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RESEARCH ARTICLE

Hospital costs associated with vagus nerve stimulation and medical treatment in pediatric patients with refractory epilepsy

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Abstract

Objectives: Refractory epilepsy is a diagnosis of recurrent seizures that requires multiple resources for optimal chronic management. The disease negatively impacts the lives of affected patients and families and poses an economic burden to the health care system. This study compares hospital costs between pediatric patients treated with antiseizure medications (ASMs) only and ASMs plus vagus nerve stimulation (VNS).

Methods: Patients 0–17 years of age who were diagnosed with refractory epilepsy between January 1, 2011 and December 31, 2016, were identified from the Children's Hospital Association's Pediatric Health Information System (PHIS) database. Patients treated with ASMs only or ASMs plus VNS were included in the study and were followed 1 year prior and 2 years after meeting pre-determined criteria for refractory epilepsy. The difference-in-difference (DID) approach along with the two-part model was used to compare the changes in mean hospital costs captured in the PHIS database over time between the two cohorts.

Results: One thousand one hundred thirteen patients treated with ASMs plus VNS and 3471 patients treated with ASMs only were included. At a follow-up time of 2 years, for the ASMs-only cohort, the adjusted all-cause and epilepsy-related mean annual total costs increased by $14 715 (95% confidence interval [CI]: $12 375–$17 055) and $18 437 (95% CI: $15 978–$20 896), respectively. By comparison, the adjusted all-cause and epilepsy-related mean annual total costs of the ASMs plus VNS cohort increased by $12 838 (95% CI: $8171–$17 505) and $15 183 (95% CI: $10 253–$20 113), respectively. Compared to ASMs only, ASMs plus VNS generated a cost savings of $3254 for epilepsy-related annual costs per year after the index date.

Significance: Compared to ASMs alone, ASMs plus VNS is a treatment modality associated with lower annual hospital costs over time. Our study shows that VNS is a cost-beneficial treatment for a national cohort of pediatric patients with refractory epilepsy.

KEYWORDS
antiseizure medication, cost analysis, health care cost, pediatric, refractory epilepsy, vagus nerve stimulation

1 | INTRODUCTION

Epilepsy is a neurological disorder affecting 0.5%–2.0% of the population in the United States[1] and is more common in children than adults.[2] The prevalence rate of childhood epilepsy is 10.2 per 1000 children.[3] Although many patients become seizure-free with antiseizure medications (ASMs) as first-line treatment, about 20% of these pediatric patients have long-term refractory epilepsy that is not controlled by multiple ASMs.[4,5] With the definition of patients with controlled epilepsy having no change in ASM monotherapy or combination therapy for ≥1 year,[5] studies demonstrate that patients with poorly controlled epilepsy have more hospitalizations, emergency department (ED) visits, and outpatient visits compared to those with controlled epilepsy. In addition, the estimated costs of treating refractory epilepsy are considerable, being 2 to 10 times greater than costs for nonrefractory epilepsy.[5,6] Taken together, it is important to explore ways to manage the care of this challenging disease in this group of patients.

The etiologies for refractory epilepsy are heterogeneous. For lesional cases and other select candidates, cranial surgery can be a good option. Some patients may not be considered ideal candidates for cranial epilepsy surgery.[7] Such patients either continue medication therapy or receive vagus nerve stimulation (VNS). Other therapies are also emerging, although without published long-term outcomes in the pediatric population to date, such as deep brain stimulation (DBS) or responsive neurostimulation (RNS), and ketogenic diet. Evidence-based clinical guidelines from the American Academy of Neurology in 2013 delineate that VNS is an effective option for treating seizures in children.[8] The efficacy of VNS in controlling seizures has been demonstrated by previous clinical studies, with seizure burden reduction (≥50% reduction) at 1 year after VNS implantation reported between 51.4% and 68%.[9–14] In general, the efficacy of VNS is at least comparable to the efficacy of the addition of new ASMs[15] in the published literature.

Comparison of health care costs associated with continued ASMs vs ASMs plus VNS for pediatric patients with refractory epilepsy is warranted. Most available publications have small sample sizes or only compare health care utilization or cost before and after VNS implantation[16–18] without a comparison group. In this study, we compare hospital costs associated with ASMs only and ASMs plus VNS in pediatric patients using a large national administrative database.

Key Points

- Hospital-based costs were compared between pediatric patients with refractory epilepsy treated with antiseizure medications (ASMs) only and with ASMs plus vagus nerve stimulation (VNS)
- Outpatient costs of ASMs plus VNS cohort increased after the implantation of VNS
- Emergency department costs decreased more in the ASMs plus VNS cohort compared with the ASMs-only cohort
- The average annual total costs increased more in the ASMs-only cohort compared with the ASMs plus VNS cohort.

2 | METHOD

2.1 | Data sources

This is a retrospective observational study using data from the Children's Hospital Association's Pediatric Health Information System (PHIS; Lenexa, KS, USA) database. PHIS represents ~15% of the national volume of non-normal newborn pediatric hospitalizations. PHIS contains inpatient, ED, ambulatory, and observation encounter level data from more than 44 children's hospitals in the United States since 2007. The PHIS database includes all charged items/services billed to the patient including: pharmacy, imaging/radiology, lab, clinical, supplies, and other charges that allow us to examine PHIS hospital system costs. It does not include professional fees or clinic visits. All encounter-level data are de-identified. This study received exempt status and was classified as non-human subjects research by our institutional review board.

2.2 | Study design and population

The study cohort (Figure 1) was assembled in a four-step process. First, we performed a retrospective query from the PHIS system using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code and 10th Revision, Clinical Modification (ICD-10-CM) codes. We extracted the data on children

(ages 0 to 17 years) discharged between January 1, 2011 and December 31, 2018 with primary diagnosis codes of epilepsy (ICD-9-CM code 345.XX and ICD-10-CM code G40.XXX) or seizure (ICD-9-CM code 780.3X and ICD-10-CM code R56.X or R56.XX). To define a cohort with epilepsy, included patients had at least two visits and met the criteria of at least one the following published algorithms[19–23] that have been published previously for identifying epilepsy with administrative data: (1) at least two encounters with the diagnosis code 345.XX or G40.XXX on separate dates in any visit (including inpatient, ED, or ambulatory care); (2) at least one encounter with diagnosis code 345.XX or G40.XXX and at least one separate encounter on a different date with diagnosis code 780.3X or R56.X or R56.XX; (3) a primary diagnosis code 345.XX or G40.XXX and a therapeutic category code indicating antiepileptic medication; (4) at least two encounters with diagnosis code 780.3X or R56.X or R56.XX and code(s) for antiepileptic medication; (5) an inpatient or ED visit with a primary diagnosis code 345.XX or G40.XXX. Second, confirmed epilepsy cases that had a diagnosis code listed in Table S1, and received at least three types of ASMs or VNS were identified as those with refractory epilepsy. Third, children with refractory epilepsy were assigned to the ASMs-only cohort if they received at least three types of ASMs or to the ASMs plus VNS cohort if they received VNS in addition to their existing medications. For the ASMs-only cohort, the first encounter date of the addition of the third type of ASMs was defined as the index date for the purpose of study tracking. The first admission date of surgery for VNS implantation was defined as the index date for the ASMs plus VNS cohort. The first date of diagnosis of epilepsy is not delineated in this data set or study design. Finally, we included patients whose index admission date was between January 1, 2011 and December 31, 2016, whose age at index date was between 1 and 17, and who had cost information available for at least 1 year before and 2 years after the index date. Patients were excluded if they had any cranial surgery for epilepsy before and within 2 years following the index date, or had missing values on key variables.

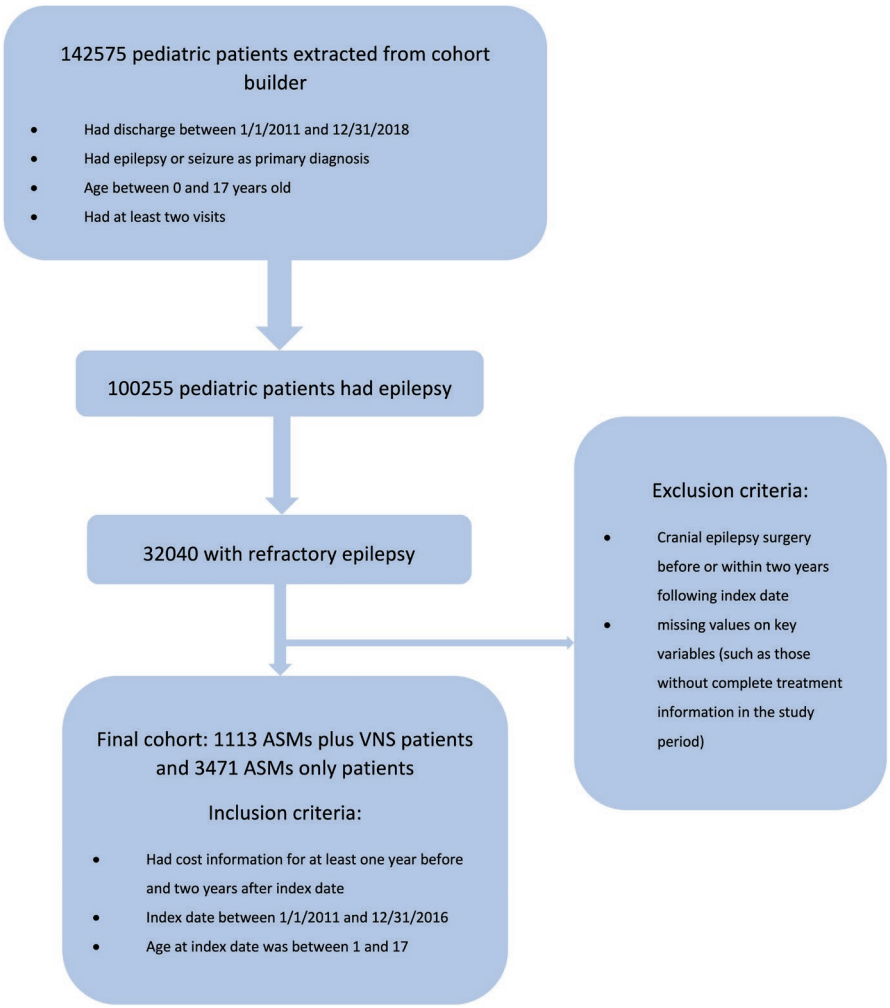

FIGURE 1 Sample selection

2.3 | Dependent variables

Cost information was extracted 1 year before the index date (pre-index period) and was followed up for 2 years after the index date (post-index period). All-cause and epilepsy-related hospital costs were calculated as mean annual costs during the pre-index and post-index periods, and included total costs, inpatient costs, outpatient (ambulatory surgery and observation unit) costs, and ED costs. The costs occurred at index date were part of the costs in post-index period. All costs were estimated from regionally adjusted charges using the Ratio of Cost to Charges (RCCs) submitted by the hospitals annually on their Medicare cost reports. Epilepsy-related costs were identified from records with 345.XX, G40.XXX, 780.3X, R56.X, or R56.XX as the diagnosis code. All costs were inflated to 2018 US dollars using the annual medical care component of the Consumer Price Index.

2.4 | Independent variables

There are three independent variables of interest in this study: "VNS," "Post," and the interaction between "VNS" and "Post." "Post" captured the periods before and after index date; "VNS" indicated the treatment the patient received. Sociodemographic and clinical characteristics are also controlled for in this study. Sociodemographic characteristics included age at index date, gender, race, insurance, and census region. Clinical characteristics included patient type at index date, epilepsy diagnosis, and pediatric complex chronic conditions (CCCs) calculated using 12 months of records in the pre-index period.[24]

2.5 | Statistical analysis

Bivariate comparisons of baseline characteristics between the two groups were conducted using Pearson's chi-square tests for categorical variables and *t* tests for continuous variables. Pre-index and post-index hospital costs were compared using Wilcoxon signed-rank tests. The difference in the changes of hospital costs between patients treated with ASMs only and ASMs plus VNS were compared using Mann-Whitney *U* test due to non-normality.

A difference-in-differences framework (DID) was used to estimate the effect of VNS on hospital costs. The DID framework is a quasi-experimental design that can estimate the effect of treatment (intervention) by comparing the changes in outcomes (eg, costs) over time between patients who received additional treatment (eg, VNS in addition to ASMs) and patients without the additional treatment (eg, ASMs).[25] In addition, because hospital costs have skewed distributions with a large proportion of zero, a two-part model was conducted to analyze hospital costs.[26] The first part of the two-part model was a logistic regression analyzing the binary dependent variable of whether there was any cost larger than zero, and the second part evaluated the continuous dependent variable capturing the annual costs for patients having costs larger than zero. Based on the results of BoxCox test and Park test, the second part of the two-part model was conducted through a generalized linear model (GLM) with gamma distribution and log link. All the sociodemographic and clinical characteristics listed in Table 1 were included in the first-part and second-part models. Because every patient in both cohorts had total hospital costs, only GLM with gamma distribution and log link was used for all-cause and epilepsy-related total costs analyses instead of using two-part models. Because the health care costs of each individual patient are nested within the hospital at which the patient received care, cluster-robust standard errors were used to adjust for interclass correlation in all cost models. In addition to reporting the odds ratios and mean cost ratios of continuous dependent variables, overall marginal effects combining the marginal effects from both parts of two-part models were also reported.[27] All analyses were performed using Statistical software SAS 9.4 and Stata 14.0. *P*-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of participants

This study included 1113 patients who received ASMs plus VNS and 3471 patients who received ASMs only. Significant variations in age, gender, census region, race and ethnicity, patient type at index date, CCCs, primary diagnosis, and insurance were identified between the two cohorts ($p < .001$). Baseline cohort characteristics and demographics are shown in Table 1. Compared to the ASMs-only cohort, those in the ASMs plus VNS group were more likely to be privately insured, non-Hispanic White, male, and residing in the Midwest or South regions of the US. The ASMs plus VNS patients were older (mean age 9.34 years, SD 4.25) and were more likely to have documented presence of comorbidities. They were more often treated as outpatient status on the index date when the classification of drug resistant epilepsy was met in the medical records. For the ASMs plus VNS cohort, the patient type at the index date would dictate the attribution of the costs

TABLE 1 Baseline patient demographics and clinical characteristics

Characteristics	Total		ASMs plus VNS cohort $N = 1113$		ASMs-only cohort $N = 3471$		p value
	Mean	SD	Mean	SD	Mean	SD	
Age in years	7.94	4.44	9.34	4.25	7.49	4.40	<.001
	N	%	*N*	%	*N*	%	
Age in years							
<4	1055	23.0	118	10.6	937	27.0	<.001
4–11	2532	55.2	659	59.2	1873	53.9	
12–17	997	21.8	336	30.2	1026	19.1	
Gender							
Male	2477	54.0	640	57.5	1837	52.9	.008
Female	2107	46.0	473	42.5	1634	47.1	
Census region							
Midwest	1243	27.1	336	30.2	907	26.2	<.001
Northeast	620	13.5	117	10.5	503	14.5	
South	1720	37.5	445	40.0	1275	36.7	
West	1001	21.8	215	19.3	786	22.6	
Race and ethnicity							
Non-Hispanic White	2500	54.5	732	65.8	1,768	50.9	<.001
Non-Hispanic Black	713	15.6	127	11.4	586	16.9	
Hispanic	1017	22.2	190	17.0	827	23.8	
Other	354	7.7	64	5.8	290	8.4	
Patient type at index date							
Inpatient	3286	71.68	312	28.1	2974	85.7	<.001
Outpatient	1298	28.32	801	71.9	497	14.3	
Comorbidity with CCCs							
No	850	18.5	43	3.9	807	23.2	<.001
Yes	3734	81.5	1070	96.1	2664	76.8	
Primary diagnosis							
Focal/Partial	565	12.3	207	18.6	358	10.3	<.001
Generalized	430	9.4	139	12.5	291	8.4	
Other	3589	76.3	767	68.9	2822	81.3	
Insurance							
Medicaid	2667	58.2	596	53.6	2071	59.7	<.001
Private	1602	35.0	435	39.1	1167	33.6	
Other	315	6.8	82	7.4	311	6.7	

of the surgical encounter for VNS implantation: 71.9% of the ASMs plus VNS cohort had outpatient VNS surgeries, whereas 28.1% had their VNS surgery encounters classified as inpatient.

3.2 | Unadjusted costs

All-cause annual hospital costs were determined for patients in the ASMs plus VNS and ASMs-only cohorts over 1 year pre-index and 2-year post-index periods, and the geometric mean costs were reported in Table 2 to account for the non-normal distribution of cost data. All-cause annual total costs were higher in the post-index period for both cohorts. The mean unadjusted all-cause annual total costs were $20 893 vs $9074 for the ASMs-only cohort, and $28 599 vs $11 414 for the ASMs plus VNS cohort. For the ASMs plus VNS cohort, the relative increase in annual total costs was driven mainly by significant increases in outpatient costs; the

TABLE 2 Unadjusted geometric mean annual hospital costs with 95% confidence intervals in pre-index and post-index periods

	ASMs plus VNS cohort			ASMs-only cohort			VNS change vs ASMs change
Variables	**Pre-index**	**Post-index**	***p* value**	**Pre-index**	**Post-index**	***p* value**	***p* value**
All-cause							
Inpatient costs	$986 ($747, $1301)	$517 ($383, $695) $2978	.932	$414 ($350, $490)	$10 876 ($9965, $11 871)	<.001	<.001
Outpatient costs	$27 ($21, $36)	($2393, $3706)	<.001	$20 ($17, $24)	$82 ($71, $95)	<.001	<.001
Emergency department costs	$21 ($16, $26)	$24 ($19, $29)	<.001	$66 ($58, $75)	$71 ($63, $81)	<.001	.843
Total costs	$11 414 ($10 525, $12 378)	$28 599 ($27 475, $29 768)	<.001	$9074 ($8609, $9564)	$20 893 ($20 046, $21 776)	<.001	<.001
Epilepsy-related							
Inpatient costs	$916 ($693, $1210)	$490 ($364, $660)	.796	$304 ($256, $360)	$10 595 ($9704, $11 568)	<.001	<.001
Outpatient costs	$17 ($13, $22)	$2572 ($2050, $3225)	<.001	$9 ($8, $11)	$45 ($39, $52)	<.001	<.001
Emergency department costs	$10 ($8, $12)	$9 ($7, $11)	<.001	$16 ($14, $18)	$17 ($15, $20)	<.001	.853
Total costs	$8200 ($7209, $9328)	$27 898 ($26 807, $29 034)	<.001	$3884 ($3503, $4305)	$19 614 ($18 809, $20 453)	<.001	<.001

Note: Means in Table 2 are geometric means.

mean unadjusted all-cause annual outpatient costs increased from $27 in pre-index period to $2978 in post-index period ($p < .001$): these post-index costs include the costs of the surgical encounters with the VNS implant and all services. The mean unadjusted all-cause inpatient costs decreased from $986 to $517, but the change in inpatient costs was not significant ($p = .932$). The mean unadjusted all-cause ED costs increased slightly from $21 to $24 ($p < .001$). For the ASMs-only cohort, the relative increase in annual total costs was driven mainly by significant increases in inpatient costs; the mean unadjusted all-cause annual inpatient costs increased from $414 in pre-index period to $10 876 in post-index period ($p < .001$). The mean unadjusted outpatient costs increased significantly from $20 to $82 ($p < .001$). The mean unadjusted all-cause ED costs increased from $66 to $71 ($p < .001$). The changes in all-cause hospital costs, which is equal to the difference in costs in the post-index period compared with the costs in pre-index period, were compared between the two cohorts. The changes in inpatient, outpatient, and total costs were significantly different between the two cohorts ($p < .001$), whereas there was no significant difference in the change in ED costs between the two cohorts ($p = .843$). Epilepsy-related costs were compared between the two cohorts. Similar directionality of results were observed in pre-index and post-index difference for epilepsy-related inpatient costs, outpatient costs, and total costs.

3.3 | Adjusted costs

To analyze the association between treatment and hospital costs, DID analyses were conducted using two-part models and GLM (Table 3, Figure S1).

3.3.1 | Inpatient costs

Significant difference in the pre- to post-index change between the two cohorts was observed for the odds of having inpatient costs (all-cause odds ratio [OR] = 0.04, 95% CI: 0.03–0.06; epilepsy-related OR = 0.05, 95% CI: 0.03–0.07) and for the annual inpatient costs among patients having inpatient costs (all-cause mean cost ratio = 0.82, 95% CI: 0.69–0.97; epilepsy-related mean cost ratio = 0.81, 95% CI: 0.67–0.98). The overall marginal effect indicated that the effect of ASMs-only treatment on all-cause and epilepsy-related annual inpatient costs was a significant increase by $14 893 (95% CI: $12 465–$17 320) and $18 038 (95% CI: $15 592–$ 20 483), whereas the effect of ASMs plus VNS on all-cause and epilepsy-related annual inpatient costs was not significant (all-cause: −$3752, 95% CI: −$8267 to $762; epilepsy-related: −$797, 95% CI: −$5941 to $4346).

3.3.2 | Outpatient costs

The odds of having outpatient costs increased significantly more in the ASMs plus VNS cohort compared with the ASMs-only cohort (all-cause OR = 5.34, 95% CI: 3.51–8.14; epilepsy-related OR = 4.37, 95% CI: 2.87–6.66). Among patients having outpatient costs, the pre- to post-index change in outpatient costs was different between the two cohorts (all-cause mean cost ratio = 3.59, 95% CI: 3.04–4.27). More than 70% of ASMs plus VNS patients were classified as outpatient at the index date, which means the cost of their VNS surgeries was attributed to outpatient surgical encounters. The overall marginal effect indicated that the adjusted all-cause and epilepsy-related annual outpatient costs of the ASMs plus VNS cohort increased significantly by $8912 (95% CI: $7705–$10 120) and $8916 (95% CI: $7556–$10 275), respectively. The effect of ASMs-only treatment on all-cause and epilepsy-related annual outpatient costs was not significant (all-cause: −$216, 95% CI: −$516 to $83; epilepsy-related: $264, 95% CI: −$18 to $546).

3.3.3 | Emergency department costs

The pre- to post-index change in the odds of having ED costs was not significantly different between the two cohorts (all-cause: OR = 1.01, 95% CI: 0.84–1.21; epilepsy-related: OR = 0.96 95% CI: 0.79–1.15). Among patients having ED costs, these costs decreased significantly more (from pre-index to post-index periods) in the ASMs plus VNS cohort compared with the ASMs-only cohort (all-cause mean cost ratio = 0.86, 95% CI: 0.76–0.97, epilepsy-related mean cost ratio = 0.84, 95% CI: 0.74–0.96).

3.3.4 | Total costs

The adjusted all-cause and epilepsy-related annual total costs of ASMs plus VNS cohort increased by $12 838 (95% CI: $8171–$17,505) and $15 183 (95% CI: $10 253–$20 113), respectively. For the ASMs-only cohort, the adjusted all-cause and epilepsy-related annual total costs increased by $14 715 (95% CI: $12 375–$17 055) and $18 437 (95% CI: $15 978–$20 896). There was no significant difference in the pre-index to post-index changes between the ASMs plus VNS cohort and the ASMs-only cohort observed for all-cause annual total costs (all-cause mean cost ratio = 0.88, 95% CI: 0.76–1.02), whereas the

TABLE 3 Difference-in-difference models of hospital-based costs

	Inpatient costs		Outpatient costs		Emergency department costs		Total costs
	First part	Second part	First part	Second part	First part	Second part	GLM
Variables	OR (95% CI)	Mean cost ratio (95% CI)	OR (95% CI)	Mean cost ratio (95% CI)	OR (95% CI)	Mean cost ratio (95% CI)	Mean cost ratio (95%CI)
All-cause							
VNS[a]	5.63 (4.17, 7.63)*	1.16 (0.99, 1.35)	0.40 (0.29, 0.54)*	0.79 (0.68, 0.92)*	0.59 (0.46, 0.75)*	1.08 (0.94, 1.23)	1.27 (1.09, 1.49)*
Post[b]	13.57 (10.68, 17.26)*	1.15 (1.06, 1.26)*	1.90 (1.66, 2.18)*	0.73 (0.68, 0.79)*	0.93 (0.85, 1.03)	0.73 (0.68, 0.79)*	1.57 (1.46,1.69)*
VNS*Post[c]	0.04 (0.03, 0.06)*	0.82 (0.69, 0.97)*	5.34 (3.51, 8.14)*	3.59 (3.04, 4.27)*	1.01 (0.84, 1.21)	0.86 (0.76, 0.97)*	0.88 (0.76, 1.02)
Mean marginal effect							
Post vs Pre							
VNS	$−3752 (−$8267, $762)		$8912 ($7705, $10 120)*		−$394 ($−518, −$269)*		$12 838 ($8171, $17 505)*
ASMs	$14 893 ($12 465, $17 320)*		−$216 ($−516, $83)		−$337 (−$425, −$248)*		$14 715 ($12 375, $ 17 055)*
Epilepsy-related							
VNS	4.91 (3.64, 6.65)*	1.17 (1.08, 1.36)*	0.51 (0.37, 0.69)*	0.82 (0.69, 0.99)*	0.88 (0.68, 1.17)	1.08 (0.93, 1.24)	1.35 (1.16, 1.58)*
Post	14.85 (11.83, 18.65)*	1.25 (1.16, 1.36)*	2.33 (2.04, 2.65)*	0.77 (0.70, 0.84)*	1.15 (1.04, 1.23)*	0.71 (0.66, 0.78)*	1.81 (1.67, 1.96)*
VNS*Post	0.05 (0.03, 0.07)*	0.81 (0.67, 0.98)*	4.37 (2.87, 6.66)*	3.63 (3.00, 4.37)*	0.96 (0.79, 1.15)	0.84 (0.74, 0.96)*	0.83 (0.71, 0.96)*
Mean marginal effect							
Post vs Pre							
VNS	$−797 (−$5941, $4346)		$8916 ($7556, $10 275)*		−$263 (−$355, −$170)*		$15 183 ($10 253, $20 113)*
ASMs	$18 038 ($15 592, $20 483)*		$264 (−$18, $546)		−$165 (−$230, −$101)*		$18 437 ($15 978, $20 896)*

Note: The first part was a logistic regression analyzing the binary dependent variable of whether there was any cost larger than zero, and the second part evaluated the continuous dependent variable capturing the annual costs for patients having costs larger than zero.

*Statistically significant at the 5% level.

[a]Reference is ASMs-only cohort. Coefficient represents the cost ratio in the pre-index period = (pre-index mean costs of VNS cohort)/(pre-index mean costs of ASMs only cohort). Ratio >1 indicates that the average annual costs of VNS cohort is higher than that of ASMs-only cohort in the pre-index period.

[b]Reference is pre-index period. Coefficient represents the cost ratio of the reference cohort (ASMs-only cohort) = (post-index mean costs of ASMs-only cohort)/(pre-index mean costs of ASMs-only cohort). Ratio >1 indicates the costs of ASMs-only cohort increased after the index date.

[c]Reference is post-index to pre-index in the ASMs-only cohort. Coefficient represents the ratio of cost ratio = (post-index mean costs of VNS cohort/pre-index mean costs of VNS cohort)/(post-index mean costs of ASMs-only cohort/ pre-index mean costs of ASMs-only cohort). If post-index mean costs of ASMs-only cohort/pre-index mean costs of ASMs-only cohort >1, ratio of cost ratio >1 indicates the cost of VNS cohort increased more than ASMs-only cohort; if post-index mean costs of ASMs-only cohort/pre-index mean costs of ASMs-only cohort <1, ratio of cost ratio >1 indicates the cost of VNS cohort decreased less than ASMs-only cohort or costs of VNS cohort increased.

results of DID analyses for epilepsy-related annual total costs indicated that the ASMs plus VNS group generated significant cost savings of $3254 per year (epilepsy-related mean cost ratio = 0.83, 95% CI: 0.71–0.96).

4 | DISCUSSION

In this study, we compared the inpatient, outpatient, ED, and total hospital costs incurred by a large national cohort of 4584 pediatric patients with refractory epilepsy in the United States: there were significant differences in these costs of care in the ASMs-only cohort vs the ASMs plus VNS cohort. We found that VNS is a cost-beneficial treatment compared to continuing on ASMs only at 2-year follow-up.

Previously, three studies[16,28,29] have compared costs of care prior to VNS therapy and after VNS therapy: control or comparison groups were not included in those studies. These studies have all reported a decrease in health care costs after VNS therapy, whereas our study found that the mean annual total costs increased in both cohorts. The timeframe for data inclusion and follow-up is different between studies. Helmers et al. used administrative data from the State Inpatient Database collected 6 months prior to VNS implantation and up to 3 years after VNS implantation, and reported that average quarterly total health care costs decreased incrementally over time after VNS implantation by $2181 and $3229 for children and adolescents, respectively. It was postulated that the health status in the 6 months before VNS implantation may be a time of relative clinical deterioration in some patients, giving patients and families the impetus to proceed with surgery; that may factor into health care costs being higher in the pre-VNS period in Helmers' study.[16] Ben-Menachem et al. compared the direct hospital costs 18 months before and 18 months after VNS implantation in 42 patients receiving VNS therapy, and reported that the total hospital costs in the post-VNS period were lower than those in the pre-VNS period by an average of $3000 per year. It is notable that some significant costs were not included in calculating costs in the post-VNS period, such as cost of the VNS therapy system, cost of the implantation surgery, and costs of the outpatient office visits for device programming. Therefore, Ben-Menachem et al. underestimated the total costs, especially for the post-VNS period.[28] This study tracks a patient population treated in the Swedish health care system and thus may not be directly comparable to health care cost studies in other countries. Boon et al. studied American adults and children (ages 5- to 71-years-old) with refractory epilepsy by comparing the direct medical costs incurred by surgery, VNS, and ASMs. They also found that the yearly epilepsy-related direct medical costs in the post-VNS period (mean 29 months; range 12–57 months) were $2496, which was lower than those in the pre-VNS period (24 months) of $4826. Their study included the costs of ASMs, clinic visits, hospital admissions, and laboratory tests.[29]

Our finding of cost efficiency of VNS is in keeping with findings of previous studies.[16,28,29] We found that the costs of care rose on average $3254 less per year for the ASMs plus VNS cohort compared to the ASMs-only cohort in epilepsy-related treatment. Prior studies have not included a comparison group beyond the VNS group themselves. Our study's inclusion of the ASMs-only cohort adds additional data to the literature with an important comparison group and a more robust study design. It is not surprising that costs of care rise every year for children with refractory epilepsy. Such a diagnosis entails a chronic disease that requires complex multidisciplinary care. Comorbidities for children with epilepsy are common, with over 80% of this population having one or more comorbidity.[30] Escalation in medical needs for this patient population at a trajectory in their disease requiring the addition of another medication or the addition of surgical intervention may occur at a time coinciding with increase in health care costs. That the addition of vagus nerve stimulation therapy was associated with lower health care costs in comparison to the medically treated group is notable. Future research with longer follow-up is warranted.

Our study also breaks down costs into inpatient, outpatient, and ED components. For chronic diseases that can have exacerbation of illness severity requiring ED care or inpatient hospitalization, more ideal care patterns would typically be regular outpatient management without ED and inpatient encounters. Outpatient care management generally represents a more stable disease state compared to ED or inpatient care. This study shows that the all-cause and epilepsy-related ED costs decreased significantly more in the ASMs plus VNS cohort compared with the ASMs-only cohort. The ASMs-only cohort incurred higher inpatient costs after the index date, whereas the overall marginal effect of VNS on inpatient costs was not significant. The ASMs plus VNS group incurred higher outpatient costs in the post-index timeframe. For 71.9% of the ASMs plus VNS patients, the surgical encounter for VNS device implantation was attributed to the first post-index year of outpatient costs. Outpatient management is expected after VNS implantation in the postoperative period during VNS device adjustment for each patient. With time, as VNS parameters are individually optimized, the intensity of outpatient encounters typically decreases. In clinical practice, outpatient programming encounters tends to decrease in frequency after titrating to an individualized setting. This temporal change is demonstrated in the results. Our data show that the geometric mean annual all-cause and epilepsy-related outpatient costs were

$3200 and $2900 in the first year after VNS implementation, and decreased to $8 and $6 in the second year (Table S2). We would expect a de-escalation of outpatient care over time, which would likely be accompanied by decreasing costs. Future studies warrant additional focus on costs and patterns of care in longer-term follow-up.

Even higher increases in inpatient costs for the ASMs-only cohort in the post-index period were noted compared to the increases in outpatient costs for the ASMs plus VNS cohort. The cost-benefit assessment in average annual costs is in favor of VNS therapy. Because outpatient management is typically considered more optimal and reflective of lower acuity than inpatient care. Shifting costs to the outpatient setting is not only cost-beneficial, but it is also likely of benefit to patients and families. We do not have such data in this study to further explore this idea: in future directions for research, qualitative and quantitative study of the patient and family stakeholder perspectives is essential.

There are known limitations to administrative data, which may be subject to errors in coding or documentation. Specifically for epilepsy, the structure of ICD-9 and ICD-10 coding is often not adequate to reveal clinical considerations that are important to clinical study and treatment. This study cohort of pediatric epilepsy is heterogeneous in etiology and behavior. A national database gives a sample size and power to study the challenging entity of refractory epilepsy with real-world data. Recognizing the inherent limitation of coding and documentation of pediatric epilepsy in the clinical context, the data quality is mitigated in multiple ways: there is an internal data verification process conducted by the Children's Hospital Association and contributing hospitals for PHIS data. Our study used published algorithms for cohort identification of children with refractory epilepsy: the combination of codes selected has been validated by other research teams and has undergone peer review. With administrative data, the rationale for clinical decision-making for each individual case is not known. Causality is also not known. In addition, it is not possible to adjust for unobservable confounding factors. Nevertheless, a national perspective of costs of pediatric epilepsy care in children with refractory epilepsy, with medication and VNS groups, provides unprecedented information. In our present study, given that the PHIS database has data only from PHIS hospitals, costs of care incurred in non-PHIS pharmacy, outpatient, ED, or inpatient settings are not known. Costs to the health care system as a whole are thus expected to be underestimated.

Diseases such as pediatric drug-resistant epilepsy represent complex conditions, which require multidisciplinary care. Understanding and quantifying direct and indirect costs of care for children and families living with chronic conditions including epilepsy are important endeavors for future research. Pursuing such research is essential for advancing the treatment of these diseases and for improving health care delivery for these challenging diseases that represent high health care burdens. In addition, the treatment pathways analyzed in this study are only two common options in the armamentarium of treatments for refractory epilepsy, which can include multiple medications, ketogenic diet, and different surgical options including resections, disconnections, and neurostimulation, among others. This study certainly cannot substitute for multicenter clinical research; however, it provides evidence to motivate future research to compare these treatment modalities for larger populations or for future clinical trial design.

5 | CONCLUSION

We conducted an analysis of the PHIS database estimating hospital-based costs of pediatric patients with refractory epilepsy on ASMs-only vs ASMs plus VNS. We show that VNS reduces total hospital-based costs compared with ASMs at 2-year follow-up. Our study suggests that VNS utilization is associated with cost savings to payors, patients, and health care systems.

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CONFLICT OF INTEREST

SKL reports an investigator-initiated study award from LivaNova to study patterns of care in pediatric epilepsy using independent national data sets, and has served as a paid consultant on advisory boards of Aesculap Academy, LivaNova, Encoded Therapeutics, and Jaguar Gene Therapy. Authors Lu Zhang and Matt Hall have no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Hauser WA, Hesdorffer DC. Epilepsy : Frequency, Causes and Consequences. Demos; 1990.
2. Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the epilepsies in children and adolescents. Epilepsia. 1989;30(1):94–106.
3. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics. 2012;129(2):256–64.

4. Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. Epilepsia. 2013;54(s2):19–22.
5. Cramer JA, Wang ZJ, Chang E, Powers A, Copher R, Cherepanov D, et al. Healthcare utilization and costs in children with stable and uncontrolled epilepsy. Epilepsy Behav. 2014;32:135–41.
6. Begley CE, Durgin TL. The direct cost of epilepsy in the United States: a systematic review of estimates. Epilepsia. 2015;56(9):1376–87.
7. Group TVNSS. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology. 1995;45(2):224–30.
8. Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;81(16):1453–9.
9. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery. 2000;47(6):1353–8.
10. Fernandez L, Gedela S, Tamber M, Sogawa Y. Vagus nerve stimulation in children less than 3 years with medically intractable epilepsy. Epilepsy Res. 2015;112:37–42.
11. Suresh G, Sirichai C, Leslie C, SooHo C, Bruce E, Jane H, et al. Neuromodulation therapy with vagus nerve stimulation for intractable epilepsy: a 2-year efficacy analysis study in patients under 12 years of age. Epilepsy Res Treat. 2016;2016:9709056–5.
12. Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure. 2006;15(7):491–503.
13. Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. Epilepsia. 2009;50(5):1220–8.
14. Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr. 2011;7(5):491–500.
15. Cramer JA, Menachem EB, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. Epilepsy Res. 2001;47(1):17–25.
16. Helmers SL, Duh MS, Guérin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical outcomes, quality of life, and costs associated with implantation of vagus nerve stimulation therapy in pediatric patients with drug-resistant epilepsy. Eur J Paediatr Neurol. 2012;16(5):449–58.
17. Patel A, Wang L, Gedela S. Health care utilization following vagus nerve stimulation therapy in Pediatric Epilepsy Patients From a Pediatric Accountable Care Organization. J Child Neurol. 2018;33(2):136–9.
18. Aburahma SK, Alzoubi FQ, Hammouri HM, Masri A. Vagus nerve stimulation therapy in a developing country: a long term follow up study and cost utility analysis. Seizure. 2014;25:167–72.
19. Helmers SL, Thurman DJ, Durgin TL, Pai AK, Faught E. Descriptive epidemiology of epilepsy in the U.S. population: a different approach. Epilepsia. 2015;56(6):942–8.
20. Pestana Knight EM, Schiltz NK, Bakaki PM, Koroukian SM, Lhatoo SD, Kaiboriboon K. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. Epilepsia. 2015;56(3):375–81.
21. Jetté N, Reid AY, Quan H, Hill MD, Wiebe S. How accurate is ICD coding for epilepsy? Epilepsia. 2010;51(1):62–9.
22. Baaj AA, Benbadis SR, Tatum WO, Vale FL. Trends in the use of vagus nerve stimulation for epilepsy: analysis of a nationwide database. Neurosurg Focus. 2008;25(3):E10.
23. Kee VR, Gilchrist B, Granner MA, Sarrazin NR, Carnahan RM. A systematic review of validated methods for identifying seizures, convulsions, or epilepsy using administrative and claims data. Pharmacoepidemiol Drug Saf. 2012;21:183–93.
24. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr. 2014;14(1):199.
25. Wooldridge J. Difference-in-Differences Estimation; 2007 [Available from: https://www.nber.org/WNE/lect_10_diffindiffs.pdf. Accessed March 1, 2021.
26. Deb P, Norton EC. Modeling health care expenditures and use. Annu Rev Public Health. 2018;39(1):489–505.
27. Belotti F, Deb P, Manning WG, Norton EC. Twopm: two-part models. Stata J. 2015;15(1):3–20. https://doi.org/10.1177/1536867X1501500102
28. Ben-Menachem E, Hellström K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology. 2002;59(6 Suppl 4):S44–7.
29. Boon P, D'Havé M, Van Walleghem P, Michielsen G, Vonck K, Caemaert J, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia. 2002;43(1):96–102.
30. Aaberg KM, Bakken IJ, Lossius MI, Lund Søraas C, Håberg SE, Stoltenberg C, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics. 2016;138(3):e20160921.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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