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Adherence to anti-hypertensive agents and their associated factors among haemodialysis patients in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia: a cross-sectional study

***Abstract*—** The study aims to determine the adherence to anti-hypertensive agents as well as the factors influencing adherence levels among patients undergoing haemodialysis in Hospital Raja Perempuan Zainab II (HRPZ II), Kelantan, Malaysia. A total of 82 patients were enrolled in this study. A convenience sampling was done based on the number of haemodialysis patients registered in the study centre (Haemodialysis Unit, HRPZ II, Kelantan, Malaysia) who were also on anti-hypertensives. A validated Medication Compliance Questionnaire which consisted of ten questions gauging drug-taking and drug-stopping behaviours among Malaysian hypertensive patients was used to measure adherence. The majority (84.1%) of patients adhere to their anti-hypertensives. Despite this fact, only 42.7% of the patients achieved the target blood pressure (BP) control. A multiple logistic regressions analysis showed that uncontrolled diastolic BP [adjusted odds ratio (OR) = 0.928 (95% CI: 0.873 – 0.987); p = 0.018] and cigarette smoking [adjusted OR = 11.62 (95% CI: 1.55 – 86.99); p = 0.017] were independent factors for non-adherence to anti-hypertensives in this study indicating that patient's education and support may be necessary. Although a good adherence to anti-hypertensives were observed among haemodialysis patients, BP control remains poor due to poor control of diastolic BP and cigarette smoking.

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1 INTRODUCTION

Hypertension is the second underlying cause that account for approximately 26% of end stage renal disease (ESRD) or stage five chronic kidney disease (CKD) in the United States [1]. Worldwide, the prevalence of hypertension among patients on dialysis is high, ranging between 70 and 90% [2,3]. In Malaysia, the prevalence of dialysis has more than doubled, from approximately 706 cases per million population (2008) to 1363 cases per million population (2018). In 2018, 21.8% of new dialysis patients has been reported to suffer from hypertension as the primary renal disease which contributes to the second leading cause of ESRD [4]. Meanwhile, the mortality rate of patients who received dialysis was 13.3% with most fatalities occurring due to cardiovascular disease (33%) [5].

Death due to cardiovascular disease is common in patients with ESRD who receive dialysis. In fact, hypertension is one of the most important modifiable risk factors in CKD patients that can reduce the risk of cardiovascular-related death [6]. Furthermore, adequate blood pressure (BP) control may delay the progression of CKD and hence slow the decline of renal function [7]. Nevertheless, a study conducted by Agarwal and colleagues [2] in the USA which is a first world country showed that nearly 60% of dialysis patients with hypertension showed inadequately controlled BP although they have been prescribed with anti-hypertensives.

A possible factor leading to the uncontrolled BP may be due to poor adherence to anti-hypertensives, which is a common clinical issue particularly in the management of chronic diseases [7]. Schmitt and colleagues [6] previously showed that approximately one third of CKD patients had poor adherence to anti-

hypertensives and that adherence declines with worsening of kidney function. In fact, poor medication adherence is also associated with a 23% higher risk of uncontrolled BP, strongly suggesting the importance of adherence to anti-hypertensives in CKD patients to improve treatment outcome.

Although poor adherence (approximately 46-56%) has previously been reported among patients who receive medications from different outpatients' clinic in Malaysia [8,9], there is limited data specifically on adherence to anti-hypertensive drugs among haemodialysis patients in Malaysia. Hypertension is a risk factor for cardiovascular disease and good BP control is associated with reduced risk of cardiovascular events and mortality in the dialysis population. Therefore, the main objective of this study is to evaluate the adherence to anti-hypertensive drugs as well as to determine factors that are associated with adherence among haemodialysis patients in a general hospital in Malaysia.

2 METHODS

This is a cross-sectional study involving ESRD patients requiring renal replacement therapy who were registered to the Haemodialysis Unit, in a general hospital in Kelantan, Malaysia. Adult patients, regardless of the diagnosis, who were on dialysis for at least two months and who required anti-hypertensive(s) were eligible for the study. All eligible patients who attended the Unit during the study duration, were invited to participate in this study.

The study was approved by the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-16-2664-33390) which complies with the Declaration of Helsinki. Written informed consents were obtained from all participating patients prior to study participation. All patients were scheduled to visit the unit three times per week for their dialysis.

Adherence was assessed using a Medication Compliance Questionnaire (MCQ) which is a tool to measure medication adherence in Malaysian hypertensive patients and is an instrument with good validity and reliability [10]. This Malay-language questionnaire was originally developed and validated in hypertensive patients in Kelantan. The MCQ consisted of ten items regarding drug-taking behaviour (Questions 1 to 7) and drug-stopping behaviour (Questions 8 to 10). The questionnaire utilises a five-level Likert scale from 1 (never) to 5 (very frequent). The total percentage score of adherences is taken from the mean of all ten items. Indirect measures, for instance the self-report adherence questionnaire, provide a practical and flexible tool to assess adherence in addition to a unique opportunity to distinguish patient's concerns [11]. The method is widely used since it is a simple, relatively inexpensive and easy method to implement in a patient's follow-up [12].

Demographic data such as age, gender, weight and relevant information including smoking status, the number of anti-hypertensives received, other medications (such as anti-cholesterol, oral anti-hyperglycaemic agents) as well as dietary and fluid restriction requirement were completed by a researcher using the patient's medical record. Illiterate patients were not included in the study. The questionnaire took approximately 10 – 15 minutes to complete. A patient was considered to adhere if the individual percentage score was 80% or greater [13].

BP was measured before dialysis after five minutes of resting. The patients were asked to sit in a comfortable position and their BPs were measured by a trained nurse using a dedicated automated electronic BP monitor. BP was recorded twice and the mean was taken. Uncontrolled BP was noted in patient's note if the value was more than 140/90 mm Hg [or <140/80 mmHg in a diabetic patient] [14].

The demographic data are presented as percentages or mean (standard deviations). The association between adherence and other factors were first investigated using a univariate analysis with independent t-test or simple logistic regression. Subsequently, multiple logistic regression analysis was conducted to determine the independent associations between adherence and the independent variables. The selection of variables to be included in the multiple logistic regression model was based on the univariate analysis with a p-value of less than 0.25. All p-values were two-tailed, and $p < 0.05$ was considered as statistically significant. The data analyses were performed using SPSS statistical software version 20 (IBM Corporation, Armonk, NY, USA).

3 RESULTS

A total of 100 participants were recruited in this

study. However, only 82 participants completed the questionnaire, giving a total response rate of 82%. Some reasons for the drop-out include respondent fatigue and doubts about the confidentiality of survey data. The responses from the participants were included in the descriptive statistics analysis.

The mean age of the patients was 49.8 ± 14.2 years (Table I). Approximately two-thirds of the patients were on one or two anti-hypertensives. All patients can identify their anti-hypertensives indicating that compliance is good. The anti-hypertensives prescribed include angiotensin converting enzyme inhibitors (such as captopril, perindopril and enalapril) or angiotensin receptor blocker (such as losartan and valsartan) and calcium channel blocker (such as amlodipine and nifedipine). A single patient was reported to consume alternative medicine for BP lowering, although it was unsure what the exact constituent were.

Approximately 70% of the patient were co-prescribed with statin (anti-cholesterol) while about 20% of the patient were co-prescribed with gliclazide modified release (oral anti-hyperglycaemic agent). Most of the patients (84.1%) adhered to their medications. However, less than 50% achieved the desired BPs. The mean systolic and diastolic BPs were 146.9 ± 20.9 mmHg and 84.3 ± 14.3 mmHg, respectively. Many of the patients (68.3%) were non-smokers or had quit smoking while nearly 60% followed some forms of diet or/and fluid restriction plan. Most patients (82.9%) already started their renal replacement therapy for more than one year.

A multiple regression analysis (Table II) indicated that adherence was associated with low diastolic BP and non-smoking status. There was no association between adherence and other demographic variables, concurrent medications with oral anti-hyperglycaemic agent and anti-cholesterol, the number of anti-hypertensives received, BP status as well as diet or fluid restrictions. There was no evidence of interaction among the independent variables as well for the model tested.

4 DISCUSSION

To our knowledge, this is the first study to investigate on adherence to anti-hypertensive agents and their associated factors among Malaysian haemodialysis patients. Hypertension is a strong risk factor associated with CKD with one factor aggravating the other. Lowering BP with anti-hypertensives reduces the risks of cardiovascular events and their associated mortality. Therefore, monitoring of BP in patients with CKD is important regardless of the underlying cause. Management of hypertension in CKD often requires institution of multi-drug therapies over a long period of time in which medication adherence becomes critical in achieving the desired therapeutic targets. Medication adherence is influenced by various factors including patient, conditions, therapy, socio-economic and healthcare system-related factors that often requires attention from clinicians to achieve the desired treatment goal [15,16].

Table I: Demographic characteristic of haemodialysis patients receiving anti-hypertensives in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia**.**

Characteristics	Quantity	n	%	Mean (SD)
Age (years)				49.8 (14.2)
Weight (kg)				57.7 (14.3)
Gender	Male	39	47.6	
	Female	43	52.4	
BP (mm Hg)	SBP			146.9 (20.9)
	DBP			84.3 (14.3)
Control of BP	Yes	35	42.7	
	No	47	57.3	
Smoking status	Active smoker	26	23.7	
	Never/ Quit	56	68.3	
Number of anti-hypertensives received	≤ 2	53	64.6	
	3-4	26	31.7	
	≥5	3	3.7	
Statin	Yes	58	70.7	
	No	24	29.3	
Gliclazide MR (OHA)	Yes	17	20.7	
	No	65	79.3	
Adherence score				89.6 (8.8)
Adherence group	Adherent	69	84.1	
	Non-adherent	13	15.9	
Diet restriction	Yes	47	57.3	
	No	35	42.7	
Fluid restriction	Yes	49	59.8	
	No	33	40.2	

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; MR, modified release; OHA, oral anti-hyperglycaemic agent; SBP, systolic blood pressure; SD, standard deviation

Table II: Factors associated with adherence to anti-hypertensives among haemodialysis patients in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia.

		Univariate analysis		Multiple logistic regression analysis		
Independent variables	Mean (SD)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	Wald-stat	p-value
Age (years)[a]		1.04	0.054			
Adherence	51.10 (13.90)	(0.998, 1.083)				
Non-adherence	42.85 (14.30)					
SBP (mm Hg)[a]		0.97	0.147			
Adherence	144.75 (18.20)	(0.942, 0.999)				
Non-adherence	158.08 (30.20)					
DBP (mm Hg)[a]		0.918	0.015*	0.928	5.637	0.018*
Adherence	81.75 (11.30)	(0.868, 0.971)		(0.873, 0.987)		
Non-adherence	98.00 (20.50)					
Weight (kg)[a]		0.998	0.916			
Adherence	57.62 (14.0)	(0.957, 1.04)				
Non-adherence	58.08 (16.2)					
Gender						
Male		1.349	0.626			
Female		(0.411, 4.428)				
Control of BP[b]		1.836	0.399			
Yes		(0.516, 6.534)				
No						
OHA[b]		1.528	0.605			
Yes		(0.305, 7.655)				
No						
Smoking status[b]		0.048	0.001*	11.62	5.701	0.017*
Active smoker		(0.008, 0.288)		(1.55, 86.99)		
Never/Quit						
Anti-cholesterol[b]		1.645	0.430			
Yes		(0.478, 5.660)				
No						
Diet restriction[b]		1.708	0.378			
Yes		(0.519, 5.624)				
No						
Fluid restriction[b]		2.816	0.096			
Yes		(0.831, 9.542)				
No						

Abbreviation: BP, blood pressure; DBP, diastolic blood pressure; OHA, oral anti-hyperglycaemic agents; OR, odds ratio, SBP, systolic blood pressure; SD, standard deviation
Univariate analysis with [a]independent t-test or [b]simple logistic regression

Despite a high adherence score yielded by the patients in this study, sadly, only 42.7% of patients achieved their desired BP target (< 140/90 or <140/80 mmHg in diabetic patient). In both adherence and non-adherence groups, the mean systolic BP was considered uncontrolled. In contrast, the target diastolic BP was achieved in the adherence but was uncontrolled in the non-adherence group. Systolic BP continues to elevate throughout life while diastolic BP tends to level off after the age of 50 years [17]. Poor systolic BP control may be responsible for poor BP control in general, suggesting that achieving target systolic BP may be more critical in all hypertensive patients including in those patients undergo haemodialysis and should be given greater emphasis in treatment plans and in research [18].

We found that diastolic BP is a significant factor associated with anti-hypertensives

adherence. Patients who do not adhere to their medication have a higher risk of having uncontrolled BP, but not systolic BP. Diastolic hypertension predominates before 50 years of age either in the presence or absence of an elevated systolic BP. Hence, as compared to systolic BP, diastolic BP is regarded as a more important cardiovascular risk factor until 50 years, after which systolic BP becomes more important [17]. The given fact corresponded with the mean age of the patients who participated in the study, suggesting that the role of diastolic BP as a factor associated with anti-hypertensives adherence is particularly relevant in patients below 50 years of age. Nevertheless, whether a systolic BP can be used to predict adherence for patients above 50 years of age remains unclear since the study sample size is relatively small (n = 82) and patients were generally from the younger age groups.

Other factor identified to be associated with medication adherence in this study was smoking status. Poor awareness of health risks, inadequate health literacy as well as socioeconomic burden among active smokers generally influence treatment goals, particularly in the management of chronic disease [19]. In this study, a non-smoker tends to adhere more to their medication as compared to the smokers. Similarly, significantly lower adherence to anti-hypertensives among active smokers were previously reported when compared to never-smokers [20]. It was suggested that smokers tend to rationalize their low compliance to treatment by giving excuses for their unhealthy practice since they have already engaged in a known unhealthy lifestyle behaviour i.e. smoking [20]. In addition, a study by Aggarwal and Mosca [21] also identified cigarette smoking to be one of the univariate predictors of non-adherence to BP medications, suggesting the information on lifestyle practice may help in identifying individuals at higher risk of non-adherence to medication(s).

Meanwhile, other factors including age, body weight, the concurrent use of other medications as well as diet and fluid restriction were not associated with anti-hypertensives adherence. Although statistically not significant, there was a trend in higher adherence to medication among the older age group compared to the younger age group. Non-adherence among younger patients was often reported worldwide [22–24]. Similarly, Chan et al. [25] reported that younger and working patients are more likely to be non-adherent to treatment plan. The age-related association may be partly due to a more structured lifestyle among older patients, while the younger generations tend to be busy with work and other commitments in their daily life which contribute to non-compliance. In addition, younger patients may have lesser concern regarding their health condition when compared to the elderly, assuming themselves to be less vulnerable to disease progression [25]. Of many factors identified to be associated with medication non-adherence, many were patient-related and were potentially modifiable through behavioural or educational interventions [26]. Hence, identifying the risks for medication non-adherence may be clinically useful to improve overall adherence and to achieve treatment goal.

This study has some limitations. First, it is a single-centre study with relatively small sample size. A larger multi-centre study involving other haemodialysis centres is therefore recommended to allow recruitment of a higher number of patients which will in turn increase the generalizability of the study. Secondly, other confounding factors such as patients' body mass index (BMI), the total number of medications as well as educational and socioeconomic statuses should also be included to identify other factors associated to medication adherence in haemodialysis patients. Third, BP monitoring or alternatively using home BP measuring whenever possible, may be a more reliable assessment than pre-dialysis BP measurement in managing hypertension. However, these monitoring methods may be limited by patient's financial constraints especially for patients coming from third world countries as well as device availability. Future investigations to explore reasons for uncontrolled hypertension despite high medication adherence should be included to improve the treatment success rate since achieving desired BP control and reducing risk of cardiovascular events is the ultimate treatment goal for the sake of patients' well-being.

5 CONCLUSIONS

Overall, although there was a high medication adherence rate to anti-hypertensives among Malaysian haemodialysis, an adequate BP control is not achieved. Diastolic BP and smoking

status are factors associated with medications adherence for anti-hypertensives among haemodialysis patients.

ETHICAL CLEARANCE & CONSENT

This study was approved by the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-16-2664-33390). Written informed consents were obtained from all participating patients prior to the study.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

FINANCIAL DISCLOSURE

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