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THE PREVALENCE OF APPARENT RESISTANT HYPERTENSION AND ASSOCIATED FACTORS AMONG ELDERLY HYPERTENSIVE PATIENTS AT TWO PRIMARY CARE CLINICSIN KLANG VALLEY, MALAYSIA

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Abstract—

BACKGROUND: Resistant hypertension has been identified as one of the causes for hypertensive patients failing to reach their blood pressure target.
OBJECTIVE: This study aims to determine the prevalence of resistant hypertension amongst elderly hypertensive patients (aged 60 years and above) and the factors associated with resistant hypertension.
METHODOLOGY: A cross-sectional study incorporating a questionnaire was used in this study and was conducted between July 2018 to February 2019. Adherence to anti-hypertensive medication was assessed by using the 14-item Hill-Bone Compliance to High Blood Pressure Therapy Scale.
RESULTS: A total of 594 patients aged ≥ 60 years were studied. The mean age was 70.28 ± 6.74 years with 57.8% (n=343) being female. The mean systolic blood pressure was 144.93 ± 14.12 mmHg while the mean diastolic blood pressure was 77.67 ± 8.64 mmHg. The proportion of patients with resistant hypertension was 66.3% (394/594). In univariate analysis, factors found to significantly associated with the presence of resistant hypertension were gender, educational level and age ($p<0.05$). In multivariate analysis, it was found that older age and those of a lower educational level were determinants of having resistant hypertension.
CONCLUSION: The prevalence of resistant hypertension among elderly patients was very high. Groups found to have a higher risk of developing resistant hypertension should be targeted during health campaigns or consultations.

Key words: resistant; hypertension; elderly; Malaysia; primary health care

INTRODUCTION

Resistant hypertension is defined as blood pressure(BP) not achieving the therapeutic target (≤140/90 mm Hg in hypertension or ≤130/80 in those with chronic kidney disease, diabetes, or previous cardiovascular event) despite adherence to at least threeoptimally dosed antihypertensive medications of different classes, one of which must be a diuretic [1,2]. Some studies on resistant hypertension in Europe show a prevalence rate of 10-20%in hypertensives patients mainly followed up on the primary care [2-4].

Meanwhile studies in Asia show a prevalence of 2%(in hypertensives patients followed-up in primary care clinics in China) -20%(in hypertensives patients followed-up under a cardiology clinic in Sri Lanka) with a large study involving 112,000 patients showing a prevalence rate of 14.6% [5-10]. Three earlier studies in Malaysia showed a prevalence of 8.8-12% [5,11,12].Resistant hypertension leads to a 50% increase in the risk of experiencing an adverse cardiovascular event compared with patients whoseBP iscontrolled by three or fewer antihypertensive agents [3].

There is a lack of research on the prevalence of resistant hypertension in elderly hypertensive patients (aged >60 years), despite these patients being at the highest risk of developing a stroke, myocardial infarction and chronic kidney disease. Therefore, this prevalence study aims to analyse this age group of patients in two primary care clinics in Klang Valley, Selangor to determine which factors are associated with developing resistant hypertension and in which group(s) intervention is needed.Hopefully this willsubsequently lead to the identification of possible secondary causes of hypertension, which is common in resistant hypertension but the exact prevalence is unknown in future studies [13). This will include common causes such as obstructive sleep apnea, renal parenchymal disease, primary aldosteronism and renal artery stenosis and uncommon causes such as pheochromocytoma, Cushing's disease,hyperparathyroidism, aortic coarctation and intracranial tumor [13]..One possible treatment includes earlyreferral for the revolutionary renal nerve denervation that has been postulated as a curative treatment for resistant hypertensionRenal nerve denervation is able to lower systolic blood pressure (SBP)by 25 ± 24 mmHg during daytimeand 26 ± 24 mm Hg during nighttime. Regarding diastolic blood pressure (DBP), a similar decrease of 12 ± 14 mm Hg during daytime and nighttime was seen, based on a study of 63 eligible patients that underwent this mode of therapy in Kazakhstan [14].The treatment of right patients with resistant hypertension may provide life-long curative treatment for this group of patients.

METHODS

A cross sectional study incorporating a questionnaire that identifiedsocio-demographic data, (age, gender, ethnicity, educational level and medical co-morbidities (diabetes, dyslipidaemia) was used in this study which was conducted between July 2018 to February 2019. Certain blood and urine parameters (glucose, fasting lipids and urine protein) from patient's medical records were also included. Anthropometric data including height and weight, biochemical parameters of glycaemia (fasting blood glucose, glycated haemoglobin), lipid profile and renal function were also collected from patient's medical records.

The patients were aged 60 years and above and registered in the primary care clinic. Patients who fulfilled the criteria of hypertension were selected for the study using a universal sampling method. As this clinic has follow-ups of patients with hypertension of varying durations, participants that fulfilled the inclusion criteria and gave informed consent to participate were recruited into the study. The inclusion criteria were patients who fulfilled the diagnosis of hypertension**,** as well as having hypertension for at least one year and on three or more antihypertensive agents, including a diuretic. The sample size was400patientstaking into account a

prevalence rate of 20% of resistant hypertension as noted in the study in Colombo, Sri Lanka and an anticipated of up to 20% non-response rate [8] . Due to the difficult logistics of the study, the actual criteria of having these three antihypertensives at maximum tolerated dose for the diagnosis of true resistant hypertension was not possible and therefore the term apparent resistant hypertension is used instead of true resistant hypertension.

BP was measured by digital BP devices at the clinic after 1 minute of rest and repeated 1 minute later as recommended by the latest local Clinical Practice Guidelines on the management of hypertension to determine the mean systolic and diastolic BP which will be used to determine the prevalence of resistant hypertension[1].Apparent resistant hypertension will be defined as those participants with mean SBP ≥ 140mmHg and/or DBP ≥ 90 mmHg despite on three or more antihypertensive agents, including a diuretic.

Determination of adherence to anti-hypertensive agents

Adherence was assessed using the14-item resilience scale and Hill-Bone compliance to the High Blood Pressure Therapy Scale (HBTS) with was used with permission that was also back and forward translated in the Malay language for use in participants that are not fluent in the English Language. A higher score indicates an increased adherence to oral anti-hypertensive agents. There arethree subscales assessing three domains of adherence: to medication, appointment keeping and salt intake.

The 14 items-scale is scored from 1 (all the time) to 4 (none of the time) with a reverse coding used for question 6(How often do you get your next appointment before you leave the clinic?). Higher scores on this scale indicate good adherence to anti-hypertensive agents.

All statistical analysis was done using SPSS v23. Multiple logistic regression analysis was used to look for the determinants of resistant hypertension. Data analysis was performed using 95% confidence intervals (CI), and the level of significance was taken as $p<0.05$.

Ethics approval was obtained fromUniversiti Putra Malaysia -Medical Research Ethics Committee (JKEUPM) and National Medical Research Register (NMRR) prior to commencement of this study.

Operational definitions:

Hypertension is defined as those with a history of hypertension (i.e. BP ≥ 140/90 mmHg) or on anti-hypertensive medication. Apparent resistant hypertension was defined as a persistent elevation of BP (≥140/90 mmHg) with continuously concomitant use of ≥3 anti-hypertensive medications, including a diuretic.

Normal controlled BPis taken as BP < 140/90mmHg for all patients as per definition by most major guidelines such as ESC/ESH 2018 and NICE 2019 [15].Body mass index (BMI) is calculated as weight in kilograms per square meter (kg/m2).

Diabetes mellitus is defined as those with known diabetes or the use of anti-diabetic agents or both.

Dyslipidaemia will be defined as those with persistently elevated blood lipid levels.

RESULTS

A total of 594patientsaged ≥ 60 years were recruited. Table 1 shows the prevalence of apparent resistant hypertension. In 594 subjects that had complete data, the prevalence of resistant hypertension was 66.3 %(n=394).

Table 1.Prevalence of resistant hypertension (N=594).

Presence of apparent resistant hypertension	**Frequency (%)**
Yes	394(66.3)
No	200(33.7)

Table 2and 3shows the univariate analysis of factors associated with the presence of apparent resistant hypertension. Based on these analyses, it was found that age (p=<0.001), gender (p=0.031) and educational level (p=0.001) were significantly associated with the presence of apparent resistant hypertension. Older patients (aged 60 years and above), Chinese ethnicity as well as those with a lower educational level had a higher prevalence of apparent resistant hypertension. The difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the those with or without apparent resistant hypertension was also statistically significant (p <0.001).

Table 2. Factors (Socio-demographic) associated with apparent resistant hypertension (N=594).

Variable	**Overall Frequency (%)**	**Apparent resistant hypertension**		**Chi-square,X^2**	**T-test,F**	**P value**
		Yes	**No**			
Age (years) Mean± SD	70.28 ± 6.74	72.98±10.04	67.19±9.87		1.347	<0.001
Gender						
Male	251(42.2)	149(59.4)	102(40.6)	4.727		0.031
Female	343(57.8)	222(64.7)	121(35.3)			
Educational Level						
Nil	22(3.7)	14(63.6)	8(36.4)	17.388		0.001
Primary	88(14.8)	64(72.7)	24(27.3)			
Secondary	318(53.6)	200(62.9)	118(37.1)			
Tertiary	166(28.0)	94(56.6)	72(43.4)			
Ethnicity						
Chinese	201(33.8)	124(61.7)	77(38.3)	0.827		0.845
Malay	204(34.4)	128(62.7)	76(37.3)			
Indian	179(30.1)	113(63.1)	66(36.9)			
Other	10(1.8)	7(70.0)	3(30.0)			

Table 3.Factors (medical comordidity, adherence and lifestyle habits) associated with the presence of apparent resistant hypertension

Variable	Overall Frequency (%)	Apparent Resistant hypertension		Chi-square,X^2	T-test,F	P value
		Yes	No			
Duration of Hypertension (years) Mean ± SD	12.71± 9.27	12.88±9.66	12.60±8.58		7.530	0.698
Family history of Hypertension						
Yes	429(72.3)	266(62.0)	163(38.0)	0.363		0.857
No	154(26.0)	98(63.6)	56(36.7)			
Unsure	10(1.7)	6(60.0)	4(40.0)			
Diabetes mellitus						
Yes	293(49.4)	182(62.1)	111(37.9)	0.090		0.798
No	301(50.6)	189(62.8)	112(37.2)			
Dyslipidaemia						
Yes	469(79.0)	287(61.2)	182(38.8)	0.033		0.856
No	125(21.0)	84(67.2)	41(32.8)			
Body mass index(n=558) Mean ± SD(kg/m^2)	27.89 ± 6.32	28.82±5.34	26.98±7.28		0.209	0.617
Current smoker past 1 week						
(n=570)	54(9.4)	34(63.0)	20(37.0)	0.028		0.889
Yes	516(90.6)	323(62.6)	193(37.4)			
No						
Shift worker(n=520)	17(0.9)	10(58.8)	7(41.2)	2.349		0.165
Yes	503(99.1)	316(62.8)	187(37.2)			
No						
SBP, mmHgMean ± SD	144.93 ± 14.12	152.09±10.85	131.32±6.31		146.047	<0.001
DBP, mmHgMean ± SD	77.67 ± 8.64	78.47±8.81	74.69±7.49		12.072	<0.001
Adherence score(n=540) Mean ± SD (Range	51.12 ± 2.40	50.17 ± 2.49	52.11 ± 2.56		0.922	0.727

Factors that had a p value of less than 0.25 were entered into the multiple logistic regression model to identify the determinants of the presence of apparent resistant hypertension as reported in Table 4. It was found that older age and those of a lower educational level are determinants of having apparent resistant hypertension. Older persons had 1.015increasedodds of having apparent resistant hypertension as compared to a younger person (95%CI 1.015-1.026, p=0.004).Those with primary education, had 1.859increasedodds of having apparent resistant hypertension as compared with those with tertiary education (95%CI 1.317-2.624, p<0.001).

Table 4. Determinants of the presence of apparent resistant hypertension.

Variable	**Odds ratio**	**95%CI**	**P value**
Age	1.015	1.005-1.026	0.004
Gender			
Male	ref		
Female	0.838	0.679-1.035	0.101
Educational level			
Nil			
Primary	1.151	0.653- 2.027	0.626
Secondary	1.859	1.317- 2.624	<0.001
Tertiary	1.257	0.955- 1.588	0.055
	ref		
Shift worker			
Yes	ref		
No	0.539	0.182-1.593	0.264

DISCUSSION

The prevalence of apparent resistant hypertension in this study is very high at 66.3%.This compares to aprevalence of only 8.8% in a previous local study done in 2007 [5].The differences could be explained by the fact that the mean age of our study population was 70.28 ± 6.74 years as compared to the previous study population whose mean age was 66.8 ± 9.7 years and of the higher mean BP noted in our study (i.e 145/78 vs 130/80).This may also be due to the fact that our study is looking at apparent resistant hypertension and not true hypertension per se.

In this study,older patients had a higher chance of having apparent resistant hypertension. This is in contrast with a previous study by Chia et al which showed that younger patients had higher odds of developingresistant hypertension [5]. However, our results were comparable to another study by Kumara et alwhich showed that there is a possibility of hypertension progression as age increases due to increased arterial stiffness that causes a rise in the rate of developing resistant hypertension [8].These once again may due to the fact that our study was on apparent resistant hypertension rather than true hypertension.

Our study found that higher education was linked with a reduced rate of apparent resistant hypertension. This could be due to the fact that those with a higher education tend to read more and have a wider access to the latest evidence-based information on hypertension and other medical conditions. No previous study has compared this variable to look at its association to resistant hypertension. Therefore, this could be a novel finding and education can be used to reduce the rates of developing apparent or true resistant hypertension.

Despite being significant in univariate logistic regression, factors such working shifts and gender did not show significance in multivariate analysis. Also, our study showed that adherence did not affect the rates of apparent resistant hypertension, however a recent study did validate that treatment non-adherence was a cause of true resistant hypertension as attested by the 60% non-adherent rate [16].This once again is

possibly due to the fact that we were looking at apparent resistant hypertension.

Another important factor to consider was metabolic syndrome that was not explored in this study. Many studies have shown that In subjects with Mets where lipid level, BMI and glucose levels are usually abnormal, age-related arterial siffnessmaycause the emergence of resistant hypertension due to Renin-Angiotensin-Aldosterone system activation, increased oxidative stress and chronic low grade inflammation and insulin resistance, among others.[17-19]

The strength of the study lies in the fact that this is one of the few studies that examines the rates of apparent resistant hypertension among a large number of elderly hypertensives in Malaysia. Limitations includes that it is a cross-sectional design that may limit the causality and generalisability of the study.

Future studies should be expanded to more centres nationwide to reflect the true prevalence of resistant hypertension amongst all age groups. Among other factors that can be possibly looked at including metabolic syndrome, sleep and exercise patterns, salt intake and other relevant variables including adherence and how does it affect the prevalence of resistant hypertension.

Alas, apparent or 'pseudo-resistant' hypertension may be difficult to separate from the actual or true prevalence of resistant hypertension. Apparent resistant hypertension has been documented to result from poor medication adherence and drugs dosages not being fully optimised besides other factors such as poor lifestyle habits, white-coat hypertension and drug-drug interactions that was not explored in this study [20-21]. Therefore, any subsequent studies should also address these factors along with other important factors such as medication availability and patient education.

As an addition, we need also consider that Increasing arterial stiffness results in impaired bar reflex mechanism resulting in episodes of hypotension with postural changes and that orthostatic hypotension in the elderly results in increased incidence of syncope and falls leading to hospitalization and functional impairment, thereby increasing CVD risk and mortality [22-23]. Other important risk factors such as hyperlipidaemia, diabetes and physical activity are also important issues to consider in tackling resistant hypertension [24-26].

CONCLUSION

The prevalence of resistant hypertension is highIn the specific group of 594 patients in primary care clinics in Klang Velley.Factors associated with resistant hypertension should be actively tackled in order to reduce the prevalence of resistant hypertension and its associated devastating complications that has be noted to be rising over the years.

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