Positive Airway Pressure Usage in Youth with Obstructive Sleep Apnea Following Transition to Adult Health Care

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Background: There is increasing prevalence of moderate to severe obstructive sleep apnea (OSA) in adolescents, the majority of whom receive treatment with positive airway pressure (PAP). Adherence to PAP is sub-optimal in adolescents with OSA. Moreover, the impact of transition from pediatric to adult healthcare system on PAP adherence is unknown. This is relevant as the transition period is a time of increased stress for youth with chronic illnesses.

Research Question: Does PAP adherence decrease during the 1-year transition period from pediatric to adult healthcare system in those with OSA?

Study Design and Methods: Youth previously diagnosed with persistent OSA and treated with PAP in a large academic center (Toronto, Canada) between 2017 and 2019 were enrolled on transfer from the pediatric to adult sleep clinic and followed at 12 months. Mixed-effects linear regression models were used to investigate the effect of time since the transfer on objective PAP adherence with adjustment for confounders.

Results: Among the 45 enrolled participants, 42.2% were female, the median age was 18 years (interquartile range [IQR]: 17–18), median BMI was 30.3 (IQR: 24.0–37.1), and the median apnea-hypopnea index (AHI) was 17.8 events/hour (11.8–30.7). In univariate analysis, we observed a significant reduction in the 12-month average PAP usage in days used at follow-up compared to PAP use at the time of enrolment: median of 5.0 hours/day (IQR: 1.3–8.0) vs 2.6 hours/day (0.0–6.4), p < 0.0001. Following adjustment for age, level of education, employment status and living arrangement, the 12-month average PAP usage in days remained significantly decreased at follow-up compared to at the time of enrolment: change in hours of −1.14; 95% CI −2.27 to −0.01.

Interpretation: Among youth with OSA treated with PAP, there is a clinically significant reduction in PAP adherence over the first year during the transition from pediatric to adult health care.

Keywords: CPAP adherence, transition care, obstructive sleep apnea, young adults, CPAP compliance

Plain Language Summary

Study Question: In youth, does the transfer from pediatric to adult sleep clinics impact adherence to PAP for OSA?

Results: This study demonstrates that in youth, PAP adherence at one year following transfer declines dramatically.

Interpretation: The negative impact of the transfer process on PAP adherence for OSA in youth requires further study to elucidate the barriers to adherence and develop specific strategies to overcome PAP treatment reluctance or resistance in this population.
Introduction

In Ontario, Canada, the majority of youth transfer to adult health services by age 18 years. The transition period between adolescence and adulthood is a time of significant change and increased psychological distress, especially, for youth with chronic health conditions. Current research has identified that young adults find the transition to adult care as disjointed and they struggle with the demands of increased responsibility for their own care. Non-adherence to medical treatments is a common challenge among adolescents. Over the last 10 years, there has been a dramatic rise in youth diagnosed with moderate to severe OSA. This increased prevalence of OSA in youth is attributed to increasing childhood obesity, to the survival into adulthood of children with previously fatal complex medical disorders and to increased awareness and diagnosis of OSA. The impact of persistent childhood OSA on future adult health outcomes is unclear but recent evidence suggests that adolescents diagnosed with OSA are more likely to have a lower employment status as young adults, earning lower income with greater dependence on social assistance and disability pension compared to those without OSA. Positive airway pressure therapy (PAP) is the mainstay of treatment for OSA in this population, and is highly efficacious. However, adherence with PAP is suboptimal at less than 50% in youth. Moreover, there are no data on whether changes in PAP adherence occur during the transition process from pediatric to adult care and over the longer term. As recent studies suggest that low use of CPAP may still be beneficial to the individual, the change in adherence over time maybe of more relevance than absolute thresholds (ie, categorizing participants into adherent or non-adherent). Accordingly, the primary objective of this study was to evaluate the change in adherence with PAP during the initial 12 months following transition from the pediatric to adult healthcare system in young adults with OSA. The secondary objective was to identify factors associated with PAP therapy poor adherence. We hypothesized that there would be a decrement in PAP adherence during the first 12 months of transfer of care to adult health service.

Methods

Study Design/Population

This was a prospective observational cohort study of young adults with OSA transferred from the pediatric sleep clinic at the Hospital for Sick Children to the Sleep Pediatric Transition (SlePT) clinic at University Health Network (UHN) for ongoing clinical care enrolled between February 2017 and December 2019. The sleep clinics at both sites incorporate recommended guidelines and processes for transition of care. Prior to transition, all patients underwent routine otolaryngology assessment and if required treatment. Dental, medical weight loss and assessment for bariatric surgery were performed if warranted. Eligible participants were those between the ages of 17 to 20 years old previously diagnosed with OSA on a level 1 overnight polysomnogram (PSG) and on treatment with PAP for a minimum of 12 months prior to transfer to the adult sleep clinic. Exclusion criteria included those who had difficulties with communication due to language barriers, and those with a PAP device without the capability of monitoring adherence.

Procedures

Participants had medical history and demographics (age, sex, body mass index (BMI), race, education and employment status), questionnaires and download of PAP adherence, assessed on enrolment (baseline) at UHN (T-0), at 6 months (T+6) and at 12 months (T+12). Participants self-identified as White/non-Hispanic, Hispanic, African American/Black, Asian, Indigenous and Other/unknown. At each time point, participant attendance at second or third level education and/or employment status was documented. Baseline PSG data were from the diagnostic PSG performed at the pediatric center closest to the time of transfer to adult care.

PAP Monitoring and Adherence

All participants had objective adherence monitored by downloading the compliance data either directly from the PAP device or through a cloud-based tracking system. Data collected included the percentage of total nights the PAP device was used, average and median usage over the total time and days used, the residual apnea-hypopnea index (AHI) and mask leak stratified into normal range or excessive as per the PAP device. Objective PAP Adherence at T-0 was
a download for the previous 12 months, at T+6 for the 6-month period from T-0, and T+12 for the 12-month period from T-0.

**Questionnaires**
1) Epworth Sleepiness Scale (ESS) a measure of subjective daytime sleepiness; 15 2) Pittsburgh sleep quality index (PSQI), which assesses sleep quality over a one-month interval; 16 3) Insomnia Severity Index (ISI) to assess the severity/presence of insomnia; 17 5) Fatigue severity scale (FSS), a measure of fatigue and its change over time; 18 6) Generalized Anxiety Disorder-7 (GAD-7) to assess for anxiety; 19 7) Patient Health Questionnaire-9 (PHQ-9) to screen for, monitor and measure depression; 20 8) CPAP perception questionnaire (PAPPQ) that assess patients’ experiences, beliefs and attitudes towards therapy on a Likert-type visual analogue scale; 21 9) EQ-5D-5L, a generic health-related quality of life questionnaire that records health status and the EQ-VAS which records the participant’s self-rated health on a vertical visual analogue scale. 22

Approval for conduct of the study was from the UHN research ethics board (UHN- REB #14-8043). Written informed consent prior to participation in the study was provided by the subjects or their legal guardians. The study was performed in accordance with the Declaration of Helsinki.

**Study Outcomes**
The primary outcome was defined as the change in objective PAP adherence measured as the average PAP usage in days used, hours per day, over the 1-year transition period (PAP adherence within 12 months before baseline and at 12-months follow-up visit). The secondary definitions were: a) the change in PAP adherence as the average number of hours use per day between T0 and T+6; and b) change in PAP adherence as the percentage of days used between T0, T+6 and T+12.

**Statistical Analysis**
Descriptive statistics were used to characterize our population of interest at baseline (T0), at 6 (T+6) and 12 (T+12) months, as applicable, using the Wilcoxon test for paired samples for continuous variables and McNemar’s test for paired samples for categorical/nominal data. The level of significance was set at p < 0.05.

For the primary analyses, PAP adherence measured by time of PAP usage per day was compared between baseline and 12-month follow-up visits using a paired Wilcoxon test. A Friedman test, as the appropriate post-hoc test is the pairwise Wilcoxon rank sum test with a Bonferroni correction was used to compare all time points. To adjust for potential confounders, risk factors, and additional time point, we used mixed-effects linear regression models to investigate the effect of time (three time points – T-0, T+6 and T+12) on PAP adherence clustered by individuals. For the main model (Model 1), as potential confounders, we selected variables with less than 10% of missing values at each time point associated with PAP adherence that would also have changed over the same time period, such as age, combined variable on the level of education and employment status and living arrangement. In Model 2, we further adjusted for potential risk factors available at baseline that may affect PAP adherence such as time on PAP therapy before transition, sex, ethnicity, a history of tonsillectomy and comorbidities with less than 10% of missing values: genetic conditions, congenital heart failure, asthma, dyslipidemia, neurological and endocrine conditions, anxiety/depression. In addition to Model 1, Model 3 included baseline OSA severity and PAP-related characteristics over time, such as baseline AHI, minimum oxygen saturation (MinSaO₂), mask type and residual AHI. Finally, in Model 4, in addition to Model 1, other variables that can change over time (at a p-value of 0.2 or lower) and may be associated with PAP adherence, but with more than 10% of missing values, were considered: weight, height, FSS, ESS, PAPPQ, and EQ-VAS.

For the secondary analyses, similar approaches described above were used to investigate the effect of time on secondary definitions of PAP adherence.

Given the relatively small sample size for the missing values’ imputation, completed case analyses were conducted. Missing values are reported in Supplemental Table 1. All statistical analyses were performed in the secure environment following provincial privacy standards using RStudio Version 1.3.1073 (www.r-project.org; ©2009–2020 RStudio, PBC).
Our preliminary sample size calculation was based on our ability to enroll 38 individuals over initial year of transition period. With this sample size, we are able to detect a difference of at least 50 min in CPAP adherence with the standard deviation ranged from 90 to 110 min at power of 80% and alpha of 0.05.\textsuperscript{23}

**Results**

Of 69 patients screened between January 2017 and December 2019, 45 were enrolled in the study (Figure 1). Baseline (T-0) characteristics are presented in Table 1. At baseline, the median age was 18 years with a median BMI of 30.3 kg/m\(^2\) of whom 42.2\% were females. The majority of participants self-reported race/ethnicity as White/non-Hispanic. A high percentage had confirmed genetic disorders (57.8\%) and at least one comorbidity was reported in 93.3\% of participants. Although, these patients were diagnosed with OSA without associated hypoventilation, a high percentage were prescribed BPAP (44\%).

The most recent diagnostic PSG had been performed a median of 2.3 years (IQR: 1–4) prior to enrolment. The median AHI was 17.8 events per hour (IQR: 11.8–30.7). The median time on PAP therapy before transition was 36 months (IQR: 18–62). The majority of subjects used fixed continuous PAP and the predominant interface was an oronasal mask (Table 1). The median average PAP usage days used was 5 hours (IQR: 1.8 to 3) for 77\% of all nights at T-0. PAP termination, contrary to medical advice, occurred in 35.5\% (n = 16) of participants over the 12-month period. No individual who discontinued PAP at T+6 resumed treatment at T+12. Two participants were lost to follow-up and could not be contacted (n = 4\%). Despite initial clinic attendance by participants, subsequent attendance demonstrated a marked decline at both T+6 (did not attend, n = 26, 57.8\%) and T+12 (n = 18, 40.0\%).

**Primary Objective: Changes in PAP Adherence Following Transition**

In univariate analysis, the average PAP usage in days used significantly decreased over time from baseline to T+12 (Table 2) for the primary outcome definition. Following adjustment for potential confounders in our main model such as age, level of education, employment status and living arrangements (Model 1) a significant reduction in average PAP
Table 1 Baseline Characteristics, Sleep, Medical and Questionnaire Data (n = 45)

| Variables | Baseline |
|-----------|----------|
| Age, years: median (IQR) | 18.0 (17.0–18.0) |
| Sex, female: n (%) | 19 (42.2) |
| BMI, kg/m²: median (IQR) | 30.3 (24.0–37.1) |
| Race, n (%) | |
| Asian | 12 (26.7) |
| White | 23 (51.1) |
| Black | 4 (8.9) |
| Indigenous | 1 (2.2) |
| Other/Mixed | 5 (11.1) |
| Education/Work Status n, (%) | |
| 2nd level education | 27 (60.0) |
| 3rd level Education (beyond high school) | 12 (26.7) |
| Working | 3 (6.7) |
| Not working/Not in School | 3 (6.7) |
| Living Independently: Yes | 1 (2.2) |
| At least one reported medical comorbidity: Yes, n (%) | 42 (93.3) |
| Dyslipidemia | 6 (13.3) |
| Syndrome - Genetic Disorders | 26 (57.8) |
| Congenital heart disease | 8 (17.8) |
| Asthma | 12 (26.7) |
| Neurological Disease | 5 (11.1) |
| Endocrine Disease | 6 (13.6) |
| Depression/Anxiety/Taking antidepressant or hypnotics | 6 (13.3) |
| Previous tonsillectomy/adenoidectomy | 21 (46.7) |
| Positive Airway Pressure-related variables, n (%) | |
| Continuous Positive Airway Pressure | 26 (57.7) |
| Automatic Positive Airway Pressure | 3 (6.6) |
| Bilevel Positive Airway Pressure | 19 (42.2) |
| Volume Assured Pressure Support | 1 (2.2) |
| Mask type: oronasal (vs nasal/others) | 29 (64.4) |
| Time on Positive Airway Pressure therapy before transition, months, median (IQR) | 36.0 (18.0–62.0) |
| Polysomnogram Variables, median (IQR) | |
| AHl (events/hour) (n missing =1) | 17.8 (11.8–30.7) |

(Continued)
usage at 12 months was noted (Table 3). A reduction in average PAP usage at 12 months remained significant additionally controlling for underlying medical co-morbidities and genetic conditions, sex and ethnicity (Model 2) (Table 3). It became non-significant (but directionality confirmed the results), additionally controlling for other covariates (Model 3 and 4), which may be impacted by >10% missing values (Supplementary Table 2) and the relatively small sample size.

Similar results were noted utilizing secondary definition for PAP adherence (Tables 2 and 3). Although significant reduction in percentage of days of PAP usage at T+12 in univariate analysis was attenuated and become non-significant after adjusting for confounders, we directionally confirmed our results as based on estimates and 95% confidence intervals.

**Secondary Objective: Factors Associated with PAP Adherence at 12 Months**

Limited by sample size and multiple comparisons, we found that self-identification of race as non-White, having a diagnosis of anxiety or depression, living independently, higher level of the minimum oxygen saturation at the diagnostic PSG and a higher PAPPQ score were significantly associated with a decrease in 12-month PAP usage (see e-Table 2 for details).

**Discussion**

This is the first prospective study from a large academic hospital to evaluate the adherence to PAP following transition of young adults from the pediatric to adult healthcare service in those with persistent OSA. In multiple analyses we demonstrated that a significant reduction in average PAP therapy usage occurred during the first year following transition.
Furthermore, a significant minority of participants (35.5%) stopped PAP therapy during the first year while in the adult healthcare system. Studies assessing medium to long-term adherence (3 to 10 years) in the adult general population show heterogeneity with adherer rates between 52% and 85%. In pediatric patients, a large cloud database study showed PAP adherence at 90 days of 61.8%. Reassuringly, a 24-month follow-up study in children showed stable adherence at greater than 50%.

Adherence at baseline in our patient group was similar to the general population, but it is most notable for the significant drop over the 12 months following transition, highlighting that transition to adult health care is a critical period in this adolescent group. While no studies have looked at dose-response of necessary PAP adherence in adolescents, in adults nightly use of

### Table 2 Univariate Changes in the Outcomes of Interest: Objective Measures of Adherence with PAP Treatment

| Outcomes, Median (IQR) | Baseline | At 6 Months | At 12 Months | P value: Baseline vs 6 Months* | P value: Baseline vs 12 Months* | Friedman Test, p value# |
|------------------------|----------|-------------|--------------|--------------------------------|--------------------------------|------------------------|
| **Primary definition** |          |             |              |                                |                                |                        |
| Average PAP usage in days used, hours per day | 5.0 (1.28–8.0) N=44 | 3.7 (0.5–6.8) N=43 | 2.6 (0.0–6.4) N=43 | 0.009 | <0.0001 | <0.0001 |
| **Secondary definition** |          |             |              |                                |                                |                        |
| Percentage of days of PAP usage | 77 (28–98) N=45 | 70 (24–98) N=44 | 44 (0–99) N=43 | 0.077 | 0.0002 | <0.0001 |

**Notes:** *Paired Wilcoxon test for continuous variables.** For a Friedman Test, the appropriate post-hoc test is the pairwise Wilcoxon rank sum test with a Bonferroni correction: a statistical difference at 0.10 or less was found only for comparison between baseline and at 12 months.

**Abbreviation:** PAP, positive airway pressure.

### Table 3 The Effect of Time (Three Time Points – Baseline, 6 Months and 12 Months) on the Objective Positive Airway Pressure (PAP) Treatment Adherence Measures

| Outcomes | Univariate* | Model 1 | Model 2 | Model 3 | Model 4 |
|----------|-------------|---------|---------|---------|---------|
| **Primary definition:** Average PAP usage in days used, hours per day | | | | | |
| Changes at 6 months | -0.67 (-1.36 to -0.03) | -0.56 (-1.39 to -0.27) | -0.79 (-1.62 to -0.03) | -0.33 (-1.25 to 0.64) | 0.11 (-1.34 to 1.61) |
| Changes at 12 months | -1.40 (-2.09 to -0.71) | -1.14 (-2.27 to -0.01) | -1.64 (-2.75 to -0.55) | -0.16 (-1.41 to 1.13) | -0.05 (-1.54 to 1.45) |

**Secondary definition:** Percentage of days of PAP usage

| Changes at 6 months | -4.42 (-12.60 to -3.74) | -1.50 (-11.18 to 8.19) | -3.91 (-13.62 to 5.62) | 2.91 (-6.60 to 12.75) | 14.81 (0.00 to 30.08) |
| Changes at 12 months | -17.34 (-25.51 to -9.17) | -11.98 (-25.15 to 1.18) | -17.68 (-30.75 to -4.94) | 0.34 (-12.91 to 13.92) | 3.67 (-11.73 to 19.25) |

**Notes:** *Clustered by individuals. Results from a multilevel mixed effects linear regression models were presented as changes in PAP adherence at 6 and 12 months and 95% confidence intervals. Model 1 (main model): fixed effect variables: demographics and socio-economic status related variables considered as potential confounders with less than 10% of missing values; age, combined variable on the level of education and employment status and living arrangements. Model 2: Model 1 + variables available at baseline: time on positive airway pressure therapy before transition, sex, ethnicity, a history of tonsillectomy and comorbidities with less than 10% of missing values: genetic conditions, congenital heart failure, asthma, dyslipidemia, anxiety/depression, neurological and endocrine conditions. Model 3: Model 1 + OSA and PAP related characteristics: baseline apnea-hypopneas index (AHI), minimum oxygen saturation (MinSpO2), mask type and residual AHI (more than 10% of missing values). Model 4: Model 1 + other variables that can change overtime with more than 10% of missing values, which were associated with changes overtime in the univariate analyses at p-value of 0.2 or lower: weight, height, Fatigue severity scale, Epworth sleepiness scale, Positive airway pressure perception score and EQ-VAS.**

**Abbreviation:** PAP, positive airway pressure.
more than 4, 6 and 7.5 hours is required to improve subjective sleepiness, memory and functional status, respectively.28 Alarmingly, most of our adolescents had PAP adherence below any of these absolute thresholds.

Factors Predictive of PAP Adherence

Secondary objectives of our study were to elicit factors that may be contributing to PAP adherence. In both adult and pediatric studies, multiple factors have been inconsistently associated with PAP adherence including socio-demographic characteristics, OSA severity, intolerance and side-effects of PAP therapy and psychosocial factors.29,30 In our study, time following transition was the most significant factor controlling for confounders. Even with concerted efforts by the clinical team, 4% (n = 2) were lost to follow-up, and in-person attendance at clinics was very low at 6 months (42%) and 12 months (60%), the reasons for which were not clear.

Neither age nor sex were predictors of adherence in our cohort. Age-related differences in adherence in large real-world database studies have found lower adherence in those aged 18 to 30 years compared to older adults31,32 and a cloud-based database cross-sectional study of 20,553 children evaluating 90-day PAP adherence also showed lower adherence in the adolescent group (15–18 years).11 In our cohort, age was not predictive most likely due to the narrow age range (17–18 years). In contrast to our study, adult studies with relatively similar sex distribution had lower adherence in females.25,32 Our results may be explained in part by the majority of young adults continuing to live at home. This may moderate peer pressure and perceived stigma associated with PAP usage in females, who endure greater societal expectations with respect to body image.31

Our cohort was representative of the diverse population in Toronto.33 Non-white race was significantly associated with lower PAP adherence. Other, but not all studies have also shown race/ethnicity to be a predictor of PAP adherence.34 The majority of US studies when adjusted for covariates have identified black race as a predictor of lower PAP usage compared to whites.35,36 The reasons for this have not been fully elucidated, as neighbourhood socioeconomic barriers were not the sole drivers for this poorer adherence.37

The presence of anxiety or depression was the only patient comorbidity negatively associated with PAP adherence. This is in keeping with other studies that identified baseline anxiety as a predictor of PAP non-adherence.38,39 These results suggest that the adequate screening for and treatment of underlying mood or anxiety disorders should be considered in this young population to aid with improved PAP adherence. Sleepiness, fatigue or quality of life as per the EQ-VAS were not predictors of PAP adherence in our study. This is consistent with other studies in the literature.36 The participant’s perceptions and attitudes to PAP were predictors of average PAP usage. This questionnaire independently predicted mean PAP adherence in the first 30 days following a PAP titration study and is also predictive in our patient group.21

Disease severity as determined by the AHI did not have an impact on PAP adherence as observed in other studies.40 However, there was an association between the minimum oxygen saturation and adherence, suggesting that those with more severe intermittent hypoxia had greater average PAP usage. The reason for the greater adherence is unclear, but may relate to previous education regarding the benefits of PAP or symptomatic improvement in these individuals. In our group, a very high proportion of patients (64.4%) were prescribed oronasal interfaces on transfer from the pediatric system. This is higher than the usual prevalence of oronasal masks in the adult population and the reasons for this are unclear. While these masks were not identified as significant predictors of adherence in our study, previous studies have identified greater patient preference for nasal masks41 and better adherence.42 Furthermore, a higher PAP pressure may be required for oronasal masks42 which may further impact PAP adherence.44,45 Over the 12 months, two patients were switched from oronasal to nasal masks. Ongoing reassessment of the mask interface may be important in this young group to promote continued adherence.

This study has a number of limitations, in particular the relatively small sample size and missing data at different time points. For some participants who did not attend follow-up clinics, some data collection was possible, for example, remote download of PAP usage but completion of questionnaires was limited. The absence of this data was an impediment to the assessment of, and adjustment for multiple confounders sequentially to assess changes in estimates after each step. This may explain the failure to elicit associations for Models 3 and 4. Our cohort had a high frequency of comorbid medical conditions, which may not be representative of young adults with OSA attending community clinics.
The changes in physician communication language and style from pediatric to adult health care, implicit biases and poor understanding of cultural beliefs may have had an impact on PAP adherence and attendance at clinics. Lastly, we did not assess self-efficacy, an important predictor of PAP adherence.46

The current SlePT clinic was established due to an increase in pediatric patients with OSA requiring ongoing adult care and to streamline the transition of young adults with sleep disorders to the adult healthcare system.14 The results from our study suggest that further modification and evaluation of the program is required to improve patient participation with the health-care team and their OSA treatment. This is important as emerging evidence in youth with OSA indicates that OSA is an independent risk factor for cardiovascular and metabolic disease, poorer psychosocial functioning and lower QOL.47–49

**Interpretation**

We have shown a significant concerning reduction in adherence to PAP in young adults in the first year following transfer to adult health care. There is an urgent need to ensure effective and sustained therapy for OSA in young adults to improve long-term clinical and psychosocial outcomes in these individuals. Further research is needed to identify critical barriers to PAP adherence in young adults. Moreover, novel strategies to promote effective engagement between adult healthcare providers and young adults are paramount to enhance attendance at clinics.

**Abbreviations**

BMI, body mass index; CI, confidence interval; ESS, Epworth sleepiness scale; FSS, Fatigue severity Scale; GAD, Generalised anxiety disorder; IQR, interquartile range; ISI, insomnia severity index; OSA, Obstructive sleep apnea; PAP, Positive airway pressure; PHQ, Patient health questionnaire; PAPPQ, CPAP perception questionnaire; PSG, polysomnogram; PSQI, Pittsburgh sleep quality index; SlePT, Sleep Pediatric Transition; UHN, University Health Network.

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**Author Contributions**

C.R. is the guarantor of the article, taking responsibility for the integrity of the work as a whole, from inception to published article. C.R., I.N. and T.K. conceptualized, designed and obtained funding for the study. A.H., U.M., C.G. C. participated in data collection and conducted the study. T.K. performed data analysis. C.R., I.N. and T.K wrote the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

**Disclosure**

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