

Stage migration of testicular germ cell tumours in Alberta, Canada, during the COVID-19 pandemic: a retrospective cohort study

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Abstract

Background: An absence of screening recommendations and the rapid progression of testicular germ cell tumours (TGCTs) offer a perspective on the potential impact of the COVID-19 pandemic on cancer presentations. We evaluated the presenting cancer stages of TGCTs in a real-world population before and during the pandemic to assess stage migration.

Methods: We performed a retrospective review of all new patients with TGCT diagnoses in Alberta, Canada, from Dec. 31, 2018, to Apr. 30, 2021, using the Alberta Cancer Registry. Because potential changes in staging should not occur instantaneously, we used a 6-month lag time from Apr. 1, 2020, for seminomas, and a 3-month lag time for nonseminomas, to compare initial cancer stages at presentation before and during the pandemic. We evaluated monthly rates of presentation by stage and histology. Exploratory outcomes included the largest tumour dimension, tumour markers and, for advanced disease, risk category and treatment setting.

Results: Of 335 patients with TGCTs, 231 were diagnosed before the pandemic and 104 during the pandemic (using a lag time). In total, 18 (7.8%) patients diagnosed before the pandemic presented with stage III disease, compared to 16 (15.4%) diagnosed during the pandemic (relative risk 1.97, 95% confidence interval [CI] 1.05–3.72). We observed no significant differences for secondary outcomes. Without a lag time, the rate ratio for a stage II presentation decreased significantly during the pandemic (0.40, 95% CI 0.21–0.72).

Interpretation: We observed signs of TGCT stage migration during the COVID-19 pandemic, driven by a decline in stage II disease and a potential rise in stage III disease. Management of TGCTs should remain a priority, even during a global pandemic.

During the COVID-19 pandemic, population-based assessments have indicated a decline in the overall rate of reported cancer diagnoses, compared to historical controls.^{1–4} A lower number of cancer diagnoses is likely the result of delays in cancer detection and can lead to migration toward more advanced cancer stages at presentation.⁵ Disruptions to the health care system during the COVID-19 pandemic — including cancer screening programs, surgeries and other routine services — have made diagnosing cancer more challenging.^{6,7} As well, patients may be reluctant to seek care, dismiss symptoms and face additional barriers to access.^{8–10} Cancer care providers are concerned about more advanced cancer presentations, and about poorer patient outcomes as a result, but direct evidence in this area has been limited.^{5,11–16}

Testicular germ cell tumours (TGCTs) are the most common solid organ malignancy in males aged 15 to 35 years; the annual incidence in Canada is 1200 cases, representing 1% of all solid organ malignancies.¹⁷ Patients may

present with a testicular mass and can develop additional symptoms from growing metastatic lesions, but the prognosis is generally good — with 5-year survival rates of 97% — because most cases are caught early.^{17–20}

TGCTs develop and progress more rapidly than many other solid organ malignancies, and changes in staging may be more immediately apparent with delays in presentation.^{18,19} Patients with TGCTs are nearly always seen and treated by an oncologist, because cure and long-term survival are possible, even if they are more challenging with advanced presentations.^{19,20}

Competing interests: See the end of the article.

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Based on their histology, TGCTs are classified as seminomas or nonseminomas and given a stage of I to III. Stage I disease typically requires orchiectomy alone; stage II disease requires further surgery, radiation (for seminomas) or systemic therapy (for lymph nodes); and stage III disease requires systemic therapy for metastatic disease.^{19–27}

Major surgical and urological guidelines have advocated for the continued prioritization of TGCT management throughout the pandemic.^{28–30} We sought to evaluate the presentation and initial treatment of new TGCT diagnoses in Alberta, Canada, both before and during the pandemic. The main objective of this study was to investigate possible changes in the initial stage of TGCT at presentation during the COVID-19 pandemic.

Methods

Study design and setting

We performed a retrospective cohort study of all new TGCT diagnoses and Cancer Care Alberta referrals from Jan. 1, 2019, to May 31, 2021, in the province of Alberta. We evaluated the presenting stage for all TGCTs, as well as their seminoma and nonseminoma histology, before and during the pandemic, to assess for stage migration. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting.³¹

Cancer Care Alberta is responsible for the universal administration of cancer care in the province of Alberta, covering a population of approximately 4.3 million patients. It consists of 2 tertiary cancer centres (Tom Baker Cancer Centre, Cross Cancer Institute), as well as 4 regional and 11 community cancer centres. The Alberta Cancer Registry maintains the highest gold certification by the North American Association of Central Cancer Registries, and it tracks all cancer diagnoses in Alberta (www.albertahealthservices.ca/cancer/Page17367.aspx).

The first declaration of a public health emergency for COVID-19 in Alberta took place on Mar. 12, 2020, followed by a series of public health restrictions, including school closures Mar. 15, surgical postponements on Mar. 18, continuing care visitor restrictions on Mar. 20, isolation requirements for travellers on Mar. 25 and gathering restrictions on Mar. 27.³² We used Apr. 1, 2020, as the date of the beginning of the pandemic, given the dynamic changes before that date.

Data sources

We used the Alberta Cancer Registry to identify new cases of TGCTs based on *International Classification of Diseases and Related Health Problems, 10th revision*, Canadian version (ICD-CA) codes (c620, c621 and c629). Data entry for TGCTs was considered incomplete for 2021 (when the present study was conducted) because of a lack of confirmatory coding, not a lack of diagnostic information (Derek Tilley, Department of Oncology, University of Calgary, Tom Baker Cancer Centre, Calgary, Alta., personal communication, Sept. 30, 2021).

To validate the diagnostic information, R.L.-Y., N.A., N. Basappa, T.C., M.K., S.K., D.R., S.N., S.Y., B.D. and D.H. reviewed patient referral data at the 2 tertiary Cancer Care Alberta sites (with a catchment of approximately two-thirds of the province) from Jan. 1, 2019, to May 31, 2021. We compared the proportion of referrals identified by both methodologies across the years to look for any signals of diagnostic inaccuracy in the Alberta Cancer Registry in 2021.

Cancer Care Alberta has a single unified electronic medical record system (ARIA MO) that is used for all outpatient cancer management. The system includes consultation notes, progress notes, hospital admission and discharge notes, physician orders, chemotherapy orders and linkages to province-wide laboratory, pathology and diagnostic imaging results. R.G., R.N.S. and N. Bosma performed electronic chart reviews on all identified cases to verify and collect additional data elements. R.L.-Y. reviewed a random sample of 20 cases for accuracy, and identified no discrepancies.

Participants

Adult patients (age > 18 yr) with a new diagnosis of a TGCT during the study period were included. Tumours were categorized as having pure seminoma or nonseminoma (including mixed and pure nonseminoma) histology, based on pathology and tumour markers. Patients were also categorized as having been diagnosed before or during the pandemic, based on their date of diagnosis.

Because potential changes in staging should not occur instantaneously, we selected clinically relevant lag times after which stage migration could occur. Post-treatment surveillance guidelines recommend that seminomas be monitored every 4 to 6 months, and that nonseminomas be monitored every 2 to 3 months in the first 2 years of follow-up.^{18–26} Extrapolating from these recommendations, we selected a 6-month lag time for seminomas (Oct. 1, 2020) and a 3-month lag time for nonseminomas (July 1, 2020) to serve as the cut-off dates for diagnosis before and during the pandemic.

Outcomes

TGCTs were staged according to the *American Joint Committee Cancer Staging Manual* and classified as stage I, II or III.³³ Patients with advanced disease (stage II or III) were further classified by risk according to the International Germ Cell Consensus Classification (IGCCC): good, intermediate or poor (for nonseminomas).^{30,34,35} A patient's systemic treatment setting was defined as outpatient or inpatient (ward or intensive care unit [ICU]), based on where the first dose of systemic treatment was administered. Treatments administered after initiation of active surveillance were not considered.

To assess the burden of disease, the largest tumour dimension (e.g., testicular primary or metastatic lesion) was measured radiographically, using first imaging at presentation. Baseline tumour markers (α fetoprotein, β human chorionic gonadotropin and lactate dehydrogenase) were collected pre-orchiectomy (closest to the date of presentation) and post-orchiectomy for IGCCC classification.

Using established lag times, we compared cancer stage at presentation before and during the pandemic (III versus I and II), to assess for the presence of stage migration; this was the primary outcome. Secondary outcomes included 3-month incidence rates and a monthly assessment of the presenting stage of new diagnoses across the study period. Exploratory outcomes included differences in largest tumour dimension, tumour markers at presentation and (for patients with advanced disease) IGCCC risk category and systemic treatment setting.

Statistical analysis

We evaluated the incidence of TGCTs by stage and histology before and during the COVID-19 pandemic. We used χ^2 or Fisher exact tests (depending on expected cell counts) to compare categorical variables and Wilcoxon rank signed tests to compare continuous variables. To quantify the relative risk of being diagnosed with a stage III TGCT during the pandemic, we conducted a binomial regression model with a log-link. To characterize potential changes in staging further, we evaluated the proportion of TGCTs by stage and histology for each month. We compared rate ratios in the monthly incidence of TGCTs before and during the pandemic without a lag, using a Poisson regression model. We performed all statistical analyses using a 2-sided significance level of $p < 0.05$ and R statistical software (www.r-project.org).

We performed sensitivity analyses to evaluate the effect of assumptions in our study design: the use of Apr. 1, 2020 (versus Mar. 12, 2020), as a cut-off date for the beginning of the pandemic, and the use of different lag times (all 3 months or all 6 months) for seminomas and nonseminomas.

Ethics approval

This study was reviewed and approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA CC-21-0207).

Results

A total of 335 patients with TGCTs were included in the present study, of whom 192 (57.3%) were diagnosed with pure seminomas and 143 (42.7%) diagnosed with nonseminomas.

To validate Alberta Cancer Registry identifications for 2021 (which were considered incomplete), we assessed new patient referrals to the 2 tertiary centres (representing approximately two-thirds of all referrals). For diagnoses in 2019 to 2020, we identified 90 of 269 cases (33.5%) from referral review of the Alberta Cancer Registry, compared to 25 of 66 cases (37.9%) in 2021. We excluded 1 case because of an incorrectly classified histology, and added 1 case in 2020 based on tumour markers without histology, from referral review (Appendix 1, Figure S1, available at www.cmajopen.ca/content/10/3/E633/suppl/DC1). Baseline patient and presentation characteristics stratified by histology are presented in Table 1.

Table 1: Baseline patient and presentation characteristics stratified by histology

Characteristic	No. (%)*	
	Seminoma n = 192	Nonseminoma n = 143
Age, yr, mean \pm SD	38.5 \pm 14.5	32.5 \pm 11.9
Histology		
Seminoma	192 (100.0)	55 (38.5)
Embryonal	–	102 (71.3)
Yolk sac	–	69 (48.3)
Choriocarcinoma	–	20 (14.0)
Teratoma	–	74 (51.7)
Other	–	20 (14.0)
pT stage		
1	122 (63.5)	70 (48.9)
2+	66 (34.4)	52 (36.4)
0 or unknown	4 (2.1)	21 (14.7)
cN stage		
0	159 (82.8)	92 (64.3)
1	11 (5.7)	11 (7.7)
2	11 (5.7)	19 (13.3)
3	11 (5.7)	21 (14.7)
M stage		
0	185 (96.4)	120 (83.9)
1	7 (3.6)	23 (16.1)
Cancer stage		
I	159 (82.8)	88 (61.5)
II	26 (13.5)	28 (19.6)
III	7 (3.7)	27 (18.9)
Treatment location		
Tom Baker Cancer Centre	68 (35.4)	53 (37.1)
Cross Cancer Institute	80 (41.7)	60 (41.9)
Other	44 (22.9)	30 (21.0)
Orchiectomy	188 (97.9)	130 (90.9)
Radiation therapy	10 (5.2)	1 (0.7)
Systemic therapy	22 (11.5)	51 (35.7)

Note: cN = node (clinical), M = metastasis, pT = tumour (pathological), SD = standard deviation, TGCT = testicular germ cell tumour.
*Unless otherwise indicated.

Outcomes

Before the COVID-19 pandemic and during the lag periods, 231 cases of TGCTs were diagnosed in Alberta; 104 cases were diagnosed during the pandemic (after the lag times). The relative risk for diagnosis of a stage III TGCT during the pandemic (versus before the pandemic) was significantly increased (1.97, 95% confidence interval [CI] 1.05–3.72). Differences in stage, systemic treatment setting, IGCCC

risk category, largest tumour dimension and presenting tumour markers before and during the COVID-19 pandemic are given in Table 2. Among stage II and III TGCTs, the relative risk of intermediate- or poor-risk disease during the pandemic was 2.21 (95% CI 0.94–5.02). We found no cases with ICU management before the pandemic, but identified 2 during the pandemic.

Changes in the 3-month incidence of TGCTs overall and by stage are illustrated in Figure 1. The 3-month incidence of TGCTs underwent an initial decline at the onset of the pandemic, followed by a rise, with a disproportionate

amount of stage III disease. These changes are further accentuated in Figure 2, where rates and proportions are separated by seminoma and nonseminoma histology and their respective lag times. The proportion of patients with stage I disease was relatively similar in both periods, and the increase in the proportion of stage III disease was driven largely by a decrease in the proportion of stage II disease.

Table 3 delineates the monthly incidence of each cancer stage and subtype. The proportion of stage II and nonseminoma cases decreased during the pandemic. The monthly

Table 2: Differences in staging, systemic therapy setting, largest tumour dimension and pre-orchietomy markers before and during the COVID-19 pandemic

Variable	No. (%) [*]		p value
	Before pandemic† n = 231	During pandemic n = 104	
Cancer stage			0.002¶
I	166 (71.9)	81 (77.9)	
II	47 (20.3)	7 (6.7)	
III	18 (7.8)	16 (15.4)	
IGCCC risk category‡			0.07**
Good	52 (80.0)	13 (56.5)	
Intermediate	6 (9.2)	5 (21.7)	
Poor	7 (10.7)	5 (21.7)	
Systemic therapy setting§			0.1**
Outpatient	44 (78.5)	13 (61.9)	
Inpatient or ICU	12 (21.4)	8 (38.1)	
Largest tumour dimension, cm			0.06††
Mean ± SD	4.5 ± 3.6	5.1 ± 4.1	
Median (IQR)	3.6 (2.4–5.5)	4.2 (3.1–6)	
No. missing records	1 (0.4)	0 (0)	
Pre-orchietomy LDH, U/L			0.1††
Mean ± SD	288 ± 358	278 ± 476	
Median (25th–75th percentiles)	198 (170–279)	192 (167–237)	
No. missing records	49 (21.2)	20 (19.2)	
Pre-orchietomy β-HCG, IU/L			0.4††
Median (25th–75th percentiles)	5 (1.0–13.8)	5 (0.5–20.0)	
No. missing records	17 (7.4)	9 (8.7)	
Pre-orchietomy AFP, ng/mL			0.1††
Median (25th–75th percentiles)	3.6 (2.0–6.4)	3 (2.0–6.0)	
No. missing records	18 (7.8)	7 (6.7)	

Note: AFP = α fetoprotein, HCG = human chorionic gonadotropin, ICU = intensive care unit, IGCCC = International Germ Cell Consensus Classification, IQR = interquartile range, LDH = lactate dehydrogenase, SD = standard deviation, TGCT = testicular germ cell tumour.

*Unless otherwise indicated.

†Includes a 6-month lag period for seminomas and a 3-month lag period for nonseminomas.

‡IGCCC risk category was applicable only to stage II and stage III patients before (n = 65) and during (n = 23) the pandemic.

§Systemic therapy setting was applicable only to patients who received systemic treatment before (n = 56) and during (n = 21) the pandemic.

¶χ² test.

**Fisher exact test.

††Wilcoxon rank sum test.

proportion of TGCTs is shown in Figure 3, with and without the prespecified lag times. Although the total number of cases per month was low, an absence of stage II and III cases — followed by a larger proportion of stage III cases than stage II cases — is visible after the onset of the pandemic.

Sensitivity analyses

A sensitivity analysis using Mar. 12, 2020, as the index date (rather than Apr. 1, 2020) yielded similar results; 4 stage I, 1 stage II and 0 stage III cases were shifted to the pandemic period ($p = 0.003$ across stages). These shifts attenuated the relative risk of stage III disease (1.84, 95% CI 0.98–3.47). When only 3-month lag times were used, the relative risk for stage III disease was 1.63 (95% CI 0.83–3.21). When only 6-month lag times were used, the relative risk for stage III disease was 1.71 (95% CI 0.84–3.38).

Interpretation

Our population-based assessment of TGCT staging before and during the COVID-19 pandemic identified evidence of stage migration, with an increased relative risk of stage III disease when using a 6-month lag time for seminomas and a 3-month lag time for nonseminomas. This finding was attenuated by sensitivity analyses, and was driven largely by an overall decline in the rate ratio of stage II and nonseminoma disease during the pandemic; only some of these cases presented as more advanced stage III disease. Changes in other potential markers of disease severity (such as presenting tumour markers and median largest tumour dimension) were not observed. Although their numbers were limited, the subset of patients with advanced disease demonstrated a nonsignificant increase in IGCCC

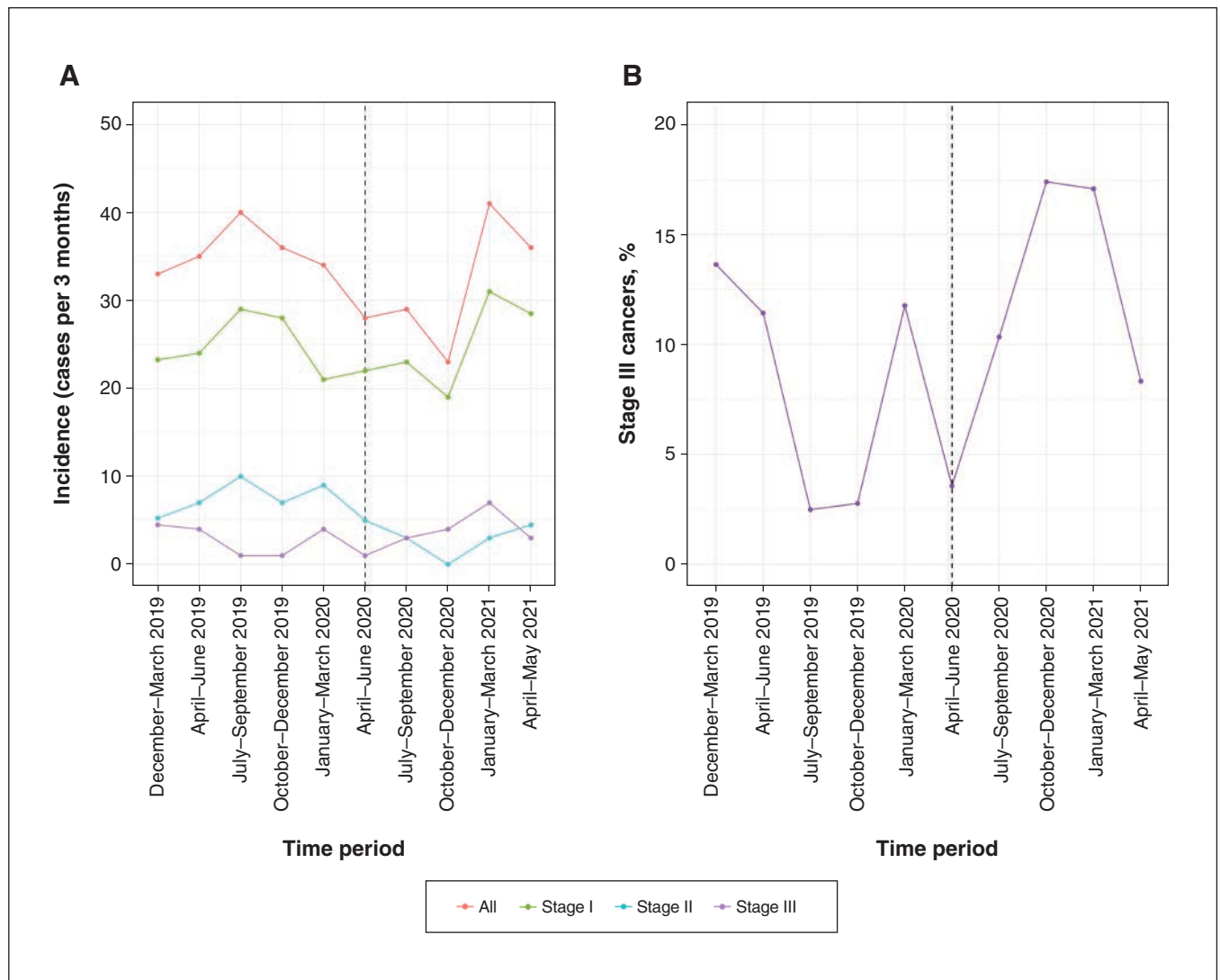


Figure 1: Changes in 3-month incidence of testicular cancer overall, by stage and for stage III before and during the COVID-19 pandemic in Alberta. The black dotted line represents the first 3-month period of the COVID-19 pandemic in our study. (A) Incidence of testicular cancer overall and by stage for each 3-month time period. (B) Proportion of stage III testicular cancers diagnosed for each 3-month period. Note: the first and last periods have been standardized to a 3-month incidence.

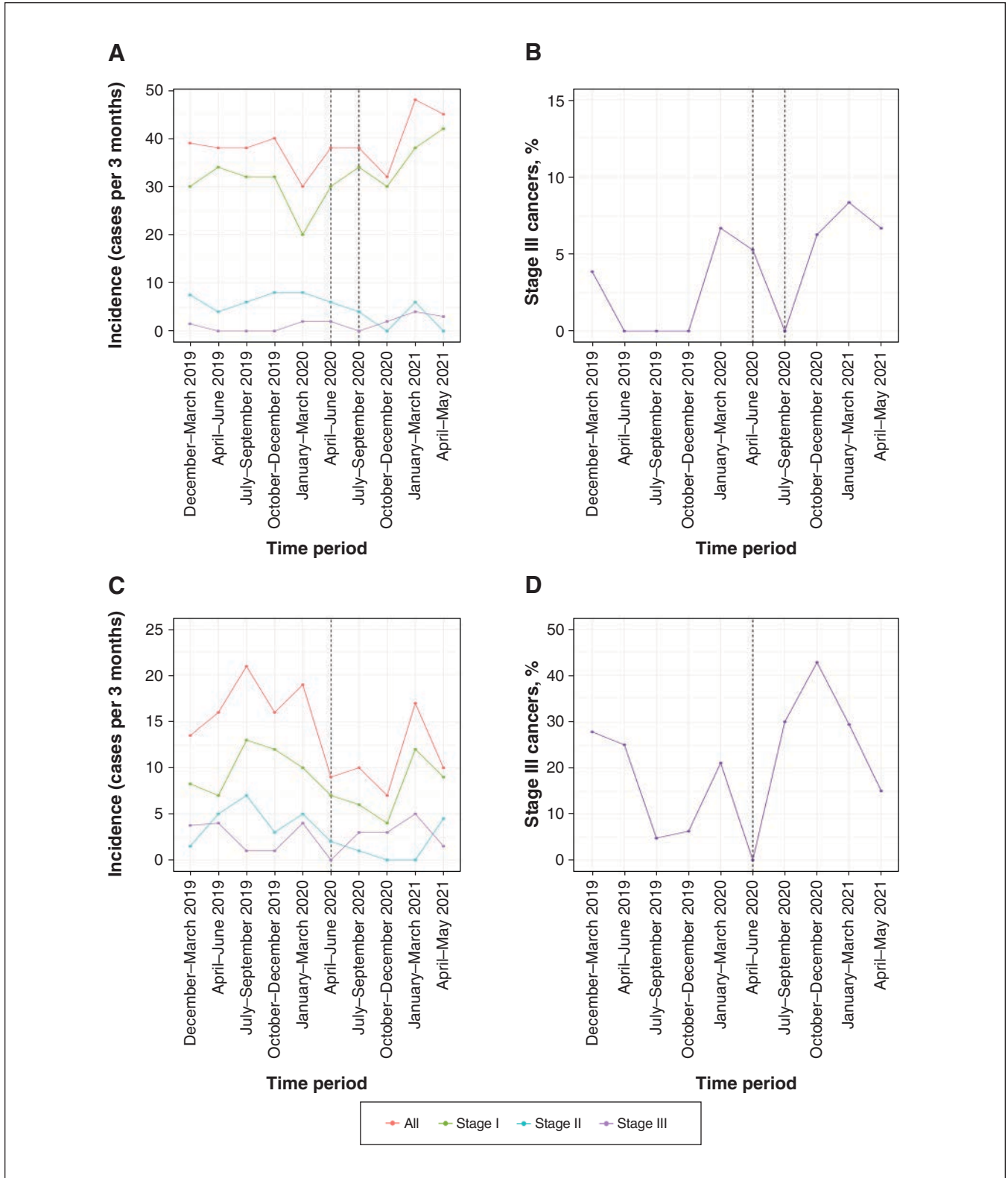


Figure 2: Changes in 3-month incidence of pure seminoma and nonseminoma testicular cancers by stage and for stage III, before and during the COVID-19 pandemic in Alberta. The first black dotted line represents the first 3-month period of the COVID-19 pandemic in our study. The second black dotted line indicates the period with the 6-month lag time for seminomas. (A) Incidence of pure seminoma testicular cancer by stage for each 3-month period. (B) Proportion of stage III pure seminoma testicular cancers diagnosed for each 3-month period. (C) Incidence of nonseminoma testicular cancer by stage for each 3-month period. (D) Proportion of stage III nonseminoma testicular cancers diagnosed for each 3-month period. Note: the first and last periods have been standardized to a 3-month incidence.

Table 3: Monthly incidence of TGCTs before and during the pandemic*

Variable	Monthly incidence		Rate ratio (95% CI)
	Before pandemic	During pandemic	
Overall	11.69	10.43	0.89 (0.72–1.11)
Stage I	8.13	8.21	1.01 (0.79–1.30)
Stage II	2.5	1.00	0.40 (0.21–0.72)
Stage III	1.06	1.21	1.14 (0.58–2.26)
Nonseminoma	5.56	3.79	0.68 (0.48–0.95)
Stage I	3.25	2.50	0.77 (0.50–1.18)
Stage II	1.38	0.43	0.32 (0.12–0.74)
Stage III	0.94	0.86	0.92 (0.52–1.97)
Seminoma	6.13	6.64	1.08 (0.82–1.44)
Stage I	4.88	5.71	1.17 (0.86–1.60)
Stage II	1.13	0.57	0.51 (0.21–1.15)
Stage III	0.13	0.36	2.74 (0.56–21.26)

Note: CI = confidence interval, TGCT = testicular germ cell tumour.
*Using Apr. 1, 2020, as the pandemic cut-off (without lag time).

intermediate- or poor-risk disease. We also found no cases of ICU management before the pandemic, but identified 2 during the pandemic.

This study provides real-world evidence of TGCT stage migration associated with the COVID-19 pandemic. A few others have demonstrated stage migration in other cancer types, but these have been limited to single-centre institutions;^{36–38} the present study provides a population-level assessment of stage migration. Most modelling studies have focused on more common cancer types to characterize the greatest impacts of the pandemic on health care systems.^{2,4–8,16,37} However, diagnostic delays in more common cancers are also affected by interruptions in screening.⁶ In contrast, an organized screening program does not exist for TGCT, so delays in presentation are more likely a reflection of general changes in the health care system and care-seeking behaviour.^{21–27,39,40} Potential mechanisms for observed stage migration in TGCT are likely relevant for all cancers.

The decline in stage II and nonseminoma TGCTs is particularly concerning, because overall rates of TGCTs have been rising in Canada, suggesting that some patients with stage II disease and nonseminomas may not have presented during the study period.⁴¹ Effective messaging for patients about identifying and addressing the symptoms of TGCT is an important step in limiting unintended impacts of the pandemic.^{39,40}

Testicular germ cell tumours are the most common solid organ cancer in males aged 15 to 35 years, a demographic that often has limited interaction with the health system.^{42,43} Those who are single, younger and of lower socioeconomic status may be particularly prone to delays in seeking care and

thus poorer cancer outcomes.^{42–45} Changes in how care is delivered could pose further obstacles. For example, a virtual assessment limits the physical detection of a testicular mass and makes it harder for potentially sensitive topics to be addressed, such as testicular health.⁴⁶ Such changes may have a differential impact on the population; patients already at risk of presenting with advanced disease may face greater barriers to care and ultimately delays in diagnosis.

Time and longer follow-up are needed to evaluate whether changes in TGCT presentation from the pandemic will affect patient outcomes. Our exploratory outcomes are underpowered, but the treatment of advanced cases can have severe immediate and potential long-term toxicities for patients, with 5-year overall survival decreasing from more than 95% with stage I disease to 67% with advanced, IGCCC poor-risk disease.^{34,35,47} Outcomes for patients with TGCT who are managed in the ICU are even worse, with 6-month mortality rates as high as 63.3%.¹⁸ Even a single case of ICU management may have marked implications for health resources, particularly in the context of COVID-19, when hospital and ICU capacity have been key indicators of health system strain.⁴⁸ Mitigating TGCT presentations that require inpatient and ICU-level care should remain a priority.

Limitations

This study was restricted by the low baseline rate of TGCT diagnosis. To illustrate stage migration, we focused on assessments of 3-month intervals to increase the stability of our observations and complemented this with monthly intervals to provide greater detail on the dynamics of how staging has changed. The COVID-19 pandemic led to dynamic changes in the health care system; low numbers prevented us from assessing the impact of specific public health measures and changes during various pandemic waves. However, the fact that a signal for stage migration was detectable despite these limitations warrants attention — from health care providers to be vigilant in diagnosing cancers, and from health system administrators to facilitate timely access to the management of more advanced cases.

Conclusion

The presence of stage migration in TGCT associated with the COVID-19 pandemic emphasizes the need for increased planning and resource allocation to mitigate and manage cancers that remain undiagnosed and may be more advanced upon presentation. Health care providers should remain vigilant in assessing patients for cancer-associated symptoms, particularly for cancers that lack robust screening programs. Targeted educational campaigns beyond the health system, with help from charitable organizations (e.g., Oneball in Calgary and Movember) and using demographic-appropriate means such as social media, may help bridge some gaps for patients who may not access care routinely. In the interim, TGCT management should remain a priority for health care providers and administrators, even amid a global pandemic.

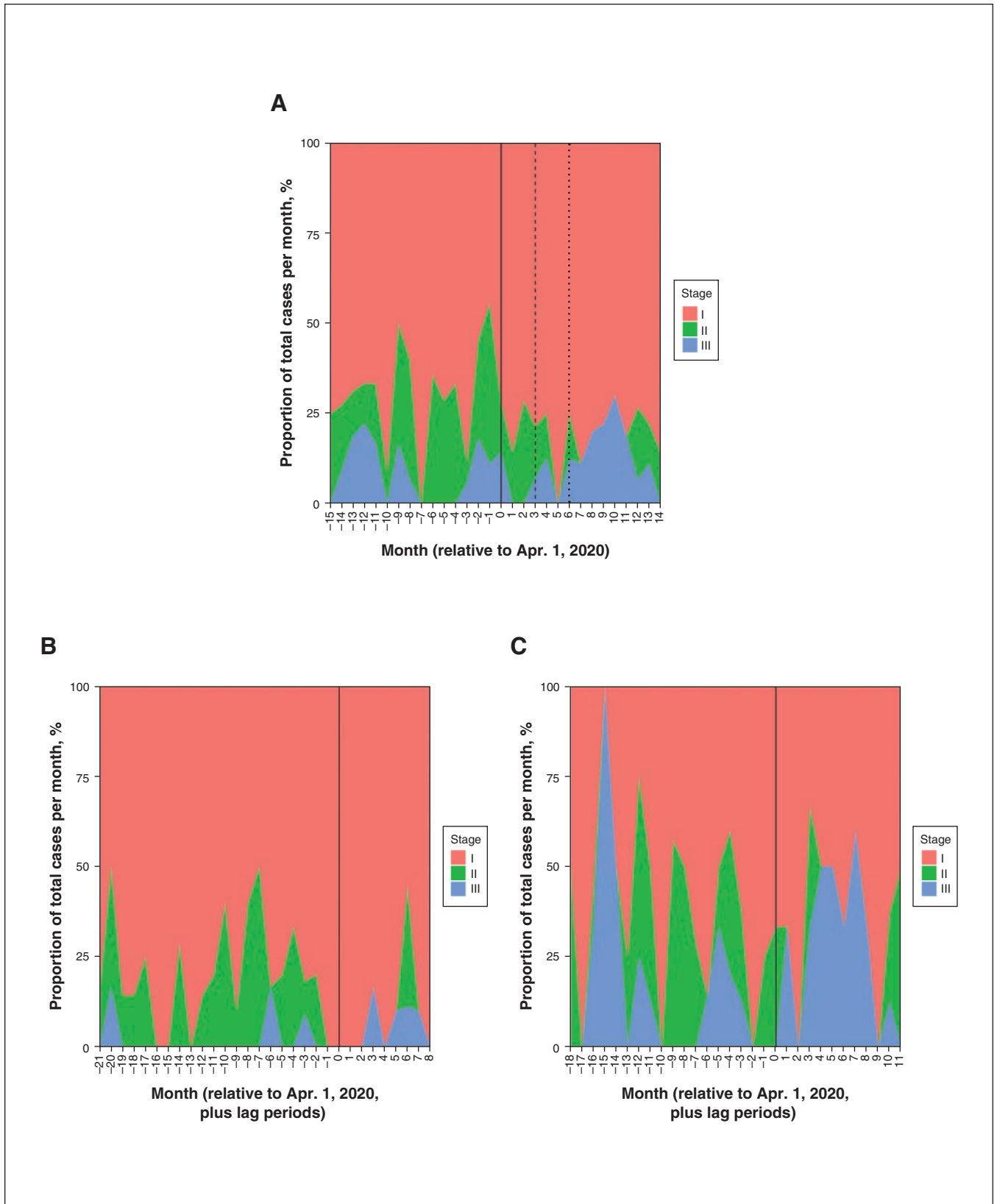


Figure 3: Monthly proportion of testicular germ cell tumours by stage. (A) All cases; time 0 (solid line) represents Apr. 1, 2020, the beginning of the pandemic in Alberta in our study; the dashed line represents the 3-month lag time for nonseminomas and the dotted line represents the 6-month lag time for seminomas. (B) Seminomas; time 0 (solid line) incorporates a 6-month lag time (Oct. 1, 2020). (C) Nonseminomas; time 0 (solid line) incorporates a 3-month lag time (July 1, 2020).

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Data sharing: Primary or supplementary data may be made available upon request from the corresponding author. Because of privacy concerns, data may be shared only in aggregate, and any data categories that may include cell counts of less than 5 will be reported as such.

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