60.5)	
	Regular	2 (3.2)	3 (4.5)	5 (4)	
BMI	< 18	--	5 (8.1)	5 (4.03)	$X^2 = 20.72$ P=0.001
	18 – 24.9	20 (32.3)	39 (93.9)	39 (31.6)	
	25 – 29.9	42 (67.7)	18 (29.1)	80 (64.5)	

***cases included stage 1 hypertensives and stage 2 hypertensives whereas comparison group includes normotensives and Pre-hypertensives**

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Table 2 Classification of study participants as per JNC VII criteria and mean systolic and diastolic blood pressure in each category

Blood pressure -JNC VII **(mm of Hg)**	No (%)	Systolic Blood Pressure* Mean (SD)	Diastolic Blood Pressure# Mean (SD)
Normotensives	21 (16.9)	115.14 (SD ± 3.14)	**77.42 (SD ± 2.57)**
Prehypertensives	41 (33.1)	128.10 (SD ± 3.16)	**82.34 (SD ± 2.68)**
Hypertensives - Stage 1	29 (23.4)	151.79 (SD ± 4.53)	**92.62 (SD ± 1.86)**
Hypertensives -Stage 2	33 (26.6)	167.45 (SD ± 4.34)	**102.27 (SD ± 6.14)**
All participants	124 (100)	138.94 (SD ± 22.35)	**88.32 (SD ± 10.16)**

***** ANOVA, F= 1345.81 p= 0.000 **#** ANOVA, F= 276.57 p=0.000

The lowest MMSE score was 14 and the highest was 30. Overall mean score was 26.73 (SD 3.44). The difference in mean MMSE score between normotensives, prehypertensives and hypertensives was statistically significant (ANOVA, F= 175.14, p=0.000). On further comparing the mean MMSE score with various stages of blood pressure on post hoc Bonferroni test, it was observed that the mean MMSE in hypertensives were significantly less than mean MMSE in normotensives (p<0.001) and prehypertensives (p<0.001), whereas the mean MMSE score in normotensives and prehypertensives was not significantly different (p>0.05). (**Table 3**)

The mean MMSE score was also significantly different between subcategory of predictors, i.e. gender (male & Female), age group (60 to69 years 70 to 75 years & 76 to 80 years), education (illiterate, secondary, higher secondary and above) smoking (non smoker & ever smoker) and alcohol (never / occasional and regular) for different stages of blood pressure level as per the JNC VII classification (p<0.05). On further comparison of mean MMSE score on post hoc test, it reveals that across all predictors, the mean MMSE score in hypertensives was significantly less than in normotensives (p<0.001) and prehypertensives (p<0.001) whereas the mean MMSE in normotensives and prehypertensives were almost similar (p>0.05) (**Table 3**).

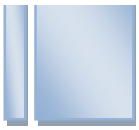


Table 3 Mean (SD) MMSE in Normotensives, Pre-hypertensives, Hypertensives

Participant characteristics		Overall (n=124)		Normo-tensives (n=21)		Pre-hypertensives (n=41)		Hypertensives (n=62)		ANOVA / t test
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Overall **(All participants)**		26.73	3.44	29.40	0.30	29.15	1.33	22.03	2.10	**F= 175.14, p=0.000**
Sex [a]	Male	26.8	3.26	29.55	0.70	29.37	0.77	23.77*	3.08	**F=185.63 P=0.000**
	Female	26.4	2.52	28.56	1.88	27.83	1.94	25.00 *	1.80	**F=21.56 P=0.000**
Age group [b] **(years)**	60 – 69	29.18	1.65	29.81	0.47	29.13	1.60	26.38 *	2.13	**F=54.92 P=0.000**
	70 – 75	26.82	2.84	29.05	1.39	29.13	0.81	24.96 *	2.35	**F=57.52 P=0.000**
	76 – 80	24.84	3.7	28.87	0.74	29.02	0.79	23.44 *	2.90	**F=141.16 P=0.000**
Education	Illiterate	26.65	3.30	29.08	1.66	28.67	1.87	24.34 *	2.68	**F=34.04 P=0.000**
	Till Secondary	26.75	2.82	29.25	0.96	29.25	1.06	24.25 *	0.96	**F=139.87 P=0.000**
	HSSC & above	26.86	3.61	29.29	0.76	29.29	0.85	24.43 *	3.74	**F=224.95 P=0.000**
Smoking	Never smoker	27.65	2.40	29.36	0.81	29.00	0.82	25.81 *	2.01	**F=135.58 P=0.000**
	Ever smoker	26.49	3.74	29.31	1.15	29.04	1.92	23.44 *	3.13	**F=116.57 P=0.000**
Alcohol	Never / Occasional	26.43	3.87	29.80	0.45	29.29	0.83	24.16 *	3.56	**F=171.52 P=0.000**
	Regular	27.60	3.29	29.81	0.26	29.00	1.29	23.97 *	2.43	**F=116.57 P=0.000**

** Significantly less as compared to mean MMSE in normotensives and prehypertensives on post hoc Bonferroni within each subcategory of predictor (p<0.001)*
a= significant only in prehypertensive group (t=0.481; p=0.001)
b= significant only in hypertensive group (ANOVA F=6.108; p=0.004)

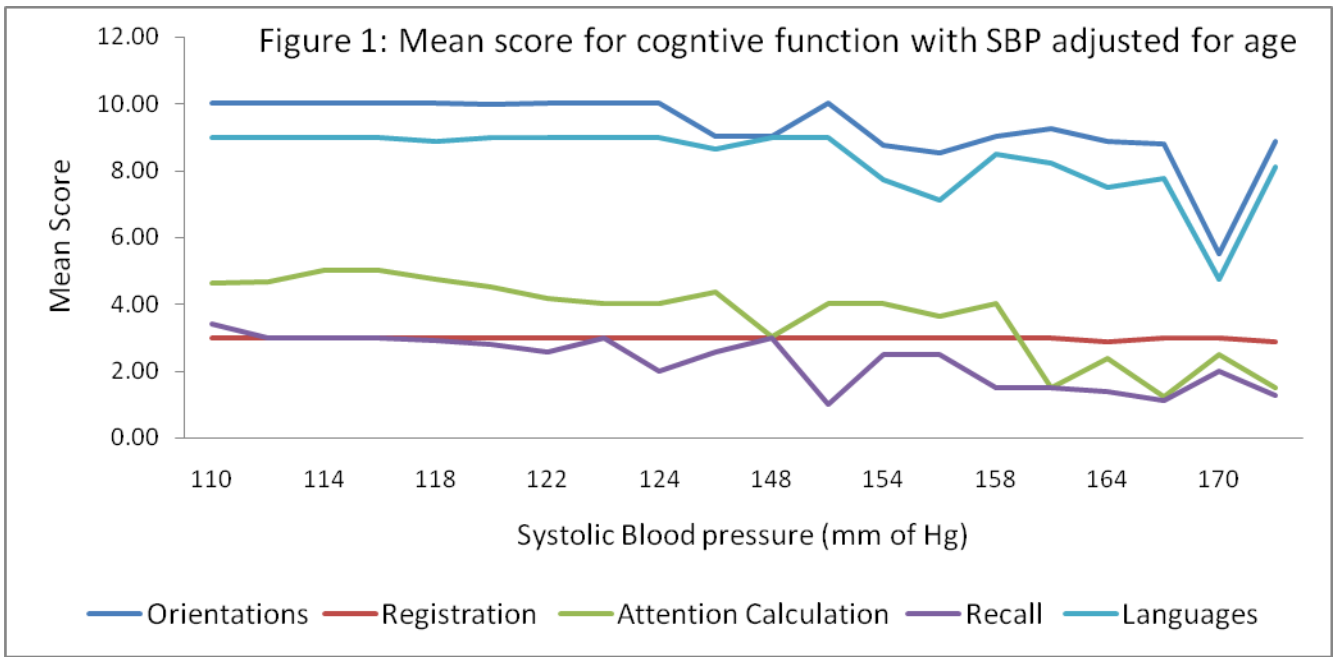
We also studied the score of each cognitive domain separately across all stages of blood pressure. The score of orientation, attention-calculation, immediate recall and language were significantly less in hypertensives compared to that of prehypertensives (p<0.001) and normotensives (p<0.001), whereas the difference in score of all cognitive domain between normotensives and

prehypertensives was not significant (p>0.05).The registration score was remain unaffected across all stages of blood pressure(p>0.05) (**Table 4**). It was also observed that the mean scores for orientation, attention & calculation, recall and languages decrease with increase in SBP & DBP after adjusting for age. The decrease is more obvious for the higher blood pressure level, in case of SBP after 124 mm of Hg and in case of DBP after 90 mm of Hg. However, the score of registration remains almost unaffected with the increasing the severity of blood pressure (**Figure 1 & 2**).

Table 4 Mean (SD) score of various cognitive domain in cases and comparison group

Cognitive domain	Overall (n=124)		Normo-tensives (n=21)		Pre-hypertensives (n=41)		Hypertensives (n=62)		ANOVA
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Orientation	9.35	1.10	9.98	0.21	9.98	0.16	8.71*	1.26	F=22.89 (p<0.001)
Registration	**2.98**	**0.13**	**3.00**	**0.0**	**3.00**	**0.0**	**2.97**	**0.18**	**F=1.89 (p=0.156)**
Attention & Calculation	3.68	1.42	4.90	0.44	4.41	0.77	2.77*	1.37	F=101.84 (p<0.001)
Recall	2.33	0.85	2.87	0.50	2.78	0.47	1.79*	0.79	F=50.79 (p<0.001)
Language	8.39	1.04	8.97	0.18	8.98	0.16	7.81*	1.21	F=23.30 (p<0.001)
Total MMSE	26.73	3.44	29.40	0.22	29.15	1.33	22.03*	2.10	F=175.14 (p<0.001)

***** Significant when compared to normotensives (p<0.001) and prehypertensives (p<0.001) on post hoc Bonferroni test



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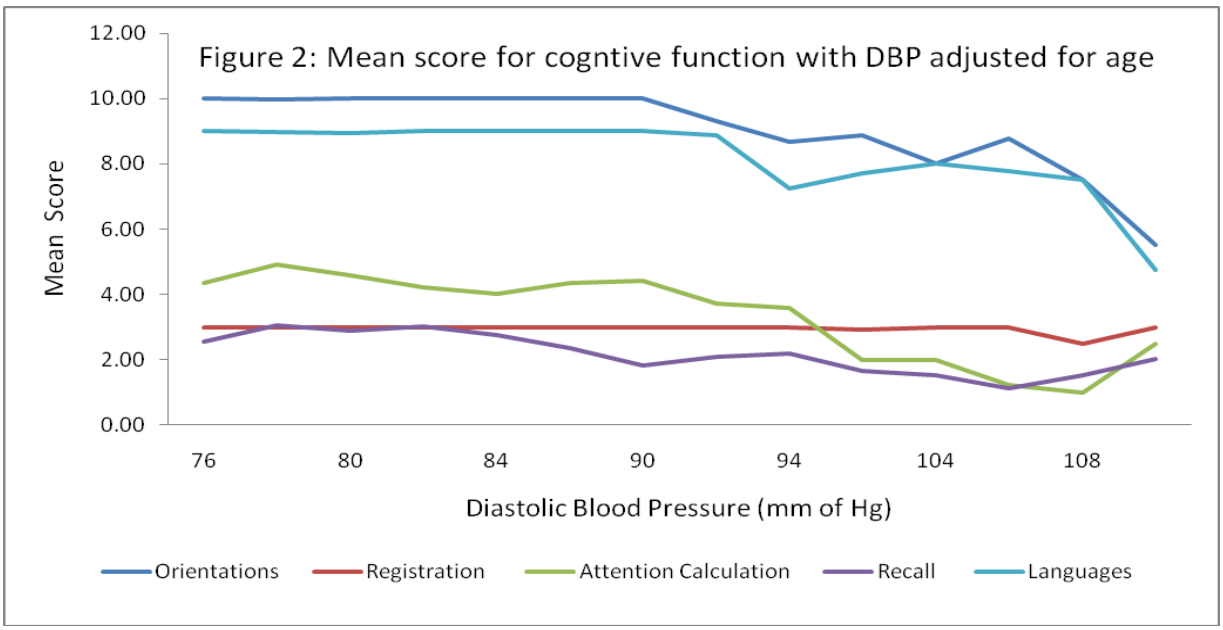

The regression analysis was performed to test the independent effect of blood pressure and age on cognition. SBP, DBP and age were included in model. Overall it was observed that the SBP, DBP and age independently shows a significant negative relationship with MMSE score. On running regression analysis separately for normotensives, prehypertensives and hypertensives, only age in prehypertensives shows significant independent effect on MMSE score, whereas in hypertensives all three, SBP, DBP and age, shows a significant negative effect on MMSE score (**Table 5**).

Table 5: Multiple linear regression to find out the independent effect of SBP, DBP and Age on MMSE score

Predictor	Overall (n=124)		Normotensives* (n=21)		Pre-hypertensives (n=41)		Hypertensives (n=62)	
	B	SE	B	SE	B	SE	B	SE
SBP	**-0.184**	**0.014**[a]	-0.509	0.026	-0.820	0.053	**-0.386**	0.021[c]
DBP	**-0.686**	**0.031**[c]	-0.377	0.094	0.114	0.060	**-0.590**	0.030[c]
Age	**-0.113**	**0.017**[b]	0.174	0.009	**-0.516**	**0.021**[c]	**-0.136**	0.023[b]
Constant	45.01		46.12		32.87		**72.63**	
R^2	0.862		0.20		0.289		**0.858**	

SBP= systolic blood pressure, DBP = diastolic blood pressure
a - Sig at p<0.05, b- sig at p<0.01, c- sig at p<0.001
* Not significant for SBP, DBP and age

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DISCUSSION

Our study reveals a declining cognitive performance in hypertensive (stage 1 and 2) compared to normotensives and prehypertensives. Hypertensives score significantly less on MMSE scale compared to normotensives ($p<0.001$) and prehypertensives ($p<0.001$), whereas the difference in mean MMSE score of normotensives and prehypertensives were not statistically significant ($p>0.05$). Several studies also mentioned that hypertension confer greater risk for cognitive impairment, independent of other factors.[10,16-18,20,23,24]The mean MMSE score for all participants was 26.73 (SD 3.44). Fourteen was the lowest and 30 the highest MMSE score of study participants. The mean MMSE score was significantly different across all stages of blood pressure as per the JNC VII criteria ($p<0.001$).

Our study also reveals that across all sub-category of predictors i.e. age group (60 to69 years 70 to 75 years & 76 to 80 years), sex (male & female), education (illiterate, secondary, higher secondary & above), smoking (ever smoker & nonsmoker) and alcohol (never / occasional & regular); hypertensives scores significantly less than normotensives and prehypertensives on MMSE scale ($p<0.001$). The findings of Dufouil C et al[28]reports that a high level of education were protected against the cognitive deterioration. However in our study in hypertensive education does not have protective effect on cognition.

On studying the effect of age on cognition in subjects with different stages of blood pressure level as per the JNV VII criteria, it was observed that with increasing age the MMSE score decreases significantly in hypertensives ($p<0.001$), but in prehypertensives and normotensives the decrease in MMSE score was not significant ($p>0.05$).On controlling for age, a decrease in cognitive function score was observed with increasing stage of systolic and diastolic blood pressure and it was more significant at higher stage of systolic and diastolic blood pressure. Many studies have reported similar findings.[17, 18]We applied a multiple linear regression analysis to find out the independent predictive effect of SBP, DBP and age on cognitive function. In hypertensives, SBP, DBP and age shows a significant negative effect on cognition; however the similar relationship was not seen in normotensives and prehypertensives. Waldstein SR[10] and Brady CB et al[18] also reports that in hypertensive individuals age was negatively related to performance on all of the cognitive tests in their studies.

On studying each cognitive domain separately across various stage of blood pressure, the score for orientation, attention-calculation, recall and language in hypertensives was significantly less when compared to prehypertensives and normotensives individuals ($p<0.001$). However, mean scores for all cognitive domains between normotensives and prehypertensives was not significantly different ($p>0.05$). For all cognitive domains, except registration, a significant inverse relationship was observed with increase in SBP and DBP. Other studies have also mentioned that hypertension does not affect all the domains of cognitive function similarly. Few studies have reported that the cognitive functions affected by high blood pressure are related to deficits in learning, memory, attention, abstract reasoning, executive functions, visuospatial, and psychomotor abilities but were unrelated to verbal intelligence or language abilities.21, 29 However, our study shows the language was significantly affected in hypertensive individuals. Framingham Heart Study16 also showed varying association of various cognitive functions with hypertension. Brady CB et al18 study reports an association of hypertensive status with category fluency and immediate recall. Waldstein et al10 reports that hypertensives perform more poorly than normotensives in virtually all domains of cognitive function. However this differing opinion on association of specific cognitive domain with hypertension in different studies may be due to different tools used for measuring cognitive performances and different inclusion criteria. But it is evident from our study and most of the reported literature that hypertension does not affect all cognitive domains uniformly.

Studies that we have discussed and compared are those that have studied cognitive function in persons with uncontrolled or long duration of hypertension. Our study includes patients of essential hypertension, may or may not on antihypertensive treatment and without evidence of complication or target organ

damage. Unlike other studies that have not studied prehypertensives categories separately, we studied the cognitive function across various stage of blood pressure as per the JNC VII classification i.e. normotensives, prehypertensives and hypertensives. However in our study the prehypertensives and normotensives score almost similar on cognitive function tests whereas, hypertensives show a significant inverse relationship systolic and diastolic blood pressure level. Similarly most of the studies that we have compared were on elderly persons i.e. more than 70 years. Considering the high risk of hypertensions in south East Asian population due to higher fat deposit at lower BMI compared to their western counterpart, we recruited relatively younger population (i.e. above 60 years of age) in our study. In-spite of difference in inclusion criteria findings of our study was comparable to those of other studies. However there are few variations with regards to association of various cognitive domains with hypertension. As already discussed these variations may be due to different scales used for studying cognitive functions apart from different inclusion criteria. Moreover the minimental status examination scale used in our study also has some inherent limitations because of its emphasis on language and its insensitivity towards mild deficits and is also influenced by age and education.[15]Although, despite variations in findings, one thing is clear from all these studies that hypertension negatively affect most of the cognitive domain, which may have negative affect the quality of life of hypertensive patients.

We have not studied the pathophysiologic mechanism and cause for decrease in cognitive performances in hypertensives and its clinical significance. It is unclear whether the impact of elevated BP on cognitive decline in late-life is mediated through its chronic and negative effect on the structural characteristics of the brain.[20, 23, 24] However several studies suggest that presence of cerebral white matter lesion (WML) is associated with impaired cognition leading to dementia and is also an important prognostic factor for the development of stroke and could be considered an early marker of brain damage.[19, 20, 23, 24, 27-29] Cardiovascular Heart Study [25] mentioned that WML and cognitive decline is associated with higher stages of blood pressure and clinical silent stroke on MRI. Mental slowing, executive deficits, memory impairment and global cognitive decline are the most common cognitive features related to WML in hypertensives.[20, 21, 26] Longstreth T et al[22] mentioned that hypertensive persons with WML are more likely to have impaired cognitive function and gait. Thus the decreased cognitive function in hypertensives could not be considered as benignand therefore it becomes imperative to study cognitive function in all hypertensive subjects, regardless the stage and duration of blood pressure.

Considering this background, and our findings that both SBP and DBP apart from age are associated with reduced cognitive function, this study may have significant health implication for improving the quality of care and life of patients with essential hypertension. In resource poor settings it would not be feasible to undertake such costly investigations like MRI to diagnose WML in all hypertensives; therefore assessing the cognitive function would be cost effective approach to suspect early cerebral white matter changes as studies have already established the association of declining cognitive function with WML and subsequently stroke and/or dementia in hypertensive patients. However, this was an observational cross-sectional study; inferences regarding a causal relationship between essential hypertension and cognitive function remain tentative. A more elaborate community based prospective study in needed to examine the temporal relation. Similarly an experimental study would be useful to study the value of assessing cognitive function in hypertensives on their quality of life and care in Indian setting.

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