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# Non-dipping blood pressure pattern is associated with higher risk of new-onset diabetes in hypertensive patients with obstructive sleep apnea: UROSAH data

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**Objective:** Impairment of circadian blood pressure (BP) patterns has been associated with cardiovascular risks and events in individuals with hypertension and in general populations, which are more likely to be found in obstructive sleep apnea (OSA). The aim of this study was to investigate the association of non-dipping BP pattern with new-onset diabetes in hypertensive patients with OSA, based on Urumqi Research on Sleep Apnea and Hypertension (UROSAH) data.

**Materials and methods:** This retrospective cohort study included 1841 hypertensive patients at least 18 years of age, who were diagnosed with OSA without baseline diabetes and had adequate ambulatory blood pressure monitoring (ABPM) data at enrollment. The exposure of interest for the present study was the circadian BP patterns, including non-dipping and dipping BP pattern, and the study outcome was defined as the time from baseline to new-onset diabetes. The associations between circadian BP patterns and new-onset diabetes were assessed using Cox proportional hazard models.

**Results:** Among 1841 participants (mean age: 48.8 ± 10.5 years, 69.1% male), during the total follow-up of 12172 person-years with a median follow-up of 6.9 (inter quartile range: 6.0-8.0) years, 217 participants developed new-onset diabetes with an incidence rate of 17.8 per 1000 person-years. The proportion of non-dippers and dippers at enrollment in this cohort was 58.8% and 41.2%, respectively. Non-dippers were associated with higher risk of new-onset diabetes compared with dippers (full adjusted hazard ratio [HR]=1.53, 95% confidence interval [CI]: 1.14-2.06, *P*=0.005). Multiple subgroup and sensitivity analyses yielded similar results. We further explored the association of systolic and diastolic BP patterns with new-onset diabetes separately, and found that diastolic BP non-dippers were associated with higher risk of new-onset diabetes (full adjusted HR=1.54, 95% CI: 1.12-2.10, *P*=0.008), whereas for systolic BP non-

dippers, the association was nonsignificant after adjusted the confounding covariates (full adjusted HR=1.35, 95% CI: 0.98-1.86,  $P=0.070$ ).

**Conclusions:** Non-dipping BP pattern is associated with an approximately 1.5-fold higher risk of new-onset diabetes in hypertensive patients with OSA, suggesting that non-dipping BP pattern may be an important clinical implication for the early prevention of diabetes in hypertensive patients with OSA.

#### KEYWORDS

New-onset, diabetes, circadian blood pressure patterns, non-dipping, obstructive sleep apnea, hypertension

## Introduction

The global number of adult patients with diabetes between 20 and 79 years reached 537 million and was responsible for 6.7 million deaths in 2021 (1). Among Chinese adults, the number of patients with diabetes was 111.6 million in 2019 and will reach 147 million in 2045 (2, 3). Early prevention for diabetes is pivotal to reduce the disease burden.

Obstructive sleep apnea (OSA), a condition characterized by intermittent hypoxia and sleep fragmentation due to a complete or partial collapse of the upper airway, is highly prevalent in parallel with the obesity epidemic trends in the general population (4), with estimated nearly one billion worldwide (5). OSA and hypertension (HTN) are highly prevalent conditions in the general population, approximately 50% of OSA patients noted to have HTN (6). Accumulating evidence has confirmed a strong association between OSA, HTN and diabetes (7–10). Shared mechanisms may involve enhanced sympathetic activity, oxidative stress, systemic inflammation, activation of the hypothalamic-pituitary-adrenal axis and alteration of circulating adipokines, induced by intermittent hypoxia and sleep fragmentation (4, 11, 12). In addition, enhanced sympathetic activity can alter circadian blood pressure (BP) rhythm resulting in a non-dipping BP pattern (11, 13), which was found to be increased by approximately 1.5 times likelihood in patients with OSA compared with non-OSA (14).

Emerging evidence has revealed that the non-dipping BP pattern is associated with adverse cardiovascular risks and events in both normal and HTN participants compared to the dipping pattern (15–18). Numerous cross-sectional studies have shown a high prevalence of non-dipping phenomenon in diabetes and even in early-stage diabetes (19–21). A recently prospective study with 21-year follow-up documented an independent association between non-dipping BP pattern and risk of new-onset diabetes in a randomly selected Finnish ( $n=449$ ), originally middle-aged population with/without HTN (22). However, the longitudinal association between non-dipping pattern and the risk of developing new-onset diabetes in hypertensive patients with OSA remains unexplored.

While OSA and HTN have been substantiated to be associated with a higher risk of new-onset diabetes overall (4, 7–10, 23), non-dipping BP pattern may be a possible mechanism to accelerate the development of diabetes in hypertensive patients with OSA. Hence, we aimed to investigate the association between circadian BP patterns

and new-onset diabetes based on Urumqi Research on Sleep Apnea and Hypertension (UROSAH) data.

## Materials and methods

### Study design and subjects

Data were obtained from the UROSAH study. The design and data collection of the UROSAH study have been described in detail elsewhere (24–26). Briefly, UROSAH is a single-center observational study to assess the association of OSA with long term cardiovascular outcomes in patients with HTN. Hypertensive patients aged  $\geq 18$  years who visited Hypertension Center between Jan 2011 and Dec 2013 were reviewed. In the current study, 1841 hypertensive patients who were diagnosed with OSA without baseline diabetes and had adequate ambulatory blood pressure monitoring (ABPM) data at enrollment were included, the patient recruitment flowchart is illustrated in Figure 1.

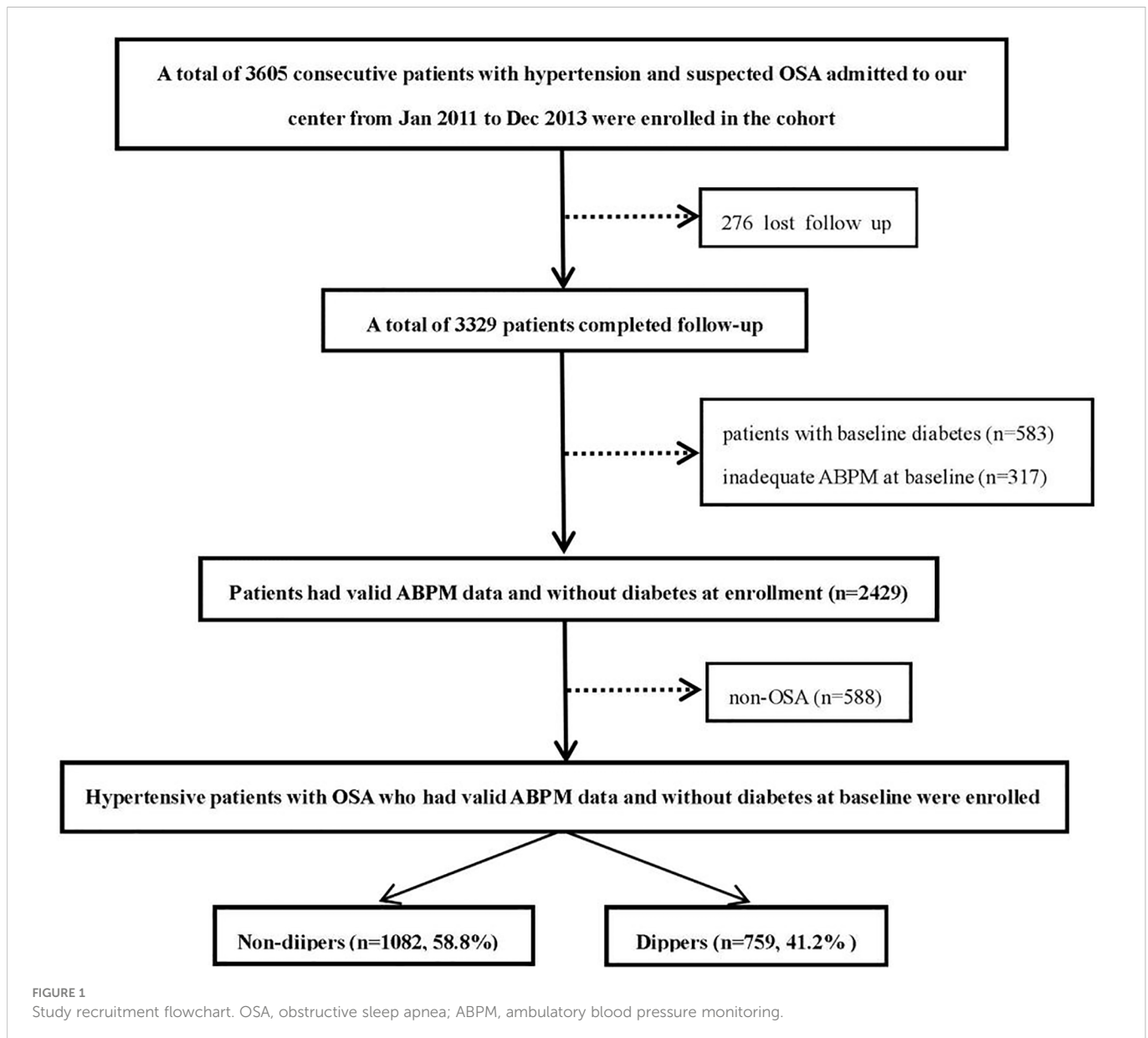
### Ethical approval

The research was authorized by the Medical Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. 2019030662) and was conducted in strict compliance with the ethical standards set forth in the Declaration of Helsinki and its subsequent amendments. Written informed consent was submitted by all patients or their legal relatives participating in this study.

### Definitions at baseline

HTN was defined according to the “China guidelines for prevention and treatment of hypertension 2010”: the resting systolic BP (SBP) of at least 140 mmHg and/or the resting diastolic BP (DBP) of at least 90 mmHg or the current use of antihypertensive drugs (27).

Smoking and drinking status were stratified into two levels: current (current smoking/drinking or quit within the past 1 year) and never or former (non-smokers/drinkers or those who quit more than 1 year).



The height and weight were measured and body mass index (BMI) was calculated by weight (kg)/height ( $m^2$ ), obesity was defined as  $BMI \geq 28 \text{ kg/m}^2$  and overweight as  $24 \text{ kg/m}^2 \leq BMI < 28 \text{ kg/m}^2$  according to the Criteria of Weight for Adults of the health industry standard of China, WS/T 428–2013.

Baseline prediabetes included impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG was defined if a fasting plasma glucose (FPG) ranged from 6.1 to less than 7.0 mmol/L, whereas 2-h glucose was less than 7.8 mmol/L; IGT was defined if 2-h glucose ranged from 7.8 to less than 11.0 mmol/L (28).

OSA was defined as an apnea-hypopnea index (AHI)  $\geq 5$  events per hour based on polysomnography (PSG) examination. Severity of OSA was defined as follows: mild OSA ( $5 \leq AHI < 15$  events per hour) and moderate-severe OSA ( $AHI \geq 15$  events per hour) (5).

Regular continuous positive airway pressure (CPAP) treatment was defined as the use of CPAP therapy for more than 70% of nights throughout the follow-up period and no less than 4 hours per night.

## Exposure of interest

The exposure of interest was the circadian BP patterns according to the ABPM parameters. Twenty-four-hour ABPM was performed at enrollment using an oscillometric recorder (Spacelabs 90217). Briefly, the cuff with appropriate size was fitted in the non-dominant arm. After device application, subjects were encouraged to follow their usual daily activity for the next 24 h. The device was programmed to automatically measure BP every 20 min during daytime (from 8:00 to 23:00) and every 30 min during nighttime (from 23:00 to 08:00). Patients were asked to go to bed at 23:00 and not to rise before 8:00 AM. Adherence to this schedule was checked from the diary card. Only ABPM reports with more than 70% of successful readings were considered valid and included in the analysis.

Dippers were participants whose nighttime (asleep) SBP and/or DBP fall  $\geq 10\%$  compared with that of daytime (awake), and those with nighttime SBP and DBP fall  $< 10\%$  were defined as non-dippers,

as indicated by the European Society of Hypertension (ESH) guidelines (29).

Elevated BP were according to the following criteria: SBP  $\geq 130$  mmHg and/or DBP  $\geq 80$  mmHg during 24-hour ABPM recording, SBP  $\geq 135$  mmHg and/or DBP  $\geq 85$  mmHg during daytime ABPM recording, SBP  $\geq 120$  mmHg and/or DBP  $\geq 70$  mmHg during nighttime ABPM recording (29).

## Follow-up and outcome

All participants were followed up through medical records, outpatient and/or inpatient visits and telephone communication. The deadline for follow-up was January 2021. All events were certified by medical documents and confirmed by the clinical event committee. Details were described in previous studies (24–26).

The outcome for the present study was defined as time from baseline to new-onset diabetes, which was determined by the WHO criteria: diabetes was diagnosed if fasting plasma glucose was  $\geq 7.0$  mmol/L and/or 2-h plasma glucose was  $\geq 11.1$  mmol/L in 2-h oral glucose tolerance test, or if a person was use of antidiabetic medications.

## Statistical analysis

The participants were divided into non-dippers and dippers according to their circadian BP patterns. Continuous variables were reported as mean  $\pm$  standard deviation (SD) if normally distributed and as median and inter quartile range (IQR) if not. The differences between the two groups were compared using independent sample t-tests for normally distributed continuous variables and Mann-Whitney U-tests for non-normally distributed continuous variables. The categorical variables were presented as observed numbers and percentages and were compared among groups using Pearson's chi-squared test.

The incidence rate of new-onset diabetes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Cumulative hazards were estimated by Kaplan-Meier curves stratified by time-updated exposure (non-dippers versus dippers) by the log-rank test. To evaluate the validity of the proportional hazard assumption, the assumption was evaluated using the log-minus-log-survival function and was found to be valid. Cox proportional hazard regression models were used to compare the risk of new-onset diabetes across groups.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated, with dippers group as the reference group. Univariate Cox regression analysis was performed to select variables for adjustment (Supplementary Table 1). Before building the Cox regression model, we evaluated the covariance between variables according to the variance inflation factor (VIF) (Supplementary Table 1). Variables with VIF  $> 5$  were considered inappropriate for inclusion in the multivariate Cox regression model. Thus, we eliminated 19 variables with multicollinearity, including waist circumference, waist-to-height ratio, serum creatinine, 24-h mean SBP, DBP, MAP and heart rate (HR), mean daytime SBP, MAP and HR, mean nighttime SBP, DBP, MAP and HR, elevated daytime BP, elevated nighttime BP, isolated

elevated nighttime BP, SBP night-to-day ratios and DBP night-to-day ratios. Variables in multivariate analyses included traditional risk factors (model 1), further plus variables that gave  $p$  values  $< 0.1$  in the univariate analyses (model 2). We performed directed acyclic graphs (DAGs) by the program DAGitty for drawing and analyzed causal diagrams between non-dipping pattern and new-onset diabetes, to identify suitable minimally sufficient adjustment sets as full adjusted model (Figure 2, model 3).

Subgroup analyses with interaction tests were also conducted (Supplementary Table 2). Stratification of the study included gender (male and female), age ( $\geq 60$  and  $< 60$  years), BMI ( $\geq 28$  and  $< 28$  kg/m<sup>2</sup>), current drinker (yes or no), hypertension duration ( $\geq 5$  and  $< 5$  years), AHI ( $\geq 15$  and  $< 15$  events/hour), angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) use (yes or no), and statins use (yes or no). Sensitivity analyses were performed in participants excluding baseline prediabetes, regular CPAP treatment, eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, statins use and normal nighttime BP (Supplementary Table 2). A competing risk analysis with death was performed using the Fine-Gray model (Supplementary Table 3). Data were analyzed using SPSS statistical software (version 25.0, SPSS Inc., Chicago, Illinois) and R (version 4.2.1) software all analyses were two-tailed and  $P$  value  $< 0.05$  was statistically significant.

## Results

### Baseline characteristics

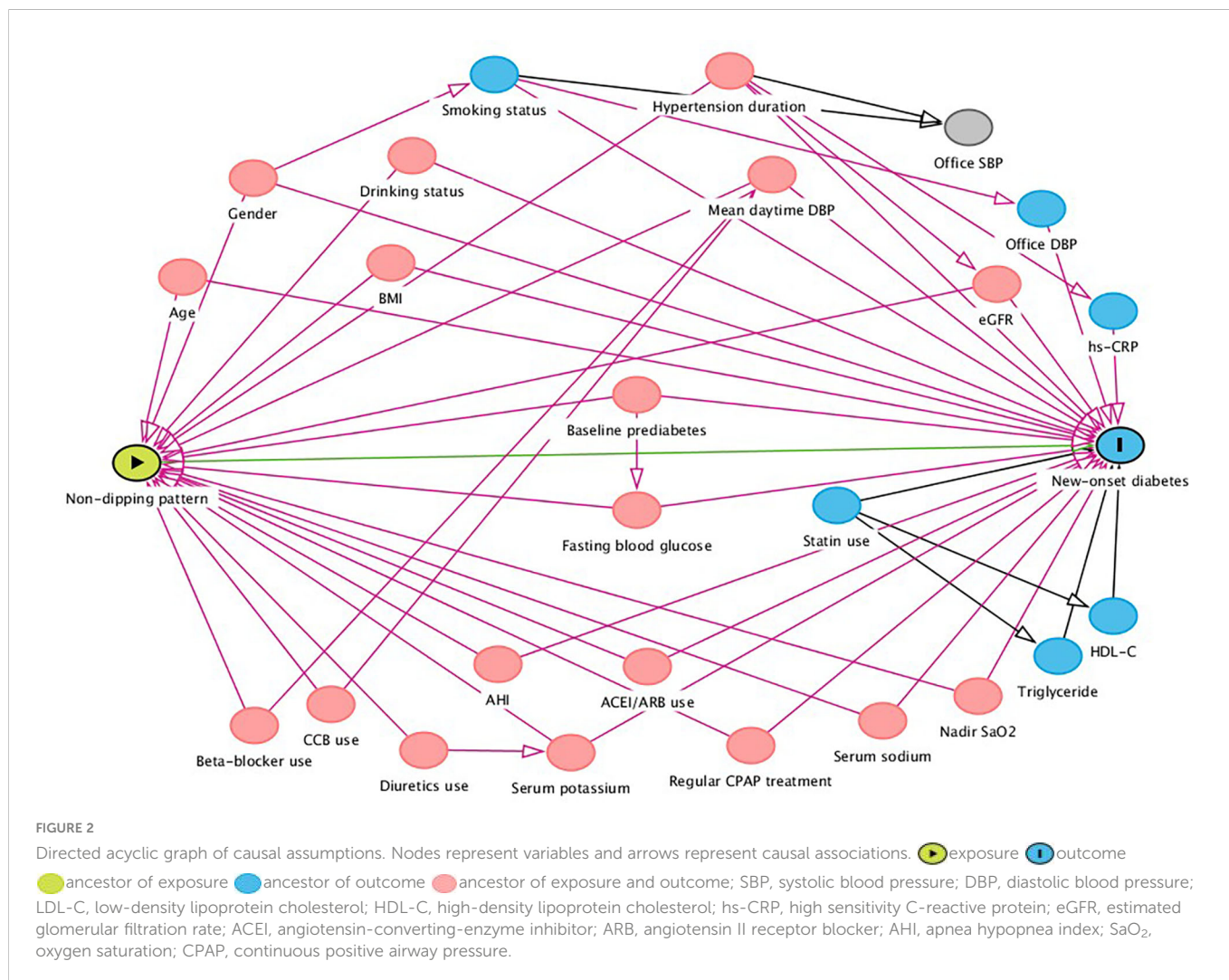
Overall, the proportion of non-dippers and dippers at enrollment in the present study was 58.8% and 41.2%, respectively. The characteristics of the study population at baseline are presented in Table 1. Compared with dippers, non-dippers had older age, less frequent male and current drinkers. No significant differences were found in BMI, waist circumference, waist-height ratio, office SBP and DBP levels, as well as in proportion of current smokers, obesity, overweight and baseline prediabetes between non-dippers and dippers.

As for clinical laboratory measurements, non-dippers had lower levels of total cholesterol, triglyceride (TG), serum potassium, eGFR and higher levels of serum sodium than dippers, no significant differences were found in levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose and serum creatinine between non-dippers and dippers.

For ABPM parameters, as expected, non-dippers had higher levels of mean 24-h and nighttime SBP, DBP and mean arterial pressure (MAP), more frequent elevated 24-h and nighttime BP, whereas lower levels of mean daytime SBP, DBP and HR, as well as less frequent elevated daytime BP than dippers.

Non-dippers received more calcium channel blockers (CCBs), diuretics and numbers of antihypertensive agents than dippers. No significant differences were found in the proportion of ACEI/ARBs and beta blockers use, as well as in major PSG parameters (e.g., AHI values, nadir SaO<sub>2</sub> levels and proportion of regular CPAP treatment) between non-dippers and dippers.





**TABLE 1** Baseline characteristics for the total, non-dippers, and dippers.

Characteristics	Total	Non-dippers	Dippers	P value
Participants, n (%)	1841	1082	759	
<b>Demographic characteristics</b>				
Male, n (%)	1273 (69.1%)	727 (67.2%)	546 (71.9%)	0.030
Age, years	48.80 ± 10.47	49.40 ± 10.49	47.96 ± 10.40	0.004
Current smokers, n (%)	656 (35.6%)	372 (34.4%)	284 (37.4%)	0.180
Current drinkers, n (%)	644 (35.0%)	353 (32.6%)	291 (38.3%)	0.011
Body mass index, kg/m <sup>2</sup>	28.23 ± 3.82	28.31 ± 3.90	28.11 ± 3.71	0.253
Waist circumference, cm	100.00 (93.00, 106.00)	100.00 (93.00, 107.00)	100.00 (94.00, 106.00)	0.739
waist-to-height ratio	0.58 (0.55, 0.63)	0.58 (0.55, 0.63)	0.58 (0.55, 0.62)	0.322
Obese, n (%)	891 (48.4%)	522 (48.2%)	369 (48.6%)	0.875
Overweight, n (%)	752 (40.8%)	446 (41.2%)	306 (40.3%)	0.698
Office SBP, mmHg	139.42 ± 19.42	139.37 ± 19.52	139.50 ± 19.27	0.892
Office DBP, mmHg	92.00 ± 13.94	92.19 ± 14.01	91.72 ± 13.84	0.471

(Continued)

TABLE 1 Continued

Characteristics	Total	Non-dippers	Dippers	P value
Participants, n (%)	1841	1082	759	
Hypertension duration, years	3.0 (1.0, 8.0)	4.0 (1.0, 8.0)	3.0 (0.8, 7.0)	0.007
Baseline prediabetes, n (%)	239 (12.9%)	146 (13.5%)	93 (12.3%)	0.436
<b>Clinical laboratory measurements</b>				
Total cholesterol, mmol/L	4.54 ± 1.19	4.50 ± 1.02	4.61 ± 1.23	0.033
Triglyceride, mmol/L	2.08 ± 1.50	2.02 ± 1.36	2.17 ± 1.65	0.031
HDL-C, mmol/L	1.11 ± 0.30	1.12 ± 0.31	1.10 ± 0.28	0.308
LDL-C, mmol/L	2.66 ± 0.79	2.65 ± 0.81	2.67 ± 0.76	0.587
Fasting blood glucose, mmol/L	4.85 ± 0.63	4.83 ± 0.60	4.87 ± 0.66	0.138
Serum potassium, mmol/L	3.91 ± 0.34	3.88 ± 0.34	3.96 ± 0.34	<0.001
Serum sodium, mmol/L	140.69 ± 2.38	140.79 ± 2.50	140.56 ± 2.20	0.036
hs-CRP, mg/mL (M, IQR)	1.95 (1.95, 3.62)	2.04 (0.98, 3.71)	1.87 (0.89, 3.50)	0.053
Serum creatinine, umol/L	77.07 ± 20.00	77.23 ± 21.26	76.84 ± 18.03	0.673
eGFR, mL/min/1.73 m <sup>2</sup>	90.18 ± 19.26	89.45 ± 18.92	91.24 ± 19.70	0.049
<b>ABPM parameters</b>				
Mean 24-h SBP, mmHg	133.16 ± 15.29	134.64 ± 15.56	131.05 ± 14.66	<0.001
Mean 24-h DBP, mmHg	85.61 ± 10.74	86.57 ± 11.00	84.23 ± 10.22	<0.001
24-h MAP, mmHg	100.49 ± 12.87	101.88 ± 12.98	98.51 ± 12.45	<0.001
Mean 24-h HR, bpm	75.63 ± 9.05	75.39 ± 9.27	75.96 ± 8.71	0.180
Mean daytime SBP, mmHg	136.40 ± 15.61	135.78 ± 15.75	137.29 ± 15.38	0.040
Mean daytime DBP, mmHg	88.32 ± 23.04	87.34 ± 11.11	89.72 ± 33.30	0.028
Daytime MAP, mmHg	102.68 ± 13.21	102.50 ± 13.00	102.93 ± 13.44	0.492
Mean daytime HR, bpm	79.81 ± 9.54	79.27 ± 9.63	80.60 ± 9.35	0.003
Mean nighttime SBP, mmHg	128.22 ± 16.88	133.47 ± 16.50	120.74 ± 14.43	<0.001
Mean nighttime DBP, mmHg	81.98 ± 11.65	85.57 ± 11.42	76.86 ± 9.94	<0.001
Nighttime MAP, mmHg	97.04 ± 13.79	101.14 ± 13.53	91.10 ± 11.89	<0.001
Mean nighttime HR, bpm	68.16 ± 8.89	68.48 ± 8.95	67.70 ± 8.79	0.064
Elevated 24-h BP, n (%)	1416 (76.9%)	858 (79.3%)	558 (73.5%)	0.004
Elevated daytime BP, n (%)	1272 (69.1%)	724 (66.9%)	548 (72.2%)	0.016
Elevated nighttime BP, n (%)	1649(89.6%)	1032 (95.4%)	617 (81.3%)	<0.001
Isolated elevated nighttime BP, n (%)	561 (30.5%)	416 (38.4%)	145 (19.1%)	<0.001
SBP night-to-day ratios	0.94 ± 0.07	0.98 ± 0.05	0.88 ± 0.04	<0.001
DBP night-to-day ratios	0.93 ± 0.08	0.98 ± 0.05	0.87 ± 0.05	<0.001
<b>Prescribed medication, n (%)</b>				
<b>Numbers of antihypertensive drugs</b>				
None, n(%)	167 (9.1%)	88 (8.1%)	79 (10.4%)	0.094
1, n (%)	528 (28.7%)	288 (26.6%)	240 (31.6%)	0.019
2, n (%)	999 (54.3%)	608 (56.2%)	391 (51.5%)	0.047
3, n (%)	147 (8.0%)	98 (9.1%)	49 (6.5%)	0.043

(Continued)

TABLE 1 Continued

Characteristics	Total	Non-dippers	Dippers	P value
Participants, n (%)	1841	1082	759	
ACEI/ARB users, n (%)	894 (48.6%)	515 (47.6%)	379 (49.9%)	0.323
Calcium channel blocker users, n (%)	1353 (73.5%)	829 (76.6%)	524 (69.0%)	<0.001
Beta blocker users, n (%)	177 (9.6%)	104 (9.6%)	73 (9.6%)	0.997
Diuretic users, n (%)	284 (15.4%)	185 (17.1%)	99 (13.0%)	0.018
Statis users, n (%)	625 (33.9%)	365(33.7%)	260(34.4%)	0.816
<b>PSG parameters</b>				
AHI, events/hour	19.00 (10.35, 31.25)	19.30 (10.50, 31.60)	18.60 (10.00, 30.10)	0.196
Moderate-severe OSA, n (%)	1025 (58.5%)	618 (59.8%)	407 (56.7%)	0.190
Nadir SaO <sub>2</sub> , %	80 (75, 84)	80 (75, 83)	80 (76, 84)	0.123
Mean SaO <sub>2</sub> , %	91.86 ± 3.66	91.76 ± 3.60	92.00 ± 3.73	0.183
Regular CPAP treatment, n (%)	49 (2.7%)	29 (2.7%)	20 (2.6%)	0.953

Non-normally distributed variables are expressed as the median (inter quartile range). All other values are expressed as mean ± SD or n, %.

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; IQR, inter quartile range; eGFR, estimated glomerular filtration rate; APBM, ambulatory blood pressure monitoring; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; BP, blood pressure; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; PSG, polysomnography; AHI, apnea hypopnea index; OSA, obstructive sleep apnea; SaO<sub>2</sub>, oxygen saturation; CPAP, continuous positive airway pressure.

## Risk of new-onset diabetes in groups by non-dippers and dippers

Among 1841 participants (mean age: 48.8 ± 10.5 years, 69.1% male), during the total follow-up of 12172 person-years with a median follow-up of 6.9 (inter quartile range: 6.0-8.0) years, 217 participants developed new-onset diabetes with an incidence rate of 17.8 per 1000 person-years. Non-dippers experienced a higher cumulative hazard of new-onset diabetes than dippers during the follow-up period ( $P=0.0019$  for log-rank test; [Figure 3A](#)). In univariate cox regression analysis ([Supplementary Table 1](#)), BMI, waist circumference, waist-to-height ratio, baseline prediabetes, TG, HDL-C, fasting blood glucose, statins use, AHI and nadir SaO<sub>2</sub> were associated with higher risk of new-onset diabetes. Apart from mean daytime DBP, SBP night-to-day ratios and DBP night-to-day ratios, no other ABPM parameter showed an association with new-onset diabetes.

Three multivariate models were performed through the following sequential adjustments: model 1 adjusted for traditional risk factors, including age, gender, drinking status, smoking status, BMI, office SBP, office DBP, hypertension duration and baseline prediabetes. Model 2 included covariates in Model 1 and further adjusted for variables that gave  $p$  values <0.1 in the univariate analyses and no multicollinearity, including TG, HDL-C, fasting blood glucose, mean daytime DBP, ACEIs/ARBs use, CCBs use, statins use, AHI and nadir SaO<sub>2</sub>. Model 3 (full adjusted model) was based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes identified by DAG ([Figure 2](#)), including age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO<sub>2</sub>, and regular CPAP treatment. Non-dippers showed an increased risk for new-onset diabetes compared with dippers in crude model with an unadjusted HR of 1.57 (95% CI 1.18-2.09,  $P=0.002$ ). The

association remained consistently in adjusted models (full adjusted HR=1.53, 95% CI: 1.14-2.06,  $P=0.005$ ) ([Table 2](#)).

We also explored association of systolic and diastolic BP patterns with new-onset diabetes separately ([Figures 3B, C](#)), and found that DBP non-dippers were associated with new-onset diabetes both in crude model (unadjusted HR=1.47, 95% CI:1.09-2.00,  $P=0.013$ ) and adjusted models (full adjusted HR=1.54, 95%CI:1.12-2.10,  $P=0.008$ ), whereas for SBP non-dippers, the association was only significantly in crude model (unadjusted HR=1.40, 95% CI: 1.02-1.92,  $P=0.036$ ), after adjusted the aforementioned covariates, the association was nonsignificant (full adjusted HR=1.35, 95% CI: 0.98-1.86,  $P=0.070$ ) ([Table 2](#)).

## Subgroup and sensitivity analysis

In subgroup analysis, as shown in [Table 3](#), compared with dippers, non-dippers exhibited higher risk for new-onset diabetes in participants whom were male, age<60 years, non-obese, current drinker, hypertension duration<5 years, moderate-severe OSA, no use of ACEI/ARBs and statins. None of above variables, substantially altered the association between non-dipping pattern and risk of new-onset diabetes ( $P$  for all interaction > 0.05).

Sensitivity analysis showed that the association of non-dipping BP pattern with the risk of new-onset diabetes didn't change in participants excluding baseline prediabetes, regular CPAP treatment, eGFR<60 mL/min/1.73 m<sup>2</sup>, statins use and normal nighttime BP ([Supplementary Table 2](#)). We also performed a competing risk analysis with death as a competing event. Sub-distribution HRs for non-dipping pattern and new-onset diabetes after competing risk analysis are presented in [Supplementary Table 3](#). The association between non-dipping pattern and new-onset diabetes remained significant in the Fine Gray model.

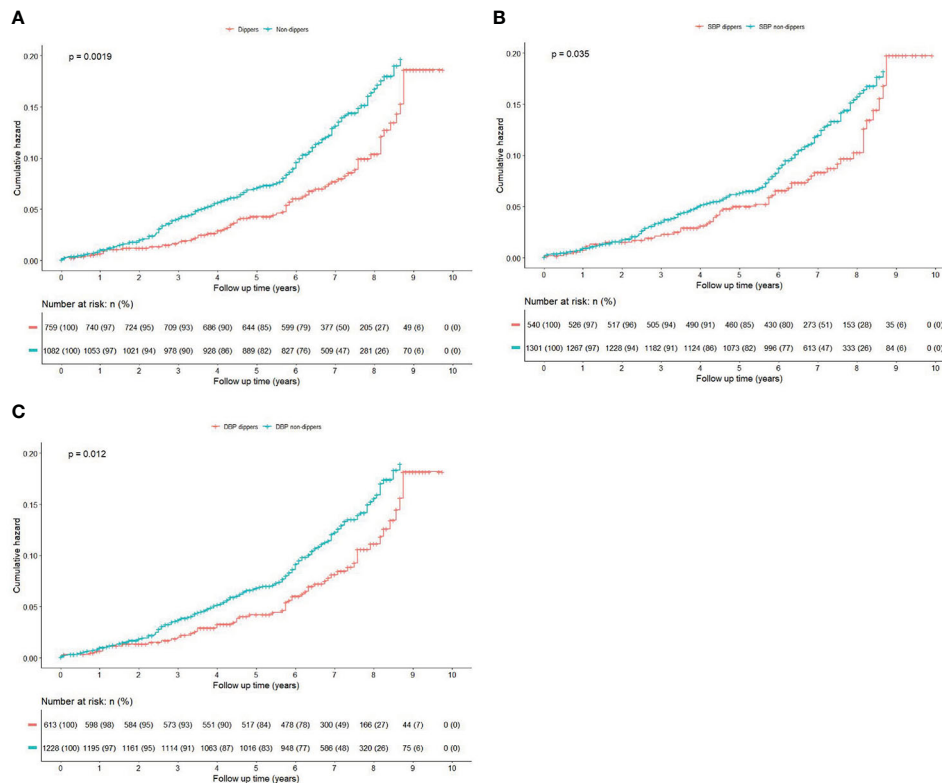


FIGURE 3

(Color online) Kaplan-Meier curves for the cumulative risk of new-onset diabetes by dipping and non-dipping pattern during the follow-up. Kaplan-Meier curves were compared with the log-rank test. (A) BP non-dippers vs dippers; (B) Systolic BP non-dippers vs dippers; (C) Diastolic BP non-dippers vs dippers.

## Discussion

The current study is, to the best of our knowledge, the first to explore the association of nocturnal BP patterns with new-onset diabetes in a relatively large cohort of hypertensive patients with OSA. Our findings suggest that non-dippers, despite having similar levels of office SBP, DBP, and even lower mean daytime SBP and DBP compared to dippers, are associated with a higher risk of new-onset diabetes in hypertensive patients with OSA.

ABPM can assess circadian BP patterns over a 24-hour period and provides more useful prognostic information than clinic measurements of BP. The proportion of non-dippers at enrollment in the current cohort was as high as 58.8%, which is consistent with previous studies. A meta-analysis involving 1562 patients with OSA and 957 non-OSA controls from 14 studies revealed that the prevalence of non-dipping patterns in patients with OSA varied widely from 36.0% to 90.0% and non-OSA from 33.0% to 69.0%, depending on demographic or clinical characteristics, definitions of OSA and non-dipping phenotypes (14).

The dipping phenomenon occurs when lying recumbent due to lower leg fluid shifts in the rostral direction, increasing carotid intravascular fluid volume and triggering carotid baroreceptors to reflexively reduce sympathetic nervous activity (SNA), thus causing a nocturnal BP dipping. The enhanced SNA caused by OSA can antagonize the natural dipping phenomenon, meanwhile, the chronic HTN leading to endothelial dysfunction, vasculature

abnormality, and insensitive baroreceptors may further inhibit the reflex dipping phenomenon (30).

In animal models as well as in humans, exposure to intermittent hypoxia and disruption of circadian rhythms have been shown to be associated with pancreatic beta cell loss and dysfunction, metabolic abnormalities, impaired function of the autonomic nervous system, renin-angiotensin system, and organ malfunction in the target organ (31, 32). Insulin resistance may in turn contribute to the development of non-dipper hypertension (33). The above superimposed changes may further aggravate metabolic abnormalities and associated cardiovascular events.

Previous studies paid more attention to SBP patterns than to DBP (34). In the present study, we explored the association of both systolic and diastolic BP patterns with new-onset diabetes and found that DBP non-dippers were significantly associated with higher risk of new-onset diabetes after adjustment for confounding factors, while SBP non-dippers were non-significant after full adjustment. Our findings are in agreement with several studies that have focused on the association of both SBP and DBP modes with OSA. A case-control study showed that patients with OSA had increased ambulatory DBP during both day and night and increased SBP during the night, compared to closely matched control subjects (35). A retrospective study found that subjects with more severe intermittent hypoxia and sleep fragmentation had significant higher SBP and DBP, and were more likely to have abnormal DBP than those with less severe intermittent hypoxia and sleep fragmentation (36). These findings



TABLE 2 Multivariate Cox regression analysis of association between circadian BP patterns and new-onset diabetes.

Variable	New-onset diabetes n (%)	Incidence rate per 1000 person-years	Crude Model		Model 1		Model 2		Model 3	
			HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<b>BP patterns (SBP and/or DBP)</b>										
Dippers (n=759)	68 (9.0)	13.4	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1082)	149 (13.8)	21.0	1.57 (1.18-2.09)	0.002	1.41 (1.05-1.89)	0.022	1.51 (1.12-2.03)	0.006	1.53 (1.14-2.06)	0.005
<b>SBP patterns</b>										
Dippers (n=540)	51 (9.4)	14.0	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1301)	166 (12.8)	19.5	1.40 (1.02-1.92)	0.036	1.25 (0.91-1.72)	0.169	1.30 (0.95-1.80)	0.106	1.35 (0.98-1.86)	0.070
<b>DBP patterns</b>										
Dippers (n=613)	56 (9.1)	13.7	1 [reference]		1 [reference]		1 [reference]		1 [reference]	
Non-dippers (n=1228)	161 (13.1)	19.9	1.47 (1.09-2.00)	0.013	1.35 (0.99-1.84)	0.057	1.52 (1.11-2.08)	0.009	1.54 (1.12-2.10)	0.008

Crude model: Unadjusted. Model 1: adjusted for age, gender, drinking status, smoking status, BMI, office SBP, office DBP, hypertension duration, baseline prediabetes. Model 2: adjusted for all the variables in model 1, plus triglyceride, HDL-C, fasting blood glucose, mean daytime DBP, ACEI/ARBs use, CCBs use, statins use, AHI and nadir SaO<sub>2</sub>. Model 3: based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes: age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO<sub>2</sub>, and regular CPAP treatment.

HR, hazard ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; AHI, apnea hypopnea index; SaO<sub>2</sub>, oxygen saturation; hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

TABLE 3 Association between non-dipping pattern and new-onset diabetes stratified by subgroups.

Subgroup	N	New-onset diabetes, n (%)	Incidence rate per 1000 person-years	Full adjusted HR (95% CI)	P	P for interaction
Gender						0.532
Male	1273	144 (11.3)	17.0	1.65 (1.15-2.36)	0.007	
Female	568	73 (12.9)	19.8	1.40 (0.83-2.37)	0.208	
Age, years						0.170
≥60	286	40 (14.0)	21.9	1.27 (0.59-2.71)	0.545	
<60	1555	177 (11.4)	17.1	1.57 (1.13-2.17)	0.007	
BMI, kg/m <sup>2</sup>						0.459
≥28	891	131 (14.7)	22.6	1.30 (0.89-1.91)	0.176	
<28	950	86 (9.1)	13.5	2.33 (1.42-3.83)	0.001	
Current Drinker						0.165
yes	644	67 (10.4)	15.4	1.90 (1.11-3.25)	0.019	
no	1197	150 (12.5)	19.2	1.40 (0.98-2.02)	0.065	
Hypertension duration						0.322
≥5 years	773	95 (12.3)	18.9	1.36 (0.86-2.14)	0.191	
<5 years	1068	122 (12.4)	17.1	1.81 (1.21-2.70)	0.004	

(Continued)

TABLE 3 Continued

Subgroup	N	New-onset diabetes, n (%)	Incidence rate per 1000 person-years	Full adjusted HR (95% CI)	P	P for interaction
AHI, events/hour						0.637
≥15	1116	153 (13.6)	20.9	1.72 (1.19-2.47)	0.004	
<15	725	65 (9.0)	13.4	1.21 (0.71-2.05)	0.490	
ACEI/ARBs use						0.677
yes	894	120 (13.4)	20.2	1.40 (0.95-2.07)	0.094	
no	947	97 (10.2)	15.6	1.78 (1.11-2.85)	0.017	
Statins use						0.817
yes	625	94 (15.0)	23.9	1.54 (0.98-2.41)	0.059	
no	1216	123 (10.1)	14.9	1.60 (1.06-2.41)	0.024	

full adjusted model: based on minimal sufficient adjustment sets for estimating the total effect of non-dipping pattern on new-onset diabetes: age, gender, drinking status, hypertension duration, baseline prediabetes, BMI, fasting blood glucose, eGFR, serum potassium, serum sodium, mean daytime DBP, ACEI/ARBs use, AHI, nadir SaO<sub>2</sub>, and regular CPAP treatment. BMI, body mass index; eGFR, estimated glomerular filtration rate; AHI, apnea hypopnea index; SaO<sub>2</sub>, oxygen saturation; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

suggest that DBP mode is more likely to be specific in patients with OSA. A longitudinal analysis of the Wisconsin Sleep Cohort indicated that there was a dose-response greater risk of developing both SBP and DBP non-dipping patterns with greater severity of OSA in rapid eye movement (REM) sleep (37). Moreover, DBP non-dipping was significantly associated with the REM AHI, but not non-REM or total AHI (37), while SBP non-dipping was significantly associated with total AHI (30). It is well established that REM sleep is associated with greater sympathetic activity and cardiovascular instability in patients with OSA, which may explain why the risk of new onset diabetes subtly differs between SBP and DBP non-dipping patterns.

Elevated sleep-time BP has also been proposed as an important prognostic marker of diabetes. MAPEC study comprising 2,656 individuals without diabetes and with baseline BP ranging from normotension to HTN, during a 5.9-year follow-up, indicated that elevated sleep-time SBP is an independent prognostic marker for new-onset diabetes and lowering asleep BP could be a significant method for reducing new-onset diabetes risk. Moreover, those with new-onset diabetes were likely to have OSA at baseline (38). Nonetheless, neither mean nighttime SBP nor DBP was found to be associated with new-onset diabetes in the present study, the main reason for this may be attributed to the relatively high percentage of participants with elevated nighttime BP, 89.6% for the whole cohort, 95.4% for the non-dippers and 81.3% for the dippers, and 90.9% of the participants were on antihypertensive treatment. In the sensitivity analysis, the association between non-dippers and the risk of new-onset diabetes was unchanged in those excluding normal nighttime BP.

Currently, solid evidences of adverse prognosis of non-dipping pattern on cardiovascular risks and events provide justification for complete 24-h BP control as the primary goal of antihypertensive treatment. We therefore support the role of ABPM as an inexpensive, widely available screening and monitoring tool for the diagnosis of abnormal BP patterns in hypertensive patients with OSA, pursuing an optimized treatment and management of non-dipping BP for preventing diabetes.

CPAP is the current standard of treatment for OSA and seems to improve nocturnal BP dipping (39). Meta-analyses have shown a significant decrease in nighttime BP as well as a long-term (12 weeks) reduction in mean and diastolic BP with CPAP device usage of 4 or more hours per night (40, 41). A meta-analyses included six randomized controlled trials revealed that CPAP therapy has a favorable effect on insulin resistance in adult participants with OSA without diabetes (42). VAMONOS study demonstrated that only an outstanding compliance (defined as ≥90% of nights and 8 h/night) to CPAP reduced fasting blood glucose in patients with OSA. Longitudinally, higher levels of therapeutic adherence may affect the rate of incident impaired fasting glucose, prediabetes, and type 2 diabetes mellitus (T2DM), despite the observed weight gains (43). A recent meta-analysis included seven trials (enrolling 691 participants) determined that CPAP treatment significantly improved glycemic control and insulin resistance in patients with T2DM and contemporary OSA (44). However, CPAP therapy remained so far mixed results in improving glucose metabolism (45), herein, non-dipping BP pattern could be an important hallmark to determine high-risk patients and may need to be considered as an important clinical implication for early prevention of diabetes in hypertensive patients with OSA.

BP lowering has been an established strategy for the prevention of new-onset type 2 diabetes in hypertensive patients (46). To achieve 24-h BP control, evening or bedtime administration of antihypertensive drugs has been proposed as a potentially more effective strategy to control nocturnal hypertension, normalize the night-time BP dip. Previous study indicated that bedtime HTN treatment, in conjunction with proper patient evaluation by ABPM to corroborate the diagnosis of HTN and avoid treatment-induced nocturnal hypotension, should be the preferred therapeutic scheme for type 2 diabetes mellitus. However, it might be argued that bedtime dosing is a reasonable approach to be applied specifically to non-dippers, or patients with isolated night-time hypertension. To date, the supporting evidence, clinical relevance and indications for bedtime dosing remain debatable. The current evidence on the

comparative impact of bedtime versus other times of antihypertensive drug dosing on 24-h BP profile and on cardiovascular morbidity and mortality is limited by insufficient design and/or rigor of the available studies. The relevant ongoing trials and their results are expected to shed light on the impact of bedtime versus morning drug dosing on outcome (47). Treatment In Morning versus Evening (TIME) study has recently revealed that evening dosing of commonly used anti-hypertensive medications is no different from morning dosing in terms of major cardiovascular outcomes in hypertensive subjects (48). However, it remains unclear which treatment (e.g., CPAP, bedtime HTN therapy or combination) is optimal for preventing diabetes in patients with non-dipping HTN and OSA, further studies may need to focus on this population (47).

Our study has some limitations. First, current guidelines recommend the assessment of average daytime and nighttime BP values to be based on the individuals' sleeping times and the diagnosis of non-dippers to be confirmed with repeat ABPM. In this study, nighttime BP values were fixed from 23:00 to 08:00 and BP patterns were assessed only at the enrolment visit without repetition. Nonetheless, it was reported that the use of fixed-time periods may be a reasonable alternative approach for self-report in ABPM (49). Second, we failed to follow up ABPM so that the change of BP pattern was unclear, however, in a prospective study, of all dippers, only 42.7% remained dippers, while of all non-dippers, 81.4% remained non-dippers in the follow-up (22). Therefore, it is unlikely to overestimate the risk of non-dipping BP pattern for new-onset diabetes in this study. Third, only 2.7% patients received regular CPAP treatment possibly due to poor compliance or acceptance, thus we could not evaluate the effect of CPAP treatment on prevention for diabetes. In addition, we failed to record the administration time of antihypertensive drugs for each patient, nonetheless, bedtime dosing was not common in the routine prescription in our clinical practice. Fourth, this study is a retrospective cohort analysis and therefore is susceptible to residual confounding biases. Finally, UROSAH cohort is constituted by Chinese population from a single tertiary center, the results may not be extrapolated to other ethnicities, as previous studies reported that nocturnal dipping pattern differed by ethnicities (50).

## Conclusions

We demonstrated that non-dippers are associated with approximately 1.5-fold higher risk for new-onset diabetes than dippers among hypertensive patients with OSA, suggesting that non-dipping BP pattern may need to be considered as an important clinical implication for early prevention of diabetes among this population.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

QL was responsible for design, data collection, analysis and writing manuscript. NL was responsible for design, conduct, data collection and guiding the whole study. QZ, XY, MW, MH, XC, JH and LG participated in conduct/data collection and analysis. AA, LY, and XL participated in conduct/data collection. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2023.1083179/full#supplementary-material>

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