Association of 24-Hour Ambulatory Blood Pressure Patterns with Cognitive Function and Physical Functioning in CKD

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Abstract

Background and objectives Hypertension is highly prevalent in patients with CKD as is cognitive impairment and frailty, but the link between them is understudied. Our objective was to determine the association between ambulatory BP patterns, cognitive function, physical function, and frailty among patients with nondialysis-dependent CKD.

Design, setting, participants, & measurements Ambulatory BP readings were obtained on 1502 participants of the Chronic Renal Insufficiency Cohort. We evaluated the following exposures: (*1*) BP patterns (white coat, masked, sustained versus controlled hypertension) and (*2*) dipping patterns (reverse, extreme, nondippers versus normal dippers). Outcomes included the following: (*1*) cognitive impairment scores from the Modified Mini Mental Status Examination of <85, <80, and <75 for participants <65, 65–79, and ≥80 years, respectively; (*2*) physical function, measured by the short physical performance battery (SPPB), with higher scores (0–12) indicating better functioning; and (*3*) frailty, measured by meeting three or more of the following criteria: slow gait speed, muscle weakness, low physical activity, exhaustion, and unintentional weight loss. Cognitive function and frailty were assessed at the time of ambulatory BP (baseline) and annually thereafter. SPPB was assessed at baseline logistic and linear regression and Cox discrete models assessed the cross-sectional and longitudinal relationship between dipping and BP patterns and outcomes.

Results Mean age of participants was 63±10 years, 56% were male, and 39% were black. At baseline, 129 participants had cognitive impairment, and 275 were frail. Median SPPB score was 9 (interquartile range, 7–10). At baseline, participants with masked hypertension had 0.41 (95% CI, −0.78 to −0.05) lower SPPB scores compared with those with controlled hypertension in the fully adjusted model. Over 4 years of follow-up, 529 participants had incident frailty, and 207 had incident cognitive impairment. After multivariable adjustment, there was no association between BP or dipping patterns and incident frailty or cognitive impairment.

Conclusions In patients with CKD, dipping and BP patterns are not associated with incident or prevalent cognitive impairment or prevalent frailty.

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Introduction

Hypertension and CKD are overlapping in nature with an intermingled cause-effect relationship. Hypertension contributes to the development of kidney disease in patients with normal kidney function and leads to worsening of kidney function in those with CKD (1). Conversely, CKD is the most common cause of secondary hypertension and is an independent risk factor of cognitive impairment, poor physical performance, frailty, and low health-related quality of life (2–6). The magnitude of risk for all of these factors has been shown to increase exponentially as the severity of CKD increases (4,5). Moreover, hypertension is an important risk factor for cognitive decline in patients with CKD (6). Impaired kidney function is associated with arterial stiffness and hypertension could subsequently damage vessels exposed to high pressure (7,8). Therefore, patients with CKD are at high risk of developing injury to the cerebral vasculature and are at risk of cognitive impairment; this is known as the vascular hypothesis (9). Hypertension has been shown to be a contributor to frailty and physical function in patients with CKD (10–12). If certain hypertension phenotypes in patients with CKD are identified as important risk factors, then interventions at modifying these phenotypes to reduce the propensity toward physical dysfunction could be instituted. The exact mechanisms of this association are unclear but inflammation might play a role (13–15).

Ambulatory BP monitoring, unlike traditional clinic-based BP, has the ability to measure BP throughout the day and night. Ambulatory BP monitoring offers additional prognostic value for individuals with hypertension (16). Furthermore, ambulatory BP monitoring is superior to office BP measurements to estimate dementia-related outcomes (17–19). An altered circadian BP pattern is hypothesized to be associated with cognitive impairment, frailty, and physical functioning. This might be due to greater brain atrophy, cerebral small vessel disease burden, and exposure to higher pulsatile blood flow that damages the cerebral microvasculature, which is observed in patients with nondipping BP patterns (8,20–22). Association of nighttime BP dipping (drop in BP from day to night) with cognitive function in patients with hypertension have been inconsistent (23–26). Note that all of these studies were done in patients without CKD and were carried out in small cohorts (<100 participants). Additionally, a cross-sectional study of 1047 community-dwelling individuals with no kidney disease in Spain found that participants with lower daytime systolic BP, less systolic BP dipping, and higher nighttime systolic BP were more likely to be frail and have lower functional status (disability) (27).

The Chronic Renal Insufficiency Cohort (CRIC) study is a prospective, observational cohort study examining the risk factors and mechanisms of CKD progression. Ambulatory BP monitoring and cognitive and physical function tests were performed on a subset of CRIC participants. It has been previously shown using a cross-sectional analysis of 1492 CRIC participants with available ambulatory BP monitoring that masked hypertension (normal clinic BP with elevated ambulatory BP) is common in patients with CKD and is associated with lower eGFR, proteinuria, and target organ damage (28). Also, in CRIC, lower levels of eGFR were shown to be independently associated with impaired cognitive functioning, especially related to tests of executive function, even after adjustment for socio-demographic and clinical factors (29). Additionally in CRIC, CKD severity was associated with lower physical performance and frailty (4). The role of circadian BP patterns among patients with impaired kidney function on cognitive impairment and overall physical functioning to our knowledge has not been studied. Understanding this association could guide future efforts to improve the well being of patients with CKD.

The primary aim of this analysis is to determine whether BP and dipping patterns are associated with incident cognitive impairment or incident frailty in patients with CKD. Our secondary aim was to study the cross-sectional association between BP and dipping patterns with cognitive function, physical functioning, and frailty.

Materials and Methods

Study Participants

The CRIC study is an ongoing, multicenter, observational cohort that recruited 3939 adults aged 21–74 years with an eGFR of 20–70 ml/min per 1.73 m^2 if aged 21–44 years, 20–60 ml/min per 1.73 m^2 if aged 45–64 years, and 20–50 ml/min per 1.73 m^2 if aged 65–74. Details of the CRIC study have been published previously (30,31). The protocol was approved by the institutional review board at each of the participating sites.

Exposure

Clinic and Ambulatory Blood Pressure Measurements. At each CRIC visit, BP was measured by a trained study staff member after a 5-minute rest period using an aneroid sphygmomanometer and following guideline-recommended protocols (32). The average of three BPs was used to define clinic BP. Ambulatory BP was obtained on a subset of patients (n=1502) who agreed to undergo ambulatory BP monitoring between 2008 and 2012 with a SpaceLabs 90207 or 90217 monitor. Participants with arm circumference >50 cm, night-shift workers, breast cancer requiring mastectomy or radiation, and patients with ESKD were excluded. The average time from the CRIC baseline visit to ambulatory BP monitoring was 5.1±1.4 years. The monitor was placed on the nondominant arm unless an arteriovenous graft or fistula was present, in which case, the dominant arm was used (28). Nighttime and daytime ambulatory BPs were defined by the average of readings between midnight to 6:00 AM, and 10:00 AM to 8:00 PM, respectively (33). A recording was considered acceptable if there were at least 14 readings between 6:00 AM and midnight and at least six readings between midnight and 6:00 AM. Participant dipping patterns were defined as follows: (*1*) normal dipping status (those who experience a 10%–20% drop in mean systolic BP from day to night—reference group), (*2*) extreme dipping status (≥20% drop in mean systolic BP from day to night), (*3*) nondippers (0%–10% decrease in mean systolic BP from day to night), and (*4*) reverse dippers (increase in systolic BP from day to night) (34). Participant BP patterns were defined as follows: (*1*) controlled hypertension (clinic BP <140/90 mm Hg and 24-hour ambulatory BP <130/80 mm Hg—reference group), (*2*) white-coat hypertension (clinic BP ≥140/90 mm Hg and 24-hour ambulatory BP <130/80 mm Hg), (*3*) masked hypertension (clinic BP <140/90 mm Hg and 24-hour ambulatory BP ≥130/80 mm Hg), and (*4*) sustained hypertension (clinic BP ≥140/90 mm Hg and 24-hour ambulatory BP ≥130/80 mm Hg). For this analysis, baseline was defined as the time ambulatory BP monitoring was done.

In sensitivity analyses, we used the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) 2017 guidelines to define BP patterns (35). Clinic BP cutoff was defined as 130/80 mm Hg and 24-hour ambulatory BP cutoff was defined as 125/75 mm Hg.

Outcomes

Cognitive Function Measures. We ascertained cognitive function by performance score on the Modified Mini Mental State Examination (3MS). 3MS was administered during annual or biannual CRIC study visits. 3MS is a brief cognitive battery that includes components testing memory, orientation, concentration, language, and praxis. 3MS scores range between 0 and 100, with higher scores indicating better cognitive functioning. For baseline measurements, we included the 3MS score for each participant performed at or before the time of ambulatory BP monitoring. We defined clinically significant cognitive impairment as having a score <85 for participants younger than

65 years, <80 for participants aged 65–79 years, and <75 for those ≥80 years (36).

Physical Functioning and Frailty. The Physical Performance Ancillary Study was conducted at four of the seven CRIC centers from April 2008 to February 2010 and assessed physical functioning and frailty. Physical performance was assessed only once. Frailty was assessed annually at CRIC in-person visits. The short physical performance battery (SPPB) score was derived from the faster of two timed, usual pace, 15-foot walks; tests of standing balance in the side-by-side, semitandem, and tandem positions, and a timed series of five attempts to stand from a chair with arms crossed on the chest (4,37). SPPB score range is between 0 and 12, and a higher score indicates better functioning. Frailty status was defined using five criteria described by Fried (yes/no answers): slow gait speed, muscle weakness, low physical activity, exhaustion, and unintentional weight loss (4,38,39). Participants who meet three or more criteria were defined as frail, those who meet one to two criteria were defined as prefrail, and others were defined as nonfrail (Supplemental Appendix). For baseline measurements, we included the SPPB score and frailty category for each participant at or before the time of ambulatory BP monitoring.

Covariates

We selected the following covariates *a priori* for our multivariable analyses: clinic site, age, race, sex, educational attainment, marital status, income, smoking status, alcohol use, illicit drug use, body mass index (BMI; kg/m^2), antihypertensive medications, past medical history (hypertension, diabetes, coronary artery disease, heart failure, peripheral vascular disease, depression, hyperlipidemia), anemia (<12 g/dl for women and 13.5 g/dl for men), and eGFR. These were assessed at the time of the ambulatory BP monitoring visit. We also included urine protein-creatinine ratio and C-reactive protein values obtained at or before the time of the ambulatory BP monitoring visit.

Statistical Analyses

We compared baseline characteristics of participants across dipping and BP patterns. Continuous variables were reported as median and interquartile range or mean with SD, as appropriate, and categoric variables are presented as proportions. Chi-squared, Wilcoxon rank-sum, and Kruskal–Wallis tests were used to compare categoric, normally distributed continuous, and non-normally distributed continuous data. We compared the mean adjusted cognitive function scores (3MS) across BP and dipping patterns using one-way ANOVA. SPPB and frailty distribution were compared across BP and dipping patterns using Kruskal–Wallis and chi-squared tests, respectively.

Longitudinal Analyses. Discrete Cox proportional hazard models were used to determine the risk of incident cognitive impairment and incident frailty by dipping and BP patterns among those who did not have cognitive impairment or frailty at baseline, respectively. For each outcome, the following models were used: model 1 adjusted for age, race, sex, education, marital status, and income; model 2 adjusted for model 1 plus smoking, alcohol use, illicit drug use; and model 3 adjusted for model 2 plus BMI, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and eGFR at the time of ambulatory BP. The proportional hazards assumption was tested.

Additionally, we used longitudinal mixed repeated measures models with unstructured variance to compare 3MS score over follow-up by dipping and BP patterns.

Cross-Sectional Analyses. Logistic regression models were used to investigate the cross-sectional association between dipping and BP patterns and clinically significant cognitive impairment and frailty as a binary variable (participants who were frail versus nonfrail). Multivariable-adjusted linear regression was performed to determine the association between dipping and BP patterns and SPPB score (physical functioning) at baseline. Additionally, we used multivariable linear regression models to study the association between continuous 3MS score and dipping and BP patterns. We also used multivariable ordinal logistic regression to determine the odds ratio associated with frailty status (nonfrail—reference, prefrail, and frail) and dipping and BP patterns. The proportional odds assumption was tested for regression analyses.

Sensitivity Analyses. We studied the longitudinal and cross-sectional association between the following continuous variables and all outcomes: clinic systolic and diastolic BP, ambulatory daytime systolic and diastolic BP, ambulatory nighttime systolic and diastolic BP, clinic pulse pressure (systolic–diastolic BP), and ambulatory pulse pressure. Additionally, we restricted our analysis to only older individuals (≥60 years old), given the age distribution of the cohort. We also looked at the association of nocturnal hypertension (nighttime systolic BP >120 mm Hg or diastolic BP >70 mm Hg) with outcomes. Analyses were performed using SAS software version 9.4 (SAS Institute) and RStudio software version 1.1.463 (R Foundation for Statistical Computing).

Results

Of the 1502 participants in CRIC with acceptable ambulatory BP monitoring readings, 17% were reverse dippers, 38% were nondippers, 36% were normal dippers, and 9% were extreme dippers. Overall, at the time of the ambulatory BP monitoring visit, participants averaged 63 years of age, 56% were males, 39% were non-Hispanic black, and 66% had some college or graduate education. Participants with normal or extreme dipping compared with reverse and nondippers were on average younger, more likely to be non-Hispanic white, had lower clinic BP, had fewer comorbidities, were on fewer antihypertensive medications, and had lower median urine protein-creatinine ratio (Table 1). Of note, 49%, 4%, 28%, and 19% of participants had controlled, masked, white-coat, and sustained hypertension, respectively. Participants with controlled hypertension were younger and were in general healthier (Supplemental Table 1). Details of ambulatory BPs across dipping and BP patters are shown in Supplemental Table 2, A and B.

Table 1. Demographic and clinical characteristics of CKD cohort with ambulatory BP monitoring based on dipping patterns

Characteristic	All Patients (n=1502)	Reverse Dipping (n=252)	Nondipping (n=572)	Normal Dipping (n=536)	Extreme Dipping (n=142)
Age	63±10	66±9	64±10	62±11	62±9
Male	841 (56)	147 (58)	332 (58)	281 (52)	81 (57)
Ethnicity					
Non-Hispanic white	681 (45)	97 (39)	237 (41)	273 (51)	74 (52)
Non-Hispanic black	582 (39)	117 (46)	249 (44)	172 (32)	44 (31)
Hispanic	182 (12)	29 (12)	69 (12)	66 (12)	18 (13)
Other	57 (4)	9 (4)	17 (3)	25 (5)	6 (4)
Income					
≤$20,000	394 (26)	85 (34)	167 (29)	114 (21)	28 (20)
$20,001–50,000	401 (27)	70 (28)	151 (26)	141 (26)	39 (28)
$50,001–100,000	335 (22)	45 (18)	121 (21)	135 (25)	34 (24)
≥$100,001	164 (11)	18 (7)	57 (10)	71 (13)	18 (13)
Marital status					
Currently married	880 (59)	137 (54)	327 (57)	323 (60)	93 (66)
Never married	193 (13)	39 (16)	66 (12)	74 (14)	14 (10)
Formerly married	429 (29)	76 (30)	179 (31)	139 (26)	14 (10)
Education					
<High school	250 (17)	57 (23)	102 (18)	69 (13)	22 (16)
High school graduate	259 (17)	53 (21)	107 (19)	82 (15)	17 (12)
Some college/ college graduate	992 (66)	142 (56)	362 (63)	385 (72)	103 (73)
Body mass index, kg/m^2	32±7	32±7	32±7	31±7	31±8
Current smoker, yes	131 (9)	26 (10)	49 (9)	43 (8)	13 (9)
Current or former use of alcohol, yes	812 (54)	111 (44)	288 (51)	329 (62)	84 (59)
Illicit drug use, yes	506 (34)	80 (32)	174 (30)	202 (38)	50 (35)
Office BP, mm Hg					
Systolic	126±20	129±22	127±21	124±20	124±18
Diastolic	69±12	69±13	69±12	70±12	71±11
Pulse pressure	57±19	61±19	58±20	55±18	53±17
Past medical history					
Hypertension	1397 (93)	245 (97)	540 (94)	491 (92)	121 (85)
Diabetes	629 (42)	133 (53)	258 (45)	193 (36)	45 (32)
Coronary artery disease	585 (39)	141 (56)	238 (42)	171 (32)	35 (25)
Heart failure	146 (10)	42 (17)	48 (8)	47 (9)	9 (6)
Stroke	174 (12)	46 (18)	70 (12)	48 (9)	10 (7)
Peripheral vascular disease	99 (7)	26 (10)	40 (7)	27 (5)	6 (4)
Depression	724 (48)	121 (48)	296 (52)	245 (46)	63 (44)
Hyperlipidemia	1027 (69)	184 (73)	390 (68)	356 (67)	67 (69)
Antihypertensive medications					
ACEI/ARB	984 (66)	160 (64)	389 (68)	350 (65)	85 (60)
Diuretic	790 (53)	161 (64)	314 (55)	248 (46)	67 (48)
Calcium channel blocker	638 (43)	133 (53)	264 (46)	192 (36)	49 (35)
β-Blocker	777 (52)	168 (67)	314 (55)	232 (43)	63 (45)
Vasodilator	197 (13)	51 (20.3)	86 (15)	42 (8)	18 (13)
Taking anti-HTN medications	1374 (92)	250 (98)	532 (93)	476 (89)	120 (85)
Total number anti-HTN medications	2.6±1.5	3.2±1.4	2.7±1.5	2.2±1.4	2.2±1.5
Anemia[a]	687 (46)	146 (58)	267 (47)	215 (40)	59 (42)
Serum creatinine	1.9±1.1	2.2±1.5	2.0±1.2	1.8±0.9	1.8±0.9
eGFR, ml/min per 1.73 m^2					
≥60	355 (24)	79 (32)	156 (28)	93 (18)	27 (19)
45 to <60	448 (30)	84 (34)	163 (29)	156 (30)	43 (30)
30 to <45	394 (27)	55 (22)	147 (26)	152 (29)	40 (28)
<30	290 (20)	31 (12)	101 (18)	126 (24)	32 (23)
Urine protein-creatinine ratio[b]	0.1 (0.06, 0.4)	0.2 (0.08, 0.8)	0.1 (0.06, 0.5)	0.09 (0.05, 0.3)	0.08 (0.05, 0.3)
C-reactive protein	4.9±8.8	6.5±9.3	5.1±10.6	4.2±6.9	4.3±6.0

Categoric values presented as mean±SD and continuous variables as n (%), unless otherwise specified. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HTN, hypertensive.
[a]Anemia defined as hemoglobin <12 g/dl for women and <13.5 g/dl for men.
[b]Urine protein-creatinine ratio presented as median (25th, 75th).

Longitudinal Analyses

Cognitive Function. Of the 1502 participants, 1500 had 3MS available at or before the time of ambulatory BP monitoring and 125 had impaired cognitive function. Of the remaining 1375 participants, 207 developed cognitive impairment over 4 years of follow-up (two cases per 100 person-years). Participants with extreme dipping had marginally greater incident cognitive impairment compared with normal dippers (hazard ratio, 1.83; 95% CI, 0.99 to 3.34). Among participants ≥60 years of age, the hazards of cognitive impairment among extreme dippers was 2.43 (95% CI, 1.17 to 5.03) times that of normal dippers (Supplemental Table 3, A and B). There was no increased risk of incident cognitive impairment with white-coat, masked, and sustained hypertension (Table 2). We found no significant association between continuous 3MS scores over follow-up and dipper or BP patterns (Figure 1, Tables 2 and 3).

Frailty. A total of 1464 participants had frailty status available at baseline, and 275 were frail. During 4 years of follow-up, 529 of 1189 participants developed frailty (6.2 cases per 100 person-years). We found no association between incident frailty and dipping or BP patterns (Tables 4 and 5).

Cross-Sectional Analyses

SPPB was obtained on 591 participants in CRIC at baseline. Details of the 3MS scores, frailty distribution, and SPPB scores across dipping and BP patterns are shown in Supplemental Table 4, A and B. After multivariable adjustment, we found no significant association between dipping and BP patterns and prevalent cognitive impairment (Supplemental Table 5) or prevalent frailty (Supplemental Table 6). However, participants with sustained hypertension had 0.87 (95% CI, −1.73 to −0.01) lower 3MS scores compared with controlled hypertension after adjustment (Supplemental Table 7).

Similarly, there was no association between dipping patterns and SPPB scores or physical functioning. However, participants with masked hypertension had 0.41 (95% CI, −0.78 to −0.05) lower SPPB scores compared with those with controlled hypertension in the fully adjusted model (Supplemental Table 8).

Table 2. Modified Mini Mental State Examination scores by dipping patterns during follow-up

Dipping Pattern	Number of Participants				
	Year 0	Year 1	Year 2	Year 3	Year 4
Dipper	648	266	338	377	383
Reverse dipper	327	126	157	174	171
Nondipper	711	352	322	401	392
Extreme dipper	179	61	91	104	96

P value comparing means across dipping patterns=0.34. *P* value after adjusting for clinic site, year, age, race, sex, education, marital status, income, smoking, alcohol use, illicit drug use, body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP.

Sensitivity Analyses

Using 2017 ACC/AHA guidelines, we similarly found no association between incident or prevalent cognitive function, baseline SPPB score, or prevalent or incident frailty with dipping and BP patterns (Supplemental Tables 9 and 10). Of note, we found no association between daytime systolic or diastolic BP, nighttime systolic or diastolic BP, ambulatory BP, clinic pulse pressure as continuous variables, or nocturnal hypertension with prevalent or incident cognitive impairment, incident or prevalent frailty or baseline SPPB scores (data not shown). Moreover, we found similar results when we studied the association of frailty as a three-level variable (nonfrail, prefrail, and frail) with dipping and BP patterns (data not shown).

Discussion

To the best of our knowledge, this is the first and largest study in both a CKD and non-CKD population to evaluate the association between dipping and BP patterns and cognitive function, physical functioning, and frailty both over follow-up and cross-sectionally. We found no consistent association between dipping and BP patterns and incident or prevalent cognitive impairment or prevalent frailty among patients with nondialysis-dependent CKD. However, among participants ≥60 years, extreme dippers had greater incident cognitive impairment compared with nondippers. In the cross-sectional analyses, we found that participants with masked hypertension had significantly worse physical functioning compared with controlled hypertension.

In our analyses, we found that participants with extreme dipping had marginally worse incident cognitive impairment than normal dippers. Similar to our results, in the Coronary Artery Risk Development in Young Adults study, nocturnal systolic dipping (<8% versus 8%–13%) and higher nocturnal diastolic BP dipping were associated with lower executive function 20 years later in midlife (40). However, there was no association with other measures of cognitive function (psychomotor speed or verbal memory). Previous research has predominantly looked at the cross-sectional association between cognitive function and ambulatory BP. Several studies have found an association between dipping and BP patterns and cognitive impairment (23,24,26,41). In a study of 144 patients (mean age, 68±7 years) in Japan, frequency of mild cognitive impairment (3MS) was higher among extreme dippers, nondippers, and reverse dippers when compared with dippers (P=0.018). Patients with abnormal dipping patterns had worse cognitive function than normal dippers (odds ratio, 3.1; 95% CI, 1.1 to 9.9) (26). On the other hand, consistent with our results, several studies have found no association between dipping and BP patterns and cognitive impairment (25,42–44). For example, Cicconetti *et al.* (42) found that, among patients who were older with newly diagnosed hypertension, nondipping was not associated with lower cognitive function. Factors related to sample size, participant selection, age of cohort, method of assessing

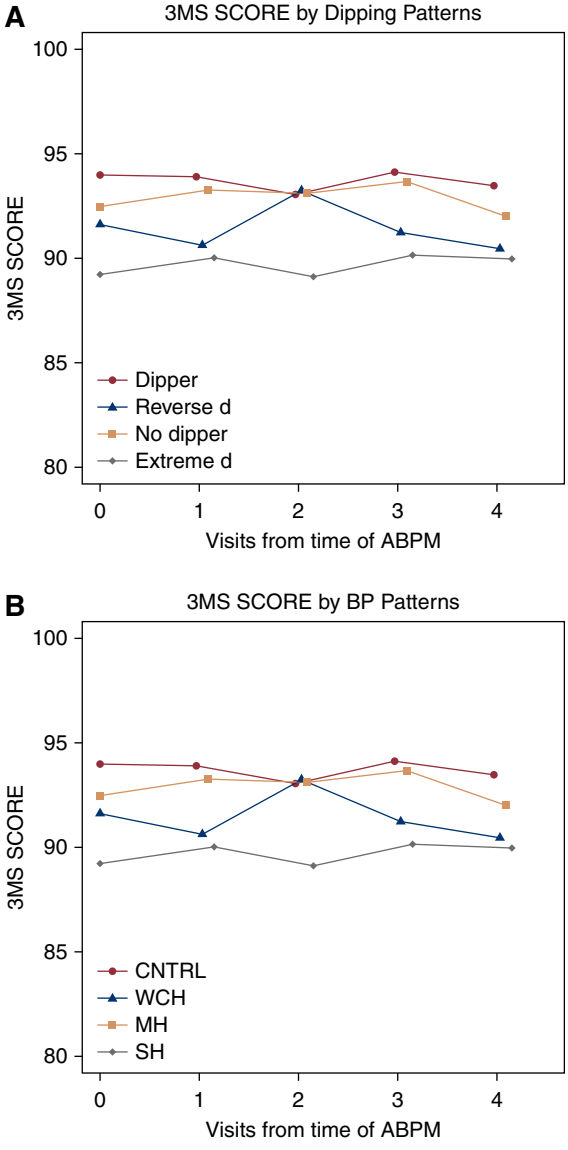

Figure 1. | 3MS score does not differ by dipping or blood pressure patterns. (A) 3MS score by dipping patterns. (B) 3MS score by BP patterns. ABPM, ambulatory BP monitoring; CNTRL, controlled BP; d, dipper; MH, masked hypertension; 3MS, Modified Mini Mental State Examination; SH, sustained hypertension; WCH, white-coat hypertension.

Table 3. Modified Mini Mental State Examination scores by BP patterns during follow-up

BP Pattern	Number of Participants				
	Year 0	Year 1	Year 2	Year 3	Year 4
CNTRL	927	411	438	560	503
WCH	66	32	28	52	52
MH	506	219	254	289	287
SH	366	143	188	155	200

P value comparing means across BP patterns=0.36. *P* value after adjusting for clinic site, year, age, race, sex, education, marital status, income, smoking, alcohol use, illicit drug use, body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP. CNTRL, controlled BP; WCH, white-coat hypertension; MH, masked hypertension; SH, sustained hypertension.

cognitive impairment, and the cross-sectional nature of the studies might explain the discrepant findings. Of note, cerebral flow increases during the night due to increased oxygen demand (45). We therefore speculate that, because many patients with CKD have vascular dysfunction, a blunted reduction in BP during the night may actually maintain adequate nighttime blood flow to the vital organs, including the brain. Therefore, among patients with vascular dysfunction, nondipping may not result in an increased risk of cerebrovascular insufficiency—a mechanism that leads to cognitive impairment. This may explain the lack of association between dipping patterns (reverse, nondippers) and cognitive impairment. Because different components of ambulatory BP affect different cerebral structure parts and functions, dipping and BP patterns may uniquely affect cognitive function (20,46). Further investigations using brain magnetic resonance imaging to understand the underlying pathways between ambulatory BP and cognitive function may be warranted. However, causal inferences from observational studies should be made with caution.

With regards to frailty, 19% of our patients who were of middle age to elderly (mean age, 63 years) were frail at baseline. We found no association between incident or prevalent frailty and BP, dipping patterns, or ambulatory BP measures. Previous studies were limited to cross-sectional analyses. Bastos-Barbos *et al.* (47) evaluated 77 frail, prefrail, and nonfrail older adults (mean age, 75 years). In contrast to our findings, participants who were frail (33%) had significantly higher 24-hour and nighttime systolic and diastolic BP than the nonfrail group. Similarly, Hajjar *et al.* (20) showed that, among 80 older adults with and without stroke, lower dipping magnitude in systolic BP was associated with slower gait speed. Our study is the first to show that participants with CKD and masked hypertension have worse physical functioning (0.41 lower SPPB score) compared with participants with controlled hypertension at time of ambulatory BP. Studies in elderly populations without CKD have shown that 0.5±1.5 points in SPPB is clinically meaningful (48). Therefore, our results may have clinical implications because individuals with masked hypertension and CKD may be at higher risk of worsening physical functioning. Given that our results are based on one measurement at baseline, we are unable to discern the temporal relationship, if it exists, between physical functioning and BP or dipping patterns. Overall, there is a paucity of literature on the association between physical functioning and frailty in patients who are non-elderly and specifically the CKD population.

Our study has a number of strengths which include the large sample size of participants with available ambulatory BP monitoring and a well characterized cohort of participants that allows us to adjust for potential confounders and enhance the robustness of our analyses. In addition, there is a dearth of evidence on ambulatory BP patterns and

Table 4. Hazard ratio and 95% confidence interval for incident cognitive impairment by dipping and BP patterns from discrete Cox proportional hazard models over 4 years of follow-up from time of ambulatory BP monitoring

Pattern	Hazard Ratio (95% CI)			
	Unadjusted[a]	Model 1[b]	Model 2[c]	Model 3[d]
By dipping pattern[e]				
Normal dipping	Reference	Reference	Reference	Reference
Reverse dipping	2.28 (1.53 to 3.41)	1.49 (0.97 to 2.29)	1.43 (0.92 to 2.21)	1.29 (0.81 to 2.05)
Nondippers	1.79 (1.26 to 2.54)	1.38 (0.95 to 1.99)	1.31 (0.90 to 1.91)	1.32 (0.89 to 1.97)
Extreme dipping	1.41 (0.81 to 2.43)	1.62 (0.89 to 2.91)	1.58 (0.88 to 2.83)	1.83 (0.99 to 3.34)
By BP pattern				
Controlled hypertension	Reference	Reference	Reference	Reference
White-coat hypertension	1.49 (0.78 to 2.83)	0.86 (0.42 to 1.73)	0.88 (0.43 to 1.78)	0.93 (0.45 to 1.92)
Masked hypertension	1.34 (0.95 to 1.89)	0.94 (0.65 to 1.36)	0.96 (0.66 to 1.40)	0.96 (0.64 to 1.42)
Sustained hypertension	2.26 (1.61 to 3.18)	0.98 (0.68 to 1.42)	0.98 (0.68 to 1.42)	0.86 (0.57 to 1.29)

P value for proportional hazard assumption (dipping patterns)=0.86. *P* value for proportional hazard assumption (BP patterns)=0.98.
3MS, Modified Mini Mental State Examination.
[a]Unadjusted: adjusting for clinic site.
[b]Model 1: adjusting for age, race, sex, education, marital status, and income.
[c]Model 2: adjusted for model 1 plus smoking, alcohol use, and illicit drug use.
[d]Model 3: adjusted for model 2 plus body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP.
[e]Clinically significant cognitive impairment based on 3MS: 3MS score <85 for participants younger than 65, <80 for participants aged 65–79, and <75 for those 80 yr or older.

longitudinal assessment of cognitive function and frailty in participants with CKD, which this study addresses. However, this study has several limitations including the observational nature of the study and that ambulatory BP monitoring was obtained on a convenience sample which could have introduced selection bias. Multiple testing conducted across categories of dipping and BP patterns needs to be considered in evaluating our results. Furthermore, only one ambulatory BP monitoring reading was obtained and classification on the basis of clinic and ambulatory BP may differ over time in up to 25% of patients (49). This may introduce misclassification bias. Although 3MS is a validated measure of cognitive function, it includes limited assessments of other domains (memory and executive function). Thus, we were unable to assess the association of BP patterns with more granular measures of cognitive impairment. The majority of participants with ambulatory BP readings had complete 3MS and frailty assessments; however, physical functioning was available in only half of the participants. Additionally, we only had longitudinal data over 4 years for 3MS and frailty status and loss to follow-up could introduce selection bias.

In conclusion, we show no association between dipping and BP patterns and cognitive impairment or frailty in

Table 5. Hazard ratio and 95% confidence interval for incident frailty by dipping and BP patterns from discrete Cox proportional hazard models over 4 years of follow-up from time of ambulatory BP monitoring

Pattern	Hazard Ratio (95% CI)			
	Unadjusted[a]	Model 1[b]	Model 2[c]	Model 3[d]
Frailty by dipping pattern[e]				
Normal dipping	Reference	Reference	Reference	Reference
Reverse dipping	1.76 (1.36 to 2.28)	1.34 (1.03 to 1.76)	1.31 (0.99 to 1.72)	1.13 (0.85 to 1.50)
Nondippers	1.38 (1.11 to 1.71)	1.17 (0.94 to 1.47)	1.17 (0.93 to 1.47)	1.08 (0.86 to 1.36)
Extreme dipping	0.94 (0.65 to 1.36)	0.91 (0.62 to 1.33)	0.92 (0.62 to 1.35)	0.95 (0.64 to 1.40)
Frailty by BP pattern				
Controlled hypertension	Reference	Reference	Reference	Reference
White-coat hypertension	0.92 (0.58 to 1.47)	0.69 (0.42 to 1.12)	0.67 (0.41 to 1.09)	0.62 (0.37 to 1.0)
Masked hypertension	1.28 (1.04 to 1.56)	1.15 (0.92 to 1.45)	1.17 (0.93 to 1.47)	1.07 (0.85 to 1.36)
Sustained hypertension	1.54 (1.25 to 1.91)	1.15 (0.90 to 1.48)	1.14 (0.88 to 1.46)	0.99 (0.76 to 1.30)

P value for proportional hazard assumption (dipping patterns)=0.99. *P* value for proportional hazard assumption (BP patterns)=0.95.
[a]Unadjusted: adjusting for clinic site.
[b]Model 1: adjusting for age, race, sex, education, marital status, and income.
[c]Model 2: adjusted for model 1 plus smoking, alcohol use, and illicit drug use.
[d]Model 3: adjusted for model 2 plus body mass index, use of antihypertensive medications, history of hypertension, diabetes mellitus, hyperlipidemia, anemia, C-reactive protein, urine protein-creatinine ratio, depression, stroke, and GFR at time of ambulatory BP.
[e]We are assessing incidence of frailty in participants who were not frail or prefrail at baseline (time of ambulatory BP monitoring).

adults with CKD. However, participants with masked hypertension had significantly worse physical functioning and participants with extreme dipping had marginally greater odds of cognitive impairment than normal dippers. Future analyses should focus on exploring the association between BP and dipping patterns and change in physical functioning over time, as well as obtaining measures of cognitive function and physical functioning over a longer follow-up time.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.10570919/-/DCSupplemental.

Supplemental Table 1. Demographic and clinical characteristics of CKD cohort with ABPM based on BP patterns.

Supplemental Table 2A. Ambulatory BP measures in each dipping pattern in CKD cohort.

Supplemental Table 2B. Ambulatory BP measures in each BP pattern in CKD cohort.

Supplemental Table 3A. Hazard ratio and 95% confidence interval for incident cognitive impairment by dipping and BP patterns from discrete Cox Proportional Hazards models over 4 years of follow up from time of ABPM for individuals aged ≥60 years.

Supplemental Table 3B. Hazard ratio and 95% confidence interval for incident frailty by dipping and BP patterns from discrete Cox Proportional Hazards models over 4 years of follow up from time of ABPM for individuals aged ≥60 years.

Supplemental Table 4A. Adjusted mean cognitive function score (3MS), short physical performance battery score and frailty status distribution by dipping patterns (adjusted for age, race, education, sex, diabetes, BMI, depression, history of stroke).

Supplemental Table 4B. Adjusted mean cognitive function score (3MS), short physical performance battery score and frailty status distribution by BP patterns (adjusted for age, race, education, sex, diabetes, BMI, depression, history of stroke).

Supplemental Table 5. Odds ratios and 95% confidence intervals of clinically significant cognitive impairment by dipping and BP patterns at baseline.

Supplemental Table 6. Odds ratio and 95% confidence interval of frail versus (pre-Frail and non-Frail) by dipping and BP patterns at baseline.

Supplemental Table 7. Parameter estimate and 95% confidence intervals of modified mini mental status examination (3MS) by dipping and BP patterns at baseline.

Supplemental Table 8. Estimate and 95% confidence interval of short physical performance score (SPPB) by dipping and BP patterns at baseline.

Supplemental Table 9. Odds ratio and 95% confidence interval of cognitive impairment and frailty; estimate and 95% confidence of short physical performance score by BP patterns.

Supplemental Table 10. Hazard ratio and 95% confidence interval for incident cognitive impairment and Frailty by BP pattern from discrete Cox Proportional Hazards models over 4 years of follow up from time of ABPM.

Supplemental Appendix. Frailty status description.

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