Am J Otolaryngol 40 (2019) 667–672

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Morbidity after tonsillectomy in children with autism spectrum disorders

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ARTICLE INFO

Keywords:
Autism spectrum disorders
Tonsillectomy
Pediatric surgery

ABSTRACT

Objectives: As the incidence of autism spectrum disorder (ASD) increases, otolaryngologists are more likely to encounter patients from this population during tonsillectomy. The purpose of this study was to examine whether outcomes differ between pediatric patients with and without ASD in a national cohort of children undergoing tonsillectomy. Understanding these differences may be used to inform future approaches to improve clinical outcomes and healthcare costs.

Methods: Data for this study were obtained from the Kids Inpatient Database (KID) of the Healthcare Cost Utilization Project. We studied pediatric patients who underwent tonsillectomy during 2003, 2006, 2009, and 2012. Tonsillectomy was identified using ICD-9-CM diagnosis codes 28.2 (tonsillectomy without adenoidectomy) and 28.3 (tonsillectomy with adenoidectomy). ASD was identified using ICD-9-CM diagnosis code 299 (autism). Outcomes including complications, length of hospital stay, and total hospitalization costs. Analyses were performed using multivariable models. Propensity score matching was used to control for covariate imbalance between patients with and without ASD.

Results: In our sample of 27,040 patients, 322 (1.2%) had a diagnosis of ASD. After controlling for potential confounders, multivariable modeling suggested patients with ASD had a shorter LOS of 0.50 days ($p < 0.0001$), were less likely to experience complications (odds ratio 0.57, $p = 0.001$), and had lower associated costs of $1308 less ($p < 0.0001$). Propensity score matching confirmed the findings of the multivariable modeling.

Conclusion: Although ASD alone does not appear to confer additional costs or morbidity, differences between children with and without ASD suggest the need for providers to address patients with ASD uniquely.

1. Introduction

Autism spectrum disorders (ASD) are lifelong conditions characterized by restricted and repetitive behaviors, interests, and activities, and deficits of social communication and interaction [1]. Between the ages of 6 and 12 months, signs of ASD begin to emerge as diminishing, delayed, or atypical development of social-communication behaviors [2]. The incidence of ASD is estimated at 1–2% of the worldwide population, with prevalence steadily increasing since the first epidemiologic study [2]. As ASD incidence grows, pediatric otolaryngologists are more likely to encounter patients from this population who require tonsillectomy. Obstructive sleep apnea, the most common indication for tonsillectomy [3], has a high incidence in children with ASD, correlating with aggravated autistic symptoms such as hyperactivity, mood variability, aggression, behavioral problems, adaptive skill maldevelopment, as well as deficits in nonverbal intelligence, communication, and academic performance [4].

Tonsillectomy is one of the most common surgical procedures performed on children in the United States with > 500,000 surgeries performed each year [2] and an average of 400 surgeries performed at our institution. This study examines the outcomes of children with and without ASD in the U.S. as they undergo tonsillectomy. We compare outcomes for the two groups by considering the following measures: length of hospital stay (LOS), complications, and cost.

Understanding the resource utilization implications of these outcomes can guide the focus of quality improvement strategies for outcomes. The long-term goal is to understand how children with ASD recover after tonsillectomy to guide improvements in healthcare costs and outcomes for these children.

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https://doi.org/10.1016/j.amjoto.2019.05.026
Received 18 February 2019

Table 1
Summary of tonsillectomy patient characteristics, stratified by ASD status.

Variable	No ASD	ASD	
	(*N = 27,040*)	*(N = 322)*	
	Mean or N (SD or %)	Mean or N (SD or %)	*p*-Value
Age, mean years	5.7 (5)	6.31 (3.7)	0.0349
0–2	9671 (35.8%)	34 (10.6%)	
3–5	7759 (28.7%)	136 (42.2%)	
6–10	4861 (18%)	103 (32%)	
11–20	4749 (17.6%)	49 (15.2%)	
Sex			< 0.0001
Male	15,433 (57.1%)	262 (81.4%)	
Female	11,607 (42.9%)	60 (18.6%)	
Race			< 0.0001
White	10,348 (38.3%)	157 (48.8%)	
Black	4825 (17.8%)	39 (12.1%)	
Hispanic	4169 (15.4%)	41 (12.7%)	
Asian	625 (2.3%)	15 (4.7%)	
Other	1233 (4.6%)	19 (5.9%)	
Unknown	5840 (21.6%)	51 (15.8%)	
APR-DRG severity			< 0.0001
0	5 (0%)	0 (0%)	
1	18,431 (68.2%)	4 (1.2%)	
2	6582 (24.3%)	233 (72.4%)	
3	1765 (6.5%)	80 (24.8%)	
4	257 (1%)	5 (1.6%)	
OSA			< 0.0001
Present	12,178 (45%)	197 (61.2%)	
Absent	14,862 (55%)	125 (38.8%)	
Insurance			0.3355
Medicaid	12,345 (45.7%)	162 (50.3%)	
Commercial	12,873 (47.6%)	143 (44.4%)	
Other	1796 (6.6%)	17 (5.3%)	
Unknown	26 (0.1%)	0 (0%)	
Hospital size			0.7934
Small	2837 (10.5%)	32 (9.9%)	
Medium	6327 (23.4%)	80 (24.8%)	
Large	16,441 (60.8%)	190 (59%)	
Unknown	1435 (5.3%)	20 (6.2%)	
Hospital type			0.519
Children's	3695 (13.7%)	48 (14.9%)	
Non-children's	23,345 (86.3%)	274 (85.1%)	
Facility location			0.157
Northeast	5715 (21.1%)	79 (24.5%)	
Midwest	6891 (25.5%)	76 (23.6%)	
South	8304 (30.7%)	85 (26.4%)	
West	6130 (22.7%)	82 (25.5%)	
Adenoidectomy			0.025
Performed	23,261 (86%)	291 (90.4%)	
Not performed	3779 (14%)	31 (9.6%)	
Additional procedures			0.316
Performed	10,098 (37.3%)	129 (40.1%)	
Not performed	16,942 (62.7%)	193 (59.9%)	

ASD = autism spectrum disorders; APR DRG = all patient-refined diagnosis related groups; OSA = obstructive sleep apnea; additional procedures = any additional procedure excluding adenoidectomy.

Table 2
Summary of outcomes following tonsillectomy, stratified by ASD status.

Variable	No ASD	ASD	
	(N = 27,040)	*(N = 322)*	*p*-Value
Length of stay (days)	3.1 (4.1)	3.2 (2.4)	0.012
Complications (%)	3856 (14.3%)	47 (14.6%)	0.002
Hemorrhage	282 (1%)	2 (0.6%)	
Cardiac	65 (0.2%)	1 (0.3%)	
Major respiratory events	754 (2.8%)	2 (0.6%)	
Minor respiratory events	2024 (7.5%)	24 (7.5%)	
Dehydration	745 (2.8%)	18 (5.6%)	
Costs (2015 US dollars)	$6539 ($12,674)	$6765 ($7516)	0.0237

2. Methods

2.1. Data

This was an institutional review board (IRB) approved retrospective cohort study using data from the Kids' Inpatient Database (KID) (2003, 2006, 2009, 2012), of the Healthcare Cost Utilization Project (HCUP) [5]. The KID is a hospital administrative dataset designed specifically to assess the use of inpatient hospital services by patients under 21 years of age. The database reports data every three years from 1997 through 2012, and encompasses data from 44 states.

2.2. Patient selection

Children undergoing tonsillectomies were identified from the KID using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 28.2 (tonsillectomy without adenoidectomy) and 28.3 (tonsillectomy with adenoidectomy). As not all states collect or report race and payer and admission data, entries with incomplete or missing admission data were retained and included in a "missing" category. Patients were stratified by an ICD-9-CM diagnosis code of autism (299).

2.3. Outcomes and covariates

Primary outcomes of interest included complications, cost, and hospital length of stay.

(LOS). Complications included hemorrhage (ICD-9-CM 998.11), cardiac complications (ICD-9-CM 997.1), major respiratory events (ICD-9-CM 518.5, 518.81, 518.82, 518.84), minor respiratory events (ICD-9-CM 786.09, 799.02, 977.39), dehydration (ICD-9-CM 276.5, 276.51) and unspecified (ICD-9-CM 998.9).

Patients were characterized by age, sex, race, All Patients Refined Diagnosis Related Groups (APR DRG), a classification system that classifies patients according to their reason of admission, severity of illness and risk of mortality, presence of obstructive sleep apnea (OSA), payer-type, hospital size and location, hospital designation as a children's hospital (according to the National Association of Children's Hospitals and Related Institutions). They were further characterized by admission type and whether additional procedures were performed.

LOS was based on duration of the index operative admission. A hospital perspective was adopted as the basis for cost analysis. Total inpatient hospital costs were calculated using hospital level ratios of costs to charges. In addition, all costs were adjusted for inflation to year 2015 dollars.

2.4. Statistical analysis

The purpose of the statistical analysis was to determine whether patients with ASD incurred significantly greater costs, had significantly longer lengths of stay, and were at significantly greater risk of post-operative complications. Univariate statistical tests were used to compare baseline patient and facility characteristics between patients with and without ASD, using chi-square and Student *t*-tests where appropriate. Post-operative complications, LOS, and cost were compared using chi-square and t-tests were appropriate. Complications were modeled using logistic regression, controlling for potential confounders. LOS and costs were modeled using a generalized linear regression model assuming a log link function and a gamma family of distributions. This was done to accommodate skewness in the data.

Given that some characteristics of children with an ASD were significantly different from those without ASD, we used propensity score matching to balance covariates and reduce the effects of selection bias. We used this methodology to compare the hospital LOS, cost, and complications between patients with ASD compared to a similar group of patients without ASD. Patients with ASD who underwent

Table 3
Summary of complications following tonsillectomy, stratified by ASD status.

Complication		No ASD	ASD	
		(N = 27,040)	*(N = 322)*	
	ICD-9 code	Mean or % (SD)	Mean or % (SD)	*p*-Value
No complications	–	23,184 (85.7%)	275 (85.4%)	0.864
Hemorrhage				0.458
Post-operative hemorrhage	998.11	343 (1.3%)	4 (1.2%)	
Cardiac				0.799
Cardiac complications	997.1	65 (0.2%)	1 (0.3%)	
Major respiratory events				0.018
Pulmonary insufficiency	518.5	504 (1.9%)	1 (0.3%)	
Acute respiratory failure	518.81	262 (1%)	1 (0.3%)	
Other pulmonary insufficiency	518.82	96 (0.4%)	2 (0.6%)	
Minor respiratory events				0.983
Other respiratory distress	786.09	1238 (4.6%)	14 (4.3%)	
Hypoxemia	799.02	692 (2.6%)	6 (1.9%)	
Other respiratory complications	977.39	282 (1%)	7 (2.2%)	
				0.002
Dehydration	276.51	745 (2.8%)	18 (5.6%)	

tonsillectomy were matched 1:1 without replacement to those without ASD who underwent tonsillectomy using a nearest neighbor approach with a caliper restriction. The selection model controlled for age, race, comorbidities, payer-type, hospital size, designation of a pediatric hospital, location, admission type, and additional procedures. After matching, differences in the distributions of patient characteristics were not statistically significantly.

The primary metric for the propensity score analysis was the average effect of treatment on the treated (ATT). This measure estimates the difference between the outcome for patients with ASD to the outcome for comparable patients who did not have a diagnosis of ASD. All statistical analyses were performed with STATA software (version 12.1, StataCorp, College Station, TX, USA).

3. Results

In our sample of 27,362 patients, 322 (1.2%) had diagnosed ASD. As seen in Table 1, these patients tended to be slightly older, much more likely to be male, white, and have significantly higher rates of obstructive sleep apnea ($p < 0.05$, all). There were no significant differences in insurance type, hospital size, treatment at a children's hospital, or facility location. Patients with an ASD diagnosis were slightly more likely to have a tonsillectomy with adenoidectomy (90.4% vs. 86%, $p = 0.025$), but not significantly more likely to have a tonsillectomy with other additional procedures.

Outcomes unadjusted for patient, procedure, or hospital characteristics are presented in Table 2. Patients with ASD had slight but significantly longer hospital LOS than patients without (3.1 days vs. 3.2 days, $p = 0.012$). They also had significantly higher rates of complications, which was mostly attributable to dehydration. Patients with ASD had greater costs than patients without ($6765 vs. $6539, $p = 0.0237$).

Specific details about complications are presented in Table 3. Although patients with diagnosed ASD were more likely to have a complication than patients without (14.60% vs. 14.26%, $p = 0.86$), the difference was small and not statistically significant. Patients with ASD were also more likely to experience dehydration than patients without ASD (5.6% vs. 2.8%, $p = 0.002$).

As seen in Table 4, after controlling for patient, disease, and facility characteristics, logistic regression modeling suggested that patients with ASD were actually less likely to experience post-operative complications than patients without ASD (odds ratio [OR] = 0.57, $p = 0.001$). Several other risk factors were associated with complications following tonsillectomy. Receiving surgery at a designated children's hospital was associated with somewhat lower risk of complications (OR = 0.80, $p = 0.013$). Patients over age 10 were less likely to have complications (OR = 0.83, $p = 0.004$). Patients with higher APR DRG severity scores were more likely to have post-operative complications, while patients with OSA were less likely to experience complications following surgery. Patients with commercial or other insurance were less likely to have complications than patients covered by Medicaid. Concomitant adenoidectomy (OR = 1.7, $p < 0.0001$) or other additional procedures (OR = 1.25, $p < 0.0001$) were also all associated with increased odds of complications.

Multivariable analysis of LOS is presented in Table 5. Patients with ASD had a shorter LOS of 0.50 days after controlling for potential confounders ($p < 0.0001$). Other factors that were significant determinants of LOS included age, race/ethnicity, APR DRG Severity score, commercial insurance, geography, and concomitant adenoidectomy or other additional procedures. Treatment at a children's hospital was associated with 0.36 day longer LOS ($p < 0.0001$).

In a generalized linear model that controlled for patient, disease and facility characteristics, patients with ASD were associated with costs of $1308 less than patients without ASD ($p < 0.0001$) (Table 6). Other factors that were significant determinants of increased cost were minority race/ethnicity, higher APR DRG severity score, OSA, small hospital size, treatment at a children's hospital, and additional procedures. Older age, female sex, coverage by commercial or other non-Medicaid insurance, and concomitant adenoidectomy were significant determinants of lower costs.

To account for the imbalance in covariates between patients with and without diagnosed ASD, propensity score matching was performed (Table 7). After matching, covariates were found to be balanced between the two groups. The propensity score analysis, which matched the 322 patients with diagnosed ASD to 322 similar patients without diagnosed ASD, largely confirmed the multivariable analyses. Patients

Table 4
Logistic regression of complications after tonsillectomy.

Variable		95% confidence		
	Odds ratio	*Low*	*High*	*p*-Value
ASD				
No	Reference			
Yes	0.5732	0.4119	0.7977	0.0010
Age (years)				
0–2	Reference			
3–5	1.1064	0.9867	1.2406	0.0830
5–10	0.9891	0.8792	1.1128	0.8550
11–20	0.8260	0.7250	0.9410	0.0040
Sex				
Male	Reference			
Female	0.9395	0.8731	1.0109	0.0950
Race				
White	Reference			
Black	1.0431	0.9377	1.1604	0.4370
Hispanic	0.9793	0.8716	1.1002	0.7250
Asian	1.0454	0.8152	1.3405	0.7260
Other	1.0894	0.9101	1.3041	0.3500
Missing	1.0386	0.9387	1.1491	0.4630
APR-DRG severity				
0–1	Reference			
2	1.8911	1.7421	2.0528	< 0.0001
3	5.3938	4.8241	6.0307	< 0.0001
4	33.4044	24.1877	46.1331	< 0.0001
OSA				
Present	0.8373	0.7760	0.9035	< 0.0001
Absent	Reference			
Insurance				
Medicaid	Reference			
Commercial	0.8470	0.7830	0.9163	< 0.0001
Other	0.8027	0.6878	0.9368	0.0050
Hospital size				
Small	1.2502	0.4513	3.4635	0.6680
Medium	Reference			
Large	1.0638	0.9327	1.2134	0.3570
Missing	0.8300	0.7563	0.9109	< 0.0001
Children's hospital				
Children's hospital	0.8006	0.6719	0.9540	0.0130
General hospital	Reference			
Facility location				
Northeast	Reference			
Midwest	0.8988	0.7992	1.0109	0.0750
South	1.6050	1.4123	1.8241	< 0.0001
West	1.7629	1.5709	1.9784	< 0.0001
Adenoidectomy				
Not performed	Reference			
Performed	1.7007	1.4992	1.9294	< 0.0001
Additional procedures				
Not performed	Reference			
Performed	1.2568	1.1140	1.4180	< 0.0001

Table 5
Generalized linear regression model of length of stay.

Variable	Marginal	95% confidence		
	Effect	*Low*	*High*	P-value
ASD				
No	Reference			
Yes	−0.4962	−0.7090	−0.2835	< 0.0001
Age (years)				
0–2	Reference			
3–5	−0.0616	−0.1500	0.0269	0.1720
5–10	−0.1820	−0.2699	−0.0942	< 0.0001
11–20	−0.1666	−0.2597	−0.0735	< 0.0001
Sex				
Male	Reference			
Female	0.0031	−0.0523	0.0586	0.9130
Race				
White	Reference			
Black	0.1905	0.1055	0.2755	< 0.0001
Hispanic	0.0745	−0.0137	0.1626	0.0980
Asian	0.0017	−0.1825	0.1859	0.9860
Other	0.1546	0.0129	0.2963	0.0320
Missing	0.0823	0.0031	0.1615	0.0420
APR-DRG severity				
0–1	Reference			
2	0.7409	0.6661	0.8157	< 0.0001
3	3.5973	3.3564	3.8382	< 0.0001
4	16.1375	14.3100	17.9650	< 0.0001
OSA				
Present	−0.0779	−0.1360	−0.0197	0.0090
Absent	Reference			
Insurance				
Medicaid	Reference			
Commercial	−0.2172	−0.2772	−0.1573	< 0.0001
Other	−0.0732	−0.1845	0.0381	0.1980
Hospital size				
Small	−0.0982	−0.1985	0.0020	0.0550
Medium	Reference			
Large	−0.0282	−0.0993	0.0429	0.4370
Missing	0.2082	0.0623	0.3541	0.0050
Children's hospital				
Children's hospital	0.3598	0.2577	0.4619	< 0.0001
General hospital	Reference			
Facility location				
Northeast	Reference			
Midwest	0.0444	−0.0462	0.1350	0.3370
South	0.1866	0.1054	0.2678	< 0.0001
West	−0.1404	−0.2256	−0.0552	0.0010
Adenoidectomy				
Not performed	Reference			
Performed	−0.3181	−0.4150	−0.2211	< 0.0001
Additional procedures				
Not performed	Reference			
Performed	0.4204	0.3591	0.4817	< 0.0001

with ASD had a significantly shorter LOS ($p = 0.02$), lower costs ($p = 0.009$), and lower rates of complications ($p = 0.013$).

4. Discussion

A diagnosis of ASD can be a challenge to pediatric surgical teams [6]. Challenging behaviors in patients with ASD include aggression, self-injury, disruption, agitation and tantrums [7]. A recent study of adolescent inpatients with ASD found that clinical severity of autistic behaviors at admission, based on the number of challenging behaviors, was correlated with a longer hospital stay [7]. However, the literature on length of stay for children with ASD is conflicting. A study on children with ASD undergoing general anesthesia for dental rehabilitation found a lack of significant postoperative behavioral problems with a shorter recovery room time [8]. The author proposed that the shorter length of stay might reflect parental desire to return the child to a familiar environment as soon as possible [8]. In our sample, the ASD group's demographics are consistent with the literature. Children with ASD are predominantly male [2] and have a greater incidence of OSA [4]. Non-Hispanic white children have a significantly higher prevalence of ASD compared to Hispanic [9] and non-Hispanic black children [10].

The findings of this observational study were consistent with Arnold et al. when other variables are taken into account. Without controlling differences in the two populations, the ASD patients undergoing tonsillectomy had a longer LOS compared to children without ASD. This can be attributed to the differences in characteristics such as sex, race, and severity score because the multivariate model agreed with the propensity score in suggesting that children with diagnosed ASD actually have a shorter LOS.

Table 6
Generalized linear regression model of length of costs. Costs are 2015 US dollars.

Variable	Marginal	95% Confidence		
	Effect	*Low*	*High*	*p*-Value
ASD				
No	Reference			
Yes	-$1308.03	-$1670.44	-$945.61	< 0.0001
Age (years)				
0–2	Reference			
3–5	-$695.91	-$853.79	-$538.02	< 0.0001
5–10	-$933.81	-$1088.36	-$779.27	< 0.0001
11–20	-$556.13	-$722.60	-$389.67	< 0.0001
Sex				
Male	Reference			
Female	-$184.94	-$286.45	-$83.42	< 0.0001
Race				
White	Reference			
Black	$603.39	$442.55	$764.23	< 0.0001
Hispanic	$662.39	$490.47	$834.32	< 0.0001
Asian	$257.07	-$96.53	$610.67	0.1540
Other	$425.07	$158.83	$691.31	0.0020
Missing	$306.04	$157.22	$454.86	< 0.0001
APR-DRG severity				
0–1	Reference			
2	$1867.07	$1723.59	$2010.54	< 0.0001
3	$9795.35	$9250.00	$10,340.70	< 0.0001
4	$51,744.62	$46,455.30	$57,033.90	< 0.0001
OSA				
Present	$460.29	$352.19	$568.39	< 0.0001
Absent	Reference			
Insurance				
Medicaid	Reference			
Commercial	-$487.46	-$597.60	-$377.32	< 0.0001
Other	-$14.65	-$223.72	$194.42	0.8910
Hospital size				
Small	Reference			
Medium	$641.53	$434.74	$848.32	< 0.0001
Large	-$105.84	-$236.51	$24.83	0.1120
Missing	$1274.71	$970.37	$1579.05	< 0.0001
Children's hospital				
Children's hospital	$1639.81	$1430.47	$1849.16	< 0.0001
General hospital	Reference			
Facility location				
Northeast	Reference			
Midwest	$177.65	$9.87	$345.42	0.0380
South	-$563.71	-$704.37	-$423.06	< 0.0001
West	$143.21	-$18.45	$304.88	0.0830
Adenoidectomy				
Not performed	Reference			
Performed	-$579.01	-$756.31	-$401.70	< 0.0001
Additional procedures				
Not performed	Reference			
Performed	$1686.56	$1567.64	$1805.49	< 0.0001

A shorter length of stay contributes to a lower cost. However, the large difference in costs for children with ASD is not fully explained by the half-day shorter length of stay. Arnold et al. found that children without ASD were twice as likely to receive morphine for pain control in the peri-operative period than children without ASD [8]. The authors proposed that less medication was given due to the difficulty of assessing post-operative pain in children with communication challenges [8]. Fewer doses of analgesics post-operatively could contribute to a lower cost.

The matched cohort examined in the propensity score analysis also suggested that children with ASD had significantly fewer complications. This likely reflects fewer major respiratory complications. This is not explainable with reference to behavioral issues that children with ASD display. Table 3 does show that more children with ASD presented with dehydration, and this seems intuitively true, as these are children who may be receiving less analgesic medication, and who may not be amenable to instructions to drink.

These results can inform improvements in management of children with ASD following tonsillectomy. A standing regimen of analgesic dosing would optimize pain control and may reduce post-operative dehydration. There are several recent studies that demonstrate good pain control alternating acetaminophen and ibuprofen on a standing basis for post-tonsillectomy patients [11,12]. To reduce post-operative dehydration rates in children with ASD, further research is needed to determine whether they require the current regimen versus a unique pain management plan.

One limitation of this study is possible miscoding, since our operationalization of an ASD diagnosis relied on ICD-9-CM diagnosis codes. The purpose of coding is for billing, not for research into specifics of patient outcomes, or even for adequately describing a patient admission. The HCUP KID provides ICD-9-CM diagnosis and procedure codes, and reliance on these codes to identify children with ASD and their complications may subject the study to inaccuracy. This database also does not connect medical treatment that occurs after discharge to the inpatient record, so we do not have information about subsequent emergency room visits.

5. Conclusion

Using a large, nationally representative sample, this study suggests that children with ASD undergoing tonsillectomy do not accrue additional costs or morbidity. This may reflect their specific disabilities –such as communication defects – reminding surgeons that special attention needs to be paid to their differences. Future studies should develop and examine specific protocols for children with ASD that may have the potential to improve clinical outcomes and healthcare costs in these vulnerable populations.

Table 7
Propensity score matching analysis.

Variable				95% confidence		
	No ASD	ASD	ATT	*Low*	*High*	*p*-Value
LOS (days)	3.14	3.21	−0.58	−1.09	−0.08	0.0229
Cost (dollars)	$8794.73	$6764.61	-$2030.12	-$3549.31	−510.92	0.0090
Complications (%)	22%	15%	−0.07	−0.13	−0.02	0.0126

Funding support

None.

Declaration of Competing Interest

None of the authors have any conflicts of interest.

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