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Risk of COVID-19 Infections and of Severe Complications Among Survivors of Childhood, Adolescent, and Young Adult Cancer: A Population-Based Study in Ontario, Canada

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abstract

PURPOSE Survivors of childhood, adolescent, and young adult cancer are at risk of late effects, including pulmonary and infectious complications. Whether survivors are at increased risk of COVID-19 infection and severe complications is unknown.

METHODS Population-based registries in Ontario, Canada, identified all 5-year survivors of childhood cancer diagnosed age 0-17 years between 1985 and 2014, and of six common adolescent and young adult cancers diagnosed age 15-21 years between 1992 and 2012. Each survivor alive on January 1, 2020, was randomly matched by birth year, sex, and residence to 10 cancer-free population controls. Individuals were linked to population-based laboratory and health care databases to identify COVID-19 tests, vaccinations, infections, and severe outcomes (emergency department [ED] visits, hospitalizations, intensive care unit admissions, and death within 60 days). Demographic, disease, and treatment-related variables were examined as possible predictors of outcomes.

RESULTS Twelve thousand four hundred ten survivors were matched to 124,100 controls. Survivors were not at increased risk of receiving a positive COVID-19 test (386 [3.1%] *v* 3,946 [3.2%]; $P = .68$) and were more likely to be fully vaccinated (hazard ratio, 1.23; 95 CI, 1.20 to 1.37). No increase in risk among survivors was seen in emergency department visits (adjusted odds ratio, 1.2; 95 CI, 0.9 to 1.6; $P = .19$) or hospitalization (adjusted odds ratio, 1.8; 95 CI, 1.0 to 3.5; $P = .07$). No survivor experienced intensive care unit admission or died after COVID-19 infection. Pulmonary radiation or chemotherapies associated with pulmonary toxicity were not associated with increased risk.

CONCLUSION Cancer survivors were not at increased risk of COVID-19 infections or severe sequelae. These results can inform risk-counseling of survivors and their caregivers. Further study is warranted to determine risk in older survivors, specific subsets of survivors, and that associated with novel COVID-19 variants.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 11, 2022 and published at ascopubs.org/journal/jco on February 28, 2022: DOI https://doi.org/10.1200/JCO.21.02592

INTRODUCTION

Survivors of childhood, adolescent, and young adult (CAYA) cancer are at significant risk of chronic morbidities because of their original cancer or cancer treatment. By age 50 years, survivors experience an average of 4.7 severe, disabling, or life-threatening conditions.[1,2] Recently, CAYA cancer survivors have been noted to be at increased risk of infection-related death from all infection types.[3]

During the COVID-19 pandemic, survivors, caregivers, and providers have been concerned that survivors may be at greater risk of developing COVID-19 infections or complications.[4-6] To date, data on the risks faced by survivors during the pandemic are extremely limited. International groups have therefore only stated that survivors may be at higher risk if they have specific comorbidities such as congestive heart failure, diabetes, or lung disease, on the basis of data from the general population and not data specific to survivors.[4] Significant anxiety persists among survivors, given this uncertainty.[5,6]

We therefore leveraged population-based clinical, health care, and COVID-19–related databases in Ontario, Canada, to determine the risk of COVID-19 infection and complications among survivors of CAYA cancer.

CONTEXT

Key Objective

Are survivors of childhood, adolescent, and young adult cancer at increased risk of COVID-19 infections or severe sequelae thereof?

Knowledge Generated

We found that compared with the general population, survivors were at no increased risk of either COVID-19 infections or of requiring emergency department visits or hospitalizations after COVID-19 infection. In this population-based cohort, no survivor experienced an intensive care unit admission or death following a COVID-19 infection.

Relevance

These findings may help inform risk-counseling of survivors and their families during the COVID-19 pandemic.

METHODS

Study Setting

We used a matched retrospective cohort design based in Ontario, Canada's most populous province. Canadian health care is delivered by provincial governments through single-payer governmental universal health insurance programs that cover all medically necessary physician and hospital services. Ontario reported its first case of SARS-CoV-2 on January 25, 2020. SARS-CoV-2 testing was available at hospitals and specialized testing centers at no cost, although testing criteria were initially restricted to certain populations (eg, working or living in high-risk settings, and hospitalized patients) because of limited availability but then broadened over time. Four SARS-CoV-2 vaccines have been approved in Canada: BNT162b2 and mRNA-1273 in December 2020, ChAdOx1-S in February 2021, and Ad26.COV2.S in March 2021. The lower age eligibility for BNT162b2 was ultimately decreased in May 2021 to those turning age 12 years or older in 2021. Eligibility was initially restricted to high-risk individuals and then broadened over time. Although a previous history of cancer was not a high-risk criteria, survivors with specific comorbidities may have been considered high risk.

Study Population and Data Sources

Survivors of CAYA cancers were identified through two population-based data sources: the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) and the Initiative to Maximize Progress in AYA Cancer Treatment (IMPACT) Cohort. Both have been described previously.[7,8] In brief, POGONIS collects detailed demographic, disease, treatment, and outcome-related data on all patients diagnosed between ages 0 and 18 years and treated at one of Ontario's five childhood cancer centers since April 1, 1985, through trained data managers embedded at each site. IMPACT includes all Ontario AYA diagnosed with one of six main cancers (acute leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, bone sarcoma, and testicular cancer) at age 15-21 years between 1992 and 2012. IMPACT data are similar to POGONIS data, but were collected retrospectively by trained chart abstractors and validated through real-time review by clinicians.

All POGONIS and IMPACT patients who survived at least 5 years from their first cancer diagnosis and who remained alive and eligible for Ontario health insurance on January 1, 2020, just before Ontario's first documented case of COVID-19, were included in the study cohort. January 1, 2020, was considered the index date for all individuals. For each survivor, potential controls from the general population were identified using the Registered Persons Database, matched by birth month (±1 year), sex, and Forward Sortation Area (first three digits of postal code) on the index date. All controls had to be alive and eligible for Ontario health insurance on the index date, and not had a previous cancer diagnosis. From all possible controls, 10 were randomly selected without replacement for each survivor to form the control cohort.

Survivors and controls were linked to population-based health services data sets using unique encoded identifiers and analyzed at ICES (formerly, the Institute for Clinical Evaluative Sciences). This allowed for identification of hospitalizations, emergency department (ED) visits, and all physician encounters. Details of the databases used in this study are shown in Appendix Table A1 (online only).

Outcomes

We examined three main categories of outcomes related to testing, vaccination, and severity of infection. *Testing-related outcomes* were obtained from the Ontario Laboratories Information System (OLIS), and included the receipt of a reverse transcription polymerase chain reaction SARS-CoV-2 test and the receipt of a positive test, defined as either positive or indeterminate for SARS-CoV-2.[9] OLIS has been shown to capture approximately 92% of all positive cases in Ontario[9]; reasons for missing cases include cases diagnosed early in the pandemic, when tests were performed at the National Microbiology Laboratory, or requisitions submitted with medical record numbers instead of health card numbers. The availability of home molecular

COVID-19 tests was severely limited in Ontario during the pandemic. Availability of rapid antigen tests was also restricted, although they were provided to some businesses and institutions for screening purposes. Persons with positive antigen results were instructed to then obtain a confirmatory polymerase chain reaction (PCR)–based test. Cases presenting to hospitals would very likely have been retested and thus captured. *Vaccination-related outcomes* were obtained from COVaxON, a comprehensive and centralized COVID-19 vaccine information system, and included both partial and full vaccination.[9] Partial vaccination was defined as 14 days after receiving one dose of any of four vaccines currently approved in Canada (BNT162b2, mRNA-1273, ChAdOx1-S, and Ad26.COV2.S). Full vaccination was defined as 14 days after receiving one dose of the Ad26.COV2.S vaccine or two of any of the other vaccines, including two doses of different vaccines. *Severe outcomes related to COVID-19 infections* were examined among those members of the cohort who tested positive, and included any ED visit, any hospitalization, any intensive care unit (ICU) admission, or death observed from 3 days before the first positive test to 60 days after, in keeping with WHO guidelines for reporting.[10] The above databases have been used by multiple authors to study vaccine effectiveness and patterns of infection, as well as by the Ministry of Health to guide policy.[9,11,12]

Covariates

Several patient, disease, treatment, and comorbidity-related factors were examined as possible predictors of our outcomes. Patient-related variables included age, sex, and neighborhood income quintile as determined by postal code on January 1, 2020, and Canadian census data (rural *v* urban quintile 1 through 5, with five representing the wealthiest neighborhoods). The presence of various comorbidities was determined through previously validated algorithms using health administrative data, including diabetes, hypertension, asthma, chronic obstructive pulmonary disease, congestive heart failure (CHF), cardiovascular disease (CVD), or any of the above comorbidities.[13-17] Appendix Table A2 (online only) shows details of these algorithms. The lookback period for all comorbidities was 5 years after the original cancer diagnosis (or dummy diagnosis for controls) to January 1, 2020. Hospitalization (yes *v* no) in the 2 years before January 1, 2020, was used as a general marker of comorbidity. Vaccination status at the time of the positive test (none *v* partial *v* full) was considered a covariate when examining infection severity outcomes.

Among survivors, disease- and treatment-related variables were also examined and included cancer type (hematologic *v* solid tumor *v* CNS tumor), previous stem-cell transplant (allogeneic *v* autologous *v* none), previous pulmonary radiation of any kind, previous exposure to chemotherapies with potential pulmonary late effects (bleomycin, busulfan, carmustine, and lomustine), cardiac radiation, and cumulative dose of anthracycline (none *v* < 100 mg/m^2 *v* 100 to < 250 mg/m^2 *v* ≥ 250 mg/m^2).[18]

Analysis

Characteristics of survivors and controls were compared using chi-square or *t*-tests, as appropriate. Our primary analyses compared testing, vaccination, and infection severity outcomes between survivors and controls. Survivors and controls were compared in terms of the crude proportion receiving (1) at least one test during the observation period (January 1, 2020-May 31, 2021) and (2) at least one positive test during the observation period. For the latter outcome, survivors who were test-negative or who were never tested were combined to reduce the likelihood of collider bias.[12] Using the index date of December 15, 2020, we examined time to partial or full vaccination using Cox proportional hazards regression models, restricted to individuals age ≥ 11 years and with the maximum follow-up of July 31, 2021. Generalized estimated equations accounted for the matched nature of the data.

All survivors and controls with at least one positive test were retained for analyses comparing severity outcomes, and were compared on their baseline characteristics. For infection severity outcomes, the date of the first positive test was considered the index date. Logistic regression was used to compare outcomes between infected survivors and infected controls, adjusting for age, sex, rurality, and neighborhood income quintile. Generalized estimated equations accounted for the matched nature of the data.

Among the survivor cohort only, predictors of outcomes were examined by using the same regression models described above. Variables significant in univariate analyses at the $P < .1$ level were included in multivariable analyses, although age and sex were a priori retained regardless of statistical significance. Statistical significance was defined as $P < .05$. Research Ethics Board approval was obtained from Sunnybrook Health Sciences Center; the need for informed consent was waived. Statistical analyses were performed using SAS software program for Unix, version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 12,721 survivors of CAYA cancer met eligibility criteria and were included in survivor only analyses. Of these, 311 (2.4%) could not be successfully matched to 10 controls; the remaining 12,410 (97.6%) survivors were successfully matched to 124,100 controls in a balanced 10:1 ratio and were included in survivors versus controls analyses. Characteristics of survivors and controls are shown in Table 1. The median age of survivors on January 1, 2020, was 24 years (interquartile range [IQR] 16-32 years, maximum age 51 years). The median time from the original cancer diagnosis to January 1, 2020, was 14.3 years (IQR 7.7-22.4 years; maximum 34.7 years). Survivors were more likely to have been previously diagnosed with

TABLE 1. Characteristics of the Overall Survivor and Cohort Cohorts

Variable	Survivors (n = 12,410)	Controls (n = 124,100)	P
Age, years, median (IQR)	24 (16-32)	24 (16-32)	.91
Sex, No. (%)			
Male	6,931 (55.9)	69,310 (55.9)	1.0
Female	5,479 (44.1)	54,790 (44.1)	
Rurality/neighborhood income quintile, No. (%)			< .001
Rural	1,259 (10.1)	12,424 (10.0)	
Urban Q1 (lowest)	1,911 (15.4)	20,587 (16.6)	
Urban Q2	2,079 (16.8)	21,290 (17.2)	
Urban Q3	2,225 (17.9)	22,341 (18.0)	
Urban Q4	2,422 (19.5)	24,115 (19.4)	
Urban Q5 (highest)	2,471 (19.9)	23,306 (18.8)	
Asthma, No. (%)			
No	11,950 (96.3)	119,927 (96.6)	.04
Yes	460 (3.7)	4,173 (3.4)	
COPD, No. (%)			
No	12,357 (99.6)	123,657 (99.6)	.22
Yes	53 (0.4)	443 (0.4)	
Hypertension, No. (%)			
No	11,942 (96.2)	121,500 (97.9)	< .001
Yes	468 (3.8)	2,600 (2.1)	
Diabetes, No. (%)			
No	12,090 (97.4)	122,519 (98.7)	< .001
Yes	320 (2.6)	1,581 (1.3)	
CHF, No. (%)			< .001
No	12,255 (98.8)	123,952 (99.9)	
Yes	155 (1.2)	148 (0.1)	
CVD, No. (%)			< .001
No	12,304 (99.1)	123,935 (99.9)	
Yes	106 (0.9)	165 (0.1)	
Any comorbidity, No. (%)			< .001
No	11,160 (89.9)	115,982 (93.5)	
Yes	1,250 (10.1)	8,118 (6.5)	
Hospitalized in previous 2 years, No. (%)			< .001
No	9,282 (74.8)	111,861 (90.1)	
Yes	3,128 (25.2)	12,239 (9.9)	
Cancer type, No. (%)			
Hematologic	5,814 (46.8)	—	
Solid tumor	2,400 (19.3)	—	
CNS tumor	2,400 (19.3)	—	
SCT, No. (%)			
None	11,573 (93.3)	—	
Autologous	413 (3.3)	—	
Allogeneic	424 (3.4)	—	
Pulmonary radiation, No. (%)			
No	11,261 (90.7)	—	
Yes	1,149 (9.3)	—	
Bleomycin exposure, No. (%)			
No	10,916 (88.0)	—	
Yes	1,494 (12.0)	—	
Busulfan exposure, No. (%)			
No	12,206 (98.4)	—	
Yes	204 (1.6)	—	
Carmustine exposure, No. (%)			
No	12,324 (99.3)	—	
Yes	86 (0.7)	—	
Lomustine exposure, No. (%)			
No	12,255 (98.8)	—	
Yes	155 (1.2)	—	
Cardiac radiation, No. (%)			
No	10,796 (87.0)	—	
Yes	1,614 (13.0)	—	
Anthracycline exposure, No. (%)			
None	6,830 (55.0)	—	
< 100 mg/m^2	1,195 (9.6)	—	
100 to < 250 mg/m^2	2,712 (21.9)	—	
≥ 250 mg/m^2	1,673 (13.5)	—	

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IQR, interquartile range; Q, quintile; SCT, stem-cell transplant.

asthma, hypertension, diabetes, and CHF (Table 1). Three thousand one hundred twenty-eight (25.2%) of survivors had been hospitalized at least once in the 2 years before the index date compared with 12,239 (9.9%) of controls ($P <$ .001). Of the survivors, 1,057 (8.5%) had experienced a relapse before the index date, whereas 197 (1.6%) had experienced a second malignant neoplasm.

Survivors were more likely than controls to have received a SARS-CoV-2 PCR test during the observation period (5,168/12,410 [41.6%] *v* 43,956/124,100 [35.4%]; $P <$ .001). Survivors also had a higher number of tests than controls (median and IQR 1 [1-3] *v* 1 [1-2]; $P <$ .001). However, survivors were no more likely to have a positive test result during the study period (386 [3.1%] *v* 3,946 [3.2%]; $P =$ .68). Survivors who received positive tests were younger than controls with positive tests (median and IQR 22 years [16-29] *v* 24 years [17-31]; $P <$ .001), but did not

TABLE 2. Variables Associated With the Receipt of a Positive SARS-CoV-2 Polymerase Chain Reaction Test Among Survivors (N = 12,721)

	Univariate		Multivariable	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	**0.99 (0.98 to 1.0)**	**.03**	**0.99 (0.98 to 1.0)**	**.03**
Sex				
Male	Ref	Ref	—	—
Female	1.1 (0.9 to 1.3)	.53	—	—
Rurality/ neighborhood income quintile				
Rural	0.7 (0.4 to 1.1)	.13	0.7 (0.4 to 1.1)	.14
Urban Q1	1.4 (1.0 to 1.9)	.07	1.4 (1.0 to 2.0)	.07
Urban Q2	1.4 (1.0 to 1.9)	.06	**1.4 (1.0 to 2.0)**	**.049**
Urban Q3	**1.6 (1.2 to 2.2)**	**.005**	**1.6 (1.2 to 2.2)**	**.005**
Urban Q4	1.2 (0.8 to 1.6)	.37	1.2 (0.8 to 1.6)	.36
Urban Q5	Ref	Ref	Ref	Ref
Asthma				
No	Ref	Ref	—	—
Yes	0.8 (0.5 to 1.5)	.51	—	—
COPD				
No	Ref	Ref	—	—
Yes	0.6 (0.1 to 4.3)	.61	—	—
Hypertension				
No	Ref	Ref	—	—
Yes	0.8 (0.5 to 1.4)	.47	—	—
Diabetes				
No	Ref	Ref	Ref	Ref
Yes	1.7 (1.0 to 2.8)	.06	**1.8 (1.1 to 3.1)**	**.03**
CHF				
No	Ref	Ref	—	—
Yes	0.8 (0.3 to 2.2)	.69	—	—
CVD				
No	Ref	Ref	—	—
Yes	0.6 (0.1 to 2.4)	.47	—	—
Any comorbidity				
No	Ref	Ref	—	—
Yes	1.1 (0.8 to 1.5)	.76	—	—
Hospitalized in previous 2 years				
No	Ref	Ref	Ref	Ref
Yes	**1.3 (1.0 to 1.6)**	**.046**	1.2 (1.0 to 1.5)	.12
Cancer type				
Hematologic	Ref	Ref	—	—
Solid tumor	0.9 (0.7 to 1.2)	.48	—	—
CNS system tumor	1.1 (0.9 to 1.5)	.39	—	—
SCT				
None	Ref	Ref	—	—
Autologous	1.1 (0.6 to 1.8)	.82	—	—
Allogeneic	0.7 (0.4 to 1.4)	.31	—	—
Pulmonary radiation				
No	Ref	Ref	—	—
Yes	1.0 (0.7 to 1.4)	.85	—	—
Bleomycin exposure				
No	Ref	Ref	—	—
Yes	1.0 (0.7 to 1.4)	1.0	—	—
Busulfan exposure				
No	Ref	Ref	—	—
Yes	1.1 (0.5 to 2.3)	.88	—	—
Carmustine exposure				
No	Ref	Ref	—	—
Yes	1.9 (0.8 to 4.8)	.16	—	—
Lomustine exposure				
No	Ref	Ref	—	—
Yes	1.2 (0.5 to 2.8)	.60	—	—
Cardiac radiation				
No	Ref	Ref	—	—
Yes	1.0 (0.7 to 1.3)	.79	—	—
Anthracycline exposure				
None	Ref	Ref	—	—
< 100 mg/m^2	0.9 (0.6 to 1.3)	.50	—	—
100 to < 250 mg/ m^2	1.1 (0.8 to 1.4)	.62	—	—
≥ 250 mg/m^2	0.8 (0.6 to 1.2)	.27	—	—

NOTE. Bold values represent $P < .05$.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; ref, reference; SCT, stem-cell transplant.

differ by sex, rurality, or distribution by neighborhood income quintile. In multivariable analyses among the full survivor cohort (N = 12,721), variables associated with an increased risk of receiving a positive test included younger age (odds ratio [OR] 0.99 per year; 95 CI, 0.98 to 1.0; $P = .03$), diabetes (OR, 1.8; 95 CI, 1.1 to 3.1; $P = .03$), and living in poorer urban neighborhoods (Table 2).

The first vaccination in either cohort occurred on December 15, 2020. By the end of the follow-up period (July 31, 2021), 6,558 (52.8%) of age-eligible survivors were fully vaccinated and another 1,341 (10.8%) were partially vaccinated, compared with 58,292 (47.0%) and 14,090 (11.4%) of age-eligible controls, respectively ($P < .001$ for both comparisons). Under time-to-event analyses, the rate of being partially or full vaccinated was 20% higher among survivors (partial vaccination: hazard ratio, 1.21; 95 CI, 1.19 to 1.24; $P < .001$; full vaccination: hazard ratio, 1.23; 95 CI,1.20 to 1.27; $P < .001$; Fig 1).

No differences in severity outcomes were seen between infected survivors and infected controls (Table 3). The median time from positive COVID-19 test to ED visit was

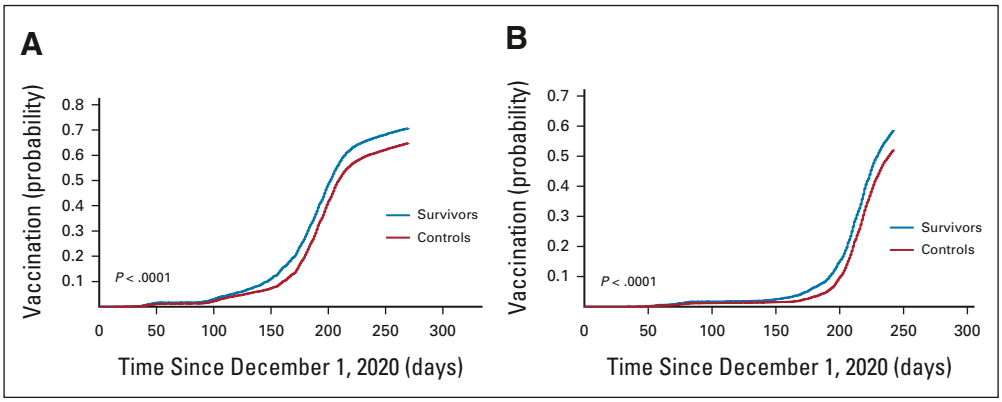

FIG 1. Cumulative incidence of (A) partial and (B) full vaccination against COVID-19 among survivors and controls age 11 years and older.

3 days (IQR 0-15 days) and to hospitalization was also 3 days (IQR 0-9 days). When adjusted for age, sex, rurality, and neighborhood income quintile, no increase in risk was observed in ED visits (OR, 1.2; 95 CI, 0.9 to 1.6; $P = .19$) or in hospitalization (OR, 1.8; 95 CI, 1.0 to 3.5; $P = .07$). No survivor was admitted to the ICU or died; logistic regression modeling was thus not performed. Adjustment for vaccine status was not feasible, given the small number of survivors and controls who were fully vaccinated (8/4,332, 0.2%) or partially vaccinated (63/4,332, 1.5%) 2 weeks before their positive test. Among survivors, only hypertension within the previous 2 years was associated with an increased risk of an ED visit following a positive test (OR, 4.1; 95 CI, 1.1 to 15.6; $P = .04$) in multivariable analysis (Table 4). Although previous allogeneic stem-cell transplant was associated with increased risk in univariate analysis (OR, 4.1; 95 CI, 1.1 to 14.9; $P = .03$), it did not retain significant in multivariable analysis (OR, 3.5; 95 CI, 0.9 to 13.1; $P = .08$). Although hypertension was also associated with risk of hospitalization in univariate analysis (OR, 8.4; 95 CI, 1.6 to 44; $P = .01$), statistical significance was lost in multivariable analyses including age and sex (OR, 5.4; 95 CI, 0.9 to 34.7; $P = .07$).

DISCUSSION

In this first population-based study to examine SARS-CoV-2 infections in survivors of childhood, adolescent, and young adult cancer, we found that survivors were not at increased risk of testing positive for infection, nor for serious sequelae when contracting infections compared with matched population controls.

Several authors have examined the impact of SARS-CoV-2 infections among children undergoing active therapy, with somewhat conflicting results. Smaller series from Greece and Brazil reported mild disease courses, whereas data from the United Kingdom and the United States noted an approximately 10% incidence of severe disease.[19-22] More recently, a large registry-based study reported a 7.4% chance of severe disease and 2% mortality in high-income countries.[23] Another large observational study of 917 American children with cancer found that 9.2% were admitted to the ICU and 1.6% died.[24] By contrast, there are very little data regarding the morbidity caused by SARS-CoV-2 infections among survivors. One study from a single institution in New York found that among 321 survivors seen over a 4-month period in their long-term follow-up clinic and assessed for COVID-19 symptoms or history, five (1.6%) reported a previous PCR-confirmed SARS-CoV-2 infection, one of whom required hospitalization.[25] A previous population-based study in Ontario found no increased risk of SARS-CoV-2 infection among survivors of childhood cancer, but did not evaluate postinfection complications or vaccine uptake patterns.[26] Consequently, there remains

TABLE 3. SARS-CoV-2 Infection Severity Outcomes Among Survivors and Controls

Outcome	Survivors (n = 386), No. (%)	Controls (n = 3,946), No. (%)	*P*	Adjusted OR (95% CI)[a]	*P*
ED visit	59 (14.8)	509 (12.9)	.30	1.2 (0.9 to 1.6)	.19
Hospitalization	11 (2.8)	68 (1.7)	.11	1.8 (1.0 to 3.5)	.07
ICU admission	0 (0.0)	6 (0.2)	NA	Unavailable[b]	—
Death	0 (0.0)	< 6[c]	NA	Unavailable[b]	—

Abbreviations: ED, emergency department; ICU, intensive care unit; NA, not available; OR, odds ratio.
[a]Adjusted for age, sex, rurality, and neighborhood income quintile.
[b]Too few events, preventing the model from converging.
[c]Privacy legislation prevents the disclosure of small cell sizes.

TABLE 4. Variables Associated With Emergency Department Visits Among Survivors With a Positive SARS-CoV-2 Polymerase Chain Reaction Test

	ED Visit			
	Univariate		Multivariable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years	0.99 (0.96 to 1.0)	.48	0.99 (0.96 to 1.0)	.40
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.8 (0.5 to 1.4)	.48	0.9 (0.5 to 1.6)	.68
Rurality/ neighborhood income quintile				
Rural	0.5 (0.1 to 2.6)	.42	—	—
Urban Q1	1.2 (0.5 to 2.9)	.76	—	—
Urban Q2	1.1 (0.4 to 2.7)	.85	—	—
Urban Q3	1.0 (0.4 to 2.4)	.95	—	—
Urban Q4	0.5 (0.2 to 1.4)	.17	—	—
Urban Q5	Ref	Ref	—	—
Asthma				
No	Ref	Ref	—	—
Yes	2.0 (0.5 to 7.5)	.32	—	—
COPD				
No	No convergence		—	—
Yes			—	—
Hypertension				
No	Ref	Ref	Ref	Ref
Yes	3.0 (0.9 to 10.4)	.08	**4.1 (1.1 to 15.6)**	**.04**
Diabetes				
No	Ref	Ref	—	—
Yes	0.8 (0.2 to 3.7)	.79	—	—
CHF				
No	No convergence		—	—
Yes			—	—
CVD				
No	No convergence		—	—
Yes			—	—
Any comorbidity				
No	Ref	Ref	—	—
Yes	1.5 (0.6 to 3.4)	.37	—	—
Hospitalized in previous 2 years				
No	Ref	Ref	Ref	Ref
Yes	1.7 (1.0 to 3.1)	.06	1.6 (0.9 to 3.0)	.12
Cancer type				
Hematologic	Ref	Ref	—	—
Solid tumor	0.8 (0.4 to 1.6)	.57	—	—
CNS system tumor	0.9 (0.4 to 1.8)	.74	—	—
SCT				
None	Ref	Ref	Ref	Ref
Autologous	1.0 (0.2 to 4.7)	.98	0.8 (0.2 to 3.8)	.31
Allogeneic	**4.1 (1.1 to 14.9)**	**.03**	3.5 (0.9 to 13.1)	.08
Pulmonary radiation				
No	Ref	Ref	—	—
Yes	1.2 (0.5 to 3.1)	.68	—	—
Bleomycin exposure				
No	Ref	Ref	—	—
Yes	0.7 (0.2 to 1.7)	.40	—	—
Busulfan exposure				
No	Ref	Ref	—	—
Yes	1.0 (0.1 to 8.1)	.97	—	—
Carmustine exposure				
No	Ref	Ref	—	—
Yes	1.2 (0.1 to 10.1)	.89	—	—
Lomustine exposure				
No	No convergence		—	—
Yes			—	—
Cardiac radiation				
No	Ref	Ref	—	—
Yes	1.1 (0.5 to 2.6)	.74	—	—
Anthracycline exposure				
None	Ref	Ref	—	—
< 100 mg/m^2	1.4 (0.5 to 3.8)	.46	—	—
100 to < 250 mg/m^2	1.1 (0.5 to 2.2)	.83	—	—
≥ 250 mg/m^2	1.6 (0.7 to 3.7)	.25	—	—

(continued in next column)

NOTE. Bold values represent $P < .05$.

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ED, emergency department; OR, odds ratio; ref, reference; SCT, stem-cell transplant.

significant uncertainty about whether young survivors may experience more substantial morbidity related to SAS-CoV-2 than the general population.

There are, however, theoretical mechanisms for why survivors may be at greater risk of COVID-19 complications. Survivors have been found to be at higher risk of infectious-

related death well after the completion of cancer treatment across infection types.[3] In addition, survivors are at higher risk of several comorbidities such as diabetes and CVD that have been shown to increase the risk of poor COVID-19 outcomes among the general population.[27,28] Of note, we also found a higher prevalence of diabetes, hypertension, and CHF among our survivor cohort. International consensus groups focused on childhood cancer survivors have thus been forced to draw on studies among the general population, and recommended that survivors with any of these comorbidities undertake additional precautionary measures to reduce risk of COVID-19 exposure/infection.[4] Nonetheless, the International Late Effects of Childhood Cancer Guideline Harmonization Group still recommends that all survivors with symptoms consistent with COVID-19 or positive COVID-19 tests seek medical advice early and alert [providers] about their cancer history and other conditions that may increase their risk for a severe course of disease.[4]

It is important to note that, as also recognized by the above guideline, survivors and their caregivers have experienced high levels of stress and anxiety during the pandemic. One group of authors found that more than 70% of childhood cancer survivors felt that they were at higher risk of experiencing severe complications of COVID-19 compared with their peers.[5] Others have reported that this anxiety has led to high rates of school and work avoidance and decreased rates of physical activity in a population already at high risk of inferior educational, occupational, and metabolic outcomes.[5,6,29,30] Accurate determination and communication of risk to survivors is thus crucial.

Survivors were more likely to undergo COVID-19 testing during the pandemic, perhaps reflecting greater anxiety or increased access to the health care system. Survivors were also getting vaccinated at a faster rate than the general population. Even without the protection afforded by vaccination, however, when contracting COVID-19, survivors were not statistically significantly more likely to suffer serious sequelae than controls. Therapy-related variables such as specific agents known to be associated with pulmonary late effects also did not increase the risk of severe disease. It may be that the protection afforded by the relatively young age of our survivor cohort (median age of 24 years, with a maximum age of 51 years) outweighs any risk associated with cancer survivorship; some studies among survivors of older adult cancer have found an elevated risk of severe disease.[31,32] The small number of severe events among our survivor cohort may also have limited our ability to detect small increases in risk either overall or associated with specific risk factors; indeed, we did find a trend toward increased risk of hospitalizations, although this was not statistically significant. Nonetheless, it is very reassuring that no survivor in our population-based cohort required ICU admission or died following a positive COVID-19 test.

Strengths of our study include the population-based nature, ability to identify COVID-19 testing and subsequent health care contacts, linkage to detailed cancer treatment data, and the use of validated algorithms to identify comorbidities. In addition to the limitations of the young age of the cohort, the small number of severe infections, and that most but not all positive tests were captured, other limitations merit note. First, our results may not be generalizable to COVID-19 infections with the Delta or Omicron variants, as our study period ended before these variants becoming dominant in Ontario. Second, our results may also not be generalizable to jurisdictions with different health care systems, different patterns of COVID-19 exposures and epidemiology, or with different underlying population demographics. Third, we did not examine chronic outcomes such as long-haul COVID-19.[33] Fourth, although able to validly identify multiple comorbidities, Ontario health care data are not able to identify and account for obesity with adequate sensitivity.[34] However, as many survivors are at increased risk of obesity,[35,36] this would bias toward an overestimation of their risk of severe COVID-19 outcomes compared with the general population, and thus not change our results. Fifth, we were unable to look at the impact of race or ethnicity, as such data are not routinely collected in Ontario. Sixth, survivors and controls may have different health care–seeking behaviors in terms of when and how they access care, which we could not account for, although this should not affect the most severe outcomes such as hospitalization and ICU admission. Seventh, we do not have access to what, if any, treatment was received following a COVID-19–positive test result. Finally, the AYA portion of our cohort, particularly those diagnosed above the age of 18 years, does not include all cancers diagnosed in this group.

In conclusion, survivors of childhood, adolescent, and young adult cancer were not at increased risk of COVID-19 infections or of severe sequelae after infection compared with matched general population controls. These results can be used to inform appropriate risk-counseling of survivors and their caregivers, particularly those in their thirties and younger. Further study is warranted to determine the risk in older survivors, specific subsets of survivors, and that associated with novel COVID-19 variants.

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DISCLAIMER

The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are based on data and information compiled and provided by the Canadian Institutes of Health Information (CIHI) and Ontario Health (OH). The opinions, results, view, and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CIHI or CCO; no endorsement is intended or should be inferred.

SUPPORT

Supported by ICES (Institute for Clinical Evaluative Sciences), which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC), as well as by the Pediatric Oncology Group of Ontario which is also supported by the MOHLTC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02592.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk of COVID-19 Infections and of Severe Complications Among Survivors of Childhood, Adolescent, and Young Adult Cancer: A Population-Based Study in Ontario, Canada

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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Consulting or Advisory Role: Jazz Pharmaceuticals

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Population-Based Health Services Databases Used in Analyses

Database	Data Elements	Description	Initiation Year
COVaxON	Vaccinations	COVID-19 vaccinations, including date and type	2020
DAD	Inpatient hospitalizations	One record per hospital admission including chart-abstracted demographic, clinical, and outcome data	1988
NACRS	ED visits	Demographic, clinical, and disposition data	2000
OHIP	Physician claims	Claims for services billed by fee-for-service Ontario physicians. Physicians under alternative funding plans are also required to submit shadow claims, ensuring capture of nearly all physician encounters	1991
OLIS	COVID-19 testing	COVID-19 tests, including date and result	2020
SDS	Same-day surgery/procedures	Demographic, clinical, and procedure data	1991

Abbreviations: DAD, Discharge Abstract Database; ED, emergency department; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan Claims Database; OLIS, Ontario Laboratory Information System; SDS, Same-Day Surgery.

TABLE A2. Algorithms Used to Identify Select Comorbidities

Comorbidity	Data Sources	Description
Diabetes	Ontario Diabetes Dataset	Captures all incident cases of diabetes since 1994 (and prevalent cases since 1991)[13]
CHF	DAD, NACRS, OHIP	Any inpatient diagnostic code indicating CHF or > 1 OHIP/ED claim indicating CHF within a 1-year time frame[14]
CVD	DAD, NACRS, OHIP	Any hospitalization/ED visit for acute myocardial infarction (AMI), stroke, percutaneous coronary intervention, and coronary artery bypass graft[14]
Hypertension	Ontario Hypertension Dataset	> 1 physician billing claim in a 2-year period or 1 hospital discharge abstract record with a diagnostic code indicated hypertension[15]
Asthma	Ontario Asthma Dataset	Captures all incident and prevalent cases of asthma since 1996[16]
COPD	COPD Database	Captures all incident cases of diabetes since 1996 (and prevalent cases since 1991)[17]

Abbreviations: CHF, congestive heart failure; COPD, Chronic obstructive pulmonary disease; CVD, cardiovascular disease; DAD, Discharge Abstract Database; ED, emergency department; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan Claims Database.