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Original Article

Generalisability of Common Oncology Clinical Trial Eligibility Criteria in the Real World

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Abstract

Aims: Strict oncology clinical trial eligibility criteria can contribute to low accrual and result in poorly generalisable study findings. Using common eligibility criteria, we sought to (i) determine how many patients would be eligible versus ineligible and (ii) describe real-world patterns of treatments and outcomes between those considered trial eligible and ineligible.

Materials and methods: The Alberta Cancer Registry was used to assemble a population-based cohort of patients diagnosed with 11 common malignancies between 2004 and 2015. We considered age >75 years, anaemia, comorbid conditions (heart disease, uncontrolled diabetes, kidney disease, liver disease) and history of a prior malignancy or immunosuppression to be exclusion criteria. Logistic regression was used to characterise the likelihood of receiving treatment. Cox regression models were constructed to determine cancer-specific and overall survival.

Results: We identified 125 316 cancer patients, of whom 53% were men; the median age was 66 (interquartile range 48–84) years. Approximately 38% of patients were considered trial ineligible. The most common reasons for ineligibility were advanced age (24%) and heart disease (16%). In this ineligible group, 12, 47 and 19% still underwent chemotherapy, surgery and radiotherapy, respectively. Compared with ineligible patients, eligible patients were more likely to undergo chemotherapy (odds ratio 1.98, 95% confidence interval 1.89–2.07, $P < 0.0001$), surgery (odds ratio 1.39, 95% confidence interval 1.32–1.46, $P < 0.0001$) and radiotherapy (odds ratio 1.46, 95% confidence interval 1.4–1.52, $P < 0.0001$). Compared with ineligible patients who did not receive treatment, those considered ineligible but who still received treatment experienced improved cancer-specific survival (hazard ratio 0.75, 95% confidence interval 0.74–0.77, $P < 0.0001$) and overall survival (hazard ratio 0.89, 95% confidence interval 0.87–0.90, $P < 0.0001$).

Conclusions: A significant proportion of real-world patients are unable to participate in clinical trials due to stringent exclusion criteria, but many still receive treatment in routine practice. The eligibility criteria of oncology clinical trials should be broadened.

Key words: Clinical trials; eligibility criteria; population-based study; real-world data

Introduction

Oncology clinical trials represent an important mechanism for the development of novel treatments for the potential benefit of patients. An important aspect of the design of clinical trials is the choice of eligibility criteria. These are the patient- and disease-specific characteristics that define the type of patients that will be included in the trial. Such criteria are important because they optimise patient safety and allow for accurate interpretation of efficacy by recruiting a homogenous sample of patients. Eligibility restrictions attempt to exclude patients who are at a higher risk for adverse events or those who are unlikely to benefit from trial participation. One of the challenges in the selection of eligibility criteria is the need to balance internal validity with external validity [1]. Overly stringent eligibility criteria may limit accrual to clinical trials and result in

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findings that may not represent the population that will ultimately use the drug(s) after regulatory approval [2].

Despite efforts to balance these factors, there continues to be concern that current eligibility criteria in most oncology clinical trials result in suboptimal representation of patients encountered in real-world practice, thus limiting generalisability [3]. In addition, there is also concern that these eligibility criteria are frequently applied from protocol to protocol without considering the differences in the treatment under evaluation or the target population where the treatment will be applied [2]. In 1996, George *et al.* [3] proposed that eligibility criteria should be broadened as much as possible and that physicians and patients should make an informed decision about clinical trial participation. Despite this, evidence suggests that contemporary oncology clinical trials remain too restrictive [4,5]. As a result, several organisations, including the American Society of Clinical Oncology (ASCO), have recently prioritised the need to re-evaluate eligibility criteria in future study designs and to expand participation in oncology clinical trials to include more patients frequently encountered in routine clinical care [6,7].

The purpose of the current study was to characterise the potential eligibility of real-world patients for oncology clinical trials. We applied common clinical trial eligibility criteria to a population-based sample of unselected cancer patients in a large Canadian province to (i) determine the proportion of patients that would be eligible versus ineligible to enrol in clinical trials and (ii) describe real-world patterns of treatments and outcomes between those considered trial eligible and ineligible. It is our hope that the study findings can be used to inform and improve the future design of oncology clinical trials.

Materials and Methods

Data Sources and Study Population

This was a large, retrospective, population-based cohort study that analysed data from the Alberta Cancer Registry (ACR). The ACR includes the province's entire population, which was estimated to be about 4 million people during the study period. All patients have access to a single-payer, universal healthcare system. The ACR prospectively collects information on patient demographics, tumour characteristics, primary treatment and oncology facility from all individuals who resided in the province at the time of their initial, confirmed cancer diagnosis. Because cancer is a reportable disease in the province, case ascertainment is complete and accurate in the ACR within 12 months of a cancer diagnosis.

The study population consisted of patients with a diagnosis of bladder, breast, colorectal, gastroesophageal, head and neck, hepatobiliary, kidney, lung, melanoma, pancreas and prostate cancer between 1 January 2004 and 31 December 2015. These are the most common, non-gynaecological, solid malignancies based on recent statistics [8]. Patients without an Alberta healthcare number (e.g. non-Alberta resident, non-Canadian citizen) or those who moved out of the province within 1 year of their primary cancer diagnosis were excluded. In patients with more than one cancer diagnosis, the most recent diagnosis was used as the cancer type. This study was designed, analysed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [9]. This study was approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC-17-0619).

Definition of Variables

Dependent Variables

The main outcomes included (i) receipt of treatment (yes/no) and (ii) survival (alive/dead). Information on treatments including radiation therapy, surgery and chemotherapy was recorded in the ACR, whereas information on cancer-specific and all-cause deaths was retrieved from Vital Statistics records.

Independent Variables

Common clinical trial exclusion criteria were defined as age $>$ 75 years, abnormal bloodwork, heart disease, uncontrolled diabetes, kidney disease, liver disease, prior malignancy and any immunosuppression diagnosed in the 5 years before their primary cancer diagnosis (Supplementary Table S1). These were identified using a combination of data from the ACR, discharge abstracts, ambulatory care and physician billing claims at the time of or preceding the cancer diagnosis using previously validated International Classification of Diseases (ICD) and Related Health Problems algorithms [10].

The American Joint Committee on Cancer (AJCC) stage, tumour grade, treating institution type (academic/community) and postal code at the time of the cancer diagnosis were obtained from the ACR. The Charlson comorbidity index (CCI) was generated using data from discharge abstracts, ambulatory care and physician billing claims [10]. Using the postal codes, neighbourhood socioeconomic status, including education and income levels, was derived based on the 2011 census. Postal codes were also used to calculate the driving time to the nearest cancer centre with the Google Maps Application Programming Interface. Driving time was categorised as $\leq$60, 61–120 and $>$ 120 min, as per previously published literature [11]. The province is divided strategically into health regions as an approach to define catchment areas, deliver care and assess outcomes at the population level [12]. Each patient was assigned to one of the health regions based on postal code.

Subgroup Analysis

We conducted a subgroup analysis to determine the impact of clinical trial eligibility on treatment and outcomes of the four most common cancers in our cohort.

Exploratory Analysis

We also conducted an exploratory analysis to evaluate the impact of broadening clinical trial eligibility criteria. We increased the age of exclusion to 80 years and eliminated the criterion of heart disease. We then determined how many additional patients would be considered trial eligible.

Statistical Analysis

Descriptive analyses were conducted to summarise patient, tumour and system characteristics. Student's *t*-test and Wilcoxon rank-sum test were used to compare continuous variables, whereas the chi-squared and Fisher's exact tests were applied to compare categorical variables. Multivariable logistic regression models were constructed to determine associations between clinical trial eligibility and cancer treatments. Unadjusted and adjusted Kaplan–Meier curves were plotted to describe survival differences between trial-eligible patients, trial-ineligible patients who received treatment and trial-ineligible patients who did not receive treatment. Comparisons across groups were conducted with the Log-rank test. Cox proportional hazards models were developed to characterise the effect of trial eligibility on cancer-specific survival (CSS) and overall survival, adjusting for measured confounders. Overall survival was defined as the time interval between the date of cancer diagnosis and the date of death from any cause, censoring at the last known follow-up. CSS was defined as the time interval between the date of cancer diagnosis and the date of death from cancer, censoring at the last known follow-up or death from non-cancer causes, whichever occurred first.

All analyses were carried out with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

In total, 125 316 patients were included in the study. The median age was 66 (interquartile range 57–75) years and 53% were men. The most prevalent cancer types were breast cancer (22%; 27 498), lung cancer (17%; 20 903) and colorectal cancer (16%; 19 625). Overall, 22% (27 277) of the study population had stage IV disease. In the entire cohort, 38% (48 149) of patients were considered trial ineligible based on common exclusion criteria. Of the ineligible patients, 12% (5891), 47% (22 629) and 19% (9113) received chemotherapy, surgery and radiation therapy, respectively. Additional details regarding the characteristics of the study population are shown in Table 1.

The reasons for trial ineligibility are summarised in Table 2. The most common factors associated with trial ineligibility were age >75 years (25%; 30 361) and the presence of heart disease (16%; 19 996).

Impact of Trial Eligibility on Cancer Treatments

We evaluated the impact of clinical trial eligibility on cancer treatment. In the univariate analysis, clinical trial eligibility was associated with a higher likelihood of receiving chemotherapy (odds ratio 3.17, 95% confidence interval 2.98–3.17, $P < 0.0001$), surgery (odds ratio 2.37, 95% confidence interval 2.31–2.42, $P < 0.0001$) or radiotherapy (odds ratio 2.15, 95% confidence interval 2.09–2.21, $P < 0.0001$). Similarly, on multivariate analysis that adjusted for age, CCI, education, income, tumour subtype, histology, grade, stage and year of diagnosis, treating facility and driving time to the nearest cancer centre and health region, trial-eligible patients continued to have a higher likelihood of receiving chemotherapy (odds ratio 1.98, 95% confidence interval 1.89–2.07, $P < 0.0001$), surgery (odds ratio 1.39, 95% confidence interval 1.32–1.46, $P < 0.0001$) or radiotherapy (odds ratio 1.46, 95% confidence interval 1.40–1.52, $P < 0.0001$) (Table 3). We further conducted this analysis for the most prevalent tumour types in our study (i.e. breast, prostate, lung and colorectal cancers). In patients with lung and prostate cancers, trial-eligible patients were more likely to receive any cancer treatment. Trial-eligible breast cancer patients were more likely to receive radiation and chemotherapy. Trial-eligible colorectal cancer patients were more likely to undergo chemotherapy and surgery (Supplementary Table S2).

Association of Trial Eligibility with Outcomes

Overall survival and CSS were evaluated using Kaplan–Meier analyses and Log-rank tests. Three groups of patients were compared: (i) patients who were trial ineligible and did not receive any treatment, (ii) patients who were trial ineligible and received any treatment (surgery and/or chemotherapy and/or radiation), and (iii) patients who were trial eligible (regardless of whether they received treatment).

The median overall survival was 135 months for the trial-eligible patients, 47 months for the trial-ineligible patients who received treatment and 3 months ($P < 0.001$) for the trial-ineligible patients who did not receive treatment. The median CSS was not reached, 99 months and 3 months ($P < 0.001$) for the trial-eligible, trial-ineligible and treated, and trial-ineligible and untreated patients, respectively.

Compared with trial-ineligible patients who did not receive treatment, those considered ineligible and who still received treatment had improved CSS (hazard ratio 0.75, 95% confidence interval 0.74–0.77, $P < 0.0001$) and overall survival (hazard ratio 0.89, 95% confidence interval 0.87–0.90, $P < 0.0001$). Patients who were trial eligible had the highest CSS (hazard ratio 0.72, 95% confidence interval 0.70–0.74, $P < 0.001$) and overall survival (hazard ratio 0.72, 95% confidence interval 0.70–0.74, $P < 0.001$) of all three groups (Table 4 and Figure 1). The association of trial eligibility on overall survival and CSS

Table 1
Characteristics of patients who would be eligible and ineligible for a cancer clinical trial in Alberta from 2004 to 2015 ($n = 125\ 316$)

Characteristic	All patients $n = 125\ 316$	Trial eligible $n = 77\ 167$	Trial ineligible $n = 48\ 149$	*P* value
Age (years)*				<0.0001
Mean/median	66/66	59/60	76/78	
≤40	4026 (3%)	3750 (5%)	276 (1%)	
41–50	12 304 (10%)	11 267 (15%)	1037 (2%)	
51–60	27 624 (22%)	23 720 (31%)	3904 (8%)	
61–70	34 605 (28%)	21 190 (35%)	7415 (15%)	
71–80	29 611 (24%)	11 240 (15%)	18 371 (38%)	
80+	17 146 (14%)	0 (0%)	17 146 (36%)	
Cancer type:				<0.0001
Breast	27 498 (22%)	20 746 (27%)	6752 (14%)	
Prostate	24 788 (20%)	17 075 (22%)	7713 (16%)	
Lung	20 903 (17%)	10 260 (13%)	10 643 (22%)	
Colorectal	19 625 (16%)	10 842 (14%)	8783 (18%)	
Melanoma	6505 (5%)	4842 (6%)	1663 (3%)	
Head and neck	4694 (4%)	3246 (4%)	1448 (3%)	
Gastroesophageal	4661 (4%)	2456 (3%)	2205 (5%)	
Pancreas	4374 (3%)	1914 (2%)	2460 (5%)	
Hepatobiliary	3724 (3%)	1199 (2%)	2525 (5%)	
Bladder	3809 (3%)	1615 (2%)	2194 (5%)	
Kidney	4735 (4%)	2972 (4%)	1763 (4%)	
Stage				<0.0001
0–1	29 170 (23%)	20 354 (26%)	8816 (19%)	
2–3	35 941 (29%)	23 743 (31%)	12 198 (26%)	
4	27 277 (22%)	15 078 (20%)	12 199 (25%)	
Unknown	32 928 (26%)	17 992 (23%)	14 936 (31%)	
CCI Score				<0.0001
0	50 156 (23%)	41 190 (53%)	8966 (19%)	
1	19 582 (16%)	12 459 (16%)	7123 (15%)	
≥2	55 578 (44%)	23 518 (30%)	32,060 (67%)	
Surgery				<0.0001
Yes	74 897 (60%)	52 268 (68%)	22 629 (47%)	
No	50 419 (40%)	24 889 (32%)	25 520 (53%)	
Chemotherapy				<0.0001
Yes	29 039 (23%)	23 148 (30%)	5891 (12%)	
No	96 277 (77%)	54 019 (70%)	42 258 (88%)	
Radiotherapy				<0.0001
Yes	34 891 (28%)	25 778 (33%)	9113 (19%)	
No	90 425 (72%)	51 389 (67%)	39 036 (81%)	

CCI, Charlson comorbidity index.
* Age at diagnosis.

was also seen when the analysis was repeated in patients with breast, prostate, lung and colorectal cancers (data not shown).

Exploratory Analysis of Broadening Trial Eligibility

In an exploratory analysis we evaluated the impact of broadening clinical trial eligibility criteria. Based on the most common reasons for trial ineligibility, we increased the age cut-off from 75 to 80 years and eliminated the presence of heart disease as an exclusion criterion.

With this manoeuvre, the percentage of ineligible patients reduced from 38% (48 149/125 316) to 25% (31 355/125 316) ($P < 0.0001$). In this new, smaller cohort of ineligible patients, 11% (3322), 45% (14 115) and 16% (4942) still received chemotherapy, surgery and radiation therapy, respectively.

Discussion

In this study, we evaluated the generalisability of common clinical trial eligibility criteria in the real world. There were several notable findings. First, we observed that these criteria, if applied strictly, would exclude almost 40% of cancer patients from participating in trials or receiving therapy. Second, although trial eligibility was associated with a higher likelihood of undergoing therapy in routine clinical practice, a fair proportion of trial-ineligible individuals still received some form of treatment, including chemotherapy and/or radiation (almost 20%) and/or surgery

Table 2
Reasons for clinical trial ineligibility among patients in Alberta between 2004 and 2015 ($n = 125\ 316$)

Criteria for ineligibility	Number of patients (%)
Age > 75 years	30,661 (25%)
Presence of heart disease	10,996 (16%)
Kidney disease	6840 (5%)
Uncontrolled diabetes	5984 (5%)
Liver disease	4778 (4%)
Abnormal bloodwork	2339 (2%)
Prior malignancy	1872 (1%)
Any immunosuppression	1642 (1%)

(almost 50%). Third, trial-eligible patients had improved outcomes compared with trial-ineligible patients. In an exploratory analysis, we also found that broadening eligibility criteria would probably have a significant impact on potential trial participation due to a significant increase in the pool of eligible patients.

Our study showed that almost 40% of patients would be considered trial ineligible based on common cancer clinical trial eligibility criteria. Our results are consistent with other similar studies. Heng *et al.* [13] showed that 35% of patients with metastatic renal cell cancer from the International Metastatic Renal Cell Cancer Database Consortium would not have met the eligibility criteria for Vascular endothelial growth factor (VEGF)-targeted therapy clinical trials based on routine exclusion criteria. In addition, a study of 326 patients with non-small cell lung cancer from Kaiser Permanente showed that 80% of patients would be ineligible for two trials involving chemotherapy and anti-angiogenic therapy [14]. The higher percentage of ineligible patients in this study may be due to the older age and higher comorbidity burden seen in patients with lung cancer. In a smaller Australian study of 62 patients with advanced non-small cell lung cancer between 2007 and 2008, Clarey *et al.* [15] showed that an average of 43% of patients were eligible for targeted therapy clinical trials. Most patients were excluded due to limited life expectancy (38%), inadequate performance status (34%) and abnormal laboratory results (32%). Furthermore, when they excluded the two trials with the least restrictive eligibility criteria, only 35% of patients would be eligible. Our study also showed that the dominant reason for ineligibility was due to comorbid conditions (i.e. heart disease, kidney disease, uncontrolled diabetes and liver disease). This finding is consistent with data from recent cancer clinical trial screening logs [16].

Despite a large number of patients in our study who were deemed ineligible based on common eligibility criteria, we also showed that a substantial number of these patients still received treatment. In the study by Clarey *et al.* [15], 66% proceeded to receive first-line treatment with either chemotherapy and/or targeted therapy, despite only 43% being considered trial eligible. Likewise, in a single-centre study from Japan consisting of patients with non-small cell lung cancer, 60% of patients between 2006 and 2014 were ineligible for first-line phase I–III clinical trials, but 54% of these patients with a performance status of less than or equal to 1 still received chemotherapy [17]. Furthermore, a study by Mitchell *et al.* [18] showed that a significant percentage of real-world patients with metastatic renal cell cancer are treated with targeted therapies for which they would have been deemed ineligible for the corresponding clinical trial. They

Table 3
Logistic regression analysis of clinical trial ineligibility on receipt of chemotherapy, surgery and radiation therapy among patients in Alberta between 2004 and 2015 ($n = 125\ 316$)

	Univariate analysis	Multivariate analysis*
Chemotherapy	OR 3.07 (95% CI 2.98–3.17, $P < 0.0001$)	OR 1.98 (95% CI 1.89–2.07, $P < 0.0001$)
Surgery	OR 2.37 (95% CI 2.31–2.42, $P < 0.0001$)	OR 1.39 (95% CI 1.32–1.46, $P < 0.0001$)
Radiation therapy	OR 2.15 (95% CI 2.09–2.21, $P < 0.0001$)	OR 1.46 (95% CI 1.4–1.52, $P < 0.0001$)

CI, confidence interval; OR, odds ratio.
* Adjusted for age, gender, tumour type, pathological T stage, pathological N stage, pathological M stage, tumour grade, chemotherapy, radiation therapy, Charlson comorbidity score, travel distance to cancer centre, neighbourhood education level, neighbourhood income level, healthcare facility type, zone name, year of diagnosis.

Table 4
Cox regression analysis of clinical trial eligibility on cancer-specific survival and overall survival among patients in Alberta between 2004 and 2015 ($n = 125\ 316$)

	Cancer-specific survival*	Overall survival*
Trial eligible	HR 0.72 (95% CI 0.70–0.74, $P < 0.001$)	HR 0.72 (95% CI 0.70–0.74, $P < 0.001$)
Trial ineligible, treated	HR 0.75 (95% CI 0.74–0.77, $P < 0.0001$)	HR 0.89 (95% CI 0.87–0.90, $P < 0.0001$)
Trial ineligible, untreated	Reference	Reference

CI, confidence interval; HR, hazard ratio.
* Adjusted for age, gender, tumour type, pathological T stage, pathological N stage, pathological M stage, tumour grade, chemotherapy, radiation therapy, surgery, Charlson comorbidity score, travel distance to cancer centre, neighbourhood education level, neighbourhood income level, healthcare facility type, zone name, year of diagnosis.

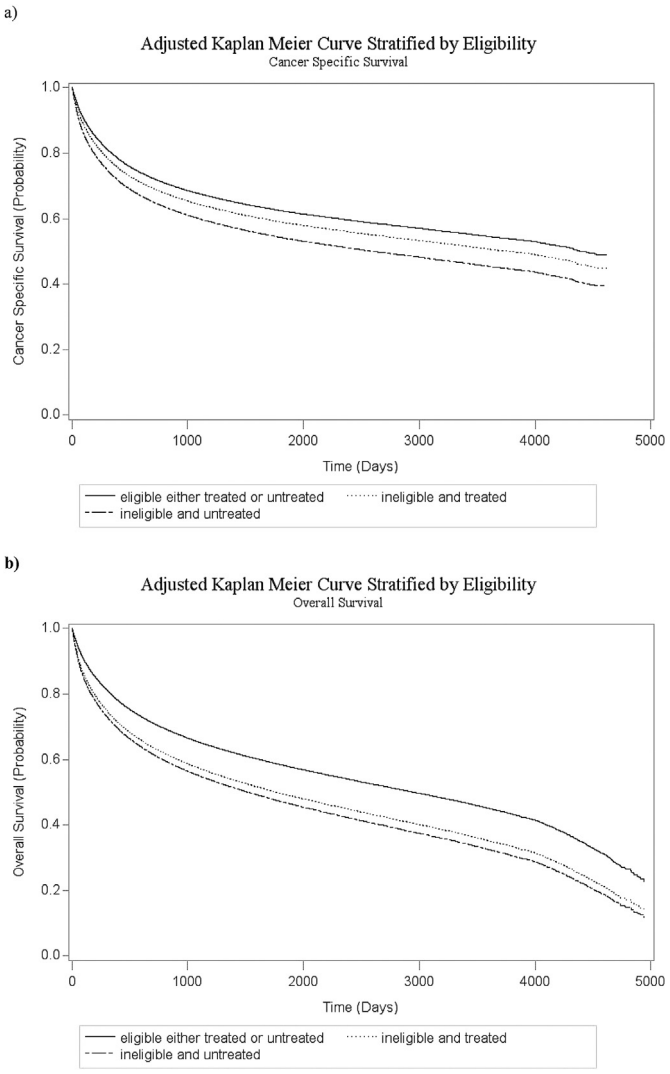

Fig 1. Adjusted cancer-specific (a) and overall survival (b) for patients based on clinical trial eligibility.

applied eligibility criteria from practice changing phase III clinical trials to a cohort of 379 registry patients in the USA, all of whom were treated in routine practice between 2007 and 2011. Almost 40% of these patients actually did not meet the eligibility criteria for the clinical trial that tested the therapy they received [18].

A number of studies have shown that trial ineligibility is a predictor of overall survival [13,17,19]. To our knowledge, however, there are few studies that have examined the impact of treatment among trial-ineligible patients. In our study, it was not surprising to find that trial-ineligible patients had poorer overall survival and CSS when compared with eligible patients. We further observed that of the trial-ineligible patients, those who received treatment in routine practice experienced better outcomes than those considered ineligible and did not receive treatment, even after controlling for known confounders. However, this finding should be interpreted with caution, as the differences in survival could be driven in part by residual confounding. We have also started work on identifying a few common treatments in routine practice (i.e. first-line chemotherapy for metastatic colorectal cancer) and comparing the survival outcomes between clinical trial-eligible and -ineligible patients with those reported in pivotal randomised controlled trials.

Finally, our exploratory analysis showed that by increasing the age limit to 80 years and eliminating a history of cardiovascular disease from the exclusion criteria, 12% more patients would be considered trial eligible. Investigators have long proposed that age should not be a barrier for clinical trial participation [20,21]. The use of age as an exclusion criterion means that most trial participants are younger and healthier [22]. As the population ages, it is important for oncologists to have objective data to ensure that new treatments are safe and effective, especially when they are used in real-world patients who are often older and more frail [23]. Recent studies continue to show that many oncology trials still include age in their eligibility criteria [4]. Likewise, an aging general population also means that there will be a larger number of cancer patients with other comorbidities, such as cardiac disease. In a systematic review of barriers to recruitment to cancer clinical trials of older individuals, Townsley *et al.* [24] found that cardiac disease may reduce enrolment of older individuals significantly. Although treatment-related cardiac adverse events may be difficult to predict, ASCO Friends of Cancer Research suggest that ejection fraction values combined with investigator assessment of heart failure related to the investigational drug may represent a more reliable way to assess eligibility rather than excluding everyone with any prior cardiac history [25].

Our study should be interpreted in the context of limitations. First, the retrospective design may subject it to selection bias. Second, performance status, which is probably a strong predictor of clinical trial eligibility, treatment and outcome, cannot be captured using administrative data. Furthermore, the assessment of comorbidity via an aggregate score (Charlson) using administrative data can be imprecise. In addition, we applied common clinical trial eligibility criteria and not those specific to individual clinical trials that were available in Alberta during this time period because the number of trials was prohibitive. Therefore, our analysis may not exactly represent the number of patients that may have been eligible versus ineligible for a specific study. However, we feel that our approach provides a more overarching estimate of the inclusiveness of clinical trials and the representativeness of their eligibility criteria. Such limitations should be weighed against the strengths of this study, including its very large sample size and its population-based study design, which are important in an analysis that focuses on generalisability.

The field of oncology strives to be evidence based and to test treatments in well-designed randomised controlled trials prior to approving them for use in the general population. However, overly stringent clinical trial eligibility criteria make it challenging to extrapolate findings to a broader population of patients. Our study has shown that although a significant number of patients would be considered ineligible for participation in cancer clinical

trials, a fair proportion of these patients still receive treatment in routine practice. This observation underscores a need to broaden clinical trial eligibility criteria and suggests that such an approach is probably safe, reasonable and potentially beneficial. Furthermore, broadening clinical trial eligibility criteria would enable greater participation in clinical trials and provide study findings that would be more representative of the phenotype of patients that clinicians encounter in routine practice. Future clinical trials should carefully examine their eligibility criteria and consider modifying them to be more inclusive. Tailoring such eligibility criteria by considering the toxicities of the specific treatment being evaluated may further lead to improved external validity.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.003.

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