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Prevalence and clinical correlates of non-dipping heart rate among adult patients with chronic kidney disease and hypertension: findings from the Ibadan CRECKID study

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1.0 Introduction

Elevated heart rate especially at night is associated with increased cardiovascular risk among individuals with cardiovascular disease and apparently normal people.[1,2] Increased heart rate is linked with heightened myocardial oxygen demand coupled with decreased diastolic filling time and coronary perfusion with a likelihood of impairment of the myocardial oxygen demand/supply balance and cardiac performance.[3,4] Additionally, increased heart rate may underlie the abnormal vascular shear and pulsatile stress associated with endothelial dysfunction, vascular stiffness and oxidative stress.[5,6]. The heart rate also undergoes circadian fluctuation like blood pressure-dependent of the sympatho-vagal balance.[7] Blunted heart rate dipping or non-dipping heart rate (<10% dip of the morning heart rate) is associated with poor cardiovascular outcomes. [8-10] The aetiology of non-dipping heart rate has been linked among many things to sustained relative sympathetic overactivation, disruption of the endogenous circadian clock in the brain and the sinoatrial node and excessive circulating neurohormonal factors including glucocorticoids and catecholamines.[11,12]

Cardiovascular disease (CVD) is a common complication of chronic kidney disease (CKD) and a major contributor to mortality. CKD is a public health problem, with a 3–18% prevalence in the general population.[1] Its increased global burden and mortality are due to the high risk of advancing end-stage renal disease (ESRD), and associated cardiovascular (CV) complications.[12-14]

Risk prediction in CKD has relied majorly on conventional parameters such as eGFR, albuminuria, and biomarkers such as cystatin C, beta-2 microglobulin, coronary artery calcium and high sensitivity troponin T with results inconsistent with outcomes in some cases.[13] Ambulatory blood pressure monitoring is a gold standard investigation to identify circadian heart rate and blood pressure variability in CKD to identify important prognostic factors such as blood pressure profile and heart rate variability (HRV). Non-dipping heart rate has been shown to increase the risk of cardiovascular and non-cardiovascular morbidity and mortality among people with CKD. Compared to blood pressure, heart rate is less dependent on increased physical activities hence making it more predictive of poor cardiovascular outcomes, especially the sleep heart rate.

Several studies have shown that non-dipping heart rate pattern may be of adverse prognostic value in the general population and other cardiovascular diseases including hypertension, CKD and type 2 diabetes mellitus. [14-16] In two studies, a 10% reduction of overnight heart rate in a general and hypertensive population was associated with an increased risk of all-cause mortality by 34 and 30%, respectively. [17,18]

Despite the increased access to 24-hour ambulatory blood pressure monitoring relatively few studies on sleep heart rate exist especially among native black Africans. The purpose of this study was to assess the prevalence and clinical correlates of non-dipping heart rate among CKD patients using data from the CRECKID study from Ibadan South-West Nigeria.

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2.0 METHODS

The Ibadan **C**ardiovascular and **R**enal **E**vents in people with **C**hronic **Ki**dney**D**isease (CRECKID) study is a prospective study of adults with CKD recruited from the medical outpatient, renal, and cardiology clinics of the Department of Medicine, University College Hospital, Ibadan, Nigeria. The CRECKID study was aimed at describing the cardiovascular risk profile of subjects with CKD using the 24-hour ambulatory blood pressure monitoring to identify those that required prompt action to mitigate their cardiovascular risk.

2.1 Study site: The University College Hospital (UCH) is the foremost teaching hospital in Nigeria established in 1957 and presently has 1000 beds. Patients from Nigeria and the West African sub-region assess healthcare services from UCH, Ibadan, Nigeria.

2.2 Procedure: A total of 173 consecutive participants with CKD defined as eGFR <60 ml/min/1.732m^2 were recruited. In other to compare with individuals with hypertension whose cardiovascular risks are also substantial, 242 hypertensive-non-CKD participants and 136 normotensive non-CKD controls were also recruited making a total of 551 participants in this study. The controls were normotensives with no report of a previous diagnosis of hypertension or CKD or were found to have the same during clinical evaluation. They were excluded if they had a history of heart failure or have had renal transplantation done. Demographic variables including age, gender, occupation and tribe were also obtained.

All the participants had a 24-hour ambulatory blood pressure monitoring done using SpaceLabs ABPM (SpaceLabs Healthcare, Issaquah, WA) which was placed on the non-dominant hand and Cuff sizes were selected after measuring participants' non-dominant arm circumference. Office blood pressure was measured with the OMRON HEM 711 DLX machine and an appropriate cuff size for each participant. Hypertension was diagnosed when repeated clinic/office blood pressure was greater than 140/90 mmHg or patients reported use of antihypertensive medications.

All patients had anthropometric measurements including height, waist circumference, hip circumference (to the nearest 0.1meters), and weight (to the nearest 0.1kilograms). The waist circumference was taken in mid expiration at the mid-point between the lowermost rib and the anterior iliac crest. Fasting blood samples were analyzed in the chemical pathology laboratory, an ISO 2000 certified laboratory for fasting plasma glucose, lipid profile, electrolytes, urea and creatinine. Heart rate dipping was estimated using the formula (1- night-time heart rate/daytime heart rate) x100. Normal dipping of heart rate was defined as a decrease in heart rate >10% while blunted dip was defined as <10%. Estimated GFR was calculated using CKD-EPI Creatinine Equation and CKD was defined as eGFR<60ml/min/1.73m^2.[16]

Ethical consideration: All subjects gave written informed consent before participation. The study was conducted according to the International Guidelines of Helsinki. Ethical approval was obtained from the Institutional Ethics & Research Board of the University College Hospital/ University of Ibadan.

2.3 Data Analysis: Data analysis was done using the Statistical Package for Social Sciences Windows version 27, (IBM, Armonk NY). Quantitative variables were summarized as means ± Standard deviation while qualitative variables were expressed in frequencies and percentages. Comparison for statistical significance was done with the Student's t-test for continuous variables and Chi-square or Fisher's Exact test for categorical variables as appropriate. The logistic regression modelwas fittedto estimatethe odds ratio for blunted heart rate dipping. P<0.05 was taken as statistically significant.

3.0 RESULTS

A total of 551 participants comprised 283(51.4%) women with mean age of 51.2 ±14.4 years. Of the participants, 242(43.9%) had hypertension without CKD; 136(24.7%) were normotensives without CKD and 173(31.4%) had CKD.

The baseline characteristics of the study participants are shown in Table 1. The mean age of hypertensive subjects was 60.1 ± 12.8 years which is significantly higher than the mean age of CKD patients (46.9 ± 17.1 years) and normal normotensive, non-CKD controls (49.4 ± 12.2 years). The office systolic and diastolic blood pressures were significantly higher among hypertensive and CKD than normotensive controls. Expectedly, serum urea (*p<0.001*) and creatinine (*p<0.001*) were significantly higher among CKD than in the other two groups. The lipid profile of participants with hypertension and CKD were similar but significantly higher than that of their normotensive non-CKD controls. However, mean 24-hour SBP (*p<0.001*), mean 24-hour DBP (*p<0.001*) and mean 24-hour heart rate (*p<0.001*) decrease significantly from participants with CKD through those with hypertension without CKD to normotensive participants non-CKD. Similar pattern was observed in the awake and sleep 24-hour blood pressure and heart rate profile.

Non-dipping heart rate was commonest among participants with CKD(73.2%) compared with 38.0% and 23.5% among hypertensive non-CKD and normotensive non-CKD participants respectively (*p<0.001*). Figure 1.

The heart rate indices in total study population among non-heart rate dippers and heart rate dippers are shown in Table 2. Participants with non-dippingheart rates were more likely to be males compared to those with normal dip patterns. Compared to heart rate dippers, non-dippers had higher mean clinic and ambulatory systolic and diastolic blood pressure parameters, mean arterial blood pressure mean heart rate and pulse pressure. The significant heart rate variation between dippers and non-dippers was majorly related to the significant difference in sleep heart rate as there was no difference between awake heart rate between dippers and non-dippers. Serum urea and creatinine were significantly higher among non-dippers compared with dippers. While the fasting serum lipid profile was similar between the two groups.

In the whole study sample consisting of the three groups, mean systolic blood pressure was significantly higher among non-dippers compared to HR dippers (*p<0.001*). Similarly, diastolic blood pressure was significantly higher among non-dippers compared to dippers (*p=0.001*). The mean BMI was significantly lower among non-heart dippers than in heart rate dippers (*p=0.024*). Serum sodium (*p<0.001*) was also significantly lower among non-dippers while serum urea (*p<0.001*) and creatinine (*p<0.001*) were significantly higher among non-dippers compared to those with normal heart rate dipping patterns. The fasting serum lipid profile was not significantly different between the two study groups. The awake and sleep systolic blood pressure, diastolic blood pressure, mean arterial systolic pressure and pulse pressure were significantly higher among non-dippers compared to dippers. Additionally, the mean nighttime heart rate was significantly higher among non-dippers compared to dippers (*p<0.05*) respectively. Overall, systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, heart rate, and gender distribution were significantly different between non-dippers and dippers. The male participants (*n=268*) were more likely to have non-dipping heart rate compared to females (*54.4% vs. 45.6%, p=0.011*).

The heart rate indices in patients with chronic kidney disease by heart rate dippers status are depicted in Table 3. The ambulatory blood pressure and heart rate profile among participants with CKD showed that age, systolic and diastolic blood pressure, serum chloride and potassium were not significantly different between CKD subjects with normal dipping pattern compared to those with non-dipping heart rate. Serum sodium (132.8 ± 6.6 vs. 136.2 ± 4.5 respectively, $p<0.05$) and body mass index (24.4 ± 4.4 vs. 27.9 ± 5.3 kg/m^2 respectively, $p<0.05$) were significantly lower among non-dippers with CKD compared to CKD patients with normal dipping pattern. CKD subjects with blunted dipping pattern had significantly higher serum urea and creatinine compared with CKD subjects with normal dipping pattern while lipid status was similar between the two groups. Overall, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate were significantly higher among CKD patients with blunted dipping pattern compared to CKD subjects with normal dipping pattern. The overall significant difference in heart rate changes was due to the sleep mean heart rate that was significantly higher among those with blunted dipping compared to CKD with normal dipping pattern (83.9 ± 12.4 vs. 69.2 ± 10.3 beats/min respectively, *p<0.001*) these parameters were reflective of significant changes in the sleep mean heart rate and systolic blood pressure.

Figure 2 revealed that non-dipping heart rate progressively predominates as the degree of kidney dysfunction increases. Participants with stages 4 (73.3%) and 5 (81.7%) had the highest prevalence of non-dipping heart rate.

Using logistic regression analysis, the estimated glomerular filtration rate was the major determinant of heart rate non-dipping pattern among CKD subjects in this study among other parameters as shown in table 4. With each ml/min/m^{2}increase in eGFR, there are 1.8% higher Odds of being heart rate dipper among the study population [AOR:1.018, (95%CI:1.009-1.027), *p<0.001*].

Table 1: baseline characteristics of study participants

Variables	CKD	Hypertension without CKD	Normotensives without CKD	P value
Age(years)	46.9±17.1	60.1±12.8	49.4±12.2	<0.0001*
Body Mass Index(kg/m²)	25.0±4.6	27.6±6.2	25.5±3.8	<0.005*
Hip Circumference (cm)	84.5±19.5	88.9±19.8	91.6±14.1	0.051
Waist circumference (cm)	81.4±13.4	85.1±18.4	83.4±11.7	0.255
Clinic SBP (mmHg)	147.7±26.2	150.9±22.1	120.7±14.8	<0.0001*
Clinic DBP (mmHg)	87.3±18.5	88.9±12.7	75.4±11.8	<0.0001*
Serum Creatinine(mg/dl)	13.3±10.8	1.2±0.7	1.1±0.2	<0.0001*
Urea (mg/dl)	149.9±98.8	33.4±15.6	24.6±7.0	<0.0001*
Total Cholesterol (mg/dl)	198.0±46.1	242.2±66.8	222.2±48.7	0.001*
Triglycerides (mg/dl)	126.0±69.1	95.0±35.1	88.6±26.1	<0.0001*
HDL Cholesterol(mg/dl)	47.6±16.7	70.7±21.9	57.1±13.7	<0.0001*
24-hour SBP (mmHg)	137.8±20.8	126.0±15.0	112.5±11.2	<0.0001*
24-hour DBP (mmHg)	85.8±16.1	75.9±9.3	71.1±8.8	<0.0001*
24-hour Heart rate(beat/min)	84.0±12.5	74.8±10.2	74.3±8.3	<0.0001*
Wake period SBP (mmHg)	138.3±20.8	127.8±14.8	115.6±11.0	<0.0001*
Wake period DBP (mmHg)	86.5±16	78.1±9.3	74.6±8.8	<0.0001*
Wake Period Heart rate(beat/min)	85.0±12.4	77.9±10.6	78.7±9.0	<0.0001*
Sleep Period SBP (mmHg)	136.3±22.3	119.2±25.2	107.0±12.7	<0.0001*
Sleep Period DBP (mmHg)	84.2±17.0	69.8±15.2	65.0±9.5	<0.0001*
Sleep period Heart rate(mmHg)	82.4±13.5	66.5±14.6	66.3±7.6	<0.0001*

*** Significant at 5% level of significance**

SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure

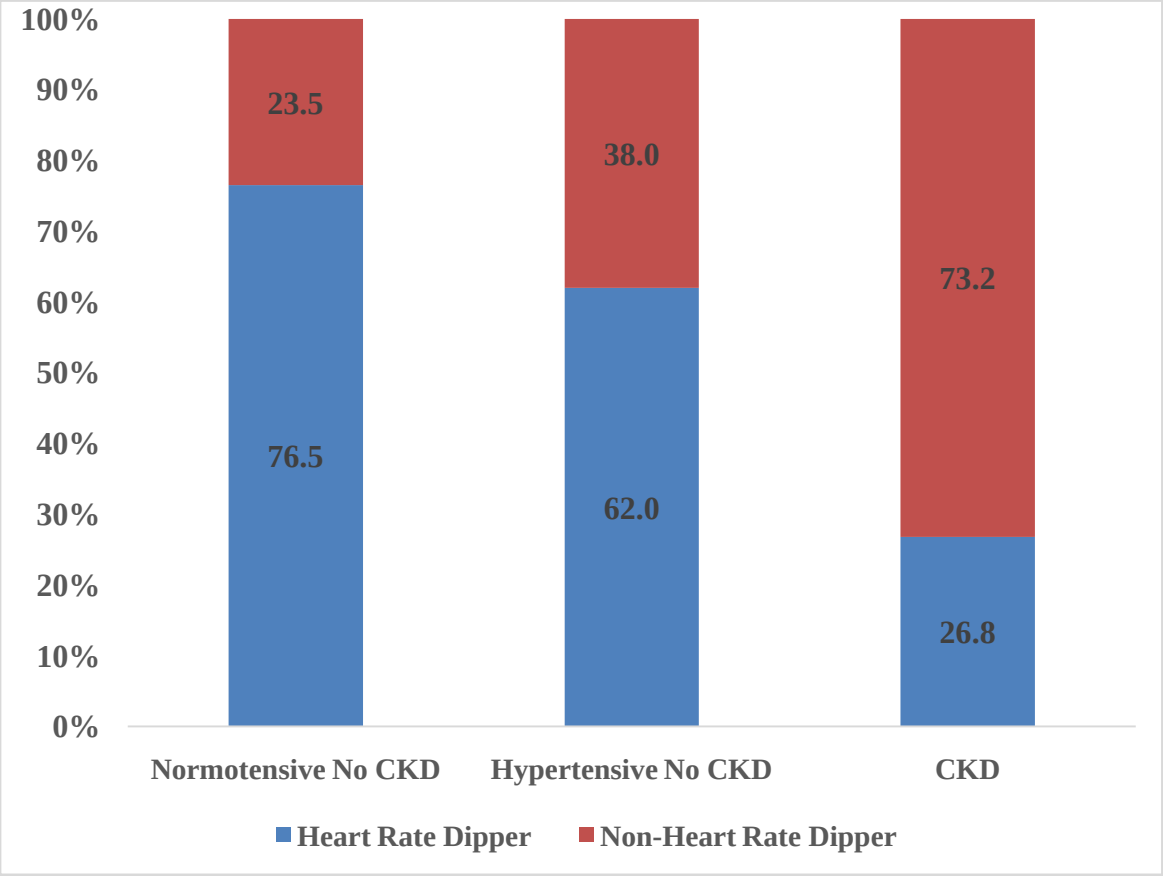


Figure 1: Frequency of Heart rate dipping among participants with CKD, Hypertensive non-CKD and Normotensive non-CKD

Table 2: Heart rate indices in total study population among non-heart rate dippers and heart rate dippers

Period	Variables	Non-Heart Rate Dippers (Mean±SD)	Heart Rate Dippers (Mean±SD)	t	p-value
Clinic	SBP	144.9±27.5	136.2±23.3	3.963	<0.001*
	DBP	89.7±17.2	85.1±14.6	3.316	0.001*
	BMI	25.5±4.7	26.9±5.7	-2.275	0.024*
	Sodium	135.4±6.2	138.6±5.1	-3.744	<0.001*
	Potassium	4.9±4.3	5.1±9.3	-0.208	0.836
	Chloride	101.6±5.3	102.6±4.3	-1.459	0.146
	Urea	109.7±100.9	39.5±42.5	7.165	<0.001*
	Creatinine	8.5±11.3	2.1±2.5	6.359	<0.001*
	Total Cholesterol	178.3±46.9	188.8±70.8	-1.211	0.228
	Triglyceride	113.8±74.4	110.6±70.4	0.515	0.756
	HDL Cholesterol	50.9±18.9	49.0±16.5	0.788	0.432
	LDL Cholesterol	109.1±38.5	119.6±60.4	-1.434	0.154
Awake	SBP	131.8±19.7	121.9±15.9	6.505	<0.001*
	DBP	82.9±14.1	77.4±9.9	5.245	<0.001*
	Map	99.7±15.4	92.9±10.9	5.904	<0.001*
	Pulse Pressure	49.0±11.2	44.9±9.3	4.610	<0.001*
	Heart Rate	81.1±12.2	80.±9.5	1.035	0.301
Sleep	SBP	128.7±22.3	115.0±16.3	7.757	<0.001*
	DBP	78.7±15.5	69.7±11.0	7.807	<0.001*
	MAP	96.1±17.5	85.6±13.1	7.874	<0.001*
	Pulse Pressure	50.1±12.2	46.2±10.4	4.025	<0.001*
	Heart Rate	78.8±12.8	66.1±8.8	13.427	<0.001*
Overall summary	SBP	130.8±20.0	120.0±14.7	7.159	<0.001*
	DBP	81.5±14.2	74.7±9.9	6.413	<0.001*
	MAP	98.3±15.8	90.5±10.9	6.681	<0.001*
	Pulse Pressure	49.3±11.2	45.5±9.8	4.257	<0.001*
	Heart Rate	80.3±12.3	75.4±9.0	5.332	<0.001*
	Gender (Males) (n=268)	142 (54.4%)	126(45.6%)	6.603	0.011*

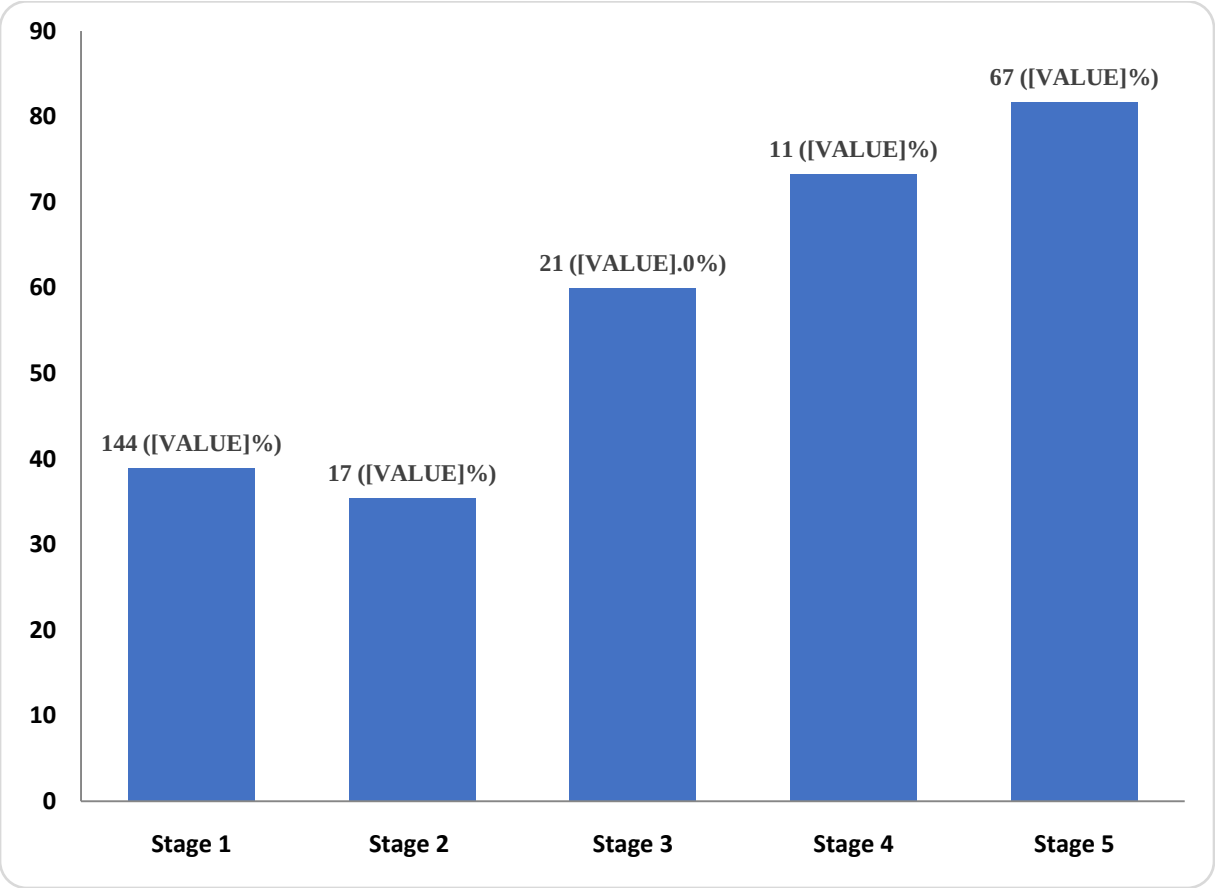
*** Significant at 5% level of significance**
SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure

Table 3: Heart rate indices in patients with chronic kidney disease by heart rate dippers status

Period	Variables	Non-Heart Rate Dipper (Mean±SD)	Heart Rate Dipper (Mean±SD)	t	p-value
Clinic	Age	46.4±14.5	51.3±15.4	-1.8	0.074
	SBP	146.5±28.3	141.1±24.2	1.053	0.294
	DBP	90.2±18.3	89.0±18.4	0.360	0.719
	BMI	24.4±4.4	27.9±5.3	-2.730	0.008*
	Sodium	132.8±6.6	136.2±4.5	-2.073	0.042*
	Potassium	4.8± 1.0	9.2±20.6	-0.941	0.359
	Chloride	101.3±6.3	103.1±5.5	-1.055	0.295
	Urea	153.8±99.5	83.3±57.3	4.596	<0.001.*
	Creatinine	11.1±8.3	4.9±3.5	5.694	<0.001*
	Total Cholesterol	170.3±45.7	224.7±114.6	-2.069	0.051
	Triglyceride	120.6±89.3	149.6±123.9	-1.131	0.262
	HDL Cholesterol	52.7±21.7	54.6±20.7	-0.327	0262
	LDL Cholesterol	99.1±37.0	139.5±91.4	-2.742	0.008*
Awake	SBP	136.9±21.0	129.4±18.0	1.969	0.051
	DBP	86.3±15.2	80.0±13.4	2.280	0.024*
	MAP	103.6±16.7	97.0±14.0	2.161	0.032*
	Pulse Pressure	50.6±11.9	49.4±11.3	0.525	0.600
	Heart Rate	84.8±12.1	81.9±10.4	1.306	0.193
Sleep	SBP	135.5±22.3	123.7±18.1	2.942	0.004*
	DBP	84.1±15.3	74.8±14.2	3.272	0.001*
	Map	101.8±17.4	92.2±14.6	3.054	0.003*
	Pulse Pressure	51.6±12.8	49.9±12.2	0.706	0.481
	Heart Rate	83.9±12.4	69.2±10.3	6.552	<0.001*
Overall summary	SBP	136.5±20.9	127.64±17.7	2.339	0.02*
	DBP	85.6±14.9	78.17±13.5	2.728	0.007*
	MAP	102.8±16.9	95.19±13.9	2.487	0.014*
	Pulse Pressure	50.9±11.8	49.47±11.5	0.626	0.532
	Heart Rate	84.5±12.0	77.31±10.0	3.271	0.001*

*** Significant at 5% level of significance**

SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure



$\chi^2 = 58.436$, df = 4; p <0.001

Figure 2: The proportion of participants with blunted heart rate dip based on the staging of CKD

Table 4: Predictors of heart rate dipper among study group

Variables	AOR	95% C.I for AOR		p-value
HYC	0.950	0.880	1.025	0.185
FGF	1.002	0.998	1.005	0.307
Age (Years)	1.008	0.983	1.034	0.535
eGFR (ml/min/m^2)	1.018	1.009	1.027	<0.001*
Sex (Males)	1.246	0.599	2.591	0.556

* Significant at 5% level of significance

[HYC- HomocysteineFGF- Fibroblast Growth FactoreGFR- estimated Glomerular Filtration Rate]

4.0 DISCUSSION

This study highlights a very high prevalence of blunted heart rate dipping among CKD patients significantly compared to hypertensive subjects and normotensive non-CKD controls. Almost four-fifth of CKD patients compared to two-fifth of subjects with hypertension and one-fifth of normal controls had blunted dipping pattern.

This reported prevalence is significantly higher than that which is reported from a cohort of predialysis patients in a study from Turkey where the prevalence of blunted HRV was 43.3%. It is however similar to what was recorded in the dialysis group in that study with a reported prevalence of 77.4%. Some but not all participants in our study were in the dialytic group based on their eGFR.[19] The same study reported a prevalence of 26.3% in the non-CKD hypertensive group similar to what was found in normal controls in this study. The linkage between heart rate variability, blunted heart rate dip, cardiovascular mortality and outcome have recently gained some attention.[2,8,11,17] This finding may suggest that increased cardiovascular risk among Black Africans compared to Asians and European counterparts may be linked in part to blunted heart rate dip among other parameters.[20,21] An accessible marker of sympathetic activity and vital stability is heart rate and it has been reported to be predictive of all-cause mortality, renal outcome and cardiovascular disease.[8,11,17] It follows circadian rhythms and it reduces by 10-20% at night due to the effect of parasympathetic system.[22-24] A study conducted by Cui and associates in 2021 demonstrated that non-dipping HR was a prognostic marker of all-cause mortality in CKD patients.[5,25]

A two-center prospective longitudinal follow-up study from China reported a prevalence of 64.2% in CKD subjects which is lower than what was reported in this study.[26] They also demonstrated that blunted HR dip was associated with renal outcome and progressive renal decline independent of blood pressure variability. There was also evidence to show that rising nocturnal heart rate is associated majorly with a progressive reduction in eGFR.[27] The circadian rhythm of the autonomic nervous system allows the parasympathetic system to be dominant at night leading to reduced heart rate. The pathophysiology of abnormal heart rate dip is very complex and relates to abnormal circadian gene expression, abnormal neurohormonal system regulation leading to increased sympathetic excitability and nocturnal elevation of heart rate causing the blunted heart rate dip.[28-30] The majority of patients with CKD in this study had blunted HR dip indicating that they already have an imbalance of the autonomic system with sympathetic drive dominance leading to significant changes, especially in nocturnal heart rate which also drives the major differences noted in the overall heart rate variability of not just the subjects with CKD, hypertension but all study participants. The effect of blunted HR dip occurs in pathological disruptions involving the heart and kidneys leading to preclinical damage, microalbuminuria, excessive cardiovascular mortality, cardiovascular complications and all-cause mortality.[31] The association with increased systolic blood pressure, diastolic blood pressure, mean arterial systolic blood pressure and significantly reduced eGFR among CKD with blunted HR lends credence to the increased CV mortality among CKD subjects with blunted HR dip compared with CKD subjects with normal HR dip pattern. This is in line with similar reports that have linked same.[18,22,29]

Elevated nocturnal heart rate is associated with increased cardiovascular mortality even in healthy people.[2] It is a predictor of target organ damage in hypertension and arterial stiffness in hypertension. Some studies have also shown that nighttime heart rate was a better predictor of cardiovascular events than daytime heart rate.[11,18] Blunted heart rate dip was commoner as kidney disease advances in line with known fact that decreasing renal function is associated with poorer prognosis. Thus, blunted heart rate seems to identify a group of cohorts who are at advanced cardiovascular risk requiring intensive management to halt their deterioration and clinical progression. The findings of this study showing that blunted heart rate or non-dipping heart rate status dominates as the degree of kidney disease advances may also explain the progressively increased cardiovascular risk associated with CKD and the excessive mortality from CVD in patients with CKD as the disease progress. It therefore suggests that blunted heart rate can be used as a biomarker of increased risk at any stage of CKD to identify those that require intensive and collaborative effort to reduce cardiovascular mortality in them.

The determinant of blunted heart rate dip was majorly estimated glomerular filtration rate. Gender, age and other demographic parameters were not significant contributors to having blunted HR dip in this study.[12,16] The associated physiological and pathological effects of blunted heart rate dip including albuminuria, left ventricular hypertrophy, and cardiovascular damage among other things contribute significantly to the prognosis of blunted heart rate dip in CKD patients. This is evidence in the findings of this study linking blunted heart rate dip with established conventional cardiovascular disease risk factors.[32-34]

This study has many strengths, first, it is the first to our knowledge on the significance of blunted heart rate dip in hypertensive and CKD patients in Black Africans with fairly large sample size. There are, however, some limitations. First, the impact of drugs taken before the ambulatory monitoring was done was not considered likewise the choice of drugs to manage cardiovascular disease patients.

4.1 Conclusions:

This study concludes that blunted heart rate dip is rather more common among Africans compared to Caucasians and is prevalent as eGFR progressively reduces with eGFR being the major determinant of having blunted heart rate dip in a cohort of hypertensive, normal and subjects with CKD in south-west Nigeria.

Blunted heart rate is related to conventional ambulatory CV risk markers and can be used to identify cohorts of CKD and hypertensive subjects requiring intensive cardiovascular

Ethics Approval and Consent to Participate: This study was performed according to the International Guideline on the Declaration of Helsinki. Institutional Ethical approval was obtained from the Research Ethics Board of University of Ibadan/University College Hospital, Ibadan. All study participants gave a written informed consent.

Availability of Data and material: The data is available on reasonable request to the corresponding author.
Competing Interest: Nil

Funding: Nil

Author's contribution:
AMA- was involved in study conceptualization, design, data obtaining, statistical analysis, review and final approval of manuscript.

AAA- conceptualization, statistical analysis, drafting the manuscript and final approval of manuscript
LA-study conceptualization, data analysis, review and final approval of manuscript
AGF- conceptualization, statistical analysis, drafting the manuscript and final approval of manuscript
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