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# Visit-to-visit blood pressure variability and sleep architecture

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## Abstract

Visit-to-visit blood pressure (BP) variability (BPV) is an independent risk factor of cardiovascular disease (CVD). Sleep architecture characterizes the distribution of different stages of sleep and may be important in CVD development. We examined the association between visit-to-visit BPV and sleep architecture using in-lab polysomnographic data from 3,565 patients referred to an academic sleep center. BPV was calculated using the intra-individual coefficient of variation of BP measures collected 12 months before the sleep study. We conducted multiple linear regression analyses to assess the association of systolic and diastolic BPV with sleep architecture—rapid eye movement (REM) and non-rapid eye movement (NREM) sleep duration.

Our results show that systolic BPV was inversely associated with REM sleep duration ( $p = .058$ ). When patients were divided into tertile groups based on their BPV, those in the third tertile (highest variability) spent 2.7 fewer minutes in REM sleep than those in the first tertile (lowest variability,  $p = .032$ ), after adjusting for covariates. We did not find an association of systolic BPV with other measures of sleep architecture. Diastolic BPV was not associated with sleep architecture either. In summary, our study showed that greater systolic BPV was associated with lower REM sleep duration. Future investigation is warranted to clarify the directionality, mechanism, and therapeutic implications.

## 1 | INTRODUCTION

Blood pressure (BP) is characterized by spontaneous fluctuations in both the short term ranging from seconds to hours and the long term ranging from days to years.<sup>1</sup> BP variability (BPV) results from a complex interplay between intrinsic cardiovascular regulation mechanisms, including humoral and neural central or reflex influences, as well as extrinsic environmental and behavioral factors.<sup>2</sup> BPV has been increasingly recognized as a prognostic marker of cardiovascular disease (CVD), independent of mean BP.<sup>3</sup> In particular, visit-to-visit BPV, which is the intra-individual BP between office visits, reflects the long-term fluctuations in BP and the BP burden on the

cardiovascular system.<sup>4</sup> Contrary to previous notions about visit-to-visit BPV as a random phenomenon, it is highly reproducible in clinical practice and has been known to have prognostic values for a wide range of health outcomes (eg, coronary heart disease, stroke, and all-cause mortality).<sup>5-7</sup> Previous work revealed that visit-to-visit variability in systolic BP improved 8-year predictions of major CVD-related health outcomes beyond those obtained from traditional risk factors.<sup>8</sup>

Sleep also plays an essential role in cardiovascular health. Abnormal sleep duration and poor quality (eg, low sleep efficiency and obstructive sleep apnea [OSA]) can contribute to disturbed BP control and cardiovascular risks, such as hypertension.<sup>9,10</sup> Sleep

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architecture is an objective measure of sleep quality assessed by polysomnography (PSG). This parameter characterizes the distributions of different stages, and it can be broadly classified into two forms: rapid eye movement (REM) and non-rapid eye movement including N1, N2, and N3 stages (collectively NREM).<sup>11</sup> A limited number of studies have suggested possible implications of sleep architecture in CVD.<sup>12,13</sup> Although visit-to-visit BPV and sleep architecture have each shown an individual link to cardiovascular health, their relationship has not been explored. In addition, past research has primarily focused on short-term variations of BP occurring over 24 hours in the context of OSA, leaving evidence for long-term BPV relatively scarce.<sup>14</sup> To address these gaps, our study examined the association between visit-to-visit BPV and sleep architecture.

## 2 | MATERIALS AND METHODS

### 2.1 | Study sample and dataset

We reviewed in-lab PSG from patients who were referred to the Sleep Center at the University of Virginia Health System between 2010 and 2017. Nearly all patients were referred to the sleep center for evaluation of sleep-disordered breathing.<sup>15,16</sup> Objective sleep measures were extracted from the PSG reports. Patients' health data, including demographic characteristics, vital signs (eg, BP measurements), medical history (diabetes and hyperlipidemia), and history of medication use, were extracted from their electronic medical records and were subsequently linked to the PSG dataset. We included the patients who met the following criteria: 1) aged over 18 years, 2) underwent a diagnostic PSG study, and 3) had at least three BP measures taken during office visits within one year prior to the sleep studies. Excluded were those who underwent split night studies, home sleep studies, or continuous positive airway pressure titration studies where sleep architecture variables were either not recorded or limited to only a small portion of the night. This study was approved by the University of Virginia Institutional Review Board.

### 2.2 | Blood pressure and blood pressure variability

All available BP readings taken during any office visits within the University of Virginia Health System and recorded in patients' electronic medical records were extracted. We used measurements taken one year before the sleep studies to calculate mean and intra-individual standard deviation (SD). BP was measured with validated and regularly recalibrated Dinamap devices by registered nurses following standard guidelines throughout the University of Virginia Health System.<sup>17</sup> The number of BP readings for each patient during the year prior to the sleep study ranged between 3 and 146, with an average of 9.8 (median = 7; interquartile range = [4, 11]). For patients who had more than 12 measures taken during this period,

12 measures were randomly selected and used to compute mean BP and BPV. Considering that mean and SD of BP measures are correlated, we used the coefficient of variation (defined as SD divided by the mean) as a measure of systolic BPV and diastolic BPV.<sup>4</sup> These two indices were then grouped into tertiles of systolic BPV and diastolic BPV, respectively.

### 2.3 | Objective sleep measures

Overnight PSGs were performed using the standard channels recommended by the American Academy of Sleep Medicine. Raw data were processed with the Embla Sandman Elite software (Natus Medical Incorporated, California, USA) and scored by registered PSG technologists. We employed the following objective sleep measures for analyses: total sleep time, sleep architecture, and apnea-hypopnea index (AHI). For the purpose of this study, sleep architecture was expressed as the duration of each sleep stage (REM and NREM [N1, N2 and N3]) (minutes) as well as their proportions relative to total sleep time (%). AHI, an index determining the severity of OSA, was derived from the number of apnea and hypopnea events per hour of sleep. We defined apnea as a reduction in airflow greater than 90% of the pre-event baseline and occurring for longer than 10 seconds using a thermocouple signal. Hypopnea events were recorded when the amplitude of the nasal pressure flow signal drop more than 30% of the pre-event baseline for longer than 10 seconds. We adopted a hypopnea definition requiring at least 4% oxygen desaturation (eg, Rule 1A for PSGs conducted between 2014 and 2018 and Rule 4B for PSGs conducted between 2010 and 2013).<sup>18,19</sup> OSA was defined by AHI greater than 5 per hour of sleep and was further classified into four levels of severity: normal (< 5.0/h), mild (5.0 - 14.9/h), moderate (15.0 - 29.9/h), and severe ( $\geq$  30.0/h).

### 2.4 | Covariates

We selected the following variables from patients' medical records as potential confounders: demographic and biometric characteristics, mean systolic and diastolic BP, diabetes, hyperlipidemia, and use of medications including antipsychotics, antidepressants, and antihypertensives which could affect BP and/or sleep architecture. Several cardiovascular risk factors including hypertension diagnosis, mean systolic BP, diabetes, hyperlipidemia, and obesity may be potential confounders in the relationship between systolic BPV and sleep architecture. They thus were identified and adjusted in multivariable models. Demographic and biometric variables included age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), and body mass index (BMI). BMI was calculated by height and weight and was then categorized into four groups (<25.0 kg/m<sup>2</sup>; 25.0-29.9 kg/m<sup>2</sup>; 30-34.9 kg/m<sup>2</sup>;

$\geq 35.0$  kg/m<sup>2</sup>). Information about the prescription of antipsychotic, antidepressant, and antihypertensive medications that are known to affect sleep was identified from medical records for the two years before the sleep studies. Patients were classified as users or non-users of antipsychotic and/or antidepressant medications. Because calcium channel blockers have been shown to reduce long-term BPV,<sup>20</sup> we grouped patients into three categories of antihypertensive medication use: non-users, calcium channel blocker users, and users of other BP medications.

## 2.5 | Statistical analysis

All statistical analyses were performed using Stata/SE version 15 (StataCorp, College Station, TX, USA). We computed Pearson coefficients among all pairs of predictors in the preliminary analyses to examine potential collinearity among the predictors. We subsequently performed multicollinearity diagnostic and confirmed that our predictors all had variance inflation factor < 4 and did not raise multicollinearity concerns. The patients' health data were compared among systolic BPV tertiles using analysis of variance or chi-square tests of independence. Multiple linear regression models were built to evaluate the cross-sectional association between visit-to-visit BPV and sleep architecture. We modeled measures of sleep architecture (N1, N2, N3, and REM sleep time) as a function of intra-individual systolic BPV and diastolic BPV, controlling for age, sex, race/ethnicity, BMI categories, diabetes, hyperlipidemia, history of medication use, mean systolic or diastolic BP, total sleep time, and AHI categories.

## 3 | RESULTS

### 3.1 | Sample characteristics

Table 1 summarizes patient demographics and biometric characteristics stratified by systolic BPV tertiles. Our final sample consisted of 3,565 patients (1,353 males and 2,212 females, mean age of  $54 \pm 15$  years). This was a racially and ethnically diverse cohort with 37% minorities. Over 91% of the sample was either overweight or obese, 36% had diabetes, and 51% had hyperlipidemia. The average BP of our sample was 132/76 mmHg. Patients with higher systolic BPV were more likely to have advanced age, higher diastolic BPV, higher AHI, and be users of antihypertensive and antipsychotic medications. Table 2 displays characteristics of sleep measures and architecture. The patients had an average total sleep time of  $339.5 \pm 88.2$  minutes. As expected, OSA was common (73%) in our study sample (mean AHI was  $16.5 \pm 18.0$ /h). Higher systolic BPV was associated with higher AHI ( $p < .001$ ). REM and NREM sleep accounted for about 17% and 84% of total sleep time, respectively. Patients with higher systolic BPV tended to have shorter REM sleep duration ( $p < .001$ ), longer N1 sleep percentage ( $p = .001$ ), and shorter N2 and N3 sleep durations.

### 3.2 | Association of systolic BPV and diastolic BPV with sleep architecture

In unadjusted analyses, systolic BP and diastolic BP coefficients of variation were correlated with REM sleep duration at  $r = -.091$  ( $p < .001$ ) and  $-0.085$  ( $p < .001$ ), respectively. There was an inverse association between systolic BPV and REM sleep duration ( $\beta = -22.2$ ,  $p = .058$ ), independent of patient demographic and biometric characteristics, diabetes, hyperlipidemia, mean systolic BP, medication use, total sleep time, and AHI (Model 1, Table 3). In Model 2 where systolic BPV tertile was a main predictor, patients in tertile 3 (highest variability) spent about 2.7 fewer minutes in REM sleep compared to those in tertile 1 (lowest variability) ( $p = .032$ ). This difference represented nearly 5% of the total REM sleep duration in this cohort. On the other hand, diastolic BPV did not show any association with REM sleep duration. Even though patients in the higher tertiles of diastolic BPV demonstrated shorter REM sleep duration, no significant difference was found between tertiles 1 and 3 (Models 1 and 2, Table 3). No associations were found between BPV and any NREM sleep durations.

## 4 | DISCUSSION

We found that systolic visit-to-visit BPV had an inverse association with REM sleep duration, independent of potential confounders including other sleep characteristics (total sleep time and OSA). When systolic BPV was divided into tertiles, patients with the highest variability (tertile 3) spent about 2.7 fewer minutes in REM sleep than those with the lowest variability (tertile 1). In contrast, no association was found between BPV and NREM sleep. To the best of our knowledge, this represents the first study to investigate the association between long-term BPV and sleep architecture.

BP is a major health factor essential for cardiovascular health, and managing BP is one of the seven recommended health behaviors included in the American Heart Association's Life's Simple 7.<sup>21,22</sup> Our findings were in accordance with prior study results demonstrating the importance of maintaining BP stability.<sup>23</sup> Growing evidence suggests that visit-to-visit BPV has important prognostic values for CVD and many other adverse health outcomes.<sup>24-26</sup> Of note, this parameter has demonstrated a comparable CVD prognosis to the 24-hour ambulatory BPV. A meta-analysis presented hazard ratios for all-cause mortality among three systolic BPV indices (visit-to-visit: 1.12 [1.05-1.20]; day-to-day: 1.15 [1.06-1.26]; 24-hour ambulatory: 1.11 [1.04-1.18]), with visit-to-visit BPV manifesting a similar strong association with cardiovascular and mortality outcomes in comparison with the other two indices.<sup>27</sup> Recently, several studies have proposed potential mechanisms by which BPV links to cardiovascular risks, such as large arterial stiffness, endothelial dysfunction, sympathetic overactivity, and autonomic imbalance.<sup>2,28,29</sup> Although poor sleep as an established CVD risk factor is linked to altered BP responses (eg, hypertension, nocturnal non-dipping BP), how BPV might be

TABLE 1 Demographic and biometric characteristics of the sample

Variable	Systolic BPV Tertiles								p-Value
	All		1		2		3		
	N	(%)	N	(%)	N	(%)	N	(%)	
All, n (Row %)	3,565	(100.0%)	1,170	(32.82%)	1,198	(33.60%)	1,197	(33.58%)	
Intra-individual Systolic BP, mean (SD)									
Mean (mm Hg)	131.73	(14.72)	129.17	(13.40)	130.92	(14.75)	135.05	(15.30)	<.001
Standard Deviation (mm Hg)	13.89	(6.40)	7.80	(2.36)	12.99	(1.99)	20.75	(5.35)	<.001
Coefficient of Variation	0.10	(0.04)	0.06	(0.02)	0.10	(0.01)	0.15	(0.03)	<.001
Maximum (mm Hg)	152.26	(21.69)	139.39	(14.87)	150.07	(17.70)	167.03	(22.08)	<.001
Minimum (mm Hg)	113.44	(14.70)	119.21	(13.29)	113.03	(14.00)	108.22	(14.66)	<.001
Number of Measures	7.45	(3.39)	6.12	(3.04)	8.06	(3.32)	8.14	(3.42)	<.001
Intra-individual Diastolic BP, mean (SD)									
Mean (mm Hg)	75.51	(8.68)	75.25	(8.56)	75.38	(8.53)	75.91	(8.94)	.142
Standard Deviation (mm Hg)	8.39	(3.55)	7.06	(3.13)	8.02	(3.06)	10.06	(3.73)	<.001
Coefficient of Variation	0.11	(0.05)	0.09	(0.04)	0.11	(0.04)	0.13	(0.05)	<.001
Maximum (mm Hg)	87.39	(11.11)	84.33	(9.95)	86.90	(10.64)	90.86	(11.67)	<.001
Minimum (mm Hg)	64.05	(10.06)	66.31	(9.38)	63.89	(9.72)	62.00	(10.57)	<.001
Number of Measures	7.45	(3.39)	6.12	(3.04)	8.06	(3.32)	8.14	(3.42)	<.001
Age at Time of Sleep Study, mean (SD)	54.17	(14.66)	51.94	(14.66)	53.90	(14.94)	56.61	(14.01)	<.001
Male Sex, N (%)	1,353	37.95%	462	39.49%	444	37.06%	447	37.34%	.414
Race/Ethnicity, N (%)									
Non-Hispanic White	2,238	(62.78%)	759	(64.87%)	753	(62.85%)	726	(60.65%)	.019
Non-Hispanic Black	862	(24.18%)	259	(22.14%)	290	(24.21%)	313	(26.15%)	
Hispanic	119	(3.34%)	40	(3.42%)	51	(4.26%)	28	(2.34%)	
Other/Unknown	346	(9.71%)	112	(9.57%)	104	(8.68%)	130	(10.86%)	
BMI (kg/m <sup>2</sup> ), mean (SD)	35.45	(8.89)	35.26	(8.63)	34.85	(8.57)	36.24	(9.37)	<.001
BMI Categories									
<25	311	(8.72%)	96	(8.21%)	118	(9.85%)	97	(8.10%)	.216
25-29.9	743	(20.84%)	256	(21.88%)	247	(20.62%)	240	(20.05%)	
30-34.9	848	(23.79%)	280	(23.93%)	299	(24.96%)	269	(22.47%)	
≥35	1,663	(46.65%)	538	(45.98%)	534	(44.57%)	591	(49.37%)	
Diabetes	1,283	(35.99%)	316	(27.01%)	417	(34.81%)	550	(45.95%)	<.001
Hyperlipidemia	1,805	(50.63%)	477	(40.77%)	610	(50.92%)	718	(59.98%)	<.001

(Continues)

TABLE 1 (Continued)

Variable	Systolic BPV Tertiles								p-Value
	All		1		2		3		
	N	(%)	N	(%)	N	(%)	N	(%)	
Antihypertensive Use, N (%)									
No Medication	1,307	(36.66%)	562	(48.03%)	444	(37.06%)	301	(25.15%)	<.001
Calcium Channel Blocker	805	(22.58%)	177	(15.13%)	273	(22.79%)	355	(29.66%)	
Other BP Medications	1,453	(40.76%)	431	(36.84%)	481	(40.15%)	541	(45.20%)	
Antipsychotic Use, mean (SD)	366	10.27%	93	7.95%	121	10.10%	152	12.70%	<.001
Antidepressant Use, mean (SD)	1,053	29.54%	292	24.96%	379	31.64%	382	31.91%	<.001

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; BPV, blood pressure variability; REM, rapid eye movement; SD, standard deviation.

TABLE 2 Characteristics of sleep variables across systolic BPV tertiles

Variable	Systolic BPV Tertiles				p-Value
	All	1	2	3	
Total Sleep Time (min), mean (SD)	339.50 (88.20)	344.69 (84.75)	342.05 (85.49)	331.87 (93.57)	<.001
AHI, mean (SD)	16.50 (18.00)	15.11 (16.75)	16.16 (17.14)	18.21 (19.81)	<.001
AHI Categories, N (%)					
<5	950 (26.65%)	344 (29.40%)	316 (6.38%)	290 (24.23%)	.009
5-14.9	1,238 (34.73%)	419 (35.81%)	412 (34.39%)	407 (34.00%)	
15-29.9	843 (23.65%)	256 (21.88%)	295 (24.62%)	292 (24.39%)	
≥30	534 (14.98%)	151 (12.91%)	175 (14.61%)	208 (17.38%)	
REM Percentage, mean (SD)	16.57 (9.06)	17.43 (9.08)	16.67 (9.12)	15.61 (8.88)	<.001
NREM Percentage, mean (SD)					
N1	9.46 (10.28)	8.75 (8.88)	9.35 (9.93)	10.27 (11.74)	.001
N2	63.12 (13.31)	62.81 (12.56)	62.89 (13.48)	63.66 (13.84)	.228
N3	12.34 (14.22)	12.90 (14.11)	12.29 (13.4)	11.85 (15.08)	.194
REM Duration (min), mean (SD)	58.94 (37.03)	62.99 (38.42)	59.13 (36.52)	54.81 (35.72)	<.001
NREM Duration (min), mean (SD)					
N1	28.41 (25.87)	27.04 (23.35)	28.71 (26.82)	29.47 (27.18)	.066
N2	214.88 (71.40)	216.69 (66.57)	215.64 (71.20)	212.35 (76.00)	.302
N3	42.90 (52.78)	45.24 (52.4)	42.93 (48.04)	40.58 (57.42)	.099

Abbreviations: AHI, apnea-hypopnea index; BPV, blood pressure variability; NREM, non-rapid eye movement; REM, rapid eye movement; SD, standard deviation.

related to sleep has not been sufficiently explored.<sup>30</sup> Existing studies were mainly focused on the association of BPV with sleep-disordered breathing, suggesting the possible contribution of OSA to increased visit-to-visit BPV.<sup>31,32</sup> In this context, we hypothesized that increased visit-to-visit BPV, an indicator of subclinical CVD, could be associated with poor sleep quality independent of OSA.

REM sleep is a distinct sleep stage that encompasses several physiological and behavioral features, such as muscle atonia, intermittent muscle twitches, and autonomic and respiratory activation.<sup>33</sup> REM

sleep that constitutes about 20% of total sleep time is considered high quality of sleep in adults.<sup>34</sup> Lower REM percentage (16.6% of total sleep time) in our study cohort is likely attributed to high prevalence of OSA, which typically results in sleep fragmentation and reduction in REM or N3 duration as shown in this study.<sup>35</sup> Moreover, since REM occurs more toward late stage in sleep, shorter sleep time expected in an in-lab environment would be associated with reduced REM percentage and REM duration. As such, our findings may be more relevant in patients with OSA.

TABLE 3 Multiple linear regression of BPV (Model 1) and BPV tertiles (Model 2) on REM sleep duration

Variable	Model 1			Model 2		
	Estimate (95% CI)		p-Value	Estimate (95% CI)		p-Value
Systolic Blood Pressure Variability						
Coefficient of Variation	-22.188	(-0.045, 0.737)	.058			
Tertiles [1 (Lowest Variability)]						
2				-2.251	(-0.005 0.135)	.064
3 (Highest Variability)				-2.700	(-0.005 -0.239)	.032
Diastolic Blood Pressure Variability						
Coefficient of Variation	-13.560	(-0.034, 7.195)	.200			
Tertiles [1 (Lowest Variability)]						
2				-0.468	(-0.003 1.905)	.699
3 (Highest Variability)				-1.761	(-0.004 0.658)	.154

Note: Reference categories are in angle brackets. The models were adjusted for age, sex, race/ethnicity, BMI, diabetes, hyperlipidemia, total sleep time, mean systolic BP, AHI, antipsychotic or antidepressant medication use, and antihypertensive medication use.

Abbreviations: BPV, blood pressure variability; CI, confidence interval.

Current investigations on REM sleep are mostly centered in the field of behavioral science. There is wide acknowledgment of the essential roles of this sleep stage in emotional regulation and memory consolidation.<sup>36</sup> While the other functions of this sleep stage remain unclear, maintaining REM sleep homeostasis is critical and may be important in cardiovascular health. A few studies have demonstrated that REM sleep-associated OSA is independently related to CVD, such as hypertension, impaired glucose metabolism, and cardiovascular end points,<sup>37,38</sup> but the role of REM sleep itself in cardiovascular health is quite limited. Pace et al<sup>39</sup> recently found that REM sleep duration was significantly reduced during the first 24 hours following stroke events in animals and that increased REM latency was linked to poor functional outcomes among post-stroke patients. Another study reported that one SD of decrease in REM sleep percentage was associated with an 18% increase in risk for atrial fibrillation, after controlling for covariates including OSA.<sup>12</sup> Our study results were consistent with the literature, supporting the growing body of evidence that linked sleep architecture to cardiovascular health. Although the absolute difference in REM sleep duration across visit-to-visit BPV tertiles was small and is of uncertain clinical significance, some clinical implications can be postulated. For example, if a patient undergoing routine PSG for OSA evaluation exhibits a significant deviation of REM sleep duration (such as absence or scarcity of REM sleep), a clinician may consider evaluating the patient's BP control, specifically BPV. Conversely, for patients with increased BPV (eg, the SD of systolic BP greater than 10 mmHg),<sup>5</sup> a clinician may consider impaired sleep quality as a possible factor.

Despite the intriguing study findings, our results require careful interpretations. Given the cross-sectional nature of this study, it is important to emphasize that this study only presents a potential interplay between visit-to-visit BPV and REM sleep rather than inferring causality, as their relationship can go in either or both directions.

The impact of cardiovascular dysfunction on objective sleep quality has not been previously examined. Thus, in this study, we were motivated to examine whether BPV, a signature of autonomic dysregulation of cardiovascular system,<sup>40,41</sup> predicts poor sleep architecture.

The strengths of this study include using a large sample and objective PSG data. Despite these strengths, several limitations should be noted. First, the results derived from a single-night, lab-based PSG may not represent the patients' natural sleep patterns because the unique assessment environment may distort their usual sleep habits. Second, since the cohort consisted of patients referred for sleep studies in one single institution, generalizability of the study findings is limited. Thus, a sample collected from multiple institutions is needed for more generalizable results. Third, medication use was obtained from prescriptions on medical records and may not represent actual use.

## 5 | CONCLUSION

In this study, we found that higher visit-to-visit BPV was associated with sleep architecture as reflected by reduced REM sleep duration. The potential pathway linking long-term BPV and sleep warrants future studies to clarify the directionality, mechanisms, and therapeutic implications. Such research studies may provide insights on stratifying individuals at high risk of CVD and developing targeted clinical interventions to reduce BP fluctuations and address sleep problems.

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## CONFLICT OF INTEREST

The authors declare no competing financial interests in relation to the work described.

## AUTHOR CONTRIBUTIONS

XL contributed to the study design, statistical design, data analysis, data interpretation, and drafted manuscript. JL and YK contributed to the study design, statistical design, and data interpretation. JML and HK contributed to the study design, data extraction, and data interpretation. MS contributed to the study conception and design, statistical design, data analysis, and data interpretation. All authors critically revised the manuscript for important intellectual content and approved the version to be submitted.

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