Medication Burden Among Pediatric Cancer Survivors: Analysis of a Population-Wide Electronic Database in Hong Kong

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Abstract

Background: Few studies have evaluated the medication burden borne by survivors of pediatric cancer. This study aimed to describe the drug utilization pattern of chronic medications in a cohort of young pediatric cancer survivors. **Methods:** This was a population-based study of patients diagnosed with cancer at age 18 years or younger between 2000 and 2013 in Hong Kong and who had survived at least 5 years postdiagnosis. The primary outcome is the use of any chronic medication (medications that were prescribed for ≥30 consecutive days within a 6-month period). Multivariable log-binomial models were used to identify factors associated with chronic medication use. Kaplan-Meier analysis was used to present the cumulative proportion of survivors initiated on a chronic medication across time from cancer diagnosis. **Results:** Of the 2444 survivors (median age = 22 years, interquartile range = 16-27 years), 669 (27.4%) required at least 1 chronic medication at least 5 years postdiagnosis. Survivors who developed a chronic health condition (CHC) had a 5.48 (95% confidence interval [CI] = 4.49 to 6.71) times higher risk of taking a chronic medication than those without CHC. At 10 years postdiagnosis, the cumulative proportion of survivors being initiated a chronic medication was 33.4% (95% CI = 31.1% to 35.6%) for the overall cohort. Higher cumulative proportions were observed in survivors with endocrine (74.6%, 95% CI = 68.4% to 79.6%), renal (68.8%, 95% CI = 54.2% to 78.7%), neurological (58.6%, 95% CI = 46.1% to 68.1%), and cardiovascular (54.7%, 95% CI = 44.0% to 63.4%) disorders. **Conclusion:** Survivors with certain CHCs had a higher risk of starting a prescription medication in the early phase of survivorship. Future studies include examining the impact of medication burden on survivors' functional status.

Advances in the treatment of cancer have led to remarkable improvements in the overall survival rate of children and adolescents diagnosed with cancer (1,2). Despite the reductions in morbidity and mortality in this population, the risk of chronic and lifelong adverse effects of cancer treatment remain a legitimate concern (3-5). Such late effects include cardiopulmonary, neurological, and musculoskeletal complications and endocrine problems such as thyroid dysfunction, growth and development delays, and infertility (5). These patients also have a risk of developing neurocognitive and psychological deficits that may affect their quality of life (6,7).

The management of cancer- and treatment-related late effects may require the lifelong use of medication (8,9). One study in the United States reported that, compared with noncancer controls, survivors of pediatric leukemia, lymphoma, and central nervous system (CNS) and bone cancers have higher rates of prescription medication use within 3 years posttherapy, suggesting the potential of emerging morbidities during the early survivorship period (10). These survivors are at risk of multiple medication use resulting in an increased medication burden. Examining the pattern of medication use in cancer survivors is important to identify individuals who should be

monitored closely for adverse health outcomes that may result from the use of multiple chronic medications.

Previous studies have typically focused on evaluating the association of chronic disease burden with functional outcomes and health-care utilization in survivors of pediatric cancer (3,4,11-14). However, few epidemiological studies have evaluated the medication burden borne by these patients. Studies on this topic have been either single-center studies (15) or confined to specific cancer diagnoses (10) or drug classes (16,17) (eg, the long-term use of psychoactive medications). To address these research gaps, the primary objective of this study was to describe the pattern of chronic medication use by a cohort of young Chinese pediatric cancer survivors, using a population-based electronic medical database in Hong Kong. The secondary objective was to identify patient characteristics associated with chronic medication use.

Methods

Study Design

This was a population-based observational study of survivors of pediatric cancer within the Hospital Authority health-care system in Hong Kong. The Hospital Authority is the sole public health-care provider in Hong Kong, and it serves more than 90% of Hong Kong residents. We conducted our study using data from the Clinical Data Analysis and Reporting System (CDARS), which is a centralized clinical data repository for all 43 public hospitals, 49 specialist outpatient clinics, and more than 70 general outpatient clinics within the Hospital Authority (18). CDARS captures patients' clinical and treatment information and has previously been validated as a data source for epidemiological studies in Hong Kong (19). This study was reviewed and approved by the Joint Chinese University-New Territories East Cluster Clinical Research Ethics Committee (reference number 2018.427).

Study Population

The study population comprised patients aged 18 years or younger who were registered with an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code of 140.00 to 209.79 between January 1, 2000, and December 31, 2013. Both incident and prevalent cases of cancer were included. Patients were excluded if they were aged older than 18 years at the time of cancer diagnosis (ie, when the ICD-9 code for cancer was first registered) or with ambiguous or uncertain diagnosis.

Medication Use

The definition used for a *chronic medication* was a medication that was prescribed to a patient with an intended duration of 30 or more consecutive days within a 6-month period or a medication that was prescribed to be used as needed but with an intended cumulative duration of 180 or more days within a 12-month period (15).

The primary outcome was the use of any newly prescribed chronic medications at 5 years or more postdiagnosis, as well as chronic medications that were prescribed at the end of therapy and were continued for more than 5 years postcancerdiagnosis. Medications were excluded from this category if they 1) were not filled or dispensed by the pharmacy, 2) had no active pharmaceutical ingredients, 3) were parenterally administered and

required inpatient admission, or 4) had no valid start date. As this analysis is focused on medications with a curative intent in survivors, medications that were dispensed 6 months prior to death were also excluded. We did not exclude chronic medications that were prescribed before cancer diagnosis because it is often difficult to tease apart preexisting health conditions or symptoms from the cancer- or treatment-related conditions.

Medications were categorized according to the British National Formulary (BNF) classification (20). The BNF is a widely accepted framework for the drug management of common diseases. All drugs within the BNF are organized by the body systems and therapeutic drug classifications. For simplicity, the drugs used by survivors of this study are presented by the therapeutic drug classifications.

The secondary outcomes were medication burden (the number of chronic prescription medications) and polypharmacy (the use of ≥5 concurrent chronic medications). These were descriptive outcomes as our previous work had shown that the rate of polypharmacy among young survivors is low (5.3%) (15).

Predictive Variables

Based on a literature review (1,8,10,15-17), several predictive factors for medication burden were identified a priori, namely primary cancer diagnosis, chronic health conditions (CHCs), and history of relapse. Primary cancer diagnoses were classified based on the Surveillance, Epidemiology and End Results Program of the National Cancer Institute classification system (21). The information on CHCs was captured electronically from CDARS. A CHC was defined as a condition with chronic implications requiring long-term management (eg, gonadal dysfunction, on-treatment epilepsy, stroke, and heart failure) or a condition that was first registered at least 5 years postdiagnosis (22).

Statistical Analysis

Descriptive statistics were used to summarize the distribution of relevant outcome variables and covariates according to reasonable groupings based on previous reports on childhood cancer (11,12,14,15,23). Multivariable models were used to identify clinical factors associated with chronic medication use, after adjustment for sex, time since diagnosis, and age at diagnosis. Consistent with other studies evaluating health outcomes in childhood cancer survivors (16,24,25), the log-binomial models (generalized linear models with Poisson error and log-link function) were used to minimize biased estimates after adjusting for confounders in cohort studies (26,27). The corresponding relative risk (RR) estimates and 95% confidence intervals (CIs) were reported. Because cancer relapse and its treatment are associated with a higher burden of comorbidities (4,28,29), a sensitivity analysis was conducted to evaluate the association between the clinical factors and chronic medication use in the cohort excluding relapsed patients.

Finally, to illustrate descriptively medication utilization from early survivorship (5 to 10 years postcancer diagnosis) to long-term survivorship (≥10 years postdiagnosis), the cumulative proportion of survivors who were initiated a chronic medication across time since diagnosis was estimated using Kaplan-Meier analysis in the overall cohort and by the type of CHC. Events including death and loss to follow-up were censored. The Schoenfeld residuals were calculated for each variable to ensure that they independently satisfied the assumptions of

Table 1. Study population demographics

Demographics	No. (%)
Total No. of patients	2444
Sex	
Male	1413 (57.8)
Female	1031 (42.2)
Age at diagnosis, y	
Median (IQR)	8 (3-14)
0 to younger than 1	144 (5.9)
1 to younger than 5	666 (27.3)
5 to younger than 10	521 (21.3)
10 to younger than 15	550 (22.5)
15 or older	563 (23.0)
Age at the last follow-up date, y	
Median (IQR)	22 (16-27)
0 to younger than 12	306 (12.5)
12 to younger than 18	434 (17.8)
18 to younger than 24	659 (27.0)
24 to younger than 30	614 (25.1)
30 to younger than 38	431 (17.6)
Most common cancer diagnosis[a]	
Leukemia	923 (37.8)
Acute lymphoblastic leukemia	652 (26.7)
Acute myeloid leukemia	164 (6.7)
Chronic myeloid leukemia	56 (2.3)
Other leukemia	51 (2.1)
Lymphoma	274 (11.2)
Non-Hodgkin lymphoma	222 (9.1)
Hodgkin lymphoma	52 (2.1)
CNS tumor	182 (7.4)
Peripheral nervous system	181 (7.4)
Bone tumor	144 (5.9)
Other soft tissue sarcoma	130 (5.3)
Retinoblastoma	106 (4.3)
Thyroid cancer	80 (3.3)
Kidney tumor	67 (2.7)
Germ cell tumor	63 (2.6)
Liver tumor	60 (2.5)
Other carcinoma	44 (1.8)
Cancer relapse	
Yes	467 (19.1)
No	1977 (80.9)
Chemotherapy	
Anthracyclines	1049 (42.9)
Alkylating agents	
Mustard gas derivatives	999 (40.9)
Heavy metals	415 (17.0)
Others	127 (5.2)
Vinca alkaloids	1013 (41.4)
Antimetabolites	
Folic acid antagonists	906 (37.1)
Purine antagonists	852 (34.9)
Pyrimidine antagonists	698 (28.6)
Others	43 (1.8)
Topoisomerase inhibitors	638 (26.1)
Asparaginase	535 (21.9)
Chronic comorbidities[b]	
No	1670 (68.3)
Any	774 (31.7)
Endocrine	300 (12.3)
Behavioral	162 (6.6)
Musculoskeletal	161 (6.6)
Cardiovascular	138 (5.6)
Respiratory	129 (5.3)

(continued)

Table 1. (continued)

Demographics	No. (%)
Renal/Urinary tract	94 (3.8)
Neurological	91 (3.7)
Vision/Hearing	80 (3.3)
Liver	26 (1.1)

[a]More than one cancer diagnosis may be present in a patient. CNS = central nervous system; IQR = interquartile range.
[b]Defined as either acute complication that occurred after the date of cancer diagnosis and chronic implications requiring long-term management (eg, gonadal dysfunction, on-treatment epilepsy, stroke, heart failure) or a condition that was first registered at 5 or more years postdiagnosis.

the Cox model. A P value less than .05 was considered statistically significant, and all tests were 2-sided. All analyses were conducted using the R program.

Results

Study Population

Between January 1, 2000, and December 31, 2013, a total of 3123 patients who were aged 18 years or younger had an ICD-9 diagnosis code of 140.00 to 209.79 registered on their records (Supplementary Figure 1, available online). Among them, 81 subjects were excluded from subsequent analyses because of the ambiguous or uncertain nature of their diagnoses. After further excluding 598 subjects who passed away and thus were lost to follow-up within 5 years postdiagnosis, 2444 subjects were included in the final analyzed cohort (Table 1).

Leukemia was the most common cancer diagnosis (37.8%), followed by lymphoma (11.2%) and CNS tumors (7.4%) (Table 1). At 5 years or more postdiagnosis, at least 1 diagnosis of CHC was documented in 774 (31.7%) survivors (Table 2). The most common CHCs were endocrine (12.3%), behavioral (6.6%), and musculoskeletal complications (6.6%). Survivors with CNS tumors were most likely to develop at least 1 CHC (58.2%), followed by survivors of sarcoma and leukemia (Supplementary Figure 2, available online). An analysis of the distribution of CHCs across cancer diagnoses showed that endocrine disorders were the most common diagnoses among survivors of CNS tumors, lymphoma, and leukemia, and musculoskeletal disorders were the most prevalent in survivors of sarcoma (Supplementary Figure 3, available online).

One-fifth of the cohort developed a relapse (19.1%; Supplementary Table 1, available online). Among survivors who relapsed, cancer recurrence occurred within 10 years from primary cancer diagnosis (77.5%). More than half of the relapsed survivors had developed a CHC (47.3%) during the time of evaluation.

Use of Chronic Medications

A subgroup of 669 survivors (27.4%) required at least 1 chronic medication (Table 2). The most commonly prescribed class of chronic medication was thyroid replacement therapy (22.7%), followed by antihistamines (17.6%) and sex hormones (15.4%). A minority (3.8%) of patients were prescribed at least 5 chronic medications (ie, polypharmacy) during the study period (Supplementary Table 2, available online).

Table 2. Chronic medication utilization at 5 or more years postdiagnosis

Characteristics	No. (%)
Total No. of patients	2444
Use of chronic medication(s) postcancer treatment[a]	
No	1775 (72.6)
Any	669 (27.4)
1 to 4 medications	575 (23.5)
≥5 medications	94 (3.8)
Subgroup with prescribed chronic medication	669
Classification of chronic medications post-cancer treatment[b]	
Thyroids and antithyroids	152 (22.7)
Antihistamines, allergy control	118 (17.6)
Sex hormones	103 (15.4)
Miscellaneous ophthalmic preparations	81 (12.1)
Drugs acting on the nose	79 (11.8)
Vitamins	65 (9.7)
Corticosteroids (endocrine)	64 (9.6)
Topical corticosteroids	63 (9.4)
Minerals	63 (9.4)
Bronchodilators	60 (9.0)
Hypothalamic and pituitary hormones and anti-estrogens	54 (8.1)
Anti-inflammatory eye preparations	51 (7.6)
Antisecretory drugs and mucosal protectant for the gastrointestinal system	47 (7.0)
Cytotoxic drugs	38 (5.7)
Drugs used in anemia and other blood disorders	37 (5.5)
Inhaled corticosteroids	36 (5.4)
Immunomodulation	30 (4.5)
Antidepressants	29 (4.3)
Drugs for hypertension and heart failure	28 (4.2)
Antipsychotics and related drugs	28 (4.2)
Laxatives	25 (3.7)
Drugs for acne rosacea	25 (3.7)
Fluids and electrolytes	25 (3.7)
Analgesics	24 (3.6)
Contraceptives	22 (3.3)
Antidiabetics	21 (3.1)
Lipid-regulating drugs	19 (2.8)
Drugs used in rheumatic diseases and gout	18 (2.7)
Drugs used in dyspepsia and gastro-oesophageal reflux disease	17 (2.5)
Beta-adrenoceptor blocking drugs	17 (2.5)
Cromoglycate, leukotriene, and phosphodesterase type-4 inhibitors	17 (2.5)
Nitrates, calcium-channel blockers, and other antianginal drugs	16 (2.4)
Mucolytics	16 (2.4)

[a]Any newly prescribed chronic medications at ≥5 years postdiagnosis as well as chronic medications that were prescribed at end of therapy and were continued beyond ≥5 years postdiagnosis.
[b]Includes the therapeutic classes prescribed to more than 2% of the cohort prescribed with chronic medications.

The most commonly prescribed medications in survivors with endocrine disorders were thyroid hormone (28.0%), sex hormone (27.7%), and hypothalamic-pituitary hormone (16.7%) replacement therapies (Figure 1). A subgroup of survivors with behavioral disorders received antipsychotics (14.2%) and antidepressants (13.0%), and survivors with respiratory disorders were most commonly treated with antihistamines and medications for allergy control (23.3%) and bronchodilators (24.8%).

Factors Associated With Chronic Medication Use

Compared with survivors of leukemia, survivors of CNS tumors were more likely to be prescribed a chronic medication (RR = 2.58, 95% CI = 1.83 to 3.64; Table 3). Among survivors of CNS tumors, the most commonly prescribed chronic medications included thyroid hormone (25.3%), hypothalamic-pituitary hormone (18.1%), and sex hormone (16.5%) (Supplementary Figure 4, available online). Survivors who developed a CHC had a 5 times higher risk of taking a chronic medication than those who did not have a CHC (RR = 5.48, 95% CI = 4.49 to 6.71). In particular, higher risks were observed in survivors with endocrine (RR = 4.95, 95% CI = 3.71 to 6.63), musculoskeletal (RR = 4.01, 95% CI = 2.74 to 5.88), and respiratory (RR = 3.92, 95% CI = 2.57 to 6.00) disorders.

Survivors who had developed a relapse demonstrated a higher risk of being prescribed a chronic medication than survivors who did not (RR = 2.97, 95% CI = 2.38 to 3.71). The sensitivity analysis showed that the predictors of chronic medication use among survivors without any history of relapse (Supplementary Table 3, available online) were similar to the primary analysis on the overall cohort.

At 10 years postdiagnosis (ie, when survivors transit into long-term survivorship), the proportion of survivors with a chronic medication was 33.4% (95% CI = 31.1% to 35.6%) for the overall analyzed cohort. Figure 2 summarizes the cumulative proportion of survivors who were initiated a chronic medication, stratified by the type of CHC. For those survivors without a CHC, the proportion was small (20.4%, 95% CI = 18.0% to 22.7%). Higher cumulative proportions were observed in those with endocrine (74.6%, 95% CI = 68.4% to 79.6%), renal (68.8%, 95% CI = 54.2% to 78.7%), vision and hearing (63.2%, 95% CI = 48.5% to 73.6%), neurological (58.6%, 95% CI = 46.1% to 68.1%), respiratory (56.2%, 95% CI = 45.9% to 64.6%), behavioral (55.6%, 95% CI = 46.3% to 63.3%), and cardiovascular (54.7%, 95% CI = 44.0% to 63.4%) disorders.

Discussion

Using real-world data from electronic health records, we sought to characterize the medication burden in a population of pediatric cancer survivors who were treated in the health-care system of Hong Kong after 2000. A subgroup (27.4%) of survivors were taking at least 1 chronic prescription medication. Overall, only a minority (3.8%) of survivors had polypharmacy. Survivors with endocrine, musculoskeletal, respiratory, and behavioral complications had the highest risk of starting a prescription medication early in the cancer survivorship continuum. This is one of the first studies to report the treatment burden of late effects borne by survivors of pediatric cancer.

Our results concur with findings from the literature showing that even contemporary treatment protocols carry a risk of late effects and may have implications on the medication burden during the early survivorship period (3). Survivors who developed at least 1 CHC were 5.48 times more likely to take a chronic medication than those who did not. The use of multiple medications in young survivors may have clinical implications, as physiological processes and neurodevelopment may be sensitive to the effects of pharmacological interventions during adolescence and young adulthood (30). For example, a previous

Group of CHC

Class of chronic medication	Endocrine	Behavioral	Respiratory	Musculoskeletal	Cardiovascular	Renal	Neurological	Vision/Hearing	Liver
Thyroid and antithyroid	28.0	9.9	8.5	8.7	12.3	13.8	16.5	20.0	23.1
Antihistamines and allergy control	8.0	11.1	23.3	11.8	9.4	10.6	8.8	18.8	
Sex hormone	27.7	11.1	7.0	8.1	15.9	13.8	15.4	13.8	19.2
Emollient and barrier preparation	5.7	7.4	13.2	11.2	9.4	9.6	7.7	10.0	3.8
Miscellaneous eye preparation	10.0	10.5	10.1	8.7	13.0	10.6	13.2	13.8	7.7
Nose preparation	4.3	6.8	17.8	6.2	5.8	4.3	4.4	11.2	7.7
Vitamin	7.3	8.0	7.0	6.8	5.8	20.2	9.9	6.2	3.8
Corticosteroid	13.0	6.8	10.1	6.8	11.6	13.8	11.0	12.5	19.2
Topical corticosteroid	4.7	4.9	9.3	6.2	8.0	6.4	6.6	6.2	7.7
Mineral	6.0	4.3	4.7	5.6	5.8	21.3	6.6	7.5	11.5
Bronchodilator	3.3	7.4	24.8	6.8	4.3	2.1	3.3	10.0	
Hypothalamic and pituitary hormone and anti-oestrogen	16.7	6.8	3.1	6.8	6.5	7.4	9.9	13.8	11.5
Anti-inflammatory	2.3	4.3	7.0	4.3	4.3	4.3	6.6	6.2	
Antisecretory and mucosal protectant	5.7	7.4	10.1	8.7	8.0	8.5	6.6	6.2	3.8
Cytotoxic	3.0	3.1	3.1	3.1	2.9	1.1	2.2	2.5	
Drug for anemia and other blood disorders	3.7	6.2	4.7	5.0	3.6	9.6	8.8	2.5	11.5
Inhaled corticosteroid	3.0	4.9	13.2	2.5	5.1	4.3	2.2	10.0	
Immunomodulator	2.7	3.1	4.7	2.5	5.8	7.4	3.3	5.0	7.7
Antidepressant	3.3	13.0	4.7	7.5	1.4	2.1	3.3	3.8	
Hypertension and heart failure	4.7	3.7	5.4	3.1	11.6	11.7	4.4	6.2	15.4
Antipsychotic	2.3	14.2	3.1	3.1	2.2	1.1	4.4	6.2	
Laxative	2.0	3.7	0.8	4.3	0.7	5.3	7.7	3.8	
Drug for acne rosacea	1.3	1.2	2.3	3.1	2.2	3.2	1.1	3.8	
Fluid and electrolyte	1.7	3.7	3.9	3.1	2.9	11.7	2.2	3.8	7.7
Analgesic	2.3	3.7	2.3	6.8	4.3	5.3	8.8	2.5	
Contraceptive	3.7	1.2	0.8	2.5	2.2	3.2		2.5	3.8
Antidiabetic	6.7	0.6	0.8	3.1	2.9	3.2	3.3	3.8	15.4

Figure 1. Chronic medication burden by drug therapeutic classes against different groups of CHC. Each number represents the proportion in percentage of the subgroup with the indicated group of CHC in the header. **Black cell** signifies zero subjects. CHC = chronic health conditions.

Table 3. Factors associated with chronic medication use

Predictive factors	Estimated RR (95% CI)	P[a]
Chronic conditions[b]		
Any chronic comorbidities	5.48 (4.49 to 6.71)	<.001
Types of chronic conditions[b]		
Liver[c]	0.803 (0.312 to 2.06)	.65
Respiratory	3.92 (2.57 to 6.00)	<.001
Renal[c]	1.30 (0.793 to 2.13)	.29
Endocrine	4.95 (3.71 to 6.63)	<.001
Vision/Hearing[c]	1.83 (1.05 to 3.20)	.03
Cardiovascular	1.31 (0.851 to 2.02)	.21
Neurological[c]	2.30 (1.34 to 3.94)	.003
Behavioral	3.50 (2.37 to 5.18)	<.001
Musculoskeletal	4.01 (2.74 to 5.88)	<.001
Groups of primary cancer diagnoses[b,d]		
Central nervous system	2.58 (1.83 to 3.65)	<.001
Germ cell tumor	0.759 (0.381 to 1.42)	.41
Hodgkin lymphoma	0.497 (0.218 to 1.03)	.08
Liver tumor	0.796 (0.379 to 1.54)	.52
Non-Hodgkin lymphoma	0.551 (0.371 to 0.802)	.002
Sarcoma	0.744 (0.531 to 1.03)	.08
Non-CNS solid tumor	0.957 (0.727 to 1.26)	.75
Cancer relapse[b]		
Any cancer relapse	2.97 (2.38 to 3.71)	<.001

[a]Log-binomial models (generalized linear models with Poisson error and log-link function) were used to calculate the P values. All tests were 2-sided. CI = confidence interval; CNS = central nervous system; RR = relative risk.
[b]Models are adjusted for sex, time since diagnosis, and age at diagnosis.
[c]Interpreted with caution because of the small sample (n < 100).
[d]Reference group is leukemia.

study showed that the use of psychoactive medications during adolescence is associated with neurocognitive impairment and poorer social attainment later in life (16). Other studies have also reported worse functional outcomes in childhood cancer survivors with endocrine complications, although the comparative contribution of hormonal and metabolic abnormalities vs medications on adverse outcomes is often hard to distinguish (13,14,31). Admittedly, the lifelong use of chronic medications is likely warranted in certain conditions, such as hormonal replacement therapy in cancer survivors with hypothalamic or gonadal dysfunction. However, the screening and early identification of modifiable risk factors for certain late effects (eg, cardiovascular diseases, diabetes, and behavioral disorders) may facilitate timely lifestyle interventions before the condition becomes chronic and requires pharmacological interventions.

A higher medication burden was observed in survivors of CNS tumors and leukemia compared with survivors of other cancers. A similar observation was found in survivors who had a relapse. This finding is consistent with previous findings that these groups of survivors demonstrate the highest cumulative burden of CHCs (4,12,15,22,32); hence, they require the use of multiple medications. It is also important to note that concurrent medication use may confound the study of cancer-related symptoms in these survivors. For example, anticonvulsants and hormonal replacement therapy may exacerbate neurological and behavioral symptoms in CNS tumor survivors (32,33). Our results reinforce the need for closer monitoring of adverse health outcomes from multiple medications in these high-risk groups. Future studies should also evaluate the well-documented burden associated with multiple medications in patients with chronic diseases, such as nonadherence to
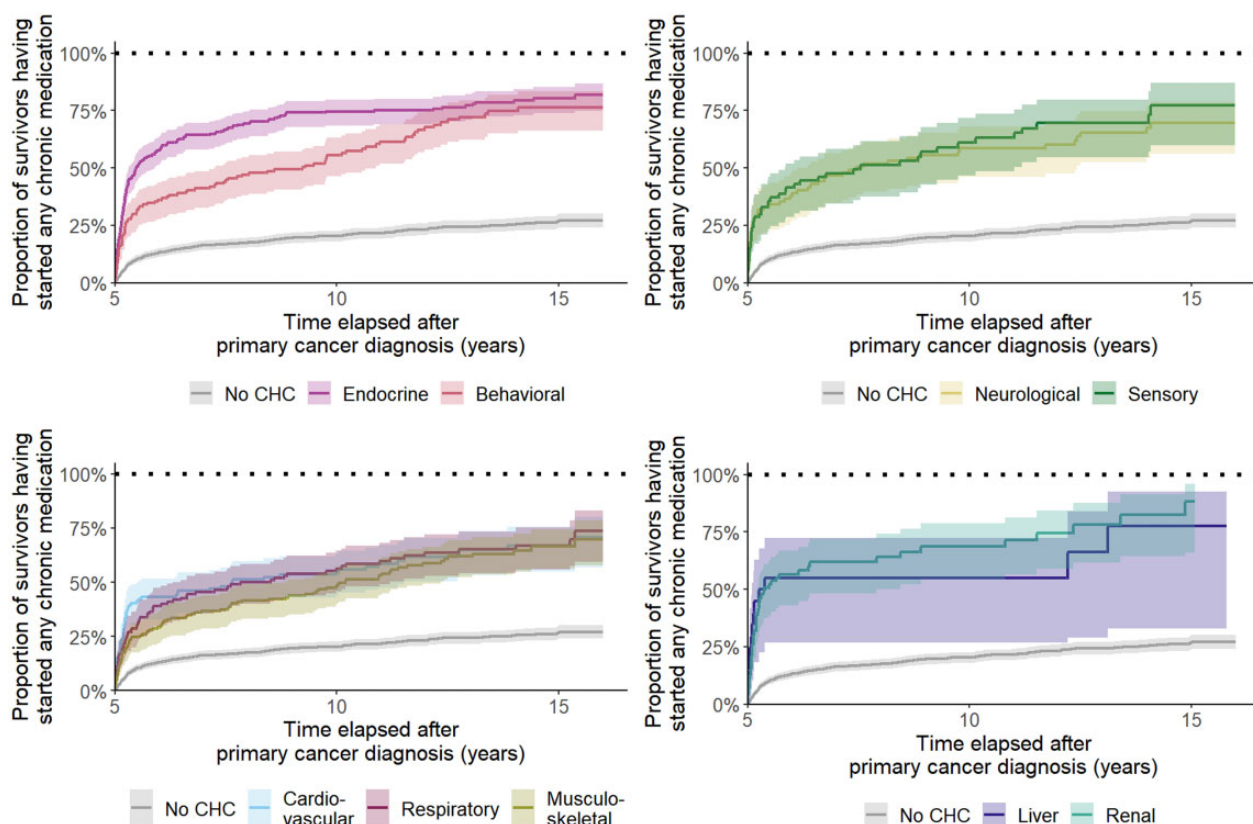
Figure 2. Cumulative proportion of survivors being initiated a chronic medication since cancer diagnosis. Kaplan-Meier plots for the initiation of chronic medication across time from cancer diagnosis (stratified by the type of CHC). CHC = chronic health conditions.

medication therapy (34,35) and inappropriate drug prescribing and drug interactions (36,37), as well as increased health-care utilization costs (9,38).

The steep slope observed on the Kaplein-Meier curves within 5 years postdiagnosis seemed to suggest that survivors tended to be prescribed a chronic medication during the early posttherapy period rather than at a later phase of the survivorship period (ie, ≥10 years postdiagnosis). This is contrary to well-established evidence that the incidence of chronic morbidities increases as survivors age (22). Our findings may reflect the initiation of medications to treat chronic conditions that occur early in the posttreatment period (eg, hormonal replacement therapy for secondary endocrinopathy). A longer follow-up time on our cohort is required to assess medication utilization in survivors as they age and as late-occurring chronic conditions emerge. Respiratory chronic conditions were recorded in 5% of our survivors, hence, the use of prescribed systemic antihistamines may be for the symptomatic relief of respiratory conditions, or it may reflect the high prevalence of allergies in the local pediatric population due to environmental factors (39). As we do not expect the prevalence of allergic conditions to differ between cancer survivors and the general population (40), these conditions might be present even prior to the cancer diagnosis and may not be related to the cancer or its treatment. Future studies should include prospectively capturing the specific indications of chronic medications and the verification with consultation notes to characterize medication use patterns in individuals with preexisting conditions.

According to a landmark study, impaired pulmonary, cardiac, endocrine, and nervous system functions were most prevalent (detected in ≥20% of participants at risk) (22). Our results showed that patients with endocrine, respiratory, and neurological conditions were at the highest risk of being prescribed a chronic medication. However, cardiovascular conditions were not associated with chronic medication use in our multivariable analysis. Our cohort is still relatively young. The estimated prevalence of clinically significant cardiovascular conditions in survivors aged 40 years and younger was around 5% (22,41). Therefore, the non-statistically significant finding should be interpreted in light of the low proportion of survivors with documented cardiovascular conditions (5.6%) and with consideration that 54% of these survivors were on a chronic medication by the time they were 10 years postdiagnosis. On the contrary, even though the prevalence of renal late effects (5%) was substantially less common (22), our study found that the medication burden in this minority is high; 68% of patients with a renal condition were initiated a chronic medication at long-term survivorship. The medication burden for this group is likely to be higher when their renal health declines as they age. Future studies with a longer follow-up should investigate the evolving profile of morbidities and medication burden in high-risk groups of survivors.

The major strength of this study is the use of a large sample size of pediatric patients diagnosed with cancer in the public health-care network of Hong Kong. However, the findings of this study should be considered in the context of several limitations. First, this study did not include an age-matched healthy comparison control group. However, the prevalence of CHCs identified here (13.0%) is higher than the rates reported by the latest Hong Kong Census and Statistics Department (3.5% to

5.1% for individuals aged 15 to 39 years) (42). Given the high prevalence of CHCs reported in childhood cancer survivors (4,7,22), it is reasonable to speculate that the medication burden may be considerably higher in cancer survivors than in the age-matched general population. Notably, our reported prevalence of CHCs was substantially lower than previously published estimates, as most previous studies have performed systematic screening of late effects (4,22) or captured self-reported late effects (11,23). The confounding effects of the different chemotherapy drugs cannot be accounted for. This is because although CDARS has a high reported level of completeness for demographic and prescription data (19), there may be a certain degree of inaccuracy in cancer treatment data because of the use of paper forms for chemotherapy orders in the pediatric wards of some hospitals in the early 2000s. Therefore, some chemotherapy drugs may not have been captured electronically. Moreover, CDARS does not include dosimetry data; hence, we were unable to evaluate the effects of radiation on late effects and chronic medication use.

This is the first study harnessing population-based electronic health data to examine drug use patterns in a cohort of relatively young Chinese survivors of childhood cancer. Although polypharmacy was observed in a minority of the survivors in this study, chronic medication use was a common occurrence and has the potential to contribute to the future medical burden, particularly in survivors with endocrine, behavioral, and musculoskeletal late effects, as well as individuals who survived a relapse. These high-risk groups should be monitored closely for drug-drug interactions and adverse events during follow-up care, as well as nonadherence to drug therapy and increased cost associated with health-care services utilization. Future studies should also include examining the impact of multiple chronic medication use on the health status of survivors as they age.

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Notes

Data Availability

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