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RESEARCH

Improvement in patient-reported pain among patients with metastatic cancer and its association with opioid prescribing

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Abstract

Purpose Opioids are a mainstay of cancer pain management; however, patients with metastatic cancer are often excluded from studies, leading to a lack of evidence on whether increased prescribing (dosage and/or duration) results in improved outcomes for this population. This study aimed to investigate whether increased opioid prescribing is associated with an improvement in patient-reported pain among patients with metastatic cancer.

Patients and methods A retrospective cohort of all adult patients diagnosed with stage IV cancers, who completed at least two patient-reported outcomes (PROs) within 30 days of each other, was identified from administrative data. Opioid prescriptions were categorized by dosage level and number of prescription days. Multivariable logistic regression was used to investigate the association between opioid prescribing and clinically important improvement in pain score (≥ 1 point change on the Edmonton Symptom Assessment System).

Results A total of 2169 patients were included, 770 (35.5%) of whom had active opioid prescription between PROs, with an average daily dosage of 86.1 mg of oral morphine equivalent. Active prescription was associated with improvement in pain (OR = 2.17, $P < 0.001$). However, among patients with active prescription, neither dosage nor number of prescription days was significantly associated with pain improvement.

Conclusion Opioid prescription is important for treating cancer-related pain; however, increased dosage or duration may not be leading to greater improvements in pain. Patients with metastatic cancer who are receiving increased opioid prescribing may have difficult-to-treat pain and may benefit from multidisciplinary pain management strategies to supplement opioid prescription and improve outcomes.

Keywords Opioids · Analgesia · Patient-reported outcomes · Cancer pain · Metastatic cancer · Administrative data

Introduction

Patients with metastatic cancer face a unique set of challenges and concerns, which are not well-researched or understood by the medical community [1, 2]. These patients face incurable diagnoses and experience ongoing physical,

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emotional, social, financial, and existential issues as a result [3]. In addition, they often have a greater symptom burden than early-stage cancer patients [4] and require treatment which is palliative rather than focused on curative intent [5]. Over recent years, the development of new treatment options has allowed patients with metastatic cancer to have increased survival times, with 5-year survival rates found to significantly increase for various cancer types [6, 7]. Where once patients would only survive for a matter of months, a large number of patients are living with their diagnosis and its ramifications for years. While researchers and oncologists have done important work to understand and document cancer survivorship after treatment has ended, there is much less information about the implications of living with chronic incurable cancer, ongoing treatments, multiple cancer diagnoses, and the impact of these factors on patient quality of life (QoL) [8].

Pain, one of the most prevalent and highest-concern cancer-related symptoms [9], is reported to occur in 39.3% of patients after curative-intent treatment compared to 66.4% among patients with advanced, metastatic, or terminal cancers [10]. The treatment of cancer-related pain (CRP) is heavily reliant upon the use of opioids, which are the first choice for the treatment of moderate-severe CRP [11]. As a result, opioids are commonly prescribed to patients with metastatic cancer [12]. However, these patients are often excluded from studies on opioid use [13, 14], justified by a greater need for palliative care and shorter prognosis times. In light of recent advances in treatment options and increased survival times, these issues are becoming more relevant and likely to impact these patients, necessitating increased study for the metastatic population.

In addition to concerns regarding the risks of opioid prescribing, there are issues relating to the appropriate and sufficient treatment of CRP. Over recent years, studies have reported a decline in opioid prescribing by oncologists, particularly for patients with metastatic cancers [15, 16] which may be caused by a variety of factors. Meta-analyses have shown that more than a third of cancer patients are undertreated based on their pain severity [17], an issue which could be exacerbated by these declines as well as stigmas surrounding opioid use [18]. There are many unanswered questions regarding the cause of these declines in prescribing and whether they are disproportionately affecting patients with metastatic cancer and have consequences for pain management, overall QoL, or the incidence of adverse events [19].

Opioid prescribing for this population is a complex balance that requires more information about the efficacy of opioids for treating chronic CRP, the risks associated with its use, and how to best manage and alleviate the plethora of other symptoms which affect patients with metastatic cancer. Due to the limited information on opioid use among this population, our study aimed to use administrative data to investigate the association between opioid prescribing and changes in patient-reported outcomes (PROs) for patients with metastatic cancer.

Methods

Data sources

Retrospective provincial health data including the Alberta Cancer Registry (ACR), Pharmacy Information Network (PIN), Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), and Surveillance & Reporting PRO data were used to abstract all study variables.

The ACR records population-based data on incident cancer patients in the province of Alberta, Canada, and maintains the highest certification from the North American Association of Central Cancer Registries [20]. The ACR was used to define demographic, treatment, cancer type, and vital status variables for our cohort. Geographic regions within the province were defined based on patients' diagnosis zone, as outlined by Alberta Health Services [21]. The PIN records data on medication prescribed to patients, including dosage, drug identification number (DIN), dispensing dates, and length of prescription for all filled prescriptions in the province. PIN data was used to define prescription subgroups and create a variable for prior opioid use, defined as the presence of opioid prescription filled in the 3–12 months prior to questionnaire completion. The DAD records data on all patients discharged from hospitals, while the NACRS records data from all hospital-based and community-based ambulatory care visits. Diagnoses in the DAD and NACRS are coded using the International Classification of Disease version 10, Canadian codes (ICD-10-CA), which were used to create a variable for the history of mental illness within our cohort (Supplementary Table 1).

Since 2016, clinical practice at all ambulatory cancer centers in the province of Alberta has included the use of patient-reported outcomes (PROs) to allow for expanded patient-centered care and research [22]. Patients complete a questionnaire called Putting Patients First (PPF) (Supplementary Fig. 1) at each visit, which includes the well-validated Edmonton Symptom Assessment System, revised version (ESASr) [19]. The ESASr captures symptoms commonly experienced by cancer patients (i.e., fatigue, pain, nausea, depression, anxiety, lack of wellbeing, etc.), rated on a 0 to 10 scale (0 representing no symptom experience and 10 being the worst possible symptom experience). The change in score on the ESASr pain scale was used as the outcome of our analysis to assess patient pain experience. Our team has extensive experience working with these provincial

administrative datasets, which have been widely used and validated. This study was approved by the Health Research Ethics Board of Alberta—Cancer Committee (reference number: HREBA.CC-21–0074).

Cohort and subgroup definition

All patients diagnosed with metastatic (stage IV) solid cancer in the province of Alberta, Canada, who had completed at least two post-diagnosis PROs within a maximum of 30 days from each other were included in our cohort. A window of 30 days was selected based on the distribution of time between PRO measures for our cohort as well as previous studies monitoring change in ESASr scores over time [23, 24]. The cohort was divided into those with an active opioid prescription between their PROs (Rx1 subgroup) and those without an active opioid prescription (Rx0 subgroup). A prescription was defined as being active from the date of dispensing to the patient and considered active for the number of days prescribed following the dispense date.

Individuals in the Rx1 subgroup were categorized into dosage subgroups based on the mean daily oral morphine equivalent (OME). OME was calculated using DIN and opioid equianalgesic dose conversion [25]. Low dosage was defined as ≤ 30 mg OME, moderate dosage as > 30 mg and ≤ 100 mg OME, and high dosage as > 100 mg OME based upon clinically relevant dosage for cancer patients [26, 27], as well as the distribution within our cohort. Individuals were additionally categorized by prescription length, defined by the number of prescription days in the time between PROs, with subgroups for ≤ 7 prescription days, > 7 and ≤ 14 prescription days, and > 14 prescription days.

Statistical analyses

Demographic and cancer-related variables, as well as PRO scores, were compared between subgroups using descriptive statistics. Univariate analyses and multivariable logistic regression were used to identify the factors associated with improvement in pain intensity rating among the full cohort and the Rx1 subgroup. Improvement in pain intensity was used as the outcome measure, with a minimal clinically important difference in the ESASr pain score defined as a 1-point change [23]. Modification by prescription length was tested using an interaction term with dosage level and found to be insignificant. Little's test was used to determine if PRO data was missing completely at random [28]. Sensitivity analyses were conducted in order to test the categorization of opioid dosage level and prescription days, as well as the maximum number of days allowed between PRO measures. Stratified analyses were carried out based on cancer type. Data analysis was carried out using RStudio Version 1.4.1106.

Results

Cohort definition

We identified 6488 patients with metastatic solid cancers who had completed at least one post-diagnosis PRO; 4741 of these individuals (73.1%) had completed a second PRO, while only 2169 (33.4%) had completed a second PRO (PRO2) within 30 days of their first PRO (PRO1) (Fig. 1). Comparison of patients with and without a second PRO found that patients lacking a second PRO were older, were more likely to be deceased at the time of data pulling, and were more likely to have a higher Charlson Comorbidity Index (CCI) score (Supplementary Table 2).

Opioid use in the time between PROs

Within our cohort ($N = 2169$), 770 (35.5%) patients had an active opioid prescription in the time between their PROs and comprised the subgroup with an active opioid prescription (Rx1 subgroup). Individuals without an active opioid prescription ($N = 1399$, 64.5%) comprised the Rx0 subgroup (Fig. 2). The Rx1 subgroup had a mean daily OME of 86.1 mg (SD 122.7 mg, range 3.8–1866.7 mg) and an average of 13.0 prescription days (SD 8.0 days, range 1–30 days) in the time between their PROs. The most common types of opioids prescribed in the time between PROs were hydromorphone (38.1% of prescriptions), morphine (17.3% of prescriptions), and oxycodone (11.8% of prescriptions) (Supplementary Table 3).

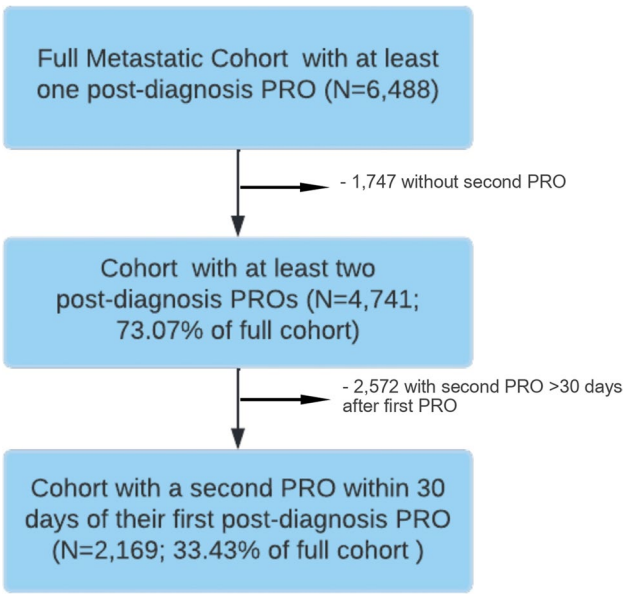

Fig. 1 Summary of cohort definition based on patient-reported outcome completion

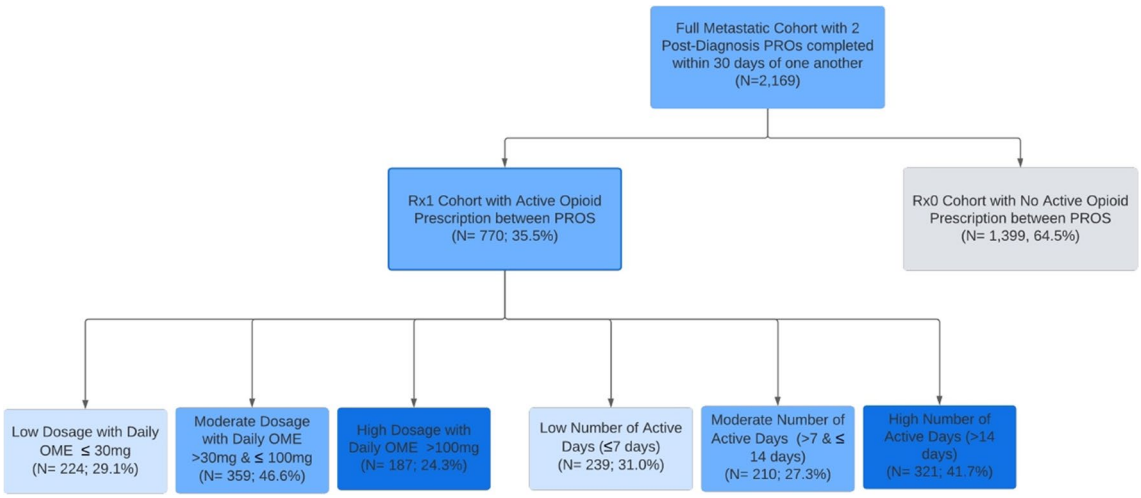

Fig. 2 Summary of cohort definitions based on opioid prescribing in the time between PROs

Of individuals with active prescription, 224 (29.1%) were categorized as having low opioid dosage, 359 (46.6%) as moderate opioid dosage, and 187 (24.3%) as high opioid dosage. Two hundred thirty-nine (31.0%) had ≤ 7 prescription days, 210 (27.3%) had > 7 and ≤ 14 prescription days, and 321 (41.7%) had > 14 prescription days in the time between PRO1 and PRO2 (Fig. 2).

Demographic and cancer-type information

There were significant differences between subgroups with and without an active opioid prescription (Table 1). Individuals with active opioid prescription were younger on average, more likely to be male, more likely to be deceased, more likely to have a higher comorbidity score, and more likely to have had prior opioid use compared to those without active opioid prescription. Individuals in higher opioid dosage subgroups were younger on average and more likely to be male, compared with individuals in lower dosage subgroups (Supplementary Table 5).

The most common cancer types for our cohort were bronchus/lung cancer (26%), colorectal cancer (18%), and other gastrointestinal (GI) cancers (13%) (Table 1). Individuals with bronchus/lung, prostate, or other GI cancers were more likely to have an active opioid prescription, while individuals with lymphoma, colorectal, or breast cancers were less likely to have an active opioid prescription.

Patient-reported outcome scores

At both PRO1 and PRO2, scores for every ESAS domain were significantly higher for the Rx1 subgroup compared to the Rx0 subgroup (Table 2). The domains with the highest scores for our cohort were tiredness and wellbeing. For individuals with active opioid prescription, pain was the third most highly scored symptom on both PROs, whereas individuals without active prescription reported pain as the 7th highest average symptom score at both PROs.

Pain and wellbeing domains were found to be significantly different between PRO1 and PRO2 for the Rx1 subgroup (Table 2). On average, people with active opioid prescription were reporting less pain intensity and better wellbeing at PRO2 compared to PRO1 (pain: 4.27 vs. 3.71; wellbeing: 4.45 vs. 3.95). This was a statistically significant but not clinically important difference in the mean score [23]. In contrast, no domains were found to be significantly different, and mean symptom scores remained relatively unchanged between PROs for individuals in the Rx0 subgroup. While individuals with active opioid prescription were more likely to report clinically important improvement in pain and wellbeing domains, dosage level or prescription length subgroups were not significantly associated with thechange in ESAS symptom scores from PRO1 to PRO2 among patients with an opioid prescription (Supplementary Table 6).

Factors associated with improvement in pain score

Multivariable logistic regression for the full cohort identified active opioid prescription as significantly associated with improvement in pain intensity rating (OR: 2.17 (95% CI: 1.72–2.74), $P < 0.001$). Recent chemotherapy was found to be significantly associated with an improvement in pain intensity (OR: 1.55 (95% CI: 1.21–1.97)), while age, sex, and socioeconomic status were not found to be significantly associated with the improvement in pain intensity (Table 3).

In multivariable analysis, among individuals with an active opioid prescription, diagnosis zone, cancer type,

Table 1 Demographic and cancer type information for opioid prescription Ssubgroups

	Active opioid prescription (Rx1)	No active opioid prescription (Rx0)	Total cohort	*P*-value
N	770	1399	2169	
Age at metastatic diagnosis (years)[1]	61.78 (11.52)	63.03 (12.49)	62.58 (12.17)	0.019
Sex[2]				
Male	446 (57.92%)	746 (53.32%)	1192 (54.96%)	0.039
Female	324 (42.08%)	653 (46.68%)	977 (45.04%)	
Vital status[2]				
Alive	203 (26.36%)	680 (48.61%)	883 (40.71%)	< 0.001*
Deceased	567 (73.63%)	719 (51.39%)	1108 (59.29%)	
Charlson comorbidity index[2]				
0	321 (41.69%)	698 (49.89%)	1019 (46.98%)	0.001*
1	242 (31.43%)	374 (26.73%)	616 (28.40%)	
≥ 2	207 (26.88%)	327 (23.37%)	534 (24.62%)	
Cancer site[2]				
Bronchus/lung	232 (30.13%)	327 (23.37%)	559 (25.77%)	< 0.001*
Colorectal	96 (12.47%)	287 (20.51%)	383 (17.66%)	
Lymphoma	37 (4.81%)	167 (11.94%)	204 (9.41%)	
Prostate	71 (9.22%)	99 (7.08%)	170 (7.84%)	
Other gastrointestinal	148 (19.22%)	144 (10.29%)	292 (13.46%)	
Head & neck	40 (5.19%)	80 (5.72%)	120 (5.53%)	
Breast	49 (6.36%)	116 (8.29%)	165 (7.61%)	
Other	97 (12.60%)	179 (12.79%)	276 (12.72%)	
Has multiple primary tumors[2]	117 (15.19%)	267 (19.09%)	384 (17.70%)	0.023
Has history of mental illness[2]	88 (11.43%)	120 (8.58%)	208 (9.59%)	0.031
Has history of opioid use[2]	391 (50.78%)	363 (25.95%)	754 (34.76%)	< 0.001*
Recent treatment[2,3]				
Chemotherapy[4]	232 (30.13%)	423 (30.24%)	655 (30.20%)	0.959
Radiotherapy[5]	63 (8.18%)	73 (5.22%)	136 (6.27%)	0.006*
Surgery[5]	17 (2.21%)	41 (2.93%)	58(2.67%)	0.318

*significant given $\alpha < 0.01$

[1]Data presented as mean (standard deviation)

[2]Data presented as number (%)

[3]Recent treatment defined as occurring in the 60 days prior to PRO1

[4]Window of chemotherapy treatment defined as treatment date + 30 days

[5] Window of radiotherapy treatment defined as treatment date + 7 days

and recent chemotherapy were found to be significantly associated with improvement in pain intensity (Table 4). Individuals with recent chemotherapy were more likely to report improvement in pain intensity (OR: 1.62 (95% CI: 1.08–2.45)) compared to those without recent chemotherapy. Individuals with prostate cancer were significantly more likely to report improvement in pain intensity (OR: 2.53 (95% CI: 1.26–5.14)) compared to patients with lung/bronchus cancer. Neither opioid dosage level nor prescription length was found to be significantly associated with the improvement in pain score. While the > 7 and ≤ 14 prescription day subgroup was significantly associated with pain improvement (1.66 (95% CI: 1.04–2.65)), there was not a clear relationship where a greater number of active days led to significantly increased odds of reporting improvement in pain.

Sensitivity and subgroup analyses

Sensitivity analyses revealed that prescription length was not consistently associated with an improvement in pain intensity, and the limits for subgroup categorization greatly impacted association within the multivariable model (Supplementary Table 8). The association between prescription length and improvement in pain intensity appears to be a consequence of the limits used to define subgroups; when

Table 2 ESAS symptom scores at PRO1 and PRO2 by opioid prescription subgroup

ESAS category	First post-diagnosis PRO (PRO1)			Second post-diagnosis PRO (PRO2)			PRO1 vs. PRO2	
	Rx0 ($N=1399$)	Rx1 ($N=770$)	*P*-value	Rx0 ($N=1399$)	Rx1 ($N=770$)	*P*-value	*P*-value	
							Rx0	Rx1
Pain	1.79 (2.24)	4.27 (2.72)	<0.001*	1.77 (2.71)	3.71 (2.71)	<0.001*	0.857	<0.001*
Tiredness	3.45 (2.71)	5.08 (2.71)	<0.001*	3.50 (2.73)	4.87 (2.63)	<0.001*	0.675	0.143
Drowsiness	2.09 (2.47)	3.67 (2.86)	<0.001*	2.19 (2.54)	3.58 (2.80)	<0.001*	0.364	0.569
Nausea	0.84 (1.78)	1.77 (2.42)	<0.001*	0.89 (1.81)	1.64 (2.39)	<0.001*	0.458	0.310
Appetite	1.85 (2.69)	3.60 (3.22)	<0.001*	1.89 (2.68)	3.45 (3.10)	<0.001*	0.730	0.373
Breath	1.82 (2.51)	2.88 (3.04)	<0.001*	1.80 (2.46)	2.59 (2.76)	<0.001*	0.843	0.075
Anxiety	2.02 (2.51)	2.88 (2.84)	<0.001*	1.82 (2.38)	2.49 (2.68)	<0.001*	0.039	0.011
Depression	1.50 (2.24)	2.55 (2.77)	<0.001*	1.39 (2.11)	2.32 (2.60)	<0.001*	0.183	0.032
Wellbeing	2.84 (2.55)	4.45 (2.60)	<0.001*	2.76 (2.50)	3.95 (2.60)	<0.001*	0.414	<0.001*

ESAS scores are presented as mean (standard deviation) for individuals with (Rx1) and without (Rx0) an active opioid prescription. All symptom scales range from 0, representing no symptom experience, to 10, representing worst possible symptom experience

*significant, given $\alpha < 0.01$

considered as a continuous variable, the number of prescription days was not significantly associated with improvement in pain intensity. Sensitivity analyses further demonstrated that regardless of constraints for defining dosage level subgroups, prescription dosage level was not significantly associated with improvement in pain intensity (Supplementary Table 9). Sensitivity analyses to test the maximum number of days allowed between PRO1 and PRO2 indicated that dosage level became more significantly associated with an improvement in pain intensity as the maximum number of days between PROs increased (Supplementary Table 10). Prescription length remained not significantly associated with improvement in pain intensity, regardless of the maximum number of days allowed between PROs. A stratified analysis revealed that prescription dosage level and length remain not significantly associated with improvement in pain intensity, regardless of cancer type (Supplementary Table 11). Little's test indicated that the pain intensity rating at PRO1 was missing completely at random ($p=0.11$) with respect to demographic and cancer-related variables. However, Little's test indicated that the pain intensity rating at PRO2 was not missing completely at random ($P<0.01$) (Supplementary Table 12).

Discussion

Using large population-based administrative health data, we conducted a retrospective cohort study to determine the associations between opioid prescribing and changes in patient-reported outcomes among patients with metastatic cancer. It was found that patients with active opioid prescription experienced a greater level of pain severity compared to those without active opioid prescription. Despite reporting increased levels of pain, the opioid prescription was associated with improvement in pain intensity, indicating the value of opioid prescribing for cancer pain management. Opioids have been shown to be highly effective for treating CRP in the majority of cases [29], in agreement with our findings. This justifies concerns arising due to observed declines in opioid prescribing among patients with metastatic cancer [15, 16]. Whether changes in prescribing practices are affecting patients with metastatic cancer in Alberta is not clear and requires further investigation into longitudinal trends in prescribing as well as their impact on pain management outcomes.

Within our cohort, opioids were prescribed for 35.5% of patients in the time between questionnaires. While there is limited literature on opioid prescribing for patients living with metastatic cancer, this proportion is the same as that found in a study of US patients with poor prognosis cancers in the 30 days before end-of-life or hospice enrollment [30]. However, this rate is notably lower than the rate of opioid prescribing reported in a study on patients with cancer receiving palliative care in Europe [31]. This difference in prescribing may be due to the prolonged survival time for many patients in our cohort, in contrast to this study which only included patients at the end-of-life. Secondly, our cohort received a relatively high opioid dosage level, with 24.3% of patients who had an active opioid prescription receiving a mean daily OME ≥ 100 mg. This is consequential, as the incidence of opioid-induced adverse events has previously been found to be greater as the daily opioid dose becomes higher [32, 33] and opioid dosages of this level are considered by the World Health Organization to be a risk factor for overdose in non-cancer populations [34]. However, it is not clear whether these dosage levels are associated with a higher incidence of adverse events among patients with

Table 3 Multivariable logistic regression in full cohort to determine factors associated with improvement in patient-reported pain

Variable		Odds ratio (95% CI)	*P*-value
Presence of active opioid prescription		2.17 (1.72–2.74)	< 0.001*
Age (in years)		1.00 (0.99–1.01)	0.405
Sex	Female	Reference	0.009*
	Male	0.73 (0.57–0.92)	
Charlson comorbidity index	0	Reference	0.440
	1	1.05 (0.81–1.36)	
	≥ 2	1.20 (0.91–1.58)	
Diagnosis zone	Calgary	Reference	0.105
	South	1.30 (0.92–1.85)	
	Central	1.01 (0.73–1.38)	
	Edmonton	1.38 (1.00–1.91)	
	North	1.39 (0.97–1.99)	
Cancer type	Bronchus/lung	Reference	0.017
	Lymphoma	0.79 (0.51–1.21)	
	Colorectal	1.03 (0.73–1.44)	
	Prostate	1.97 (1.27–3.05)	
	Other gastrointestinal	1.03 (0.71–1.49)	
	Head & neck	0.94 (0.54–1.58)	
	Breast	1.43 (0.92–2.20)	
	Other	1.18 (0.81–1.72)	
Year of metastatic diagnosis	2004–2009	Reference	0.369
	2010–2014	0.70 (0.35–1.42)	
	2015–2019	0.64 (0.34–1.23)	
Has multiple primary tumors		1.14 (0.87–1.50)	0.341
Has history of mental illness		1.13 (0.79–1.61)	0.509
Has history of opioid use		0.77 (0.61–0.98)	0.035
Received recent chemotherapy		1.55 (1.21–1.97)	< 0.001*
Received recent radiotherapy		0.95 (0.61–1.46)	0.816
Received recent surgery		1.19 (0.64–2.17)	0.583
Educational attainment of neighborhood (% who completed high school)	1st quintile	Reference	0.514
	2nd quintile	1.26 (0.90–1.76)	
	3rd quintile	1.15 (0.80–1.65)	
	4th quintile	1.01 (0.69–1.47)	
	5th quintile	1.24 (0.84–1.84)	
Neighborhood annual income per capita	1st quintile	Reference	0.009*
	2nd quintile	0.68 (0.49–0.95)	
	3rd quintile	0.63 (0.45–0.89)	
	4th quintile	1.04 (0.73–1.47)	
	5th quintile	0.77 (0.54–1.12)	

*significant, given $\alpha < 0.01$

metastatic cancer. Further studies are needed to examine the incidence of opioid-induced adverse events in this population as well as their impact on patient symptom burden, QoL, and survival.

Although the presence of an opioid prescription was associated with improvement in patient pain intensity, neither dosage level nor the number of prescription days was significantly associated with pain improvement among patients with active prescriptions. Previous studies have demonstrated that daily dose of opioids tends to increase as patients near the end-of-life [35, 36] which agrees with our findings as we observed signs of more terminal disease and greater symptom burden among patients receiving opioids. Some patients may experience diminishing opioid efficacy over time which may be a result of the development of opioid tolerance, opioid-induced hyperalgesia, or individual factors [37]. However, it is important to note that opioid dose escalation is likely linked with disease

Table 4 Multivariable logistic regression in Rx1 cohort to determine factors associated with improvement in patient-reported pain

Variable		Odds ratio (95% CI)	*P*-value
Dosage category	Low	Reference	0.365
	Moderate	0.81 (0.53–1.23)	
	High	1.09 (0.67–1.79)	
Number of prescription days	≤ 7 days	Reference	0.087
	> 7 & ≤ 14 days	1.66 (1.04–2.65)	
	> 14 days	1.42 (0.92–2.18)	
Age (in years)		1.01 (0.99–1.02)	0.480
Sex	Female	Reference	0.250
	Male	0.79 (0.53–1.18)	
Charlson comorbidity index	0	Reference	0.904
	1	1.09 (0.72–1.66)	
	≥ 2	1.09 (0.69–1.70)	
Cancer type	Bronchus/lung	Reference	0.042*
	Lymphoma	0.61 (0.23–1.51)	
	Colorectal	1.05 (0.58–1.90)	
	Prostate	2.53 (1.26–5.14)	
	Other gastrointestinal	0.71 (0.41–1.20)	
	Head & neck	0.72 (0.29–1.70)	
	Breast	1.25 (0.58–2.69)	
	Other	1.15 (0.62–2.12)	
Year of metastatic diagnosis	2004–2009	Reference	0.998
	2010–2014	1.05 (0.26–4.83)	
	2015–2019	1.04 (0.28–4.44)	
Has multiple primary tumors		1.40 (0.86–2.29)	0.181
Has history of mental illness		1.00 (0.57–1.75)	0.997
Has history of opioid use		0.79 (0.54–1.14)	0.205
Received recent chemotherapy		1.62 (1.08–2.45)	0.020☆
Received recent radiotherapy		0.91 (0.47–1.76)	0.779
Received recent surgery		1.04 (0.33–3.19)	0.941
Educational attainment of neighborhood (% who completed high school)	1st quintile	Reference	0.081
	2nd quintile	1.55 (0.92–2.62)	
	3rd quintile	1.47 (0.82–2.66)	
	4th quintile	0.92 (0.49–1.71)	
	5th quintile	1.86 (0.98–3.60)	
Neighborhood annual income per capita	1st quintile	Reference	0.126
	2nd quintile	0.79 (0.47–1.34)	
	3rd quintile	0.52 (0.30–0.90)	
	4th quintile	0.93 (0.53–1.66)	
	5th quintile	0.63 (0.34–1.14)	
Diagnosis zone	Calgary	Reference	0.027*
	South	1.71 (0.95–3.07)	
	Central	1.78 (1.06–2.98)	
	Edmonton	2.23 (1.32–3.82)	
	North	1.85 (1.01–3.41)	

*significant given $\alpha < 0.05$

progression and terminal-stage disease, causing increased pain severity, rather than the development of pharmacological tolerance [38]. This may explain the lack of association between dosage level and pain improvement, which may be indicative of a more progressive or advanced disease course among these patients. Further studies would be beneficial to better understand the reasons for elevated symptom burden among patients who are receiving high

dosage or longer length opioid prescriptions, as well as how to alleviate this burden.

Due to the increased likelihood of moderate-severe pain reporting among patients with high-dose opioid prescriptions [39] without the increased likelihood of reporting alleviation, our findings indicate that these patients are prime candidates for increased palliative care and symptom management interventions. For about 1-in-5 cases, CRP cannot be controlled with simple treatments [40], and the use of nonpharmacological approaches and/or second-line agents is central to providing these patients with the best possible care. There are several evidence-based non-pharmacological strategies for the treatment of cancer pain, including both physical and psychological approaches [9]. Increased information on and availability of resources such as mind–body approaches [41] or other psychosocial interventions [42] may be useful in addressing the increased pain and symptom burden observed among these patients. While there are encouraging preliminary results for non-pharmacological interventions such as music therapy, more research is needed on these topics [43]. Additionally, early referral to palliative care services has been found to improve pain management and QoL for patients with advanced cancer and may be useful for addressing the elevated symptom burden in this population [44]. Further trials are warranted to investigate the feasibility and efficacy of implementing multidisciplinary management strategies for treating CRP among patients with metastatic disease who are receiving opioid prescriptions.

Limitations

Due to the retrospective, quantitative design of our study, we are unable to determine if the associations reported in this study are causally related. Furthermore, we were unable to ascertain information on patient compliance with prescription instructions, which may impact our findings and result in patients being misclassified based on the prescription length or dosage level. In this population, deviations from prescription instructions generally tend toward opioid-restricting behaviors [45] and may thereby result in an underestimation of the association in our study. Interventional studies would be useful to validate the efficacy of increased opioid prescribing for a reduction in metastatic cancer pain, and qualitative studies would be beneficial to determine the causes of increased symptom burden within this population. Additionally, the ESAS measure is designed to capture patients' symptom experience at the time of questionnaire completion and may not be representative of symptom experience over more extended time periods.

The cohort for our study was limited to patients with de novo metastatic cancer (stage IV at diagnosis), as we were unable to identify patients with metastasis due to progression or recurrence using administrative health data. Studies which would facilitate the identification of progressive disease and recurrent metastasis would be useful to enable population-based studies of the full metastatic cancer population. Additionally, our study cohort consisted of individuals with > 1 PRO measure, resulting in selection bias for the included cohort. This may have impacted the results of our analysis, as the patients with only 1 PRO measure were older on average, more likely to be deceased at the time of data pulling, and had a higher comorbidity score. These findings may therefore not be applicable to patients with more aggressive or terminal-stage metastatic disease.

Conclusions

Opioid prescribing is associated with improvement in pain among patients with metastatic cancer and is important for cancer pain management. However, patients with higher dosage or duration prescriptions are not more likely to experience improvements in their pain when compared to patients with lower dosage or shorter duration prescriptions, potentially due to experiencing more advanced disease and symptom complexity. Patients with increased levels of opioid prescribing may therefore be ideal targets for increased palliative care, including multidimensional pain management strategies to improve pain management outcomes. Further e studies are warranted to evaluate the reasons for elevated symptom intensity among patients receiving opioid prescriptions and the utility of multidisciplinary pain management strategies to improve patient outcomes within this population.

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Data Availability All data used for the analyses in this paper were abstracted from provincial administrative data sources in Alberta, Canada.

Declarations

Ethics approval This study was approved by the Health Research Ethics Board of Alberta and was completed in accordance with ethical standards outlined in the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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