

Influence of Sleep Stage on the Determination of Positional Dependency in Patients With Obstructive Sleep Apnea

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Objectives. The supine sleep position and the rapid eye movement (REM) stage are widely recognized to exacerbate the severity of obstructive sleep apnea (OSA). Position-dependent OSA is generally characterized by an apnea-hypopnea index (AHI) that is at least twice as high in the supine position compared to other sleep positions. However, this condition can be misdiagnosed if a particular sleep stage—REM or non-REM (NREM)—predominates in a specific position. We explored the impact of the sleep stage on positional dependency in OSA.

Methods. Polysomnographic data were retrospectively analyzed from 111 patients with OSA aged 18 years or older, all of whom had an AHI exceeding five events per hour and slept in both supine and non-supine positions for at least 5% of the total sleep time. The overall ratio of non-supine AHI to supine AHI (NS/S-AHI ratio) was compared between total, REM, and NREM sleep. Additionally, a weighted NS/S-AHI ratio, reflecting the proportion of time spent in each sleep stage, was calculated and compared to the original ratio.

Results. The mean NS/S-AHI ratio was consistent between the entire sleep period and the specific sleep stages. However, the NS/S-AHI ratios for individual patients displayed poor agreement between total sleep and the specific stages. Additionally, the weighted NS/S-AHI ratio displayed poor agreement with the original NS/S-AHI ratio, primarily due to discrepancies in patients with mild to moderate OSA.

Conclusion. The weighted NS/S-AHI ratio may help precisely assess positional dependency.

Keywords. Diagnosis; Polysomnography; Obstructive Sleep Apnea; Sleep Stages; Supine Position

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by the repetitive collapse of the upper airway during sleep, leading to hypoxia and frequent awakening. OSA not only compromises sleep quality but can also lead to complications such as myocardial infarction, stroke, arrhythmias, and other cardiovascular diseases, necessitating active management. Polysomnography

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(PSG) is the standard diagnostic test for OSA. A diagnosis of OSA is made when the apnea-hypopnea index (AHI) derived from PSG is five or higher, accompanied by symptoms such as excessive daytime sleepiness [1]. Treatment options for OSA vary according to its severity, with an AHI of 15 or higher indicating moderate OSA and an AHI of 30 or higher indicating severe OSA [2,3].

The severity of OSA is affected by various factors, including sleep position, sleep stage, body weight, alcohol consumption, and drug use [4]. Notably, the supine sleep position is known to exacerbate OSA severity due to the gravitational effect, which increases the likelihood of upper airway collapse [5,6]. Patients who exhibit a marked increase in OSA severity when sleeping in the supine position are considered to have positional dependency (PD). PD is typically indicated by a supine AHI that is at least twice as high as the non-supine AHI [7]. Another factor that can significantly worsen OSA severity is rapid eye movement (REM) sleep. Patients with a substantial increase in AHI during REM sleep compared to non-REM (NREM) sleep are characterized as having REM-dependent OSA [8]. If such a patient primarily experiences REM sleep in the non-supine position and NREM sleep in the supine position, the supine AHI may be underestimated, and the non-supine AHI may be overestimated. This can lead to the false impression that PD is absent in a patient who actually has PD OSA. Conversely, if REM sleep occurs predominantly in the supine position, the supine AHI might be overestimated and the non-supine AHI underestimated, potentially resulting in the misclassification of non-PD OSA as PD OSA. In PSG reports, the impact of sleep stage is not typically accounted for when calculating PD-related parameters. This could lead to misinformed decisions regarding the application of positional therapy [7,9,10]. Therefore, in the present study, the authors analyzed the prevalence of changes in PD status when the

influence of sleep stage is considered, using data from patients who underwent PSG for OSA diagnosis. Additionally, we developed a modified parameter that incorporates the influence of sleep stage.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (No. 2021-04-029-013) and was exempt from obtaining patient consent.

We retrospectively analyzed data from adult patients aged 18 years and above who underwent in-laboratory PSG (Grael 4K PSG; Compumedics) at Gyeongsang National University Hospital and were diagnosed with OSA with an AHI ≥ 5 . All the patients were instrumented with standard PSG recording sensors: nasal pressure transducer, oronasal thermistor, electroencephalography, left and right electrooculography, electrocardiography, submental and leg electromyography, pulse oximetry probe, and respiratory effort belts around the chest and abdomen. We excluded cases from the analysis where either the supine or non-supine positions accounted for less than 5% of the total sleep time, as it was deemed difficult to define PD in such cases [11]. Consequently, the dataset included 111 patients (96 [86.5%] males, mean age of 46.6 years, mean body mass index [BMI] of 26.6 kg/m², mean AHI of 32.0). Consistent with the conventional definition, we defined PD as a ratio of non-supine AHI to supine AHI (NS/S-AHI ratio) of 0.5 or less. We calculated the overall NS/S-AHI ratio during the entire sleep, i.e., total sleep time, and that during REM sleep (NS/S-AHI ratio in R) and during NREM sleep (NS/S-AHI ratio in NR). For evaluating the agreement among these three NS/S-AHI ratios, group-wise comparisons were performed between each pair of ratios (i.e., overall NS/S-AHI ratio vs. NS/S-AHI ratio in R, overall NS/S-AHI ratio vs. NS/S-AHI ratio in NR, and NS/S-AHI ratio in R vs. NS/S-AHI ratio in NR). Furthermore, we calculated the weighted NS/S-AHI ratio by multiplying the proportion of REM and NREM sleep during the total sleep time by the respective NS/S-AHI ratios in each sleep stage, as shown below.

Weighted NS/S AHI ratio

$$= \left(\frac{\text{Non-supine AHI during REM}}{\text{Supine AHI during REM}} \times \frac{\text{REM sleep time}}{\text{Total sleep time}} \right) + \left(\frac{\text{Non-supine AHI during NREM}}{\text{Supine AHI during NREM}} \times \frac{\text{NREM sleep time}}{\text{Total sleep time}} \right)$$

We compared the difference between the weighted NS/S-AHI ratio and the original overall NS/S-AHI ratio. Statistical analyses were conducted with R software version 4.1.2 (R Core Team, R Foundation for Statistical Computing). The paired *t*-test, Bland-Altman plot, and Lin concordance correlation coefficient (CCC) were employed to assess and quantify the agreement of the NS/S-AHI ratios between entire sleep and REM sleep, en-

HIGHLIGHTS

- The ratios of non-supine to supine apnea-hypopnea index (AHI) for rapid eye movement (REM) sleep, non-REM (NREM) sleep, and the entire sleep period demonstrated poor agreement.
- The calculation of a weighted non-supine/supine AHI ratio, which involved multiplying the ratios obtained for REM and NREM sleep by their respective time proportions within the total sleep period, revealed discrepancies compared to the original non-supine/supine AHI ratio, which did not account for sleep stages.
- These discrepancies were especially pronounced in patients with mild obstructive sleep apnea (OSA).
- The weighted non-supine/supine AHI ratio appears to represent a useful metric for accurately diagnosing positional dependency, especially in patients with mild OSA.

tire sleep and NREM sleep, and original value and weighted value. The values of CCC were regarded as follows: <0.90, poor; 0.90 to 0.95, moderate; 0.95 to 0.99, substantial; and >0.99, almost perfect. A *P*-value <0.05 was considered statistically significant.

RESULTS

Of the 111 patients, 75 (67.6%) exhibited PD (65 [86.7%] male; mean age, 47.8 years; mean BMI, 25.7 kg/m²; mean AHI, 29.3), and 36 (32.4%) did not have PD (31 [86.1%] male; mean age, 44.1 years; mean BMI, 28.2 kg/m²; mean AHI, 45.8). The mean value of the overall NS/S-AHI ratio was not significantly differ-

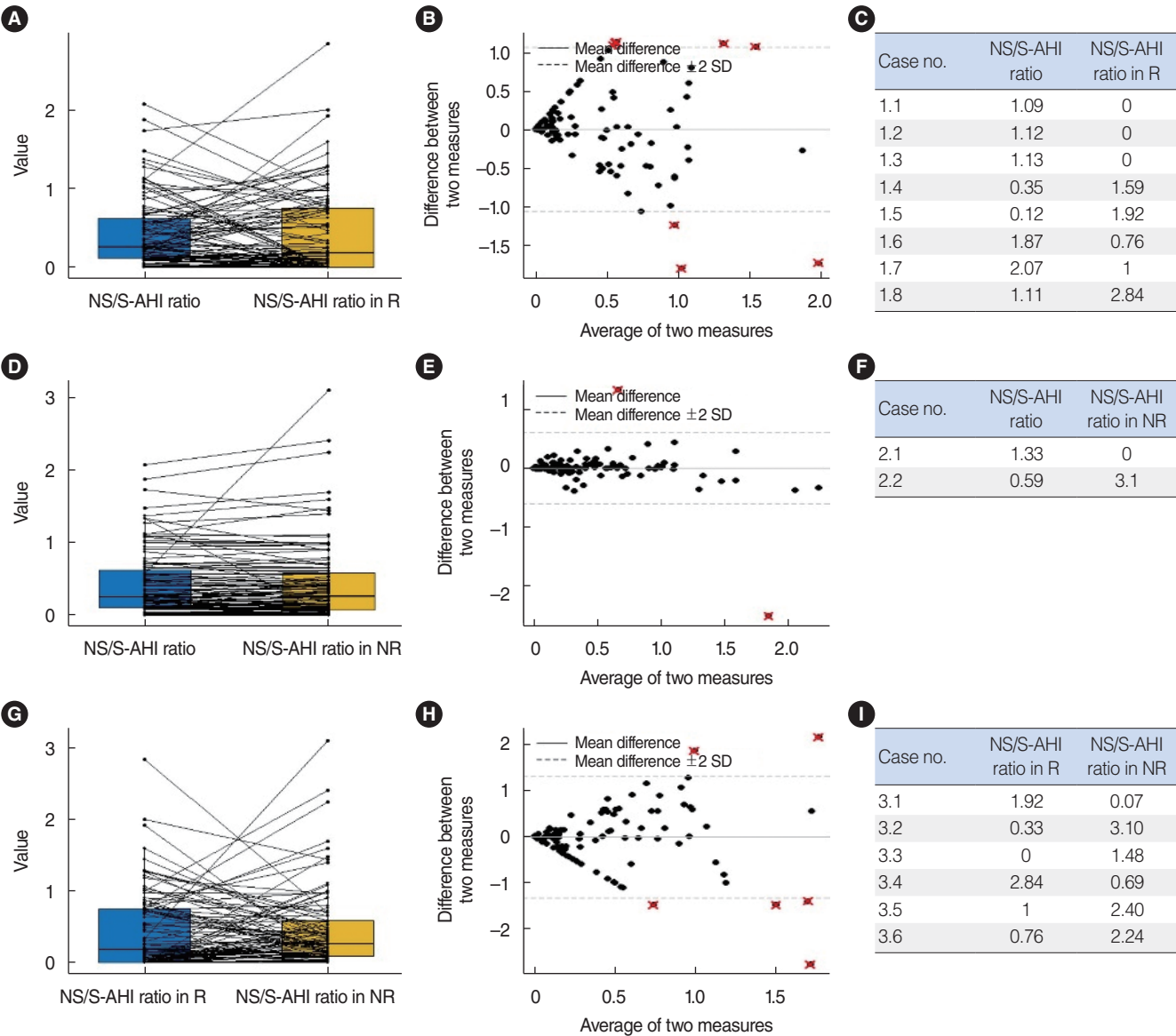


Fig. 1. Comparison of the ratio of non-supine apnea-hypopnea index (AHI) to supine AHI (NS/S-AHI ratio) during total, rapid eye movement (REM), and non-REM (NREM) sleep. The mean value of the NS/S-AHI ratio during the entire sleep period did not differ significantly from that during REM sleep (A), but the values for individual patients displayed poor agreement (Lin concordance correlation coefficient [CCC], 0.43; 95% confidence interval [CI], 0.26–0.57). Eight outliers (7.2%) were present beyond ± 2 standard deviations (SDs) from the mean difference between these two ratios (B, C). Similarly, the mean value of the NS/S-AHI ratio during the entire sleep period was not significantly different from that during NREM sleep (D), but the values for individual patients also showed poor agreement (CCC, 0.81; 95% CI, 0.74–0.86). Two outliers (1.8%) were found beyond ± 2 SDs from the mean difference between those two ratios (E, F). Likewise, the mean values of the NS/S-AHI ratio during REM and NREM sleep were not significantly different (G), but the patient-specific values again showed poor agreement (CCC, 0.25; 95% CI, 0.06–0.43). Six outliers (5.4%) were observed beyond ± 2 SDs from the mean difference between those two ratios (H, I). R, REM sleep; NR, NREM sleep.

ent from that during REM sleep (Fig. 1A), but the values for individual patients displayed poor agreement (CCC, 0.43; 95% confidence interval [CI], 0.26–0.57). When the difference between these two ratios was examined, eight outliers (7.2%) were identified beyond ± 2 standard deviations (SDs) from the mean (Fig. 1B). Among these, three patients (case numbers 1.1–1.3) were categorized as exhibiting PD during REM sleep but not based on the overall NS/S-AHI ratio. Conversely, two (case numbers 1.4–1.5) were not considered PD during REM sleep but were counted as PD according to the overall NS/S-AHI ratio. Considerable discrepancies were also observed between the two ratios in the remaining three patients (case numbers 1.6–1.8), although their PD status, as defined by a ratio of 0.5, did not change (Fig. 1C). In comparing the NS/S-AHI ratios between the entire sleep period and NREM sleep, the mean value of the overall ratio did not differ significantly from the ratio for NREM sleep (Fig. 1D). However, the values for individual patients also showed poor agreement (CCC, 0.81; 95% CI, 0.74–0.86), albeit less poor than that between total sleep and REM sleep. Regarding the difference between these ratios, two outliers (1.8%) were found beyond ± 2 SDs from the mean (Fig. 1E). One of these patients (case number 2.1) was considered to exhibit PD during NREM sleep, but the overall NS/S-AHI ratio did not indicate PD. In the other patient (case number 2.2), a marked discrepancy was observed between the two ratios, but the PD status—based on the criterion of a 0.5 ratio—did not change (Fig. 1F). When these two outliers were excluded, the agreement of the NS/S-AHI ratio between the entire sleep period and NREM sleep became substantial (CCC, 0.96; 95% CI, 0.94–0.97). Similarly, when comparing the NS/S-AHI ratios during REM and NREM sleep, the mean values were not significantly different (Fig. 1G), but the patient-specific values showed poor agreement (CCC, 0.25; 95% CI, 0.06–0.43). Six outliers (5.4%) were identified beyond ± 2 SDs from the mean in this comparison (Fig. 1H). Among them, one

(case number 3.1) was categorized as displaying PD during NREM sleep but not during REM sleep. Another two (case numbers 3.2 and 3.3) exhibited PD during REM sleep but not during NREM sleep. The remaining three patients (case numbers 3.4–3.6) also showed considerable discrepancies between the two ratios, but their PD status based on the 0.5 criterion did not change (Fig. 1I). Lastly, the weighted NS/S-AHI ratio did not significantly differ from the overall NS/S-AHI ratio (Fig. 2A), but the two measures showed poor agreement for individual patients (CCC, 0.86; 95% CI, 0.80–0.90). When examining the difference between these ratios, three outliers (2.7%) were found beyond ± 2 SDs from the mean (Fig. 2B). None exhibited PD based on the overall NS/S-AHI ratio. When the weighted NS/S-AHI ratio was applied, one patient (case number 4.1) was identified as having PD. The other two also exhibited notable changes in ratio values, but their PD status based on the 0.5 criterion did not change (Fig. 2C). All three outliers exhibited OSA of mild or moderate severity (AHIs of 9.7, 5.5, and 24.0 for case numbers 4.1, 4.2, and 4.3, respectively). After these outliers were excluded, the agreement between the overall and weighted NS/S-AHI ratios became substantial (CCC, 0.98; 95% CI, 0.97–0.98). When the degree of agreement between the overall NS/S-AHI ratios and weighted NS/S-AHI ratios was compared according to OSA severity, poor agreement was found in patients with mild to moderate OSA ($n=49$; CCC, 0.69; 95% CI, 0.52–0.81) (Fig. 3A), while substantial agreement was observed in those with severe OSA ($n=62$; CCC, 0.99; 95% CI, 0.98–0.99) (Fig. 3B).

DISCUSSION

Positive airway pressure (PAP) therapy is considered the cornerstone treatment for patients with moderate to severe OSA due to its safety and efficacy [12]. However, patients seek not only

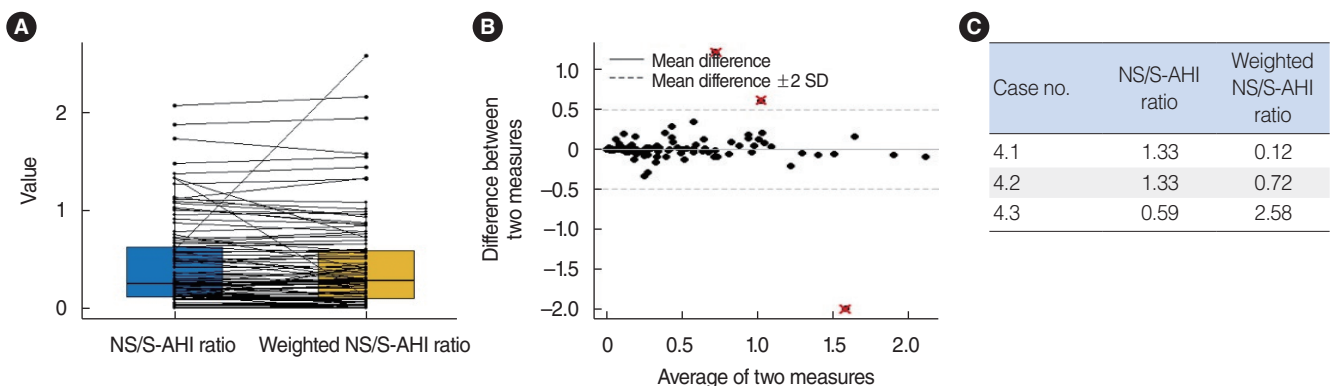


Fig. 2. Comparison between the overall and weighted ratio of non-supine apnea-hypopnea index (AHI) to supine AHI (NS/S-AHI ratio). The mean value of the weighted NS/S-AHI ratio did not differ significantly from the overall ratio (A). However, three outliers (2.7%) were found beyond ± 2 standard deviations (SDs) from the mean difference between these two ratios (B, C). None of these outliers represented positional dependency based on the overall NS/S-AHI ratio. When the weighted NS/S-AHI ratio was applied, one case (number 4.1) was identified as having positional dependency. The other two cases also demonstrated noticeable changes in their values; however, their positional dependency status did not change, according to the 0.5 criterion (C).

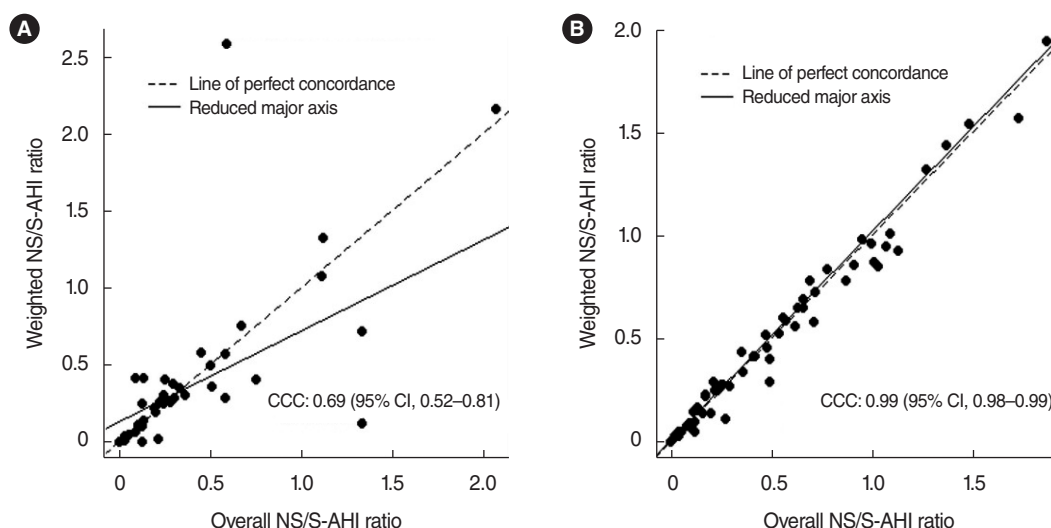


Fig. 3. Agreement between the overall and weighted ratio of non-supine apnea-hypopnea index (AHI) to supine AHI (NS/S-AHI ratio) ratios according to the severity of obstructive sleep apnea. In patients with mild to moderate obstructive sleep apnea ($n=49$), poor agreement was observed (Lin concordance correlation coefficient [CCC], 0.69; 95% confidence interval [CI], 0.52–0.81; A). In contrast, substantial agreement was found in patients with severe obstructive sleep apnea ($n=62$; CCC, 0.99; 95% CI, 0.98–0.99; B).

to treat OSA but also to achieve comfortable sleep. The inconvenience of wearing a mask during sleep and the effort required to clean the equipment contribute to a low long-term compliance rate, which is about 50% [13]. This means that nearly half of patients with OSA eventually discontinue treatment, facing outcomes like those of patients who never received treatment. Consequently, alternative non-PAP therapies are clinically necessary. Among these alternatives are treatments such as the mandibular advancement device (MAD) or hypoglossal nerve stimulation [14]. Additionally, for patients with positional OSA, various positional therapies can be considered as alternatives to PAP. These range from simple solutions like using a tennis ball to more sophisticated methods that involve vibratory or auditory alarms or vests [15].

The prevalence of PD OSA is reported to be between 23% and 63% [16,17]. This concept of positional therapy originated from a pioneering study by Cartwright, which indicated that many patients with OSA exhibit an AHI in the supine position that is at least twice as high as their AHI in the lateral position. This trend was inversely associated with obesity, prompting the suggestion that positional therapy could represent a viable treatment option for patients with OSA who exhibit PD and have a normal body weight. Additionally, the study reported that 20.8% (5/24) of the patients with PD achieved an AHI below 5 when sleeping on their side [7]. The article also noted that differences in AHI between sleep positions may be influenced by the sleep stage. Nevertheless, it was presumed that sleep position-dependent changes in AHI are independent of sleep stage alterations, as the ratio of supine to non-supine AHI remained consistent despite significant individual variations in the proportion of each sleep position throughout the total sleep time [7]. Contrasting

with these results, the findings of the present study indicated poor agreement between the NS/S-AHI ratio during REM and NREM sleep (Fig. 1G and H), suggesting that the prior assumption may not be valid. Furthermore, individuals displayed significant variation in the NS/S-AHI ratio during REM and NREM sleep. Some patients had a low NS/S-AHI ratio during REM sleep, which significantly increased during NREM sleep, while others exhibited the reverse pattern (Fig. 1G). The underlying reasons for these divergent patterns in patients remain unclear, highlighting the need for further detailed research to uncover the mechanisms or risk factors responsible for these differences. A significant difference in the NS/S-AHI ratio between total sleep and NREM sleep was observed in only a few patients (Fig. 1E and F). Consequently, the clinical impact of this discrepancy may be limited. Indeed, when two outliers were removed from the analysis, the agreement of the NS/S-AHI ratio between the entire sleep period and NREM sleep improved significantly, with the CCC increasing from 0.81 (95% CI, 0.74–0.86) to 0.96 (95% CI, 0.94–0.97). A similar improvement was seen when comparing the overall and weighted NS/S-AHI ratios after excluding outliers (from 0.86 [0.80–0.90] to 0.98 [0.97–0.98]). Overall, since positional therapy can be beneficial for some patients with OSA, a reliable indicator for accurately identifying PD remains clinically useful.

PD not only influences the selection of positional therapy but also impacts the outcomes of other treatments for OSA. For example, one study demonstrated that the effectiveness of MAD use was more pronounced in patients with supine-dependent OSA, with a median reduction in AHI from 41 to 5.9, compared to those with non-supine-dependent OSA, among whom the median AHI decreased from 44 to 21 [18]. Consequently, patients

with PD are likely to benefit from MAD treatment as well. However, caution should be exercised when interpreting these results, as the study's definition of PD did not align with the commonly accepted "twice as high" criterion requiring that the supine AHI be at least twice the non-supine AHI. In this context, the criteria for successful MAD treatment were an AHI of less than 10, with position-dependent OSA being defined as a supine AHI of 10 or greater and a non-supine AHI of less than 10.

A consensus on the definition of PD is essential for guiding the selection of appropriate treatment strategies. The "twice as high" rule has been widely accepted as a definition for PD since its introduction [7,19,20]. Some studies have incorporated additional criteria, such as a non-supine AHI of less than five, to more precisely define PD OSA [10]. Using this definition, 27.4% of all patients with OSA were classified as having PD. More specifically, 50% of patients with mild OSA were identified as exhibiting PD, while only 20% and 6.5% of those with moderate or severe OSA, respectively, were placed in this category. This suggests that positional therapy could represent a valuable treatment option, especially for patients with mild OSA. Interestingly, in the current study, two of the three outliers with discrepant results between the overall and weighted NS/S-AHI ratios were cases of mild OSA. Furthermore, the weighted NS/S-AHI ratio demonstrated poor agreement with the overall NS/S-AHI ratio in individuals with mild to moderate OSA, whereas it showed substantial agreement in those with severe OSA (Fig. 3). Previous research has indicated that with increasing OSA severity, shifts in sleep stages occur more frequently, suggesting reduced sleep stability [21]. Therefore, one might anticipate a significant difference between the overall NS/S-AHI ratio and the weighted NS/S-AHI ratio in cases of severe OSA. However, the findings exhibited the opposite trend. This could be attributed to the decreasing prevalence of PD and the proportion of REM sleep within the total sleep time as OSA severity increases [10,22]. Consequently, the identification of PD in patients with severe OSA remained accurate without requiring a precise formula to account for the influence of sleep stage shifts. Thus, employing the weighted NS/S-AHI ratio may be clinically valuable, particularly in cases of mild OSA where an accurate diagnosis of PD is critical.

In another study, PD was defined differently: an overall AHI of 15 or greater, a minimum sleep duration of 20 minutes in all positions, and a supine AHI at least double that of the non-supine AHI, provided the non-supine AHI remained below 15 [23]. The inconsistency in defining PD across various studies is apparent. In a study involving group meetings of experts, additional criteria were introduced: spending at least 10% of the total sleep time in each position, an overall AHI of 40/hour or more, and a reduction in AHI by at least 25% in the non-supine position. The objective of these criteria is to identify patients who would benefit from positional therapy [24]. A separate study proposed the modified Cartwright index as a measure for PD, acknowledging the wide variation in sleep position proportions among

patients [6]. The modified index is calculated by multiplying the proportion of time spent supine (time in supine position/total sleep time) by the ratio of supine AHI to total AHI (supine AHI/total AHI). Additionally, this index applies only to patients with an overall AHI of 15 or higher, indicating at least moderate severity. The study also indicated that the classic Cartwright index, which relies on the "twice as high" rule, does not predict the success of non-PAP therapies, such as upper airway surgery [25]. However, no alternative cut-off ratio was proposed.

In that study, a modified indicator for REM dependency was suggested, based on a principle resembling that used for PD: the ratio of REM AHI to total AHI (REM AHI/total AHI) multiplied by the proportion of time spent in REM sleep during the total sleep time (time in REM sleep/total sleep time). However, the study did not account for the potential influence of sleep stage distribution when determining PD. In contrast, the present study assessed the impact of sleep stage on PD by comparing the weighted NS/S-AHI ratio with the conventional ratio. Consequently, 2.7% (3/111) of the patients displayed marked differences. When the "twice as high" rule was applied, the PD status changed in only 0.9% (1/111) of the patients. Nevertheless, the "twice as high" rule is a conventional guideline rather than a gold standard supported by robust scientific evidence. This study highlights the need for a discussion on developing a modified ratio for PD.

This study has several limitations, including its retrospective design and the relatively small sample size of 111 patients. The possibility that significant differences between the weighted NS/S-AHI ratio and the conventional overall NS/S-AHI ratio may be present in only a minority of patients could limit the clinical impact of the findings. Nonetheless, given the key role of accurate PD diagnosis in determining the suitability of positional therapy, the modified value proposed by the authors may still hold value, even if it benefits only a subset of patients. To establish the clinical utility of the weighted NS/S-AHI ratio, future prospective studies must demonstrate that using this metric to select patients for positional therapy leads to a higher success rate compared to selections made using the conventional overall NS/S-AHI ratio. Furthermore, this study was based on a single-night PSG test performed in an unfamiliar sleep environment. Thus, the potential influence of night-to-night variability on the accuracy of the weighted NS/S-AHI ratio was not evaluated. Given that night-to-night variations can distinctly impact a patient's OSA severity [26], future multi-night studies are warranted to assess whether the weighted NS/S-AHI ratio offers definitive advantages over the conventional overall NS/S-AHI ratio, particularly in cases of mild to moderate OSA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: SWK. Methodology: BML, SWP. Formal analysis: SCK, RBK. Project administration: SWK, YJJ, YHJ, HJC. Writing—original draft: SR, SWK. Writing—review & editing: SWK, SCK, RBK, BML, SWP, YJJ, YHJ, HJC. All authors read and agreed to the published version of the manuscript.

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