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Original Article

ORIGINAL ARTICLE

The burden of obstructive sleep apnea in pediatric sickle cell disease: a Kids' inpatient database study

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Abstract

Study Objectives: Obstructive sleep apnea (OSA) is associated with cardiovascular and cerebrovascular morbidity. Patients with sickle cell disease (SCD) are at increased risk for both neurologic complications (NC) and OSA. However, the relationship between OSA and SCD complications is unclear. We hypothesized that there would be an association between OSA diagnosis and SCD complications.

Methods: Hospital discharge records of patients with SCD aged < 19 years were obtained for the years 1997, 2000, 2003, 2006, 2009, and 2012 from the Kid's Inpatient Database. The primary outcome, NC, a composite of stroke, transient ischemic attack, and seizures. Secondary outcomes included acute chest syndrome (ACS), vaso-occlusive crisis, length of hospital stay, and inflation-adjusted cost of hospitalization. Multivariable regression was conducted to ascertain the association of OSA with primary and secondary outcomes. Analyses were adjusted for the use of noninvasive mechanical ventilation (NIMV) to determine its role as NC risk modifier.

Results: There were 203,705 SCD discharges included in the analysis, of which 2,820 (1.4%) and 4,447 (2.2%) also included OSA and NC diagnoses. Multivariable logistic regression indicated that OSA was associated with NC (adjusted odds ratio [OR], 1.50 [95% CI 1.02–2.21], $p = 0.039$) and ACS (OR, 1.34 [95% CI 1.08–1.67], $p = 0.009$) in children with SCD. In the multivariable analysis adjusted for NIMV, the significant association between OSA and NC was no longer observed (OR, 1.39 [95% CI 0.94–2.05], $p = 0.100$).

Conclusions: OSA is associated with a 50% increase of odds of NC in children with SCD in this nationwide dataset. The use of NIMV to treat OSA may modify the risk of OSA-associated NC.

Statement of Significance

In this cross-sectional study of 203,705 children with sickle cell disease discharged in the United States from 1997 to 2012, children with obstructive sleep apnea (OSA) were at 50% increased odds of having neurologic complications (NC) as compared with those without OSA. Importantly, the use of noninvasive mechanical ventilation may modify the risk of NC.

Key words: neurologic complications; obstructive sleep apnea; hospitalization; Kids' inpatient database; sickle cell disease

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Introduction

Sickle cell disease (SCD) is a hemoglobinopathy with a prevalence of 17 cases per 10,000 people among African Americans [1]. The point mutation in the β-globin gene results in sickle hemoglobin that is less soluble and more prone to polymerization during deoxygenation [2, 3]. This feature leads to various acute and chronic complications that impose great health and economic burden [4]. Common complications associated with SCD include acute chest syndrome (ACS), pain crisis, neurologic complications (NC; e.g. stroke and seizures), anemia, and infection [5, 6]. Stroke, for example, affects about 0.001%–0.01% of the general pediatric population in the United States [7, 8], while occurs in approximately 10% of children with hemoglobin SS under the age of 20 years [9, 10]. Seizures are considered part of NC as they can be the first manifestation of strokes in children [11, 12].

Obstructive sleep apnea (OSA) is a disorder of breathing during sleep that results in fragmented sleep and intermittent hypoxemia from recurrent partial or complete obstruction of the upper airway [13]. In children, untreated OSA results in multiple adverse health outcomes, including neurobehavioral problems and cardiovascular complications [14–16]. In adults, OSA is associated with increased risks of NC, such as stroke and transient ischemic attack (TIA) [17–19]. OSA has a prevalence of 1%–5% among children in the United States and has been reported to be higher in children with SCD [1, 14, 20]. The higher prevalence of OSA among SCD children has been partially attributed to the adenotonsillar hypertrophy as a compensatory mechanism for the loss of splenic function [21]. It has been posited that nocturnal hypoxemia from OSA would exacerbate the NC of SCD [1, 22].

Several studies have examined the association between OSA and NC in patients with SCD [23–25], and the effect of adenotonsillectomy on the reduction of NC in SCD, but the results are mixed due to small sample sizes [26, 27]. The mixed results from previous studies might be partially explained by the inability to account for confounders and the limited statistical power as NC were not as prevalent among children. Therefore, we aimed to address this issue by utilizing the Kids Inpatient Database (KID) [28], a US nationwide inpatient database to assess the association between OSA and NC in children with SCD. We hypothesized that OSA would be associated with NC among children with SCD.

Methods

Study design and population

This retrospective cohort study was conducted using the hospital discharge data from patients with SCD aged 0–18 years for the years 1997, 2000, 2003, 2006, 2009, and 2012 from the US Representative Kids' Inpatient Database (KID) [28]. The KID is an administrative all-payer inpatient care database made of a stratified sample of pediatric discharges from all short-term, nonfederal, general, and specialty hospitals and includes sampling weights to generate national estimates of annual pediatric hospitalizations, outcomes, and healthcare costs [28]. The KID data are released every 3 years with approximately 3 million pediatric discharges in each sample from participating states [28]. As all data obtained were deidentified, IRB approval was not needed.

Hospitalized children with SCD were identified using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) code. SCD was defined based on the diagnostic codes in any diagnosis fields validated by previous studies (Supplementary Table S1) [29–31].

Measurements of variables

The following patient characteristics were included in the analyses: age, gender, race, type of insurance, median household income quartiles based on counties of residence, and admission season. Hispanic is included as part of the race instead of ethnicity per the reporting method of KID. Hospital characteristics were also included in the analyses, including hospital region, teaching status of the hospital, and hospital size depending on the region of the hospital. Comorbidities, procedures or treatments of patients ascertained using diagnostics codes validated in previous studies were also included, including OSA, sleep-disordered breathing (SDB), hypertension, obesity, congenital heart diseases, coagulopathy, types of SCD, diabetes mellitus (DM), asthma, iron-deficiency anemia (IDA), central sleep apnea (CSA), blood transfusion, cranial angiography, tonsillectomy and/or adenoidectomy (AT), and noninvasive mechanical ventilation (NIMV). Supplementary Table S1 provides the full list of ICD-9-CM codes used in the analysis.

Definition of outcomes

The primary outcome was NC. This is a composite outcome consisting of stroke (e.g. ischemic stroke and hemorrhagic stroke), TIA, and seizures. Seizures were included as a part of NC as they can be the first manifestation of strokes in children [11, 12]. Secondary outcomes included ACS, vaso-occlusive crisis (VOC), length of hospital stay in days, and inflation-adjusted cost of hospitalization. To allow for direct comparisons between years for hospital charges accounting for inflation, we converted all charges to 2012 US dollars using the average Consumer Price Index. Similarly, ICD-9-CM codes validated in previous studies were used to ascertain the abovementioned outcomes (Supplementary Table S1) [31–34].

Statistical analysis

Categorical variables were presented as counts and proportions, and the differences between groups were tested using Pearson's χ^2 test. Continuous variables were summarized as mean with standard deviation (*SD*), and the differences between groups were examined using the *t*-test. Two-way analysis of variance was performed for seasonal variations. It was determined a priori to conduct comparisons between patients with and without OSA, and between years. For comparison between years, three subperiods were created: subperiod 1 (years 1997 and 2000), subperiod 2 (years 2003 and 2006), and subperiod 3 (years 2009 and 2012).

To determine the association between OSA and NC in children with SCD, multivariable logistic regression analyses adjusting for patient characteristics, hospital characteristics, patients' comorbidities, and treatment received were performed. The final model was adjusted for the following variables: age categories, gender, race, hospital region, hospital size, household

incomes, congenital heart disease, coagulopathy, obesity, hypertension, asthma, types of SCD, blood transfusion, and AT. Variables adjusted in the model initially were determined based on potential relevance given the literature and then were further refined using a statistical backward selection approach. Similar analyses were also performed for binary secondary outcomes, including ACS and VOC. Of note, patients in 1997 and 2000 were not included in the analyses for ACS as the ICD-9 codes for ACS (517.3) was not coined during these years. For continuous secondary outcomes, including the length of hospital stay and inflation-adjusted cost of hospitalization, multivariable linear regression analyses accounting for the abovementioned variables were also conducted. Analyses were conducted with and without the inclusion of NIMV or AT as both were considered effective treatments for OSA [14, 35]. If the association between OSA and NC altered after inclusion of the treatment for OSA (e.g. NIMV and AT), it would suggest that the treatment may modify the risk of NC associated with OSA in SCD patients. A sensitivity analysis that combined OSA with SDB was performed to further delineate the association of the big SDB umbrella with primary and secondary outcomes.

All the analyses were accounted for sampling weights provided in the KID. Data were presented consistent with Healthcare Cost and Utilization Project reporting methodologies [28]. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using Stata 14.0 (Stata Corp, College Station, TX)

Results

Demographic and patient characteristics

There were 203,705 SCD discharges during the study period (Figure 1). There was a total of 36,382 patient discharges in 1997, 31,218 in 2000, 35,557 in 2003, 32,613 in 2006, 34,422 in 2009, and 35,512 in 2012 among children with SCD. Among discharged children with SCD, 1.38% (n = 2,820) carried a diagnosis of OSA. Compared with children with SCD without OSA, those with OSA were older, more likely to utilize public insurance (e.g. Medicare/Medicaid), and more likely to receive care at teaching hospitals and hospitals in the western United States (Table 1). Additionally, children with OSA were more likely to have hypertension, DM, asthma, and congenital heart disease; and more likely to receive AT, transfusion, cranial angiography, and NIMV. Across the subperiods, there were notable trend changes regarding age, female sex, race, season of hospital admission, household income, hospital region, hospital size, teaching status of hospitals, hypertension, DM, IDA, congenital heart disease, OSA, blood transfusion, NIMV, and cranial angiography (Supplementary Table S2). The proportion of hospitalizations associated with NC among children with SCD across study periods were stratified by age categories and months (Supplemental Figure S1). Children aged 15–18 years old accounted for the majority of the discharges. However, there were no significant changes across months (p = 0.97).

Primary outcome

There were 4,447 (2.18%) patients with NC among hospitalized children with SCD (n = 203,705). These consisted of ischemic stroke (n = 702), hemorrhagic stroke (n = 137), TIA (n = 291), and seizures (n = 3,415). Compared with the non-OSA group, the OSA group was more likely to have seizures (2.91% vs. 1.66%, p = 0.0003) but not stroke (0.51% vs. 0.34%, p = 0.4729). Compared with children without OSA, children with OSA were more likely to have NC (3.45% vs. 2.17%, p = 0.0014; Table 1).

In multivariable logistic regression models adjusted for age categories, gender, race, hospital region, hospital size, household incomes, congenital heart disease, coagulopathy, obesity, hypertension, asthma, transfusion, and AT, OSA (adjusted odds ratio [OR], 1.50 [95% CI 1.02–2.21], p = 0.039) was significantly associated with NC (Table 2). Multivariable logistic regression models were also performed to explore the impact of OSA on stroke (adjusted OR, 1.37 [95% CI 0.54–3.46], p = 0.510) and seizures (adjusted OR, 1.43 [95% CI 0.96–2.13], p = 0.077; Supplementary Table S3).

Given that intermittent hypoxemia associated with OSA could be a mechanism leading to NC that might be ameliorated by AT or NIMV, we adjusted for both treatments of OSA in the multivariable logistic regression model. The adjustment of NIMV made the initially significant association (adjusted OR, 1.50 [95% CI 1.02–2.21], p = 0.039) between OSA and NC non-significant (adjusted OR, 1.39 [95% CI 0.94–2.05], p = 0.10; Table 2), suggesting that NIMV may modify the risk of NC. However, this observation was not seen in the AT-adjusted model. The association between OSA and NC did not change significantly before (adjusted OR, 1.19 [95% CI 0.83–1.72], p = 0.34) and after (adjusted OR, 1.39 [95% CI 0.94–2.05], p = 0.10) including AT in the multivariable logistic regression model.

Secondary outcomes

There were 12,108 (9%) patients with ACS among hospitalized children with SCD (n = 136,104) from 2003 to 2012. Compared with children without OSA, children with OSA were more likely to have ACS (11.27% vs. 8.85%, p = 0.003; Table 1). There were 126,562 (62.13%) patients with VOC among hospitalized children with SCD (n = 203,705). Compared with children without OSA, children with OSA were less likely to have VOC (45.92% vs. 62.36%, p < 0.0001; Table 1). In multivariable logistic regression models adjusted for aforementioned variables, OSA was significantly associated with ACS (adjusted OR, 1.34 [95% CI 1.08–1.67], p = 0.009; Supplementary Table S4). The association became non-significant with the inclusion of NIMV (adjusted OR, 1.13 [95% CI 0.89–1.43], p = 0.319), suggesting that NIMV may modify the risk of ACS. OSA was not significantly associated with VOC on multivariable logistic regression models (adjusted OR, 0.96 [95% CI 0.81–1.15], p = 0.664), and was not affected by the inclusion of NIMV in the regression model (adjusted OR, 0.94 [95% CI 0.79–1.12], p = 0.490).

Hospital utilization and healthcare cost for SCD

Among children with SCD, the mean inflation-adjusted cost of hospitalization was 17,184 (*SD*, 465) US dollars, and the mean length of hospital stay was 4.01 (*SD*, 0.04) days. Compared with children without SCD, those with SCD have a higher inflation-adjusted cost of hospitalization (17,084 [*SD*, 459] vs. 24,223 [*SD*, 1,409], p < 0.0001) but similar length of hospitalization (4.01 [*SD*, 0.04] vs. 3.94 [*SD*, 0.15], p = 0.611; Table 1). Trend analyses

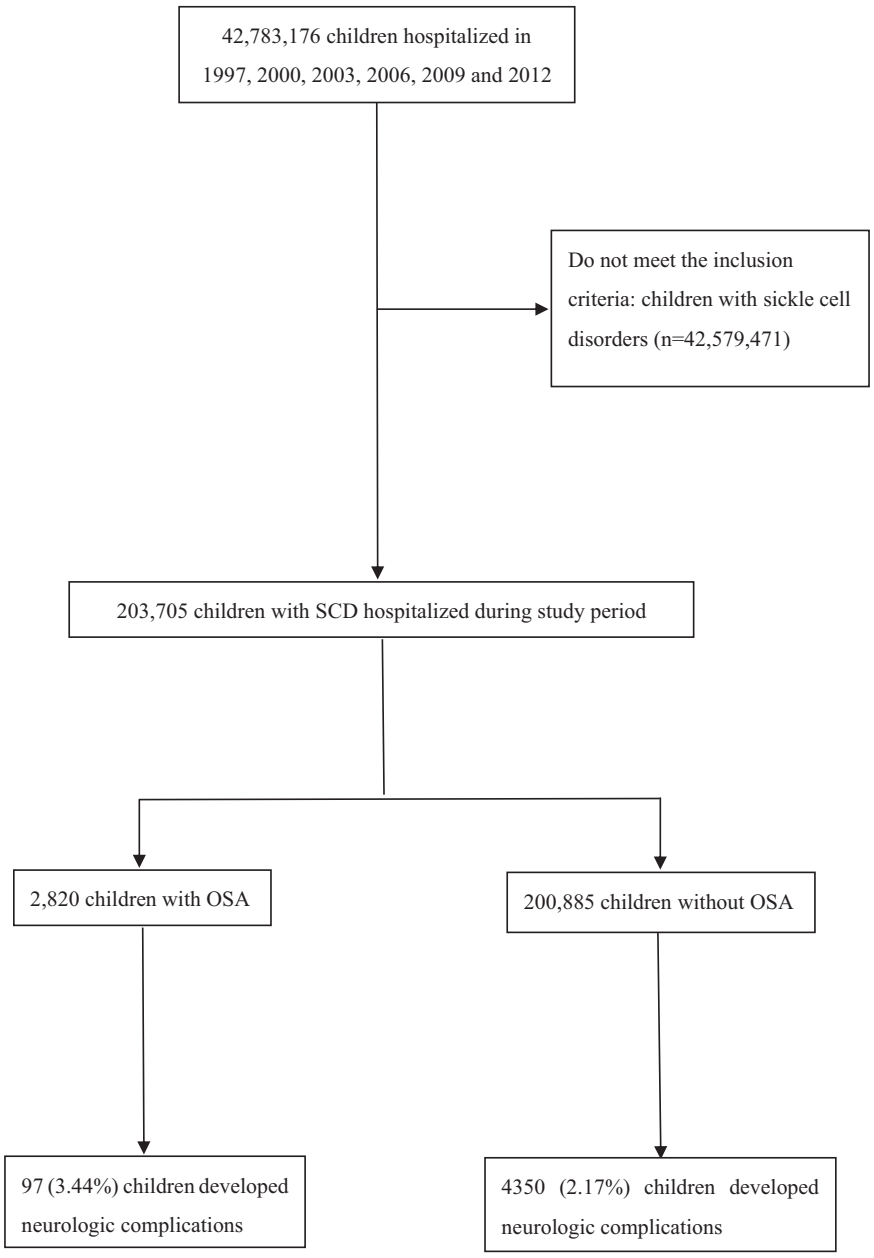

Figure 1. Construction of the study cohort. Schematic illustrating of the construction of the study cohort using the KID.

were performed comparing different subperiods and showed a significantly shorter length of hospitalization ($p < 0.001$), and higher inflation-adjusted cost of hospitalization ($p < 0.001$) in the subperiod of 2009 and 2012 as compared with two other subperiods (Supplementary Table S2).

In multivariable linear regression models adjusted for aforementioned variables, OSA was significantly associated with inflation-adjusted cost (adjusted β, 5,163 [95% CI 2223–8102], $p < 0.001$) but not length of hospitalization (adjusted β, 0.02 [95% CI–0.28–0.33], $p = 0.881$; Table 3).

The result of sensitivity analyses that combined SDB and OSA to assess the association with primary and secondary outcomes are detailed in Supplementary Tables S5 and S6. SDB was significantly associated with higher odds of NC and ACS, and longer hospital stay.

Discussion

This nationwide study showed that OSA was an independent risk factor for NC in children with SCD, and confirmed that OSA is an independent risk factor for ACS [36]. In addition, this study adds to the literature that NIMV might modify the risk of NC associated with OSA in this population. These findings highlight the public health burden of OSA on children with SCD, and possible ways to remediate the risk associated with OSA.

Several mechanisms have been proposed to explain the association between NC and OSA among children with SCD [37]. First, nocturnal hypoxemia from untreated OSA may promote polymerization of sickle hemoglobin [38–40], the adhesion of red blood cell to endothelium via binding molecules (e.g. ICAM-1 and P-selectin) [41–43], and hypercoagulable state due

Table 1. Characteristics of children with SCD stratified by obstructive sleep apnea

	Total (*n* = 203,705)	No OSA (*n* = 200,885)	OSA (*n* = 2,820)	*P*-value
Demographic characteristics				
Age, mean (*SD*)	9.34 (0.05)	9.33 (0.05)	9.92 (0.17)	0.0001
Age categories				
0–4 years, *n* (%)	56,787 (27.88)	56,359 (28.06)	428 (15.19)	<0.0001
5–9 years, *n* (%)	43,075 (21.15)	42,147 (20.98)	928 (32.91)	
10–14 years, *n* (%)	49,693 (24.39)	48,871 (24.33)	822 (29.17)	
15–18 years, *n* (%)	54,149 (26.58)	53,508 (26.64)	641 (22.74)	
Gender				
Female, *n* (%)	99,400 (48.80)	98,055 (48.81)	1,345 (47.70)	0.3179
Obesity, *n* (%)	1,103 (0.54)	925 (0.46)	178 (6.31)	<0.0001
Race				
White, *n* (%)	3,368 (1.65)	3,313 (1.65)	55 (1.95)	0.4912
Black, *n* (%)	156,650 (76.90)	154,415 (76.87)	2,235 (79.27)	
Hispanic, *n* (%)	8,886 (4.36)	8,779 (4.37)	107 (3.80)	
Asian or Pacific Islander, *n* (%)	393 (0.19)	N/A	N/A	
Native American, *n* (%)	149 (0.07)	N/A	N/A	
Others, *n* (%)	3,519 (1.73)	3,476 (1.73)	43 (1.51)	
Admission season				
Spring (Mar–May), *n* (%)	44,133 (21.67)	43,441 (21.62)	692 (24.56)	0.0058
Summer (Jun–Aug), *n* (%)	39,377 (19.33)	38,775 (19.30)	602 (21.34)	
Fall (Sep–Nov), *n* (%)	43,327 (21.27)	42,690 (21.25)	637 (22.58)	
Winter (Dec–Feb), *n* (%)	45,915 (22.54)	45,305 (22.55)	610 (22.55)	
Insurance				
Public, *n* (%)	118,348 (58.10)	116,512 (58.00)	1,836 (65.12)	0.0001
Private, *n* (%)	49,117 (24.11)	48,501 (24.14)	616 (21.84)	
Others, *n* (%)	36,008 (17.68)	35,649 (17.75)	359 (12.73)	
Median household income				
0–25%, *n* (%)	87,794 (43.10)	86,586 (43.10)	1,208 (42.83)	0.6028
26–50%, *n* (%)	49,930 (24.51)	49,277 (24.53)	653 (23.15)	
51–75%, *n* (%)	34,876 (17.12)	34,379 (17.11)	497 (17.63)	
76–100%, *n* (%)	25,752 (12.64)	25,356 (12.62)	395 (14.01)	
Hospital region				
Northeast, *n* (%)	50,037 (24.56)	49,336 (24.56)	702 (24.89)	0.014
Midwest, *n* (%)	34,828 (17.10)	34,420 (17.13)	408 (14.47)	
South, *n* (%)	98,632 (48.42)	97,333 (48.45)	1,299 (46.06)	
West, *n* (%)	20,208 (9.92)	19,796 (9.85)	411 (14.59)	
Hospital size				
Small, *n* (%)	29,447 (14.46)	29,081 (14.48)	366 (12.96)	0.0846
Medium, *n* (%)	41,981 (20.61)	41,432 (20.62)	549 (19.48)	
Large, *n* (%)	125,497 (61.61)	123,754 (61.60)	1,743 (61.83)	
Teaching hospital, *n* (%)	161,407 (79.24)	158,985 (79.14)	2,422 (85.89)	<0.0001
Comorbidity				
Sickle cell anemia type				
SS, *n* (%)	185,206 (90.92)	182,654 (90.92)	2,553 (90.54)	0.9273
S Beta, *n* (%)	6,066 (2.98)	5,987 (2.98)	79 (2.81)	
SC, *n* (%)	7,038 (3.45)	6,929 (3.45)	109 (3.88)	
Asthma, *n* (%)	28,620 (14.05)	27,340 (13.76)	980 (34.76)	<0.0001
Hypertension, *n* (%)	755 (0.37)	731 (0.36)	24 (0.84)	0.0030
Diabetes mellitus, *n* (%)	481 (0.24)	460 (0.23)	21 (0.74)	0.0216
Coagulopathy, *n* (%)	788 (0.39)	770 (0.38)	18 (0.63)	0.4098
IDA, *n* (%)	558 (0.27)	N/A	N/A	0.1348
Congenital heart diseases, *n* (%)	1,058 (0.52)	1,029 (0.51)	29 (1.05)	0.0022
Treatment				
Transfusion, *n* (%)	38,562 (18.93)	37,703 (18.77)	859 (30.48)	<0.0001
Cranial angiography, *n* (%)	632 (0.31)	610 (0.30)	21 (0.75)	0.0065
NIMV, *n* (%)	977 (0.48)	870 (0.43)	106 (3.77)	<0.0001
AT, *n* (%)	1,434 (0.70)	523 (0.26)	911 (32.31)	<0.0001
T&A, *n* (%)	1,190 (0.58)	373 (0.19)	816 (28.95)	<0.0001
Tonsillectomy, *n* (%)	75 (0.04)	46 (0.02)	29 (1.03)	<0.0001
Adenoidectomy, *n* (%)	169 (0.08)	103 (0.05)	66 (2.34)	<0.0001

Table 1. Continued

	Total (*n* = 203,705)	No OSA (*n* = 200,885)	OSA (*n* = 2,820)	*P*-value
Outcomes				
Neurologic complications, *n* (%)	4,447 (2.18)	4,350 (2.17)	97 (3.45)	0.0014
Ischemic stroke, *n* (%)	702 (0.34)	688 (0.34)	14 (0.51)	0.4729
Hemorrhagic stroke, *n* (%)	137 (0.07)	N/A	N/A	
TIA, *n* (%)	291 (0.14)	N/A	N/A	0.8903
Seizures, *n* (%)	3,415 (1.68)	3,333 (1.66)	82 (2.91)	0.0003
ACS, *n* (%)	12,108 (8.90)	11,842 (8.85)	266 (11.27)	0.0028
VOC, *n* (%)	126,562 (62.13)	125,268 (62.36)	1,295 (45.92)	<0.0001
Cost of hospitalization*, mean (*SD*)	17,184 (465)	17,084 (459)	24,223 (1,409)	<0.0001
Length of hospitalization (d), mean (*SD*)	4.01 (0.04)	4.01 (0.04)	3.94 (0.15)	0.611
Mortality, *n* (%)	246 (0.12)	N/A	N/A	0.0132

OSA, obstructive sleep apnea; TIA, transient ischemic attack; IDA, iron deficiency; NIMV, noninvasive mechanical ventilation; ACS, acute chest syndrome; VOC, vaso-occlusion crisis; *SD*, standard deviation; *n*, sample size; d, day; N/A, not available as weighted frequency less than 10.
*Cost was adjusted to 2012 USD using an average consumer price index.

to platelet activation, thrombin generation, and endothelial dysfunction [44, 45]. Inflammation also plays an important role in vaso-occlusion in SCD. Inflammatory status caused by recurrent tissue ischemia from microvascular obstruction and infection due to functional asplenia could enhance vaso-occlusion as it increases the interaction of leukocytes and endothelial cell and hypercoagulable status [46–49]. Furthermore, it has been hypothesized that persistent inflammatory status and functional asplenia are associated with a higher prevalence of adenotonsillar hypertrophy in children with SCD that could lead to further nocturnal hypoxemia [21]. Additional comorbidities (e.g. hypertension) commonly seen in OSA and SCD were also identified as risk factors for NC [9]. To test the hypothesis that OSA is an independent risk factor for NC in children with SCD, it is important to account for the aforementioned contributing and confounding factors.

The findings that OSA is an independent risk factor for NC among SCD children are in agreement with the literature. In a case–control study, Katz et al. demonstrated that children with OSA and SCD were more likely to have neurologic and cardiovascular complications compared with children with SCD alone using descriptive statistics ($p < 0.01$) [23]. Similarly, in a survival analysis by Kirkham et al., central nervous complications were associated with nocturnal hypoxemia (<96% SaO_2) on Kaplan–Meier curves ($p = 0.0026$), but not OSA based on polysomnography (PSG) results on Cox regression analysis (Hazard ratio 1.41 [95% CI 0.45–4.38], $p = 0.55$) [25]. Expanding on their findings, we not only reconfirmed the association between OSA and NC among children with SCD on descriptive statistics, but also quantified the risks of NC associated with OSA while accounting for potential confounders. Furthermore, these data showed an association between OSA and ACS, one of the secondary outcomes, in children with SCD. This finding is consistent with the results of Takahashi et al. [36]. It suggests that many SCD complications might share similar underlying mechanisms associated with nocturnal hypoxemia that could be contributed to OSA.

Ascertainment of the association between OSA and NC in children with SCD is important as the introduction of specific interventions for OSA could modify the risk of NC. An interesting finding of the current study is that patients who received AT had lower odds of NC compared with those who did not. The protective effect was also seen in previous studies. Using administrative data, Tripathi et al. suggested that AT was associated with a reduced rate of visits for cerebrovascular ischemia (e.g. stroke and TIA) in children with SCD [27]. Finch et al. also demonstrated a significant improvement of the apnea–hypopnea index and reduction in oxyhemoglobin desaturation by comparing pre- and post-adenotonsillectomy status among children with OSA and SCD [26]. However, sometimes children still suffer from persistent OSA after AT, which could explain the need of NIMV [50, 51]. Our finding that NIMV might modify the risk of NC conferred by OSA in SCD patients is crucial as it provides evidence to support the use of NIMV in this specific population. NIMV can stabilize the upper airway and favor lung recruitment, consequently improving nocturnal hypoxemia [52, 53]. Yet it is intriguing that the use of NIMV was associated with increased odds of NC. This paradoxical finding could be partially explained by reverse causation as sicker patients (e.g. those with more severe OSA) might have been more likely to receive NIMV. Further large prospective research on this topic is needed.

There were a few intriguing findings of this study. First, the OSA group was less likely to have VOC as compared with the non-OSA group (Table 1). This could result from reverse causality: As compared with SCD patients without OSA, those with OSA with frequent nocturnal hypoxemia might be more likely to receive hydroxyurea and other disease-modifying therapies (e.g. Voxelotor) to prevent VOC and other SCD complications and consequently decrease the probability of having VOC. Another explanatory factor could be hypoxic training from chronic hypoxemia leading to increased red blood cell mass and consequently oxygen-carrying capacity [54]. However, it is unclear if the increased RBC mass from hypoxia training, or chronic hypoxemia, will benefit the SCD patients as the main pathophysiology of sickle cell anemia results from the qualitative change of the hemoglobin rather from an inadequate quantity of RBC [2]. These hypotheses could not be tested using the KID administrative database which does not capture pharmacologic treatment information. To definitively answer this question, future studies are needed. Second, seizures accounted for the majority of NC seen in SCD patients, especially in the OSA group (2.91% vs. 1.66%, $p = 0.0003$). The observed association between OSA and seizures is pathophysiologically plausible. First of all, the intermittent nocturnal hypoxemia from OSA might lead to polymerization of sickle hemoglobin and subsequent development of SCD complications, such as seizure, established morbidity [55]. Second, OSA and seizures may mutually affect each other. Described adverse effects of antiepileptic drugs include weight

Table 2. Association between NC and obstructive sleep apnea among children with SCD

	Neurologic complication			
	NIMV not included		NIMV included	
Predictors	OR (95% CI)	P-value	OR (95% CI)	P-value
Age				
0–4 years	0.51 (0.41–0.63)	<0.0001	0.51 (0.41–0.63)	<0.0001
5–9 years	1.08 (0.90–1.31)	0.408	1.08 (0.89–1.31)	0.421
10–14 years	1.13 (0.94–1.37)	0.182	1.13 (0.94–1.36)	0.193
15–18 years	Ref		Ref	
Gender				
Female	0.99 (0.85–1.15)	0.874	0.99 (0.85–1.16)	0.887
Black	0.98 (0.82–1.17)	0.822	0.99 (0.83–1.18)	0.899
Insurance				
Public	Ref		Ref	
Private	0.86 (0.70–1.04)	0.128	0.86 (0.71–1.05)	0.130
Others	0.92 (0.74–1.15)	0.459	0.92 (0.74–1.15)	0.473
Median household income				
0–25%	Ref		Ref	
26–50%	1.08 (0.87–1.34)	0.487	1.08 (0.87–1.34)	0.490
51–75%	1.11 (0.89–1.39)	0.346	1.11 (0.89–1.38)	0.359
76–100%	1.11 (0.89–1.41)	0.336	1.12 (0.89–1.40)	0.341
Season				
Spring	Ref		Ref	
Summer	1.16 (1.03–1.31)	0.013	1.16 (1.03–1.31)	0.012
Fall	1.17 (1.02–1.33)	0.021	1.17 (1.02–1.33)	0.022
Winter	1.00 (0.89–1.13)	0.989	1.00 (0.89–1.13)	0.949
Hospital region				
Northeast	Ref		Ref	
Midwest	1.11 (0.83–1.48)	0.475	1.12 (0.84–1.50)	0.424
South	0.99 (0.76–1.27)	0.909	0.99 (0.77–1.28)	0.946
West	1.17 (0.84–1.64)	0.360	1.19 (0.85–1.67)	0.310
Hospital size				
Small	Ref		Ref	
Medium	1.04 (0.75–1.44)	0.831	1.04 (0.75–1.45)	0.824
Large	1.30 (0.98–1.72)	0.067	1.30 (0.98–1.71)	0.071
Asthma	1.14 (0.96–1.35)	0.138	1.13 (0.95–1.34)	0.164
HTN	2.60 (1.66–4.08)	<0.0001	2.58 (1.65–4.05)	<0.0001
Obesity	0.98 (0.47–2.05)	0.957	0.93 (0.44–1.97)	0.859
Congenital heart diseases	5.69 (3.53–9.19)	<0.0001	5.50 (3.38–8.95)	<0.0001
Coagulopathy	5.78 (3.15–10.61)	<0.0001	5.65 (3.06–10.45)	<0.0001
SS SCA	1.35 (1.11–1.64)	0.003	1.36 (1.12–1.65)	0.002
Obstructive sleep apnea	1.50 (1.02–2.21)	0.039	1.39 (0.94–2.05)	0.100
Central sleep apnea	17.12 (1.32–222.89)	0.030	17.49 (1.30–234.88)	0.031
AT	0.48 (0.24–0.94)	0.032	0.51 (0.26–1.01)	0.052
NIMV	N/A	N/A	2.66 (1.46–4.84)	0.001
Transfusion	1.84 (1.57–2.16)	<0.0001	1.81 (1.54–2.12)	<0.0001

CI, confidence interval; OR, odds ratio; HTN, hypertension; IDA, iron deficiency; NIMV, noninvasive mechanical ventilation; AT, adenotonsillectomy; SCD, sickle cell disease; ACS, acute chest syndrome; VOC, vaso-occlusion crisis.

gain and decreased upper airway tone, both of which may contribute to a higher prevalence of OSA [56]. Conversely, OSA may cause suboptimal epilepsy control via several mechanisms, such as sleep deprivation, cerebral hypoxemia, decreased cardiac output, and cardiac arrhythmias [56]. Several studies have shown that treatment of OSA may lead to improved control of epilepsy in the general population [57, 58]. Similar principles should be applicable to SCD patients with OSA and seizures. The association between OSA and seizures was non-significant on multivariable analysis possibly because we are examining a relatively uncommon pediatric pathology specifically among SCD patients.

As reported by others [30, 36], our data also showed elevated inflation-adjusted costs of hospitalization in children with SCD. This could be a reflection of several factors. The use of newer treatment and testing for SCD at higher costs could also partially explain the observation [36]. Other contributory factors included changes in prevalence or incidences of diseases (e.g. obesity and asthma), changes in service utilization, changes in service price as well as intensity across the study period [59]. The combinational effect of these factors could subsequently lead to a surge in the inflation-adjusted cost of hospitalization.

This study should be interpreted in the context of its strengths and limitations. Our analyses validated OSA as an independent risk factor for NC among children with SCD. Furthermore, it has shown that treatment for OSA, including AT and NIMV, could potentially modify the risk of NC associated with OSA among children with SCD. However, this study

Table 3. Association between secondary outcomes and obstructive sleep apnea among children with SCD

	Length of hospital stay (d)		Cost of hospitalization (USD)*	
Predictors	β (95% CI)	P value	β (95% CI)	P value
Age				
0–4 years	−1.39 (−1.52 to −1.25)	<0.0001	−5060 (−5952 to −4167)	<0.0001
5–9 years	−1.23 (−1.36 to −1.10)	<0.0001	−3404 (−4394 to −2414)	<0.0001
10–14 years	−0.71 (−0.82 to −0.60)	<.0001	−1986 (−2773 to −1198)	<0.0001
15–18 years	Ref		Ref	
Female	0.11 (0.03 to 0.19)	0.007	330 (−327 to 987)	0.324
Black	−0.06 (−0.21 to 0.08)	0.394	−190 (−1539 to 1159)	0.783
Insurance				
Public	Ref		Ref	
Private	−0.03 (−0.14 to 0.09)	0.649	1285 (283 to 2286)	0.012
Others	0.18 (−0.02 to 0.38)	0.083	−877 (−2615 to 862)	0.323
Median household income				
0–25%	Ref		Ref	
26–50%	0.15 (0.05 to 0.24)	0.003	992 (169 to 1814)	0.018
51–75%	0.10 (−0.03 to 0.24)	0.142	1105 (82 to 2127)	0.034
76–100%	0.04 (−0.10 to 0.18)	0.584	500 (−951 to 1952)	0.499
Season				
Spring	Ref		Ref	
Summer	−0.01 (−0.10 to 0.08)	0.839	1292 (595 to 1989)	<0.001
Fall	0.05 (−0.05 to 0.14)	0.339	1189 (541 to 1837)	<0.001
Winter	−0.02 (−0.11 to 0.07)	0.674	−6 (−610 to 599)	0.985
Hospital region				
Northeast	Ref		Ref	
Midwest	−0.19 (−0.42 to 0.03)	0.090	−3134 (−6032 to 236)	0.034
South	−0.37 (−0.56 to −0.19)	<0.0001	−5129 (−7679 to −2579)	<0.0001
West	0.19 (−0.15 to 0.54)	0.264	5789 (1953 to 9626)	0.003
Hospital size				
Small	Ref		Ref	
Medium	0.13 (−0.14 to 0.40)	0.347	−2041 (−5799 to 1717)	0.287
Large	0.13 (−0.10 to 0.36)	0.281	−1066 (−4590 to 2459)	0.553
Asthma	0.06 (−0.05 to 0.17)	0.262	2875 (1917 to 3833)	<0.0001
HTN	5.20 (3.89 to 6.50)	<0.0001	62462 (44915 to 80009)	<0.0001
Obesity	0.45 (0.04 to 0.86)	0.031	4468 (374 to 8561)	0.032
Congenital heart diseases	5.38 (3.82 to 6.93)	<0.0001	34538 (24751 to 44325)	<0.0001
Coagulopathy	3.72 (2.23 to 5.21)	<0.0001	47104 (28016 to 66192)	<0.0001
SS SCA	0.09 (−0.03 to 0.22)	0.152	−4004 (−5149 to −2859)	<0.0001
Obstructive sleep apnea	0.02 (−0.28 to 0.33)	0.881	5163 (2223 to 8102)	0.0001
Central sleep apnea	−0.58 (−1.18 to 0.29)	0.062	891 (−5504 to 7285)	0.785
AT	−1.21 (−1.52 to −0.90)	<0.0001	−4379 (−6693 to −2065)	<0.0001
Transfusion	1.51 (1.31 to 1.70)	<0.0001	13379 (11456 to 15303)	<0.0001

CI, confidence interval; OR, odds ratio; HTN, hypertension; IDA, iron deficiency; NIMV, noninvasive mechanical ventilation; AT, adenotonsillectomy; SCD, sickle cell disease; ACS, acute chest syndrome; VOC, vaso-occlusion crisis; USD, US dollars; d, days.
*Cost was adjusted to 2012 USD using an average consumer price index.

bears several limitations. A major limitation inherent to the use of administrative databases for healthcare research is the risk of misclassification bias due to miscoding. For instance, OSA status was determined using ICD-9 codes in our study instead of polysomnography (PSG), the gold standard. Additional to diagnostic inaccuracies from miscoding, the lack of PSG information prevents us from stratifying the severity of OSA for more analyses. Furthermore, the KID database does not contain detailed information regarding patients' clinical presentation, laboratory findings, PSG, and medical treatment (e.g. hydroxyurea) either. Second, the KID database does not contain unique patient identifiers to distinguish recurrent admission or for longitudinal studies. Therefore, the significant association between NC and OSA could be potentially driven by a small population with a history of recurrent admission as repeated measurements were not appropriately adjusted. Third, differences in socioeconomic status (SES), insurance status, and access to medical care (teaching vs. non-teaching hospital) between OSA and non-OSA group may introduce confounding effects that bias the association between OSA and NC. To prevent the confounding effects from these factors, we adjust for the insurance status, SES, regions of residence, and size of the hospitals in the multivariable logistic regression to ensure the association between OSA and NC is valid. Fourth, NC, a composite of stroke, seizures, and TIA, were used as the primary outcome. This could introduce heterogeneity and make interpretation more difficult as compared with using a stroke or seizure alone. However, one should note that seizures and stroke are not mutually exclusive. This is particularly true in children as seizures can be the first manifestation of strokes [11, 12]. Those with the diagnostic codes of seizures alone without stroke might have subclinical strokes that were not captured clinically or by the ICD-9 codes.

Furthermore, a study has reported that seizures and epilepsy are more common in children with SCD as compared with the general population based on a Jamaica sickle cell cohort, suggesting NC of SCD were not solely limited to cerebrovascular events [55]. Therefore, we consider it is a reasonable practice to report the composite outcome, NC, in addition to reporting stroke and seizures alone. Fifth, one should note that the KID database only allows for analyses of hospitalized patients. This results in a selective population that is generally sicker or needs hospitalization for certain treatments or procedures. Therefore, making epidemiologic estimates, such as the prevalence of OSA among children with SCD, would be undesirable as it does not include patients in outpatient settings. However, our assessment of the association between NC and OSA among children with SCD should be valid as NC would usually require hospitalization for diagnosis and treatment. Moreover, we could not ascertain whether NIMV was initiated as a result of NC, ACS, CSA, or OSA. Limited by the nature of the administrative database, the unclear temporal association between outcomes and NIMV and AT the study design prevented us from establishing causality. Prospective studies will be needed to address this issue.

Conclusion

This study summarized the epidemiology of hospitalized children with SCD using a US nationwide database, and confirmed OSA as an independent risk factor for NC among hospitalized children with SCD. Results indicated that NIMV but not AT might modify the risk of NC associated with OSA among this vulnerable population. Prospective studies are needed to validate whether the association between OSA and NC among children with SCD observed in this study is of causality, and the best OSA treatment to mitigate NC complications.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Author contribution

Drs Po-Yang Tsou, Yu-Hsun Wang, and Pei-Lun Kuo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design were carried out by Po-Yang Tsou and Ignacio Tapia. Drafting of the manuscript by Po-Yang Tsou and Ignacio Tapia. Critical revision of the manuscript for important intellectual content by Christopher Cielo, Melissa S. Xanthopoulos, Yu-Hsun Wang, Pei-Lun Kuo, and Ignacio Tapia. Statistical analysis by Po-Yang Tsou. Supervision by Ignacio Tapia.

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