Original Article

Impact of Multimorbidity Subgroups on the Health Care Use of Early Pediatric Cancer Survivors

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BACKGROUND: Although pediatric cancer survivors in the United States are at an increased risk of developing chronic conditions, to the authors' knowledge there is limited information regarding the types and combinations of conditions they experience in the years immediately after the completion of cancer therapy. **METHODS:** An observational cohort study of early pediatric cancer survivors (children who were ≥2 years from the end of therapy and aged ≤18 years) was conducted using the Truven Health MarketScan (r) Commercial Claims and Encounters database (2009-2014). Latent class analysis was used to identify comorbidity groups among the subset with ≥2 conditions. Group-level health care use was compared with survivors without chronic conditions using multivariate regression. **RESULTS:** A total of 3687 early survivors were identified, of whom approximately 41.2% had no chronic conditions, 22.5% had 1 chronic condition, and 36.3% had ≥2 chronic conditions. Among those with ≥2 chronic conditions, 5 groups emerged: 1) general pediatric morbidity (35.4%); 2) central nervous system (CNS) (22.4%); 3) mental health conditions (22.2%); 4) endocrine (26.2%); and 5) CNS with endocrine (3.8%). The CNS group experienced the highest expenditures, at $17,964 more per year (95% CI, $1446-$34,482) compared with survivors without chronic conditions. The CNS group also had the highest odds of an emergency department visit (adjusted odds ratio, 1.71; 95% CI, 1.15-2.56). The endocrine group had the highest odds of hospitalization (odds ratio, 2.29; 95% CI, 1.24-4.22). **CONCLUSIONS:** Multimorbidity is common among pediatric cancer survivors. The current study identified 5 distinct comorbidity subgroups, all of which experienced high, yet differential, rates of health care use. The results of the current study highlight the complex health care needs of early survivors and provide evidence for the design of targeted survivorship services and interventions. ***Cancer*** **2020;126:649-658**.

KEYWORDS: child, delivery of health care, health expenditures, multimorbidity, neoplasm, survivorship.

INTRODUCTION

In the United States, an estimated 10,590 new pediatric cancer cases are diagnosed every year.[1] Advancements in detection and treatment have increased the average 5-year survival rate across pediatric cancers to >80%. Improved survival is contributing to a growing population of survivors of pediatric cancer whose past cancer experience puts them at an increased risk of secondary chronic conditions, including cardiometabolic complications, central nervous system (CNS) disorders, and mental health effects.[2-5] By the time children survive ≥5 years, approximately two-thirds are estimated to have a chronic condition.[6] Adult survivors of pediatric cancer have 3 times the risk of developing a chronic condition compared with nonsurvivors, and >25% experience a severe or life-threatening condition.[7]

Although the increased association between pediatric cancer and chronic conditions in adulthood has been well studied, the conditions experienced by early survivors–children and adolescents who are only a few years out from the completion of therapy–are unclear.[8] This population has been shown to fill more prescriptions from more drug classes, and to be at an increased risk of having a hospitalization, compared with children who have not experienced cancer.[9,10] Unfortunately, existing evidence does not consider the variety of combinations of conditions these children might experience, and the way those conditions relate to one another. Some conditions may be treatment-related disorders (eg, cisplatin-induced hearing loss) or stress-related mental health disorders, whereas others may reflect underlying chronic illness independent of the cancer process (eg, asthma, allergies).[4,11] Adverse outcomes may be dependent on tumor type, and can extend to social and behavioral effects. For example, social difficulty and impairment has been well documented in adolescent survivors of CNS cancers, with recent evidence highlighting the interplay between physical and cognitive limitations.[12]

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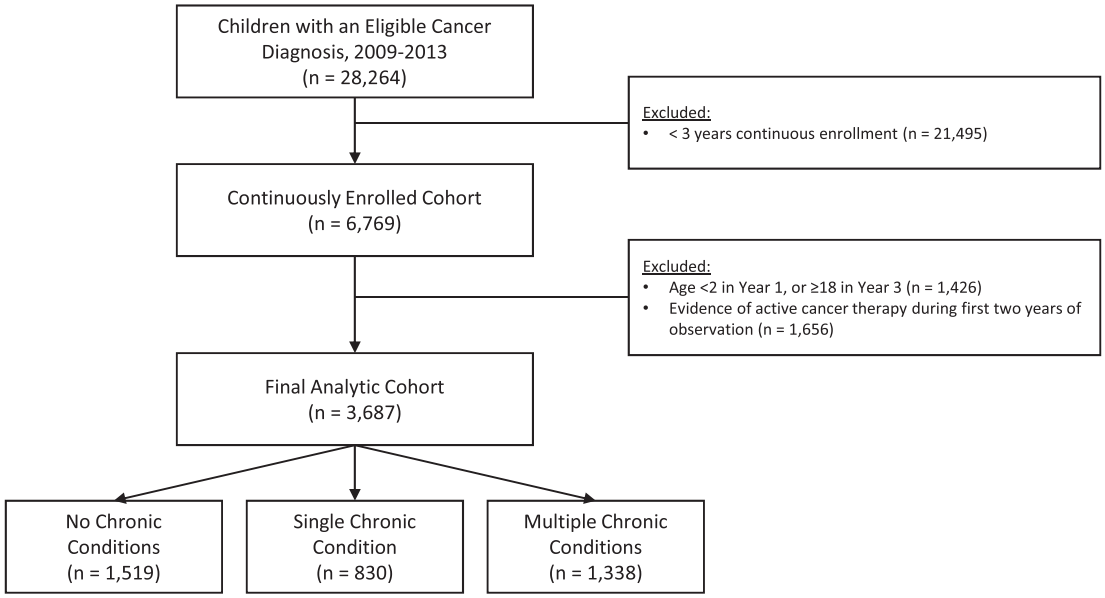

Figure 1. Cohort attrition diagram documenting the application of inclusion and exclusion criteria to arrive at the final analytic cohort.

There is a need for additional information regarding the chronic condition profiles and care patterns of the early posttherapy pediatric cancer population. Pediatric cancer guidelines stress the importance of coordinated care teams and structured transitions from cancer care back to the primary care setting.[13] A better understanding of chronic condition profiles at the time of, or shortly after, transition could lead to more informed decision making, as well as more coordinated care targeted toward high-risk populations. The objective of the current study was to identify and describe morbidity groups among early survivors of pediatric cancer, and to explore differences in demographic and clinical characteristics between these groups. To further identify groups with increased health care needs who might benefit from targeted intervention, the study also examined the association between morbidity groups and markers of health care use, including emergency department (ED) visits, hospitalizations, and total health care expenditures.

MATERIALS AND METHODS

Data Source and Study Design

A retrospective cohort study was conducted using the Truven Health MarketScan (r) Commercial Claims and Encounters (CCAE) database from January 2009 through December 2014. The database contains deidentified commercial insurance claims from approximately 350 private payers across the United States, representing around 50 million patients, annually. Information regarding subject enrollment and outpatient, inpatient, and pharmacy use is available. This includes *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, as well as procedure codes, costs, and prescription dispensing details.

Cohort selection is described in Figure 1. Children were required to be aged ≥2 and ≤18 years, with a diagnosis of at least 1 of the following cancer types: leukemia, bone/connective tissue, brain/CNS, lymphoma (Hodgkin and non-Hodgkin), or gonadal (testicular or ovarian). These cancers represent a majority of pediatric cancers, and claims-based algorithms are available to identify both diagnosis and cancer-specific active therapy.[6,9] Subjects were observed for a total of 3 years, during which time they must have been continuously enrolled. The population of interest was early survivors of pediatric cancer, defined as children and adolescents who were a minimum of 2 years out from the end of cancer therapy. To identify this population, subjects were excluded if they had any evidence of active cancer therapy (ie, any inpatient, outpatient, or pharmacy claims for radiotherapy, chemotherapy, or surgical treatment) during the first 2 years of observation.[9] Subject characteristics, including chronic condition profile, were measured over the first 2 years,

whereas health care use outcomes were measured in the third and final year.

Identification of Chronic Conditions and Generation of Morbidity Groups

Chronic conditions were assessed over the first 2 years of observation. ICD-9-CM diagnosis codes from all outpatient office visits and inpatient encounters were collected and categorized using the pediatric modification of the Agency for Healthcare Research and Quality Clinical Classification Software (CCS) and Chronic Condition Indicator (CCI) algorithms.[14-16] Together, these tools generated a systematic classification of distinct chronic clinical conditions.[17-19] Conditions that were identified as chronic by the CCI, and that appeared in 2 outpatient office visits on different dates or in 1 inpatient hospitalization, were retained in analysis. Children were classified as having none, 1, or multiple (≥2) chronic conditions (Fig. 1).

Among the subset of children with ≥2 chronic conditions, latent class analysis (LCA) was used to identify mutually exclusive morbidity groups. LCA is a model-based clustering method that can identify underlying subgroups within a population by examining a set of observed indicator variables in the data. In this analysis, chronic conditions with a prevalence of ≥3% in the cohort were used as subject-level indicators. There were no assumptions regarding the number of underlying groups, or the specific conditions that might contribute to them. A series of models were developed starting from a single class model and increasing incrementally one class at a time. The final model was selected based on statistical properties (convergence and fit) and clinical interpretability.[20-22] Fit was assessed using Bayesian information criterion, model entropy, and the Lo-Mendell-Rubin adjusted likelihood ratio test. Subjects were assigned to a morbidity group based on their highest predicted probability of membership, as calculated by the model from their individual profile of chronic conditions.

Variables

Three outcomes were measured during the last year of observation: 1) presence of an ED visit; 2) presence of an inpatient hospitalization; and 3) total health care expenditures. Total expenditures were calculated as the sum of direct annual outpatient, inpatient, and pharmacy expenditures measured via total payments on paid claims. Annual expenditures were winsorized at the 0.5% and 99.5% percentiles to account for possible data errors or extreme observations.[23] Estimates were adjusted for inflation and are presented in 2017 US dollars.[24]

Additional demographic, prior resource use, and clinical variables were measured in the second year of observation to characterize the observed population and to allow for the control of potential confounders during multivariate analysis. Demographic variables included age, sex, geographic region, and rural residence. Prior health care use variables included insurance plan type, provider type dispersion (a modified Bice-Boxerman Continuity of Care Index, with lower values indicating more dispersion across specialties), and percentage of total expenditures that were out of pocket (categorized in quintiles).[25] Cancer type was included as a dichotomous variable: blood (leukemia and lymphoma) and solid tumor (all others).

Statistical Analysis

Children in each of the morbidity groups were compared with a reference group of early survivors with no chronic conditions. In descriptive analysis, categorical variables were compared using chi-square tests and continuous variables were compared using Kruskal-Wallis tests.

Differences in ED visits and inpatient hospitalization were examined using multivariate logistic regression, with the results presented as adjusted odds ratios and 95% CIs. Differences in total expenditures were modeled using a 2-part approach. The first step modeled the probability of having zero versus nonzero expenditures (generalized linear model with log link), whereas the second step modeled the effect of the group of interest (chronic condition group) on the nonzero expenditure outcomes (generalized linear model with gamma distribution, log link). This method is recommended for analyses of health care cost data, in which a bulk of zeros and a skewed nonzero distribution are anticipated.[26,27] To examine the impact of remaining outliers, a sensitivity analysis was conducted excluding children above the 99th percentile of total annual expenditures. Results are presented as the mean change from the reference population, with 95% CIs.

Multimorbidity can be characterized as a combination of the specific combinations of clinical conditions experienced and the total number of conditions experienced. To explore the relationship between these factors and to determine whether results were robust regardless of condition count, sensitivity analyses were conducted with and without adjustment for the number of chronic conditions and both sets of results are presented.

Analyses were conducted using SAS 9.4 statistical software, MPLUS 8.0 statistical software, and STATA

TABLE 1. Baseline Characteristics of the Early Pediatric Cancer Survivor Cohort

Characteristic		
Demographics	Overall No. (%)	
Sample size	3687	
Mean age (SD), y	11.4	(4.1)
Age group, y		
2-6	528	(14.3)
7-11	1183	(32.1)
12-18	1976	(53.6)
Female sex	1671	(45.3)
Geographic region		
South	1226	(33.3)
North Central	932	(25.3)
Northeast	784	(21.3)
West	695	(18.9)
Unknown	50	(1.4)
Rural	475	(12.9)
Insurance type		
PPO	2,259	(61.3)
HMO	552	(15.0)
Other	876	(23.8)
Cancer diagnosis		
Leukemia	1459	(39.6)
Bone	576	(15.6)
Brain/CNS	1123	(30.5)
Non-Hodgkin lymphoma	367	(10.0)
Hodgkin lymphoma	185	(5.0)
Testicular	34	(0.9)
Ovarian	71	(1.9)
Chronic condition count		
None	1519	(41.2)
1	830	(22.5)
≥2	1338	(36.3)

Abbreviations: CNS, central nervous system; HMO, health maintenance organization; PPO, preferred provider organization.

14.0 statistical software. A P value <.05 was considered to be statistically significant. The current study was determined to be nonhuman subjects research by the Office for the Protection of Research Subjects of the University of Illinois at Chicago.

RESULTS

A total of 3687 children were included in the current study cohort (Fig. 1). The majority of exclusions were due to failure to meet continuous enrollment criteria. Among individuals excluded for this reason, the mean age was 11.0 years (SD, 5.5 years) and approximately 44.1% were female. Excluded individuals had a lower prevalence of brain/CNS cancer compared with the analytic cohort (26.1% vs 30.5%), and a higher prevalence of testicular cancer (2.6% vs 0.9%) and non-Hodgkin lymphoma (11.2% vs 10.0%).

The final analytic cohort was 45.3% female, with a mean age of 11.4 years (SD, 4.1 years) (Table 1). The Southern geographic region was found to have the highest percentage of children (33.3%), and approximately 12.9% of children resided in a rural area. Chronic conditions were observed in a majority of the cohort, with 41.2% of survivors having none, 22.5% having 1, and 36.3% having ≥2 chronic conditions. Leukemia was the most common single cancer type experienced overall (39.6%), both among survivors without chronic conditions (49.8%) and among those with a single chronic condition (37.8%). Brain/CNS cancer was the most common diagnosis among survivors with multimorbidity (47.2%).

Identification of Morbidity Groups

LCA of survivors with ≥2 chronic conditions (1338 survivors) identified 5 morbidity subgroups. Demographic and clinical characteristics by morbidity group are presented in Table 2. The general pediatric morbidity group accounted for largest percentage of survivors with multimorbidity (35.4%). The most prevalent chronic conditions in this group were allergic rhinitis (27.9%) and asthma (26.4%). Among all groups, the general pediatric morbidity group was the only group in which leukemia was the most prevalent cancer diagnosis (44.0%). The CNS group (22.4% of the current study cohort) primarily experienced conditions of the brain and neuropathies (59.3%) and hereditary CNS conditions (including hydrocephalus) (41.0%), followed by several related conditions including paralysis (26.3%) and epilepsy (26.0%). The mean age of survivors in this group was 9.2 years (SD, 4.5 years), which is the youngest age across all groups. The most prevalent conditions in the mental health conditions group (22.2% of the study cohort) were mood disorders (42.8%), attention deficit hyperactivity disorder (42.1%), anxiety disorders (34.7%), and adjustment disorders (32.7%). This was among the oldest groups, with a mean age of 12.5 years (SD, 3.6 years), and had the lowest percentage of girls (41.1%). In the endocrine group (16.2% of the study cohort), nonthyroid endocrine disorders (82.9%) and thyroid disorders (58.1%) accounted for the majority of chronic condition diagnoses. Finally, the CNS with endocrine group comprised 3.8% of the multimorbidity cohort. This was the most complex group, in which 7 chronic conditions had a prevalence of ≥30%: brain conditions and neuropathies (92.2%), hydrocephalus and other hereditary CNS conditions (78.4%), vision loss and disorders (45.1%), nonthyroid endocrine disorders (41.2%), other eye disorders (39.2%), mood disorders (33.3%), and adjustment disorders (31.4%). The CNS with endocrine group had the highest percentage of girls (58.8%), and the overwhelming majority had a diagnosis of brain/CNS cancer (82.4%).

TABLE 2. Characteristics of Model-Derived Chronic Condition Comorbidity Groups Among Early Pediatric Cancer Survivors

	Chronic Condition Group										
	General Pediatric Morbidity		CNS		Mental Health Conditions		Endocrine		CNS With Endocrine		
Class Name	No.	%	No.	%	No.	%	No.	%	No.	%	*P*
Sample size	473	35.4	300	22.4	297	22.2	217	16.2	51	3.8	—
Mean age (SD), y	10.9	4.3	9.2	4.5	12.5	3.6	12.5	3.4	12.1	4.4	<.001
Female sex	223	47.1	149	49.7	122	41.1	96	44.2	30	58.8	.08
Geographic region											.01
South	168	35.5	104	34.7	77	25.9	75	34.6	24	47.1	
North Central	93	19.7	75	25.0	92	31.0	58	26.7	10	19.6	
Northeast	121	25.6	57	19.0	80	26.9	39	18.0	7	13.7	
West	82	17.3	56	18.7	44	14.8	40	18.4	10	19.6	
Unknown	9	1.9	8	2.7	4	1.3	5	2.3	—	—	
Rural	59	12.5	35	11.7	31	10.4	29	13.4	5	9.8	.83
Insurance type											.53
PPO	286	60.5	175	58.3	194	65.3	141	65.0	28	65.0	
HMO	75	15.9	47	15.7	28	9.4	34	15.7	7	15.7	
Other	112	23.7	78	26.0	75	25.3	42	19.4	16	19.4	
Cancer type											
Leukemia	208	44.0	31	10.3	92	31.0	51	23.5	7	13.7	<.001
Bone	92	19.5	29	9.7	43	14.5	14	6.5	5	9.8	<.001
Brain/CNS	106	22.4	238	79.3	110	37.0	135	62.2	42	82.4	<.001
Non-Hodgkin's lymphoma	57	12.1	9	3.0	42	14.1	9	4.1	2	3.9	<.001
Hodgkin's lymphoma	24	5.1	4	1.3	19	6.4	9	4.1	1	2.0	.03
Testicular	4	0.8	2	0.7	4	1.3	—	—	—	—	.47
Ovarian	6	1.3	1	0.3	4	1.3	6	2.8	1	2.0	.22
Chronic condition characteristics											
Mean no. of conditions (SD)	3.0	1.7	3.9	2.0	3.5	1.8	3.4	1.8	9.2	4.1	<.001
Mean no. of involved organ systems (SD)	2.5	1.2	2.7	1.3	2.3	1.1	2.7	1.2	5.4	1.8	<.001
Presence of ≥1 mental health conditions	98	20.7	104	34.7	295	99.3	43	19.8	41	80.4	<.001

Abbreviations: CNS, central nervous system; HMO, health maintenance organization; PPO, preferred provider organization.

Health Care Resource Use Across Morbidity Groups

Annual expenditures of the early pediatric cancer survivor cohort totaled $77.8 million, of which $49.9 million was generated by survivors with multiple chronic conditions. Among those with multimorbidity, the general pediatric morbidity group accounted for the largest percentage (41.1%; $20.6 million), followed by the CNS group (24.2%; $12.1 million). The mental health conditions and endocrine groups had similar total expenditures ($6.7 million and $6.9 million, respectively). Annual expenditures in the CNS with endocrine group were $3.6 million. The group-specific distributions of average individual annual expenditures by type of service (inpatient, outpatient, and pharmacy) are described in Figure 2.

In the outcome year, ED visits occurred in approximately 27.0% of survivors with multimorbidity, compared with 14.4% of survivors without chronic conditions ($P < .001$). Inpatient hospitalizations were experienced by approximately 14.8% of survivors with multimorbidity and 7.7% of survivors without chronic conditions ($P < .001$). Hospitalizations varied significantly across morbidity groups ($P < .01$), whereas variation in the occurrence of ED visits across groups was marginally statistically significant ($P = .046$). The CNS group had the highest percentage of children with an ED visit (30.7%), whereas the CNS with endocrine group had the highest percentage of children with hospitalizations (31.4%). The lowest rates of both ED visits and hospitalizations were found in the general pediatric morbidity group (24.3% for ED visits and 12.7% for hospitalizations).

Differences also were observed with regard to the number of inpatient and ED encounters between groups (see Supporting Table 1). Survivors without chronic conditions averaged 0.2 ED visits (SD, 0.6 ED visits) and 0.1 inpatient encounters (SD, 0.8 inpatient encounters) in the outcome year. Among survivors with multimorbidity, the endocrine group averaged the lowest number

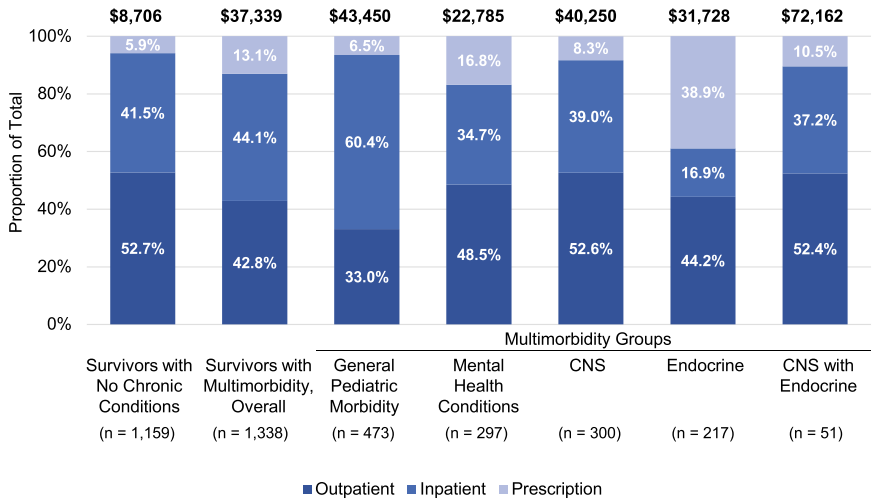

Figure 2. Distribution of average, individual annual health care expenditures among children with chronic conditions, overall and by condition group. This figure shows the distribution of average, individual, total annual health care expenditures by type of service (inpatient, outpatient, and pharmacy). The label above each column presents the total average annual expenditures per person in 2017 US dollars. The figure presents an overall breakdown for all early survivors, survivors with multimorbidity, and survivors by morbidity group. CNS indicates central nervous system.

of encounters (inpatient encounters, 0.2 [SD, 0.5 inpatient encounters] and ED encounters, 0.3 [SD, 0.8 ED encounters]), whereas the CNS with endocrine group averaged the highest number of encounters (inpatient encounters, 0.8 [SD, 1.5 inpatient encounters] and ED encounters, 1.1 [SD, 2.1 ED encounters]).

In adjusted multivariate analysis (Fig. 3), survivors in the CNS with endocrine group were found to have 2.6 times higher odds of an ED visit (95% CI, 1.4-4.8) and 5 times the odds of a hospitalization (adjusted odds ratio, 5.0; 95% CI, 2.3-10.7) compared with survivors without chronic conditions. In general, the magnitude of effect was higher for the hospitalization outcome than the ED outcome across morbidity groups.

Although the CNS with endocrine group also had the highest adjusted increase in expenditures, costing $35,096 more than survivors without chronic conditions, the results were not statistically significant. The CNS group had the next highest increase in expenditures ($25,370; $P < .001$), whereas the mental health conditions group had the lowest increase at $11,103 ($P = .03$).

The results of sensitivity analyses are presented in Supporting Table 2. In an analysis adjusting for the number of chronic conditions, the effects were attenuated; however, significant increases still were observed across multiple groups. The highest increase in expenditures was observed in the CNS group ($17,964; $P = .03$) and the lowest was observed in the mental health conditions group ($5522; $P = .30$). In analysis excluding children above the 99th percentile in total annual expenditures, the absolute change in adjusted annual expenditure in comparison with survivors with no chronic conditions was <10% in the mental health conditions group (+6%), CNS with endocrine group (−6%), and endocrine group (−3%). After excluding outliers, the CNS group cost $19,126 more than survivors with no conditions (−33% from primary analysis), and the general pediatric morbidity group cost $15,917 more (−35% from primary analysis).

DISCUSSION

In the current retrospective analysis of 3687 early survivors of pediatric cancer, there were 3 main findings. First, early survivors aged <18 years have high rates of multimorbidity, similar to adult survivors of pediatric cancer.[7] Second, this multimorbidity can be classified into 5 groups based on observed concurrent diagnoses, and these groups are predictive of health care resource use. Third, early survivors use a large amount of health care and financial resources, thereby identifying a potential target for care improvement efforts.

Multimorbidity was observed among 36.3% of early survivors in this commercially insured sample. This figure closely mirrors estimates from a study of adult survivors (mean age, 27 years), among whom 37.6% had ≥2 chronic conditions.[7] Future studies could elucidate whether the

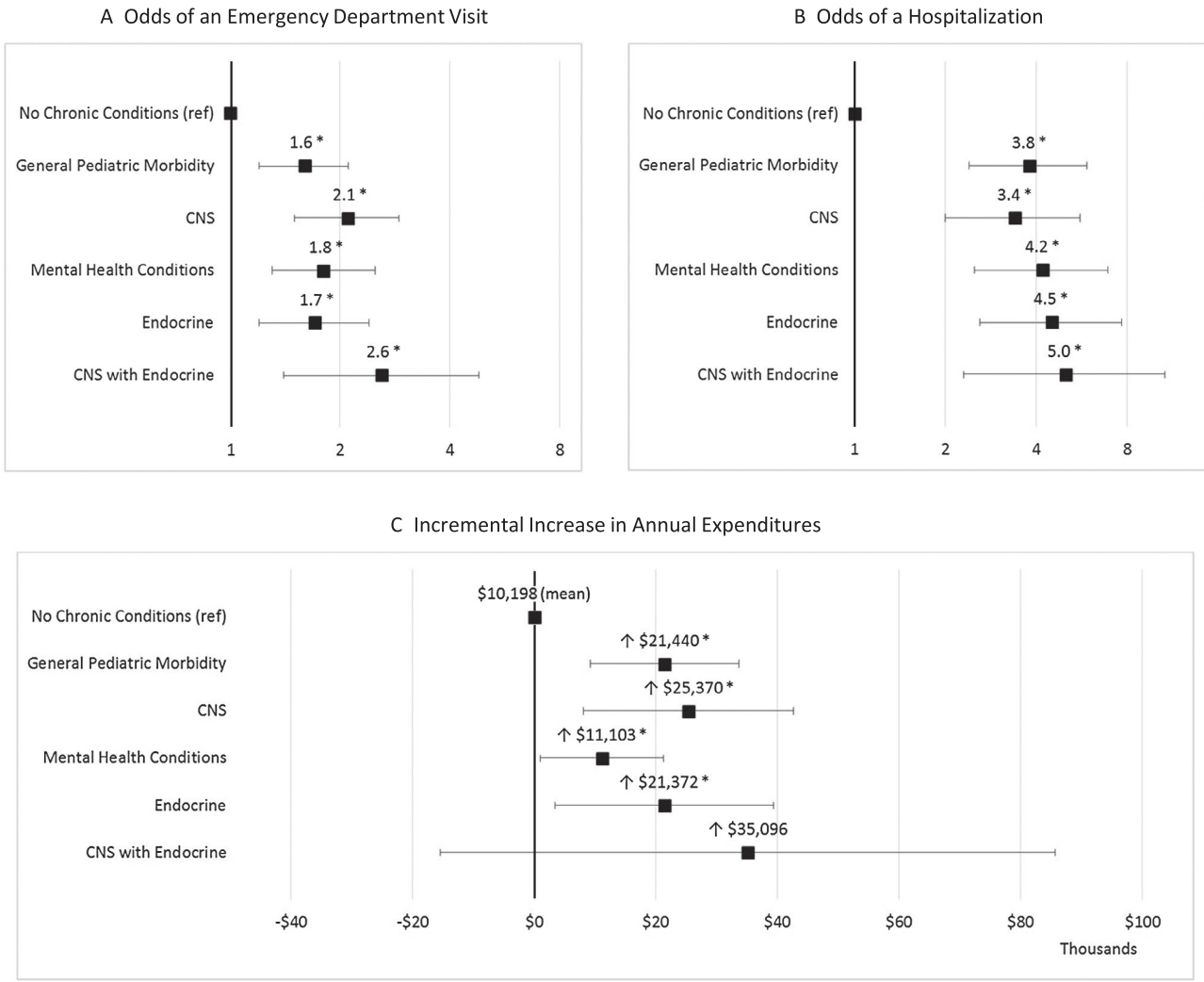

Figure 3. Adjusted associations between comorbidity groups and measures of health care use. (A) Adjusted odds of an emergency department visit by comorbidity group compared with survivors with no chronic conditions. (B) Adjusted odds of hospitalization by comorbidity group compared with survivors with no chronic conditions. (C) Additional cost experienced by each comorbidity group annually compared with survivors with no chronic conditions. Analyses were adjusted for age group, sex, geographic region, insurance type, emergency department visits within the prior year, hospitalizations within the prior year, percentage of total cost that was out of pocket within the prior year (shown by quintile), and provider dispersion within the prior year (continuous). Costs are presented in 2017 US dollars. CNS indicates central nervous system; ref, reference group. Asterisks (*) indicate a *P* value <.05.

same conditions persisted from the early posttreatment period into later life, or whether earlier conditions resolved and were replaced. Regardless, this suggests that multimorbidity-related care complexity (and challenges) are experienced equally by early and adult survivors.[28] The total annual health care expenditures in the current study cohort were just under $80 million in 2017 US dollars. This figure represents just a portion of the total national expenditure of early survivors, because cohort entry was restricted by several factors and also does not reflect costs incurred by the publically insured pediatric population. Although all these children could be considered high cost compared with survivors without chronic conditions, their expenditures varied significantly, averaging between $22,785 (mental health conditions group) and $72,162 (CNS with endocrine group) per child per year. This is substantially higher than estimated annual expenditures among the general population of children with chronic illness, which range from $2801 for children with a noncomplex chronic condition to $12,569 for those with a complex chronic condition.[29] Children who had been diagnosed with brain/CNS cancers were

both more likely to have multimorbidity and more likely to be in high-use morbidity groups compared with children who experienced a non-CNS cancer.

The use of LCA in the current study provides information regarding clinically relevant subgroups, which is an advantage over more simplistic counts or frequency-based measures of morbidity.[21,30] Similar methods have been used previously to identify patterns of patient-reported symptoms among children undergoing cancer therapy, and to identify symptom clusters or trajectories among adult survivors of pediatric cancer.[31-33] However, to the best of our knowledge, no prior study to date has examined subgroups of chronic illness, or the early survivor population specifically. Another approach previously used to examine morbidity in this population has been classification by condition severity.[6] Although useful, such an approach ignores the potential for joint comorbidity between more severe conditions and common pediatric illnesses. By allowing observed diagnoses to drive the identification of subgroups, rather than prespecifying a fixed list of chronic conditions, this study benefited from an expanded ability to detect condition combinations.[34] Of the 5 multimorbidity groups identified by the current study, 3 were defined by combinations of CNS and/or endocrine conditions. The remaining survivors with multimorbidity experienced combinations of more traditional pediatric chronic conditions, including a group of children who were characterized by mental health comorbidity (22.2%). The observed defining role of CNS and endocrine conditions in a majority of morbidity groups is supported by the documented effects of pediatric exposure to radiation and chemotherapy.[8] However, the specific prevalence of these subgroups, and the detection of the high-complexity, high-use CNS with endocrine group, has to our knowledge not been reported previously. Among physical manifestations of chronic illness, the CNS with endocrine group also experienced elevated rates of mental health conditions, suggesting that a multispecialty care plan is needed to manage the needs of these children.

Analyses examined the effect of morbidity group with and without adjustment for the number of conditions and found that, although adjustment for the number of conditions attenuated effect estimates, the majority of groups remained at a significantly increased risk of ED visits and hospitalizations. This suggests that the specific combination of conditions has a meaningful impact on use outcomes independent of the complexity introduced by the number of conditions. One group for which this did not hold was the CNS with endocrine group, in which all use measures became nonsignificant after adjustment for the number of conditions. Children in this group experienced an average of 9.2 conditions, compared with 3 to 4 conditions among children in other groups. This indicates that, at the extreme, the number of conditions may be the primary driver of health care use. Given the small sample size of the CNS with endocrine morbidity group in the current study, this population would benefit from additional research.

The results of the current study present an opportunity to build more robust transition plans for early survivors. The Children's Oncology Group recommends risk-based, systematic care plans for the long-term follow-up of survivors of childhood cancer.[8] The findings of the current study support the integration of a survivor's early morbidity profile into care planning immediately after the completion of therapy. This includes assessment of conditions present at the time of diagnosis and their management, in addition to conditions that develop during or immediately after treatment. This is in keeping with the American Society of Clinical Oncology's recommendations for components of high-quality survivorship plans.[35] Plans informed in this way may help to prevent potentially avoidable ED visits or hospitalizations, or to reduce expenditures in a population already experiencing financial stress.[36] The association between morbidity groups and cancer diagnosis also may allow for more proactive planning for the transition of a survivor's care from the oncology clinic to a pediatrician. This is important both for the clinicians contributing to the care team and for the parents and caregivers of early survivors. As a next step, additional research is needed to identify whether there are treatment-related factors predictive of multimorbidity group membership that are potentially modifiable and can be targeted directly for intervention.

The use of commercial claims data introduces several limitations. Individuals transition in and out of insurance plans, limiting the time each can be observed continuously. As a result, the current study lacked visibility to details of the natural history of cancer and treatment, thereby preventing the examination of the chronic condition profile using these clinical factors. The history of the onset of chronic conditions also could not be observed consistently for similar reasons, and future research is warranted to better understand the relationship between time of diagnosis and health care resource use among the early survivor population. The results of the current analysis may not be generalizable to those children who were excluded for a lack of sufficient continuous enrollment, whose chronic condition profiles may differ from those

of the observed population. Socioeconomic and health behavior variables that may confound the relationship between multimorbidity and health care use also were not available in the claims data. Restriction to a commercially insured cohort may partially control for this, although it reduces generalizability. Finally, the use of paid claims to calculate expenditures represents only the health system perspective, and does not reflect societal costs such as out-of-pocket expenditures, lost parental wages, or transportation. Many of these limitations highlight opportunities for further research in this area. In particular, replication of identified subgroups in alternative data sources and populations would strengthen the generalizability of findings across this early survivor population. The use of registry or longitudinal cohorts also may provide additional opportunities to identify variations in condition profiles among survivors of specific cancer types.

Conclusions

The growing number of childhood cancer survivors in the United States demonstrates the power of therapeutic advances to improve health outcomes. However, these same advances have resulted in a population of individuals at an increased risk of adverse health experiences later in life, including chronic illness. In addition to addressing the needs of adult survivors of pediatric cancer, it is imperative that clinical guidelines and health care systems recognize and meet the complex needs of the early survivor population. The results of the current study provide evidence that children and young adults only a few years out from active therapy experience high rates of chronic illness, including a high prevalence of multimorbidity. This multimorbidity presents in distinct groups, each of which experiences differential health care use. These findings highlight opportunities to better target early survivorship care, particularly for children experiencing combinations of CNS and endocrine conditions.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualization, writing–review and editing, and final approval of the article. Additional contributions are as follows: **Rachel L. Harrington:** Methodology, formal analysis, and writing–original draft. **Todd A. Lee:** Supervision.

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