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RESEARCH ARTICLE

Factors associated with the frequency of antihypertensive drug adjustments in chronic kidney disease patients: a multicentre, 2-year retrospective study

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Abstract

Background Optimum antihypertensive drug effect in chronic kidney disease is important to mitigate disease progression. As frequent adjustments to antihypertensive drugs might lead to problems that may affect their effectiveness, the modifiable factors leading to frequent adjustments of antihypertensive drugs should be identified and addressed. *Objective* This study aims to identify the factors associated with frequent adjustments to antihypertensive drugs among chronic kidney disease patients receiving routine nephrology care. *Setting* Nephrology clinics at two Malaysian tertiary hospitals. *Method* This multi-centre, retrospective cohort study included adult patients under chronic kidney disease clinic follow-up. Demographic data, clinical information, laboratory data and medication characteristics from 2018 to 2020 were collected. Multiple logistic regression was used to identify the factors associated with frequent adjustments to antihypertensive drugs (≥ 1 per year). *Main outcome measure* Frequent adjustments to antihypertensive drugs. *Results* From 671 patients included in the study, 219 (32.6%) had frequent adjustments to antihypertensive drugs. Frequent adjustment to antihypertensive drugs was more likely to occur with follow-ups in multiple institutions (adjusted Odds Ratio [aOR] 1.244, 95% confidence interval [CI] 1.012, 1.530), use of traditional/complementary medicine (aOR 2.058, 95% CI 1.058, 4.001), poor medication adherence (aOR 1.563, 95% CI 1.037, 2.357), change in estimated glomerular filtration rate (aOR 0.970, 95% CI 0.951, 0.990), and albuminuria categories A2 (aOR 2.173, 95% CI 1.311, 3.603) and A3 (aOR 2.117, 95% CI 1.349, 3.322), after controlling for confounding factors. *Conclusion* This work highlights the importance of close monitoring of patients requiring initial adjustments to antihypertensive drugs. Antihypertensive drug adjustments may indicate events that could contribute to poorer outcomes in the future.

Keywords Adjustments · Antihypertensive drugs · Chronic Kidney Disease

Impacts on practice

- Frequent adjustment of antihypertensive drugs was associated with follow-ups in multiple institutions
- Use of traditional/complementary medicine
- Poor adherence
- eGFR changes
- As well as albuminuria.
- The factors associated with frequent antihypertensive drug adjustments could contribute to poorer outcomes of chronic kidney disease over time.
- Close monitoring by pharmacists is recommended for patients requiring adjustments to antihypertensive drugs

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Introduction

Chronic kidney disease (CKD) is a global concern with an estimated worldwide prevalence of 9.1% [1]. Currently, there are no medications to treat the disease itself [2]. As such, CKD patients require multiple drugs to manage the various co-morbidities, to slow disease progression, and to mitigate complications [2, 3]. This gives rise to a substantially high medication burden, especially among advanced CKD patients, with some requiring more than 10 types of medication daily [2–5]. However, the use of more medications does not ensure a more positive clinical outcome. Therefore, optimisation of pharmacotherapy is vital for CKD patients, to ensure long-term effectiveness [6].

Adjustments to medications are an inevitable part of pharmacotherapy optimisation, to control risk factors of CKD progression, achieve therapeutic targets and accommodate changes in renal function [7]. Frequent adjustments to medications might indicate an underlying suboptimal disease control, poor control of CKD co-morbidities, or poor tolerance of current medication regimen, which are risk factors that predispose patients to CKD progression. However, some adjustments are preceded by preventable events, such as poor disease control due to medication non-adherence [7, 8]. There has been little research examining medication changes made during the treatment of long-term illnesses, due to difficulty retrieving complete data [3, 9]. Furthermore, patients may visit multiple institutions for follow-up on other conditions without complete reporting in medical records [3, 9].

Frequent adjustments to medications for patients with multiple medications can lead to various problems, including poor adherence, adverse effects and concerns about the new treatment [10]. These problems might be augmented in CKD patients with increased complexity to their medication regimens requiring patients to adapt to new routines, leading to other practical difficulties associated with medication changes [11]. Furthermore, the addition of medications increases the likelihood of receiving inappropriate medication, given the higher chance of drug-drug interactions among CKD patients who have an existing complex medication profile and altered pharmacokinetic profile [5, 12]. Frequent medication adjustments might also lead to harm if changes are not adhered to, such as unanticipated adverse events or drug interactions resulting from persistent use of medications that have been discontinued by the prescriber, or failure to achieve efficacy when the medicines were not adjusted as instructed [11].

Antihypertensive drug therapy is ubiquitous among CKD patients, due to hypertension being a common cause and consequence of CKD, and could improve outcomes and slow CKD progression [3, 13]. Optimised effect of antihypertensive drugs in CKD patients is important, as many antihypertensive drugs have multiple functions beyond blood pressure regulation, by mitigating hypertension-induced renal damage, reducing proteinuria and providing renoprotection [14]. Very often, antihypertensive drugs are changed due to uncontrolled blood pressure [14]. However, frequent changes may have a negative impact on the effectiveness of therapy. Therefore, other modifiable factors leading to frequent adjustments of antihypertensive drugs should be identified and prevented.

Aim of the study

The aim of this study was to identify factors associated with frequent adjustments to antihypertensive drugs among CKD patients receiving routine nephrology care.

Ethics approval

The study was approved by the appropriate institutional and national research ethics committees, the Ministry of Health Medical Research and Ethics Committee (KKM.NIHSEC.P19-2320(11)) and the Universiti Kebangsaan Malaysia Research Ethic Committee (JEP-2020-048). The study was performed in accordance with the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Consent waiver was granted, due to the retrospective and non-interventional nature of the study.

Method

Study design

This multi-centre, retrospective cohort study was conducted in two tertiary hospitals with nephrology clinics. Included in the study were adult CKD patients (≥ 18 years) scheduled for a nephrology clinic follow-up during March and April 2020, with a history of at least 2 years of nephrology CKD clinic follow-up and prescribed at least one medication. Patients were excluded if they attended less than two nephrology CKD clinic visits between 2018 and 2020, and if their medication regimen was not recorded. Patients were identified and screened for eligibility based on data from electronic medical records and eligible patients were assigned using the IBM SPSS random number generator [15].

Sample size

A minimum sample size of 600 subjects was required, based on the estimation of $n = 100 + 50(i)$, where 'i' refers to the number of independent variables in the final model, with an

estimation of ten variables [16]. A total of 660 subjects were targeted to allow for possible exclusion of patients.

Data collection

Demographic data, clinical information, laboratory data and medication characteristics for each patient were collected from the electronic medical record systems. Demographic data that were collected included age, gender and ethnicity.

The clinical information included the primary cause of CKD, co-morbidities, including obesity (defined as body mass index (BMI) of ≥ 30 kg/m^2) and smoking status. Co-morbidities were coded based on the International Classification of Diseases (ICD-10) [17]. The laboratory data collected were serum creatinine and albuminuria/proteinuria status during the study period. Patients' renal function were quantified via estimated glomerular filtration rate (eGFR), calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation, and proteinuria status, categorised as per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [18]. Blood pressure was monitored by clinicians using an oscillometric device.

Details of the medication regimen were recorded for each patient visit during the study period, from the chartings of clinic visits and prescription records. The data collected were the number of adjustments to medications (including changes of drug, dose and frequency) and traditional/complementary medication (TCM) use. Medications used were recorded and coded in accordance with the World Health Organization Anatomical Therapeutic Classification (ATC) system [19]. Adherence to medication regimen was assessed using prescribers' charting and prescriptions issued in the medical records.

Study definition

CKD classification and albuminuria categorisation were based on the eGFR level, as per the KDIGO CKD guidelines [18]. The definitions for each category are detailed in Table 1. Rapid progression of CKD was defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/year [18].

Changes to antihypertensive drugs were categorised as minimal (less than once yearly) and frequent (at least once yearly) based on the median value [20], and included

Table 1 Terminologies and their definition pertaining to the study

Terminologies	Definition
Chronic kidney disease classification [18]	
Stage 1	Normal or elevated GFR, with GFR of 90 ml/min/1.73 m^2 and above
Stage 2	Mildly decreased GFR of 60–89 ml/min/1.73 m^2
Stage 3a	Mild to moderately decreased GFR of 45–59 ml/min/1.73 m^2
Stage 3b	Moderately to severely decreased GFR of 30–44 ml/min/1.73 m^2
Stage 4	Severely decreased GFR of 15–29 ml/min/1.73 m^2
Stage 5	Low eGFR of less than 15 ml/min/1.73 m^2
Albuminuria categorisation [18]	
A1	Protein-to-creatinine ratio (PCR) of less than 15 mg/mmol and below or negative to trace from urine protein reagent strip
A2	PCR of 15-50 mg/mmol or trace to + from urine protein reagent strip
A3	PCR of more than 50 mg/mmol, or greater than + from urine protein reagent strip
Changes to antihypertensive drugs [20]	
Frequent change	Changes to antihypertensive drugs more than once over 2 years
Minimal change	Changes to antihypertensive drugs once or less over 2 years
Types of non-adherence [21]	
Initiation phase	The medication is not taken by patient at all
Implementation phase	A dose is missed, omitted or an extra dose taken
Persistence phase	The medication is ceased without the instruction of prescriber
Others	
Traditional/complementary medication (TCM)	The use of biological therapies other than conventional treatment or medicine from hospitals and primary care clinics, which include the use of herbs, botanicals, nutritional and dietary supplements. [35]
Non-steroidal anti-inflammatory drug (NSAID) use	NSAIDs being taken by patients as prescribed by practitioners or obtained from pharmacists at community pharmacies; as prescriptions are not mandatory for most NSAIDs in Malaysia, these fall under the Group C Poison category

changes in dosage, frequency or cessation, or commencement of new antihypertensive drugs.

Adherence was considered to be poor if there was a discrepancy between the prescribers' order and actual medication taken at any of the three phases of the medication adherence process [21]. The 2-year follow-up timeframe is consistent with a similar study on medication adherence [22].

Statistical analyses

Statistical analysis was performed using IBM SPSS [15]. The results were presented as frequencies and percentages for categorical data. Descriptive statistics for numerical data were presented as mean ± standard deviation (SD) for normally distributed data, or as median (range) for non-normally distributed data, based on the inspection of histograms. The correlation between antihypertensive drug adjustments and subsequent changes following initial adjustments (not normally distributed) was estimated via Spearman correlation coefficient. To identify the factors associated with frequent changes, multiple logistic regression was used. A univariate logistic regression was first performed to determine factors associated with frequent antihypertensive drug adjustments at a level of significance of $p \leq 0.05$, followed by an examination of multicollinearity and correlation between the factors. A multiple stepwise logistic regression was then performed with factors with $p \leq 0.25$. Variables with $p \leq 0.05$ were considered factors associated with frequent adjustments to antihypertensive drugs [23]. The Hosmer–Lemeshow goodness-of-fit test, classification tables and area under the receiving operator characteristic (ROC) curve were examined to investigate any misrepresentation of data [24].

Results

Demographic data

A total of 671 patients were included in the study. There was a slight predominance of males (n = 379, 56.5%). The mean age was 61.4 ± 16.8 years (range 19–94 years). The ethnic distribution of the study sample was consistent with the demographic distribution of the population of Malaysia [25], with the highest cases recorded among Malays (n = 422, 62.9%), followed by Chinese (n = 183, 27.3%), Indians (n = 53, 7.9%), and others (n = 13, 1.9%). During the study period, 158 (23.5%) patients had uncontrolled blood pressure of > 130/80 mmHg [26].

Clinical information

Diabetes was the most common cause of CKD (n = 268, 39.9%), with similar proportions of patients with hypertension (n = 107; 15.9%) and systemic lupus erythematosus (SLE; n = 90; 13.4%) as the cause. Most patients had hypertension (n = 516, 76.9%), while almost half (n = 329, 49.0%) had diabetes. About one-quarter of patients (n = 163, 24.3%) had ischaemic heart disease or cerebrovascular diseases. Table 2 provides a summary of demographic and clinical information.

Renal function and level of albuminuria

At baseline, nearly half of the patients had an albuminuria category of A1 (n = 321, 47.8%), 139 (20.7%) in the A2 category, and the remainder in the A3 category (n = 211, 31.4%). Most patients were in Stage 3b (n = 182, 27.1%) or Stage 4 (n = 175, 26.1%) CKD (Table 2).

The mean eGFR declined by 3.1 ± 10.7 ml/min/1.73 m^2 by the end of the study period. The eGFR improved in 125 (18.6%) patients, while 200 (29.8%) patients had a decline of not more than 5 ml/min/1.73 m^2. There were 306 (45.6%) patients who had rapid CKD progression. Most of the 37 patients with renal replacement therapies (RRT) had existing RRT, while 11 (1.6%) developed end-stage renal disease (ESRD). The decline in the mean eGFR by the end of the study period was significantly greater among those with frequent changes to antihypertensive drugs (-6.1 ± 11.6 ml/min/1.73 m^2) than those who had minimal changes to antihypertensive drugs (-2.9 ± 8.8 ml/min/1.73 m^2) ($p < 0.001$).

Medication characteristics

Fifty-three (7.9%) patients reported taking TCM, while 41 (6.1%) patients used non-steroidal anti-inflammatory drugs (NSAID)s. About one-third of patients had poor adherence to medications. The types of antihypertensive drugs at the baseline are illustrated in Fig. 1. Out of the 671 patients, 36.8% had an increase in their medications by the end of the study period. The frequency of adjustments to medications ranged from 0 to 51, with a median value of 3. Adjustment of antihypertensive drugs was the most common change (n = 948, 25.8%), followed by insulins (n = 388, 10.6%). The number of antihypertensive drug adjustments per patient ranged from 0 to 17, with a median value of 1. From the categorisation based on the median split, 219 (32.6%) patients had frequent adjustments to antihypertensive drugs, while the remaining 452 (67.4%) were classified as having minimal adjustments. A summary of the medication changes is provided in Table 3.

The most common class of antihypertensive drug adjusted was calcium channel blockers (n = 288, 30.4%),

Table 2 Demographic factors

Characteristics	Total (N = 671)
Gender, n (%)	
Male	379 (56.5)
Female	292 (43.5)
Age, mean ± SD (range)	61.4 ± 16.8 (19–94)
Ethnicity, n (%)	
Malay	422 (62.9)
Chinese	183 (27.3)
Indian	53 (7.9)
Others	13 (1.9)
Primary cause of CKD, n (%)	
Diabetes Mellitus	268 (39.9)
Hypertension	107 (15.9)
Systemic lupus erythematosus	90 (13.4)
Glomerulonephritis	63 (9.4)
Others	143 (21.3)
Presence of co-morbidities, n (%)	
Diabetes Mellitus	329 (49.0)
Hypertension	516 (76.9)
Ischaemic heart diseases and cerebrovascular diseases	163 (24.3)
Obesity	77 (11.5)
Gout	144 (21.5)
Smoking status, n (%)	
No	639 (95.2)
Yes	32 (4.8)
Use of traditional/complementary medicines, n (%)	53 (7.9)
Use of NSAIDs, n (%)	41 (6.1)
Poor adherence to medications, n (%)	202 (30.1)
Changes to eGFR (ml/min/1.73 m^2/year), mean ± SD	− 3.1 ± 10.7
Changes to eGFR, n (%) [18]	
Improved	125 (18.6)
Rapid CKD progression (decline of greater than 5 ml/min/1.73 m^2/year)	306 (45.6)
Static (0 ml/min/1.73 m^2/year)	3 (0.4)
Declined (decline of 0 to 5 ml/min/1.73 m^2/year)	200 (29.8)
Not applicable (patients with RRT)	37 (5.5)
Degree of albuminuria[a], n (%)	
A1	256 (38.2)
A2	147 (21.9)
A3	223 (33.2)
Unspecified	45 (6.7)
Number of adjustments to medications over 2 years , median (range)	3 (0–51)
Changes to number of medications over 2 years , n (%)	
Increased	247 (36.8)
Decreased	221 (32.9)
No change	203 (30.3)

CKD, Chronic kidney disease; GFR, glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; RRT, Renal replacement therapy; SD, Standard deviation

[a]Category A1 is defined as Protein-to-creatinine ratio (PCR) of less than 15 mg/mmol and below or negative to trace from urine protein reagent strip. Category A2 is defined as PCR of 15-50 mg/mmol or trace to + from urine protein reagent strip, and Category A3 is defined as PCR of more than 50 mg/mmol, or greater than + from urine protein reagent strip [18]

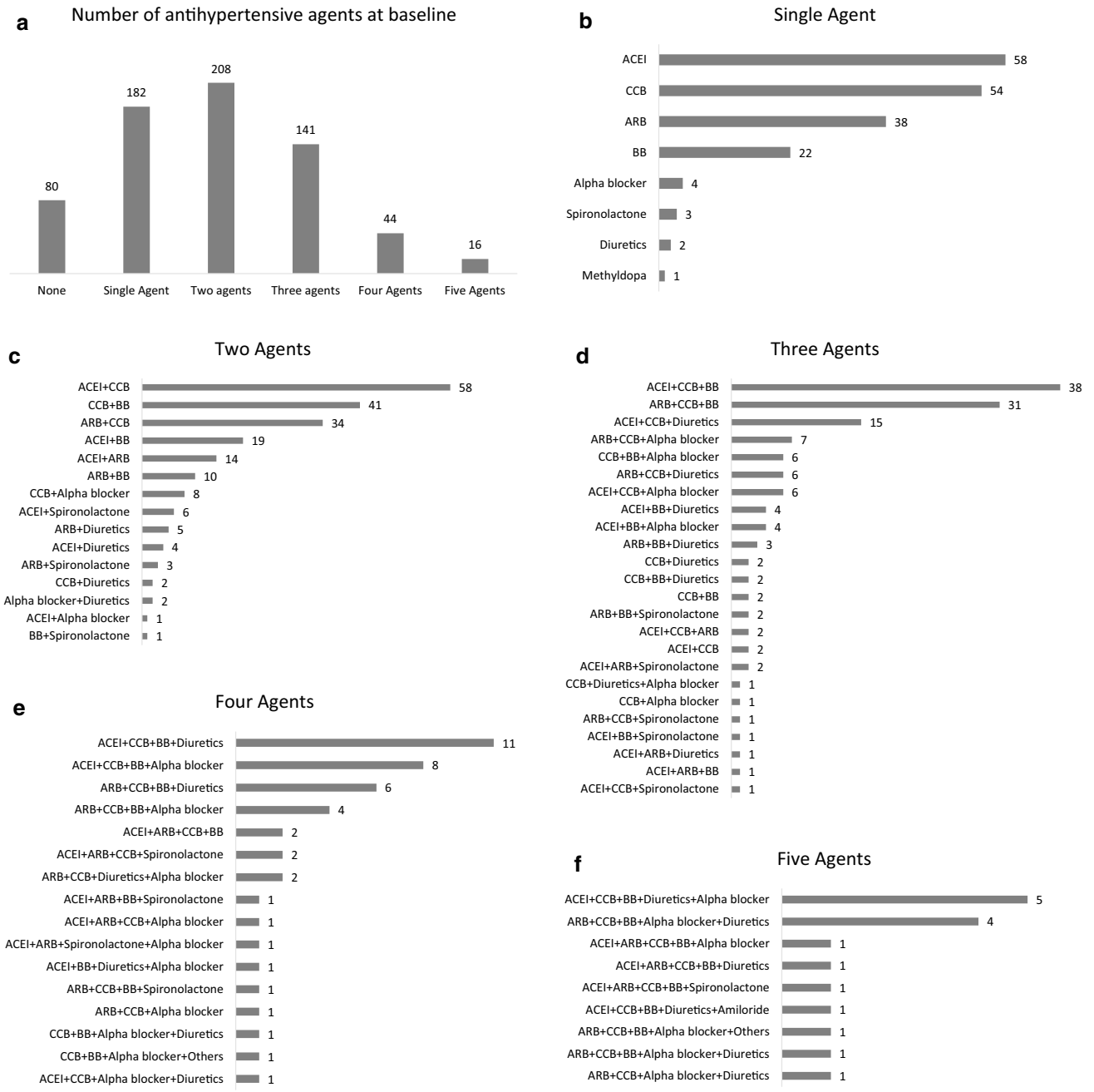

Fig. 1 Types of antihypertensive agents used at baseline. **a**. Number of antihypertensive agents used at baseline. **b** Types of antihypertensive agents used by patients with a single antihypertensive. **c** Types of antihypertensive agents used by patients with two antihypertensive drugs. **d** Types of antihypertensive agents used by patients with three antihypertensive drugs. **e** Types of antihypertensive agents used by patients with four antihypertensive drugs. **f** Types of antihypertensive agents used by patients with five antihypertensive drugs. ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin II Receptor blockers; BB, beta-blockers; CCB, Calcium channel blockers

followed by ACE inhibitors (n = 166, 17.5%), beta-blockers (n = 148, 15.6%) and ARBs (n = 143, 15.1%), as displayed in Table 4. Out of 671 patients, 310 (46.2%) had at least one adjustment made to their antihypertensive drugs and 158 (51.0%) of these patients had uncontrolled blood pressure of > 130/80 mmHg [26] when adjustment(s) were made. Thirty-three (10.6%) patients with antihypertensive drug

Table 3 Number of adjustments to the five most commonly adjusted medications, by types

Medications	Year 1 n = 1680 (45.76%)[a]	Year 2 n = 1991 (54.24%) [a]	Total N = 3671 (100.00%) [a]
Antihypertensive drugs	437 (11.90%)	511 (13.92%)	948 (25.82%)
Insulins and analogues	196 (5.34%)	192 (5.23%)	388 (10.57%)
Immunosuppressants	137 (3.73%)	196 (5.34%)	333 (9.07%)
Other drugs	132 (3.60%)	191 (5.20%)	323 (8.80%)
Drugs for anaemia	127 (3.46%)	171 (4.66%)	298 (8.12%)

[a]Totals may not correspond with the sum of the separate figures, as only the five most commonly adjusted medications were included in the table for clarity

adjustments had hyperkalaemia with serum potassium level of > 5 mmol/L.

Factors associated with frequent adjustments to antihypertensive drugs

A simple logistic regression analysis demonstrated that male gender, increasing number of follow-ups from various institutions, diabetic kidney disease, SLE, TCM use, poor adherence to medications, lower baseline eGFR, decline of eGFR during the study period and albuminuria categories of A2 and above, were factors associated with frequent antihypertensive drug adjustments with $p < 0.05$ (Table 5). When all variables with p-value of < 0.25 were included in the multiple logistic regression analysis, follow-ups from multiple institutions (adjusted Odds Ratio [aOR] 1.244, 95% confidence interval [CI] 1.012, 1.530), TCM use (aOR 2.058, 95% CI 1.058, 4.001), poor adherence to medications (aOR 1.563, 95% CI 1.037, 2.357), change in eGFR during study period (aOR 0.970, 95% CI 0.951, 0.990), and albuminuria categories of A2 (aOR 2.173, 95% CI 1.311, 3.603) or A3 (aOR 2.117, 95% CI 1.349, 3.322) were found to be factors associated with frequent adjustments to antihypertensive drugs, after controlling for other confounding factors (Table 5).

Medication changes after adjustments to antihypertensive drugs

Fifty-six (18.1%) of the 310 patients reported subsequent antihypertensive medication changes following their initial adjustments, with most reasons being adverse effects of the antihypertensive drugs (n = 42, 75.0%). Uncontrolled hypertension was another reason for subsequent adjustments of medications (n = 11, 19.6%). In addition, a significant correlation was observed between adjustments to antihypertensive drugs and adjustments to other medications, such as antidiabetics (r = 0.207, $p < 0.001$), antiplatelets (r = 0.182, $p < 0.001$), lipid-modifying agents (r = 0.118, $p < 0.001$), gastrointestinal drugs (r = 0.143, $p < 0.001$), antianaemic drugs (r = 0.164, $p < 0.001$), immunosuppressants (r = 0.119, $p = 0.002$) and drugs for mineral-bone disease (r = 0.143, $p < 0.001$). The full list is available in supplementary material.

Discussion

Medication changes have rarely been studied, as medication use is commonly reported at one point in time [3, 9], and most studies have limited applicability to CKD patients because they were not CKD-specific [9, 27]. There is a vital need to track changes to medications, as they are associated with increased hospitalisation risk [27] and frequent adjustments may lead to confusion and errors in medication-taking, especially among CKD patients with complex medication regimens. To the best of our knowledge, this is the first study that has evaluated factors associated with frequent antihypertensive drug adjustments among CKD patients. The findings indicated that follow-up in multiple institutions, TCM use, poor adherence, declining eGFR and albuminuria are factors associated with frequent adjustments to antihypertensive drugs among CKD patients, which warrant additional attention to patients with such risk factors. These factors may also facilitate triaging of patients for ambulatory-care visits, especially in areas with limited resources and a high-volume of patients, or during the challenging times of the COVID-19 pandemic.

The association between frequent changes of antihypertensive drugs and multi-disciplinary follow-up warrants increased pharmacist care for such patients. Follow-ups with multiple disciplines might predispose patients to suboptimal adjustments to their medication regimen, based on inaccurate medication history and care transition errors, given that medication information is generally not shared between institutions [11]. Pharmacists could prevent such errors by performing medication reconciliation for patients who have multiple follow-ups and ensuring that accurate information on medications is well communicated to all prescribers [11].

The use of TCM might be driven by dissatisfaction with conventional treatments, as well as the belief that TCM have less adverse effects than conventional medicines [28]. TCM

Table 4 Number of adjustments to antihypertensive drugs by types

Type of medications	Number of users at baseline, n	Drug added n = 314	Drug stopped n = 347	Dose increased n = 154	Dose decreased n = 99	Frequency increased n = 23	Frequency decreased n = 10	Total, n (%) n = 948	Total adjustments per user
Calcium channel blockers	377	110	85	50	12	11	6	288 (30.4%)	0.764
ACE inhibitors	274	38	64	47	14	2	1	166 (17.5%)	0.606
Beta-blockers	238	50	55	9	33	1	0	148 (15.6%)	0.622
Angiotensin II blockers	191	55	62	16	9	0	1	143 (15.1%)	0.749
Alpha-blockers	74	41	26	28	8	8	2	113 (11.9%)	1.527
Low-ceiling diuretics	84	10	27	0	6	0	0	43 (4.5%)	0.512
Other antihypertensive drugs (methyldopa, minoxidil, spironolactone)	29	6	18	4	3	1	0	33 (3.5%)	1.138
Combination therapies	43	4	10	0	0	0	0	14 (1.5%)	0.326

ACE, Angiotensin converting enzyme

use among CKD patients is potentially hazardous, as the impairment of renal excretory functions predisposes patients to the risk of toxicity [29]. Drug responses might be altered with concurrent TCM ingestion, as evidenced by herb-drug interactions that attenuate antihypertensive drugs' effects [29]. Furthermore, the pharmacokinetic properties of drugs with concurrent TCM use might be unpredictable, due to the presence of multiple bioactive constituents in various TCM used by CKD patients [29, 30]. There might be a greater need for drug adjustments in CKD patients following TCM use, due to drug-TCM interactions or acceleration of renal damage [29].

Poor adherence increases the risk of adverse events or medication efficacy loss, which then require frequent adjustments to, or intensification of medication regimen [8, 11]. Poor adherence is multifactorial [2, 4, 31, 32], with high medication burden and complex administration regimen often associated with poor adherence [32]. In addition, poor adherence is associated with poorer blood pressure control [4] and increased risk of CKD progression [4, 31], which ultimately lead to changes in medications.

It is not surprising that advanced baseline albuminuria and declining eGFR were found to be factors of frequent antihypertensive drug adjustments among CKD patients. Albuminuria is often a marker of cardiovascular disease risk and kidney damage, and a factor for rapid CKD progression [13, 18]. The involvement of various antihypertensive drugs in albuminuria management among CKD patients explains the more frequent adjustments of antihypertensive drugs for patients with greater albuminuria severity [13, 18]. In addition, the antihypertensive drugs were adjusted when eGFR declined, to slow renal disease progression [1, 13]. Moreover, frequent adjustments to antihypertensive drugs might be due to suboptimal medication effect, resulting from changes in pharmacokinetic parameters driven by a decline in the eGFR [7].

When adjusting antihypertensive drugs, it is important to balance the risks of adverse effects, without compromising the opportunity of enhanced therapeutic benefits in delaying the progression of CKD. However, about one-fifth of our patients had subsequent medication changes, suboptimal conditions and significant correlation with adjustments in other drugs following the change to antihypertensive drugs. Our findings warrant in-depth, long-term studies to draw conclusions on the overall health outcomes following frequent changes to antihypertensive drugs.

To that end, it is vital that CKD patients requiring their first change of antihypertensive drug be monitored closely for adherence, albuminuria and TCM use. The current work clearly demonstrates that those who require antihypertensive drug adjustment may be at risk of poor CKD control over time. Interestingly, this work demonstrates the need for pharmacists to strengthen CKD patient care,

Table 5 Factors associated with frequent changes to antihypertensive drugs (simple and multiple logistic regression)

Factors	b	OR (95% CI)	*p*-value
Simple logistic regression (Reference)			
Male gender (Female)	0.266	1.305 (0.944, 1.806)	0.108
Age (years)	− 0.003	0.997 (0.988, 1.007)	0.574
Ethnicity (Malay)			
Chinese	− 0.277	0.758 (0.519, 1.108)	0.152
Indian	− 0.103	0.902 (0.490, 1.662)	0.741
Others	0.177	1.194 (0.384, 3.716)	0.760
History of defaulting follow-ups (None)	0.103	1.108 (0.649, 1.892)	0.706
Number of follow-ups from various institutions	0.186	1.205 (1.007, 1.440)	0.041
Primary cause of CKD (Glomerulonephritis)			
Diabetes mellitus	0.701	2.016 (1.272, 3.196)	0.003
Hypertension	0.352	1.422 (0.806, 2.510)	0.224
Systemic lupus erythematosus	0.705	2.024 (1.137, 3.604)	0.017
Others	0.364	1.439 (0.741, 2.796)	0.282
Number of co-morbidities	0.056	1.057 (0.957, 1.169)	0.275
Obesity (BMI > 30 kg/m^2) (No obesity)	− 0.375	0.687 (0.422, 1.118)	0.131
Smoking (Not smoking)	0.224	1.251 (0.569, 2.751)	0.578
Use of traditional/complementary medicines (None)	0.669	1.951 (1.109, 3.435)	0.020
Use of NSAIDs (None)	0.045	0.956 (0.485, 1.883)	0.896
Poor adherence to medications (None)	0.551	1.735 (1.219, 2.470)	0.002
Baseline eGFR (ml/min/1.73 m^2/year)	− 0.006	0.994 (0.988, 0.999)	0.018
Change to eGFR during study period (ml/min/1.73 m^2/year)	− 0.035	0.966 (0.948, 0.983)	< 0.001
Degree of albuminuria (A1)			
A2	0.774	2.168 (1.327, 3.542)	0.002
A3	0.955	2.600 (1.696, 3.984)	< 0.001
Multiple logistic regression			
Factors	b	Adjusted OR (95% CI) [a]	*p*-value
Number of follow-ups from various institutions	0.218	1.244 (1.012, 1.530)	0.038
Use of traditional/complementary medicines (None)	0.722	2.058 (1.058, 4.001)	0.033
Poor adherence to medications (None)	0.447	1.563 (1.037, 2.357)	0.033
Change to eGFR during study period	− 0.030	0.970 (0.951, 0.990)	0.003
Degree of albuminuria (A1)			
A2	0.776	2.173 (1.311, 3.603)	0.003
A3	0.750	2.117 (1.349, 3.322)	0.001

BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, Standard deviation

[a]Multiple stepwise logistic regression model was applied. Uncontrolled blood pressure was not included in the model due to collinearity [36]. Multicollinearity and interaction terms of the remaining predictors were checked and not found. The model's fitness was checked using Hosmer–Lemeshow test ($p = 0.275$), classification table (overall correctly classified percentage = 68.5%) and area under the Receiver Operating Characteristic (ROC) curve (67.2%, 95% CI 62.4%-72.0%)

among those with antihypertensive drug adjustments, via monitoring their medication adherence, TCM use, albuminuria status, as well as education on correct medication knowledge, belief and management skills [31, 33]. Knowledge of CKD and treatment delays CKD progression and minimises CKD complications [2]. The potential benefits of pharmacist involvement are beyond the improvement of medication adherence, ranging from reduced hospitalisation rates to increased savings to healthcare systems [34].

This study is limited by its retrospective nature, such that causal inferences could not be drawn. As such, the outcomes of frequent adjustments to antihypertensive drugs are limited, due to the complexity of the various interactions between social, clinical and behavioural aspects. Irrespective of the causal mechanisms, we found a strong association

between poor medication adherence, TCM use and frequent adjustments to antihypertensive drugs. In addition, poor adherence might have been underestimated by physicians, due to the lack of a structured work-up, as it is subject to recall and interviewer bias. The use of TCM and NSAID might have been underestimated, due to the retrospective nature of the study. Furthermore, host genetics in the dose–response relationship of antihypertensive drugs is a possible factor that was not examined and warrants verification in future research.

Conclusion

Medication management can be complex in patients with CKD. Given that the pharmacologic treatment of hypertension is an important consideration for CKD management, this work suggests enhanced monitoring of patients who require initial adjustments of antihypertensive drugs. The need to adjust antihypertensive drugs may be indicated by patients receiving follow-ups in multiple institutions, use of TCM, poor adherence, declining eGFR and albuminuria, all of which could eventually progress to poorer CKD outcomes.

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Appendix 1

See Table 6.

Table 6 Medication changes following a change to antihypertensive drugs (n = 56)

Reason for subsequent adjustment	Number of patients, n (%)	Subsequent actions (n)
Hypotension	7	Drug withdrawn (4) Dose decreased (2) Dose decreased and subsequently ceased (1)
Adverse effects other than hypotension: Hyperkalaemia (n = 6) Impaired glucose intolerance (n = 3) Dizziness (n = 7) Headache (n = 5) Cough (n = 3) Impaired uric acid balance (n = 2) Acute kidney injury (n = 3) Deranged lipid profile (n = 1) Bradycardia (n = 1) Chest discomfort (n = 2) Palpitation (n = 1) Pedal edema (n = 2) Unspecified intolerance cause (n = 1)	37	Drug withdrawn (8) Replacement with another antihypertensive drug (10) Addition of new medications (9) Dose decreased (1) Dose decreased and subsequently ceased (1) Converted back to previous medication (6)[a] Dosing administration adjusted (1) Dose addition of non-antihypertensive drug (1)
Uncontrolled hypertension	11	Drug restarted (4) Replacement with another antihypertensive drug (6) Addition of new medications (1)
Suboptimal drug combination	1	Replacement with another antihypertensive drug (1)

[a]Five patients were subsequently given new antihypertensive drugs

Appendix 2

See Table 7.

Table 7 Correlation of changes in other medications after changes to antihypertensive drugs

Variables	Correlation coefficient	*p*-value
Changes to antidiabetics	0.207	< 0.001
Changes to external medications	0.051	0.188
Changes to antiplatelet drugs	0.182	< 0.001
Changes to lipid-modifying drugs	0.118	< 0.001
Changes to other cardiovascular drugs	0.170	< 0.001
Changes to analgesic drugs	0.066	0.090
Changes to gastrointestinal drugs	0.143	< 0.001
Changes to antigout drugs	0.051	0.187
Changes to antianaemic drugs	0.164	< 0.001
Changes to immunosuppressive drugs	0.119	0.002
Changes to diuretics	0.246	< 0.001
Changes to drugs for electrolyte imbalances	0.021	0.586
Changes to drugs for mineral-bone disease	0.143	< 0.001
Changes to other drugs	0.061	0.116

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