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Prognostic value of nocturnal blood pressure dipping on cardiovascular outcomes in Chinese patients with hypertension in primary care

Ling Lo MBChB | Sandra W. S. Hung MBChB | Sara S. W. Chan MBChB | Chui-Ling Mak MSc | Pang-Fai Chan FHKAM | David V. K. Chao FRCGP

Department of Family Medicine and Primary Health Care, Kowloon East Cluster, Hospital Authority, Hong Kong, China

Correspondence
Ling Lo, Department of Family Medicine and Primary Health Care, United Christian Hospital, Hospital Authority, Hong Kong, China.
Email: lol1@ha.org.hk

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Abstract

Meta-analyses showed that non-dipping of nocturnal blood pressure on ambulatory blood pressure monitoring (ABPM) was associated with adverse cardiovascular prognosis. However, these prognostic studies were mainly conducted in Caucasian and Japanese populations. Whether this association applies to Chinese patients remained uninvestigated. A total of 1199 Chinese patients with hypertension undergoing ABPM between January 2012 and December 2014 were recruited retrospectively from five public hypertension referral clinics in Hong Kong. Patients were followed up for a mean 6.42 years for cardiovascular morbidity and mortality and all-cause mortality. Time to event of different dipping patterns was compared by Kaplan-Meier curves. Hazard ratios (HR) were obtained by Cox proportional hazard models with patient demographics and confounding factors adjusted in multivariate regression. A total of 163 end point events occurred in the period. Normal dipping was observed in 446 patients (37.2%), non-dipping in 490 (40.9%), reverse dipping in 161 (13.4%), and extreme dipping in 102 (8.5%). Kaplan-Meier analyses showed inferior survival in non-dippers and reverse dippers for total cardiovascular events and coronary events but not cerebrovascular events. After adjusting for confounding factors, Cox regressions showed HRs 1.166 (CI 0.770-1.764) and 1.173 (CI 0.681-2.021) in non-dippers and reverse dippers for total cardiovascular events, and HRs 1.320 (CI 0.814-2.141) and 1.476 (CI 0.783-2.784) for coronary events. Nocturnal blood pressure non-dipping, and to a greater extent reverse dipping, demonstrated adverse cardiovascular prognosis in a cohort of Chinese patients with hypertension in Hong Kong. Further focused studies on cerebrovascular events and reverse dippers were warranted to refine risk stratification.

1 | INTRODUCTION

The first ambulatory blood pressure monitoring (ABPM) device was developed in 1962.[1] It realized non-invasive measurement of out-of-office blood pressure (BP) and informed BP level at sleep time, enriching BP's clinical role in cardiovascular (CV) health beyond clinic BP in the era. The human circadian BP follows a diurnal variation, and most people exhibit a 10%-20% BP drop at night. Certain

normotensive and hypertensive subjects do not demonstrate such a reduction and were postulated to bear a higher CV risk. This prognostic query was addressed in the 1980s, when O'Brien et al first reported a higher prevalence of stroke in hypertensive patients with a blunted nocturnal BP dip and named these patients "non-dippers."[2] Since then, several prospective studies reported on the prognostic significance of nocturnal BP fall both in hypertensive patients and in population-based cohorts.[3]

However, most of these studies were conducted in Europe and Japan. There was a paucity of prognostic reports on nocturnal BP drop in patients of Chinese ethnicity. The presentations of hypertension also demonstrated major ethnic[4-7] and regional[8-13] differences. For instance, the contribution of BP for CV events was higher in Asian populations than in Western populations.[14] These diverging characteristics call for local interpretation and refinement of international best practice to benefit specific populations.[15]

To date, local studies of circadian BP profiles on ABPM remain little reported. This report is the first ABPM prognosis study on CV outcomes in Hong Kong. It aims to investigate the prognostic significance of nocturnal BP dipping on CV outcomes in a retrospective cohort of Chinese patients with hypertension. Other objectives include the reporting of the prevalence of different BP dipping profiles and the real-life incidence of CV outcomes in the local primary care setting.

2 | METHODS

The Risk Assessment and Management Programme—Hypertension (RAMP-HT) was established under the Hospital Authority of Hong Kong in 2011, aiming to improve the quality of care for patients with hypertension in primary care. Its RAMP-HT Clinics were hypertension referral clinics. They received referrals of patients with suspected white coat hypertension, hypertension with white coat component, or refractory hypertension from affiliated public primary care clinics. ABPM was performed for those patients with persistent high clinic BP suspected to be due to white coat effect. The study population was a retrospective cohort of Chinese hypertensive patients undergoing ABPM in five RAMP-HT Clinics between January 1, 2012 and December 31, 2014. Sample size, accrual, and follow-up periods were set on practical grounds with reference to individual studies heretofore published. An initial 1576 subjects were recruited. Patients of non-Chinese ethnicity, and those with secondary hypertension, known sleep disorders (eg, obstructive sleep apnea), or lower urinary tract symptoms were excluded. Recordings were only valid for analysis with a minimum of 14 daytime and 7 nighttime readings according to standardized program guidelines. Two cases with incomplete computer data not supplemented by paper records were not analyzed. A final cohort of 1199 patients was included. Background demographics and baseline clinical parameters were collected and subsequently adjusted for in multiple regression.

All patients received clinical assessment by family medicine specialists, and education from program nurses before ABPM was performed. Patients were offered ABPM over 24 hours on a weekday, with measurements in every 30 minutes in day time and 60 minutes in night time (22:00-06:00). Awake and sleep time periods were defined by patient diary. ABPM was recorded by a validated oscillometric device (A&D Co., Ltd. Model: TM-2430)[16] and analyzed by the original software in all centers. Dipping status was assessed by three classification schemes. It was first assessed numerically by *Systolic BP Night-day Ratio (SBP-NDR)* = [Daytime BP-Nighttime BP] / Daytime BP. It was also classified categorically into two traditional dipping patterns, namely *Dippers* (SBP-NDR ≤0.9) and *Non-dippers* (SBP-NDR >0.9). And with reference to the latest meta-analysis,[3] nocturnal dipping pattern was further sub-grouped into:

Normal dipper	= SBP-NDR >0.8 to ≤0.9
Non-dipper	= SBP-NDR >0.9 to ≤1.0
Reverse dipper (riser)	= SBP-NDR >1.0
Extreme dipper	= SBP-NDR ≤0.8

2.1 | Follow-up and outcomes

All patients were followed up in the RAMP-HT Clinics and eight affiliated general outpatient clinics for usual BP management. The end of follow-up was defined at March 1, 2020, when patients' computer medical records were reviewed for CV outcomes in both public and private sectors. Seventeen patients (1.4%) with more than one ABPM performed were analyzed on their last ABPM to allow for possible anxiety with the procedure. CV outcomes assessed included the following: 1. Acute (non-fatal) myocardial infarction, 2. Acute (non-fatal) cerebral vascular accident, 3. Congestive heart failure, 4. Transient ischemic attack, 5. Re-vascularization, 6. CV-related hospitalization, 7. Peripheral vascular disease, 8. End-stage renal failure, 9. CV mortality, 10. Non-CV mortality, and 11. New diagnosis of coronary heart disease / cerebrovascular disease. Analyses were restricted to the first CV event under study. CV outcomes were grouped into *Total CV events*, *Major adverse cardiovascular events (MACE)*, *Coronary events*, *Cerebrovascular events*, *CV mortality*, and *All-cause mortality* for composite analysis:

Total CV events	= Outcomes 1-11 excluding 10
MACE	= Outcomes 1, 2, 3, 9
Coronary events	= Outcomes 1, 3, 5, 6, 9, 11
Cerebrovascular events	= Outcomes 2 and 4
CV mortality	= Outcome 9
All-cause mortality	= Outcomes 9 and 10

2.2 | Data analysis and statistics

Numerical data were reported as mean (and standard deviation). Baseline patient demographics were overall compared by one-way ANOVA and chi-square test. Post hoc pairwise comparisons were performed by Dunnett's test and chi-square test with Bonferroni adjustment, with normal dipping as control. Survival curves were

estimated using Kaplan-Meier product limit method and compared by the logrank statistic, with and without correction for multiple pairwise comparisons. The prognostic significance of different dipping patterns was evaluated by multivariate Cox proportional hazard regression models. Proportional hazard assumption was tested by inspection of log minus log curves. With reference to meta-analyses in this subject, hazard ratios (HR) were obtained after adjusting for multiple independent variables including mean 24-hr systolic BP (every 10 mmHg rise), sex (men vs. women), age (every 5 years rise), presence of smoking, pre-existing cardiovascular or cerebrovascular disease (CVD), diabetes mellitus (DM), hyperlipidemia, chronic kidney disease (CKD) (eGFR <60 mL/min/1.73m^2), obesity (BMI ≥25), left ventricular hypertrophy on ECG, and anti-hypertensive treatment. Hyperlipidemia was defined as elevated low-density lipoprotein or triglyceride level above treatment threshold, or the use of lipid-lowering agents. Two-sided *P* values ≤0.05 were considered statistically significant. Data were analyzed on IBM SPSS Statistics Subscription (build 1.0.0.1447).

3 | RESULTS

A total of 1199 patients were followed up for a mean 6.42 years. Their mean age was 64.5 years, and mean sleep duration was 8.35 hours. The mean number of awake and sleep time BP readings was 33.3 (range 20-39) and 9.80 (range 7-23), respectively. Normal dipping was observed in 446 patients (37.2%), non-dipping in 490 (40.9%), reverse dipping in 161 (13.4%), and extreme dipping in 102 (8.5%). Baseline characteristics of the four dipping subgroups (Table 1) were overall compared, as well as pairwise compared with normal dipping as referent. A total of 163 end point outcomes occurred in the study period (Tables 2 and 3).

We regarded total CV events as the primary end point of interest because of their comprehensive nature and large numbers, which led to more stable results. The first Kaplan-Meier curve suggested the null hypothesis that traditional dippers (SBP-NDR ≤0.9) and non-dippers (SBP-NDR >0.9) do not differ in CV outcomes was disputable (Figure 1). The logrank statistic gave a *P* value of 0.080, denoting a marginally significant difference between the two curves. In the second analysis of the four dipping subgroups, the overall logrank statistic showed a significant difference between the 4 survival curves (*P* = .001) (Figure 2). Significant pairwise differences were observed when reverse dippers (risers) were compared against all other dipping patterns (all *P* values <0.010). After multiplicity correction by the Bonferroni method, reverse dipping maintained its significance against all the other dipping patterns (*P* =.006 vs. dipper; *P* =.006 vs. non-dipper; *P* =.030 vs. extreme dipper). Other pairwise combinations were not statistically significant (Table 4). Further Kaplan-Meier survival analyses were performed on other composite end point events, that is, MACE, coronary events, cerebrovascular events, CV mortality, and all-cause mortality. Similar significant overall differences were observed in MACE and coronary events, but not in cerebrovascular events, CV mortality, or all-cause mortality. Significant pairwise subgroup differences were additionally observed in coronary events.

Tables 5 and 6 summarized further prognostic analyses of different BP dipping patterns on all CV event categories. Three sets of Cox regression were performed on the three classifications of dipping

TABLE 1 Baseline characteristics of the four dipping subgroups

	Normal dippers n = 446 (37.2%)	Non-dippers n = 490 (40.9%)	Reverse dippers n = 161 (13.4%)	Extreme dippers n = 102 (8.5%)	Overall *P* value
Independent variables					
Sex (% men)	30.3	30.0	24.8	30.4	NS
Age (year)	63.1 (9.3)	65.0 (9.8)†	67.8 (9.5)‡	63.8 (8.7)	<0.001
Smoking (% smoker)	1.3	1.4	0.0	2.9	NS
Pre-existing CVD (%)	9.0	8.4	10.6	3.9	NS
DM (%)	23.8	32.7*	30.4	18.6	0.003
Hyperlipidemia (%)	62.3	65.5	69.6	61.8	NS
CKD (%)	7.4	13.3*	12.4	3.9	0.003
Obesity (%)	40.1	38.6	35.4	33.3	NS
LVH (%)	4.3	7.3	3.7	6.9	NS
Anti-HT Rx (%)	87.7	90.0	96.9†	90.2	0.010
Day SBP	135.7 (12.6)	132.8 (12.1)†	133.8 (14.2)	140.7 (12.9)†	<0.001
Night SBP	116.3 (11.0)	125.6 (11.9)‡	140.7 (15.6)‡	107.7 (10.4)‡	<0.001
Mean 24-hr SBP	131.4 (12.1)	131.1 (12.0)	135.4 (14.3)†	133.6 (12.4)	<0.001

Note: Numerical data are reported as mean (standard deviation). Post hoc pairwise comparisons with normal dipping as control.

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular or cerebrovascular disease; LVH, left ventricular hypertrophy; NS Not significant; SBP, systolic BP.

*P <.05 †P <.01 ‡P <.001.

TABLE 2 Frequency and definition of individual CV outcomes

0	Nil		1036
1	Acute (non-fatal) myocardial infarction Diagnosis by clinical, biochemical and ECG criteria	3	
2	Acute (non-fatal) cerebral vascular accident Acute ischemic or hemorrhagic stroke confirmed on investigation	26	
3	Congestive heart failure New congestive heart failure or hospital admission for heart failure	7	
4	Transient ischemic attack Neurological deficits lasting less than 24 hours	3	
5	Re-vascularization Elective percutaneous coronary interventions	1	
6	CV-related hospitalization Cardiac arrhythmias, uncontrolled BP, stable and unstable angina	32	
7	Peripheral vascular disease Both clinical diagnosis by vascular surgeons or by investigations	0	
8	End-stage renal failure Progressive renal failure to eGFR <15 mL/min/1.73m^2 or dialysis	3	
9	CV mortality Cardiovascular or cerebrovascular cause of death	3	
10	Non-CV mortality Mortality not of cardiovascular or cerebrovascular origin	43	
11	New coronary heart disease / cerebrovascular disease Both clinical diagnosis or by investigations, without an acute event	42 Subtotal	163
		Total	1199

Abbreviation: CV, cardiovascular; eGFR, estimated glomerular filtration rate.

TABLE 3 Frequency and incidence rate of composite end point events in the four dipping subgroups

	Normal dippers n = 446 (37.2%)	Non-dippers n = 490 (40.9%)	Reverse dippers n = 161 (13.4%)	Extreme dippers n = 102 (8.5%)
Frequency (Incidence rate)				
Total CV events	40 (13.9)	45 (14.3)	29 (28.4)	6 (9.2)
MACE	9 (3.1)	20 (6.4)	9 (8.8)	1 (1.5)
Coronary events	29 (10.0)	31 (9.9)	22 (21.5)	6 (9.2)
Cerebrovascular events	10 (3.5)	13 (4.1)	6 (5.9)	0 (0)
CV mortality	1 (0.3)	1 (0.3)	1 (1.0)	0 (0)
All-cause mortality	17 (5.9)	15 (4.8)	11 (10.8)	3 (4.6)

Note: Incidence rates are per 1000 person-years of follow-up.

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular events.

(traditional dippers vs. non-dippers, the four dipping subgroups, and the continuous variable SBP-NDR). Age and sex were first adjusted for in a basic regression model (Table 5). Twenty-four hour mean BP and multiple independent variables (above) were additionally adjusted for in a subsequent full model (Table 6). For total CV events, both models suggested a higher risk for traditional non-dippers versus dippers (HRs 1.210 and 1.166 in the basic and full models, respectively). On subgroup analysis, reverse dipping showed the highest hazard ratios (HRs 1.303 and 1.173), signifying the worst prognosis. These HRs were generally attenuated in the full model and were statistically insignificant with confidence intervals spanning across 1.0.

The inferior prognosis of traditional non-dippers above was also demonstrated in MACE, coronary events, and all-cause mortality. This inferiority, however, was not consistently demonstrated in cerebrovascular events and CV mortality. As for subgroup analysis, reverse dipping was associated with the highest risk in total CV events (above),

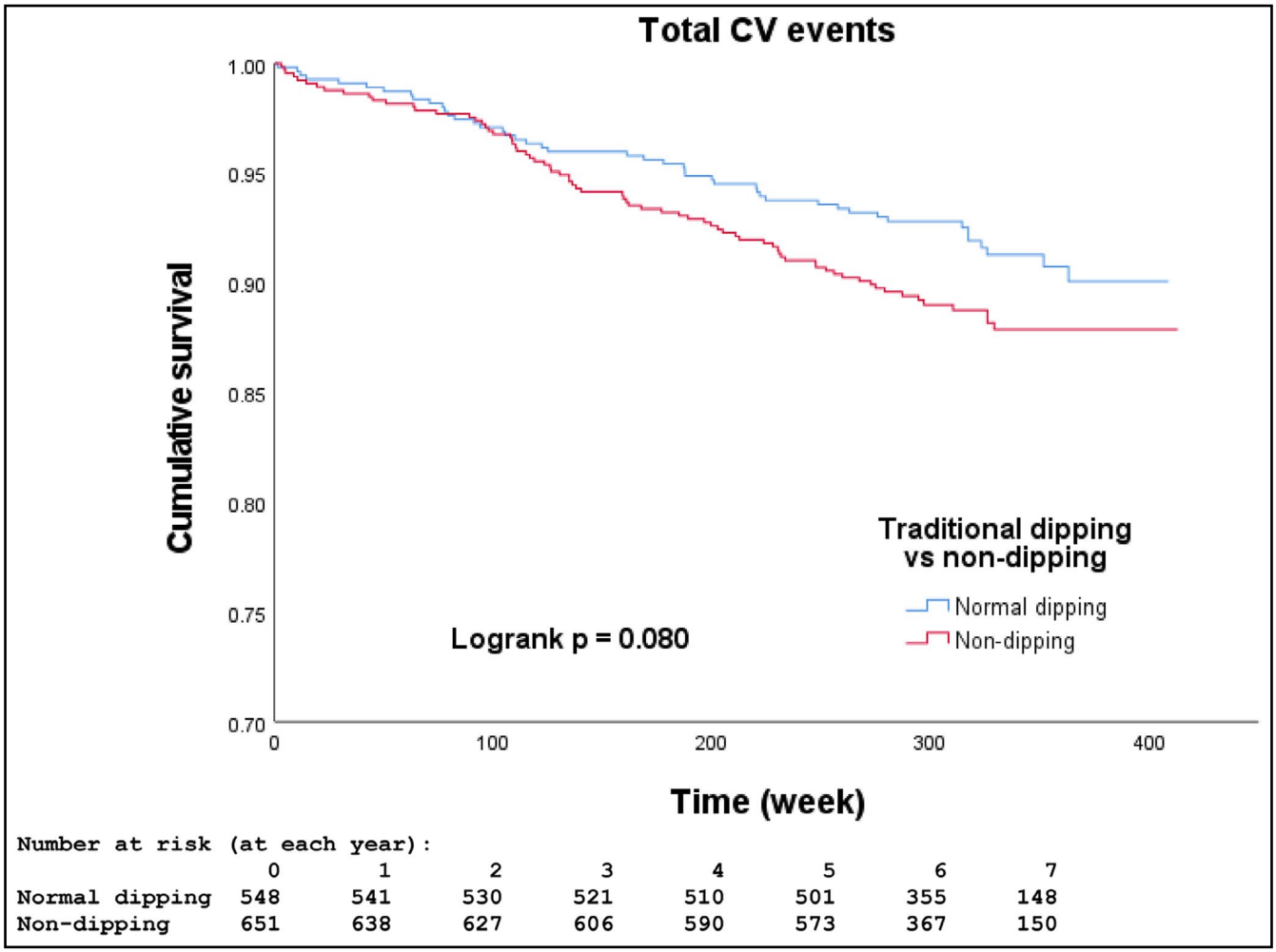

FIGURE 1 Kaplan-Meier curves for traditional dipping versus non-dipping. Abbreviation: CV, cardiovascular

coronary events, and all-cause mortality, while non-dipping was associated with the highest risk in MACE and cerebrovascular events.

On the last row of analysis by the continuous variable, every one standard deviation (= 0.0841) rise in SBP-NDR consistently demonstrated inferior survival in total CV events, coronary events, and all-cause mortality, but not in MACE, cerebrovascular events, or CV mortality. A final observation of note was the eccentric HRs for CV mortality. It was the result of a very low event rate during the study period with a mere CV mortality of three (Table 3).

4 | DISCUSSION

In the field of ABPM, a number of Asia-specific circadian hemodynamic profiles and hypertension-related CV complications are evident. For instance, masked hypertension is more common in Asia, and BP variability, especially an exaggerated morning BP surge and nocturnal hypertension, is greater in Asians than in Westerners.[15] In addition, the slope of the association between increasing SBP and the rate of cerebrovascular events is steeper in Asian than in Western populations.[17]

Published reports on ABPM and prognosis on Chinese hypertensive subjects in the literature focused on other facets of the disease different from our study. For example, the JingNing study[8] was conducted in six villages in a mountain area in mainland China, vastly different from the metropolitan background of Hong Kong. Many prognostic studies on Chinese subjects were cross-sectional rather than prospective in design.[8,18-20] A few of them focused on patients with CKD and renal damage,[21-23] while some others investigated intermediate target organ damages but not CV end points.[24,25]

The merit of the present study resides on several aspects: While many cross-sectional studies provided valuable prognostic information, they could not extrapolate association to causality. The present study followed a cohort of 1199 patients for a mean 6.42 years, commensurate with other international cohorts,[3] and reported the actual development of CV events over time. A few other studies in the literature reported intermediate target organ damages as end points. Our approach was to investigate a comprehensive range of CV outcomes and composite end point events, reflecting real-life morbidity and mortality accruals. Several other studies on Chinese patients were conducted in patients with CKD.[21-23] Our study adopted a multivariate regression method to adjust not only for the

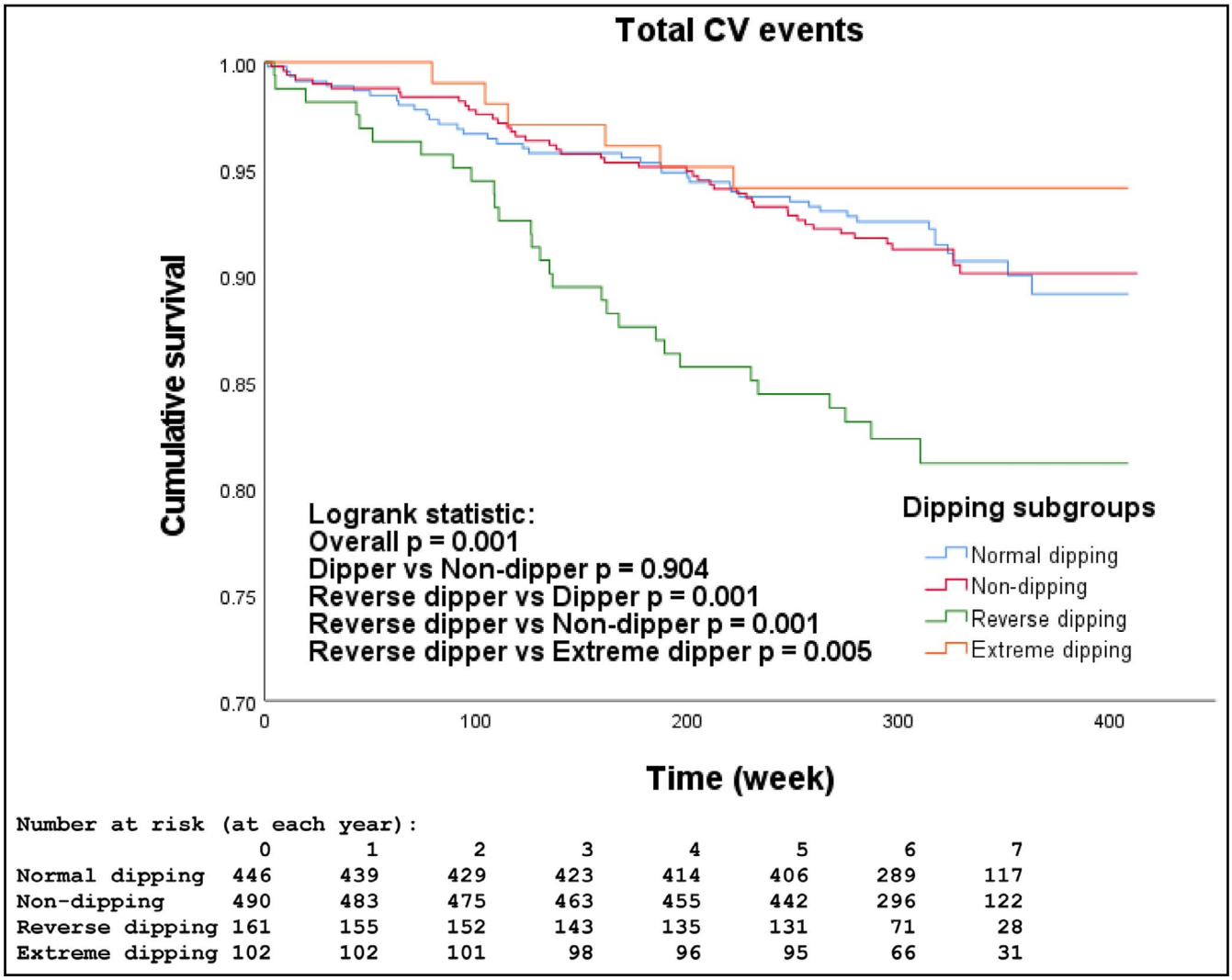

FIGURE 2 Kaplan-Meier curves for the four dipping subgroups. Abbreviation: CV, cardiovascular

TABLE 4 Kaplan-Meier analyses of all composite end point events

	Total CV events	MACE	Coronary events	Cerebro-vascular events	CV mortality	All-cause mortality
Traditional non-dippers vs. dippers	0.080	0.010	0.005	0.205	0.638	0.681
Subgroups of dipping						
Overall comparison	0.001	0.041	0.005	0.238	0.673	0.086
Non-dipper vs. Dipper	NS	NS	NS	NS	NS	NS
Reverse dipper vs. Dipper	0.001 *(0.006)*	0.016 *(0.096)*	0.002 *(0.012)*	NS	NS	NS
Reverse dipper vs. Non-dipper	0.001 *(0.006)*	NS	0.002 *(0.012)*	NS	NS	0.016 *(0.096)*
Reverse dipper vs. Extreme dipper	0.005 *(0.030)*	NS	0.037 *(0.222)*	0.045 *(0.270)*	NS	NS
Extreme dipper vs. Dipper	NS	NS	NS	NS	NS	NS
Extreme dipper vs. Non-dipper	NS	NS	NS	NS	NS	NS

Note: P values of comparisons by the logrank statistic are shown. Bonferroni adjustment for multiplicity is given in ( ). NS non-significant *P* >.05.
Abbreviations: CV, cardiovascular; MACE major adverse cardiovascular events.

TABLE 5 Adjusted hazard ratios of CV events in Cox proportional hazard models (adjusted for age and sex only)

	Total CV events		MACE		Coronary events		Cerebrovascular events		CV mortality		All-cause mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Traditional non-dippers vs. dippers	**1.210** (0.831-1.761)	0.321	**1.813** (0.871-3.774)	0.112	**1.189** (0.768-1.840)	0.979	**1.275** (0.585-2.776)	0.541	**1.733** (0.119-23.831)	0.677	**1.030** (0.565-1.880)	0.923
Subgroups of dipping (vs. Normal dipping)												
Non-dipping	**1.158** (0.752-1.783)	0.505	**1.933** (0.873-4.282)	0.104	**1.156** (0.691-1.932)	0.581	**1.183** (0.514-2.724)	0.692	**1.191** (0.065-21.863)	0.906	**0.767** (0.368-1.598)	0.479
Reverse dipping	**1.303** (0.792-2.142)	0.298	**1.319** (0.504-3.450)	0.572	**1.449** (0.812-2.585)	0.209	**0.912** (0.320-2.594)	0.862	**3.589** (0.142-90.631)	0.438	**1.349** (0.607-2.997)	0.462
Extreme dipping	**0.986** (0.406-2.396)	0.975	**0.633** (0.077-5.197)	0.670	**1.409** (0.562-3.535)	0.465	**0.000** (0.000-)	0.981	**0.000** (0.000-)	0.992	**0.619** (0.160-2.393)	0.487
SBP-NDR (every 1 SD rise)	**1.069** (0.897-1.273)	0.456	**1.067** (0.793-1.437)	0.667	**1.063** (0.865-1.306)	0.562	**1.110** (0.780-1.579)	0.563	**1.572** (0.437-5.654)	0.489	**1.163** (0.870-1.555)	0.308

Note: Hazard ratios are adjusted for age and sex only.

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; SBP-NDR systolic blood pressure night-day ratio; SD, standard deviation.

presence of CKD, but also a range of other confounding factors in the more general hypertensive patients. Finally, the current study was a multi-center study involving five primary care centers in the public sector, where most chronic disease patients in the community were taken care of in the local context.

The present study must also be interpreted within its limitations. Foremost is the possible inadequate sample size and follow-up duration. Basing on estimates of hazard ratio and event probability from meta-analyses, the calculated sample size is 2716.[26] However, recruiting this number of participants would entail a much longer accrual period or collaboration with cross-cluster centers without standardized device and practice. For the lack of local data, power analysis in the planning stage could only be based on published event probabilities. Secondly, the study population was hypertensive patients receiving ABPM in hypertension referral clinics, and they could not be assumed to be the average hypertensive patient in the community. Caution should be exercised when study results are generalized to primary care patients in the broader sense. The next potential limitation was that sleep quality was known to affect nocturnal BP and dipping status. However, the incorporation of such was not feasible with the retrospective nature of the study. Equally important was that our hypertensive patients might have been admitted to private hospitals for CV complications or mortality. These hospitalization entries might not be directly revealed in our computer record system. The investigators had endeavored to scrutinize case note details to retrieve these events. A final potential limitation in this study was the incongruent HRs on CV mortality. It was attributed to the low CV mortality rate in our patients, who were not of high background CV risk.

The results of the present study did not fully concur with findings from the latest meta-analysis.[3] This could be ascribed to the adjustment of a wider range of covariates in our multiple regressions. Notably, CKD and LVH were individually included as a covariate in several of the original studies in the meta-analysis. But none of the original cohorts adjusted for both CKD and LVH concomitantly. CKD and LVH were known to associate with BP non-dipping and adverse CV outcomes, and they exerted a major confounding effect on the causal relation. The simultaneous adjustment of both covariates in our study plausibly undermined yet perfected the HRs in the Cox regressions. This was particularly true considering the significantly higher prevalence of CKD among our non-dippers (Table 1). Apart from this, a considerably smaller sample size than a meta-analysis, a higher background of white coat component in our subjects, and a much lower percentage of smokers also accounted for the difference in results from previous studies.

Regarding statistics, the adjustment for multiple subgroup comparisons in the Kaplan-Meier survival analysis is another issue of interest. Adjustment methods such as Bonferroni, Sidak, and Holm are commonly used in the literature. However, in survival analysis, this topic has only recently been studied.[27] These post hoc correction methods are used frequently in ANOVA, but their application in survival analysis is hardly seen.[28] Out of four relevant original prognostic studies included in the latest meta-analysis, only one reported *P* values with multiplicity

TABLE 6 Adjusted hazard ratios of CV events in Cox proportional hazard models (adjusted for all covariates)

	Total CV events		MACE		Coronary events		Cerebrovascular events		CV mortality		All-cause mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Traditional non-dippers vs. dippers	**1.166** (0.770-1.764)	0.469	**1.230** (0.543-2.782)	0.620	**1.320** (0.814-2.141)	0.260	**0.778** (0.320-1.895)	0.581	**3.92E+4** (0.000-2.26E+14)	0.356	**1.147** (0.581-2.266)	0.693
Subgroups of dipping (vs. Normal dipping)												
Non-dipping	**1.169** (0.731-1.870)	0.515	**1.325** (0.554-3.171)	0.527	**1.140** (0.796-2.461)	0.243	**0.720** (0.283-1.832)	0.490	**4.10E+4** (0.000-1.37E+62)	0.875	**0.805** (0.349-1.855)	0.610
Reverse dipping	**1.173** (0.681-2.021)	0.566	**0.974** (0.338-2.803)	0.961	**1.476** (0.783-2.784)	0.229	**0.578** (0.178-1.875)	0.361	**3.59E+4** (0.000-1.73E+14)	0.356	**1.237** (0.513-2.983)	0.636
Extreme dipping	**1.029** (0.408-2.594)	0.952	**0.815** (0.092-7.235)	0.854	**1.579** (0.598-4.170)	0.356	**0.000** (0.000-)	0.982	**0.001** (0.000-1.98E+90)	0.948	**0.461** (0.103-2.067)	0.312
SBP-NDR (every 1 SD rise)	**1.018** (0.840-1.235)	0.853	**0.868** (0.607-1.242)	0.439	**1.071** (0.856-1.339)	0.549	**0.885** (0.586-1.336)	0.562	**53.75** (0.003-1.08E+6)	0.431	**1.209** (0.890-1.644)	0.225

Note: Hazard ratios are adjusted for mean 24-hr systolic BP and multiple covariates including age, sex, smoking, presence of pre-existing cardiovascular or cerebrovascular disease, diabetes mellitus, hyperlipidemia, chronic kidney disease, obesity, left ventricular hypertrophy on ECG, and hypertensive treatment.

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; SBP-NDR systolic blood pressure night-day ratio; SD, standard deviation.

adjustment.[29-32] There has been disagreement over the years on the necessity and degree of adjustment required for multiple comparisons.[33] And there are no steadfast rules for multiplicity adjustment in survival analysis, especially for subgroup comparisons planned a priori or of an exploratory nature. In this study, the application of multiplicity adjustment was pivotal in deciding the survival significance of several subgroup dipping patterns in the Kaplan-Meier analyses. Therefore, both unadjusted and adjusted *P* values were presented for valid statistical inference while keeping the results interpretable.

As a final remark, the clinical significance of the present study lay in the discrimination of CV risks of nocturnal BP dipping in non-Caucasian hypertensive patients with simultaneous adjustment for a wide range of confounding factors. At variance with previous investigations, our study showed that a non-dipping BP pattern did not consistently result in an increase in CV risk across the full range of CV events. The weakest connection seemed to reside with cerebrovascular events, where non-dipping was associated with *improved* survival in a fully adjusted regression model. This could be attributed to a higher proportion of hemorrhagic than ischemic stroke,[14,17] and a more prominent early morning BP surge in Asian hypertensive patients.[10,15] The most evident observation over all Kaplan-Meier analyses and Cox regressions in this study was that reverse dipping probably carried the worst prognosis, across total CV events, coronary events, and all-cause mortality. The worst prognosis among our reverse dippers resonated with other studies demonstrating the same adverse prognosis of the riser pattern.[34-37] Further research on the prognostic value of reverse dipping or nocturnal hypertension in Chinese hypertensive patients is desired.

5 | CONCLUSION

The present study completed the jigsaw puzzle of the prognostic value of nocturnal BP dipping on CV outcomes in Chinese hypertensive patients. In a community cohort of hypertensive patients of Chinese ethnicity in Hong Kong, nocturnal BP non-dipping and reverse dipping demonstrated prognostic importance over a range of CV events. On top of evaluating mean BP levels for CV risk stratification, clinical distinction of non-dipping and reverse dipping on ABPM is probably warranted to identify high-risk patients for more intensive treatment of reversible CV risk factors.

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CONFLICT OF INTEREST

The whole or part of the work has not been previously presented and is not under consideration by another publication.

AUTHOR CONTRIBUTIONS

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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