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ORIGINAL RESEARCH ARTICLE

Adverse Events Associated with Cumulative Corticosteroid Use in Patients with Castration-Resistant Prostate Cancer: An Administrative Claims Analysis

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Abstract

Introduction Corticosteroids are a mainstay treatment for castration-resistant prostate cancer (CRPC). Although corticosteroids have been associated with adverse events, long-term outcomes related to their sustained use have not been assessed in men with CRPC.

Objective This study evaluated the impact of cumulative corticosteroid exposure on the risk of developing specific adverse events in men with CRPC.

Methods Data were obtained from administrative claims databases. Adult chemotherapy-naïve men who initiated CRPC treatment following surgical or medical castration were selected. Patients were grouped into four cohorts based on cumulative corticosteroid dose: no exposure, low exposure (< 0.5 g), medium exposure (0.5–2.0 g), and high exposure (> 2.0 g). Time to each adverse event was assessed using Kaplan–Meier analyses and time-dependent Cox proportional hazard models, adjusting for baseline characteristics.

Results Overall, 9425 patients were included (no exposure, $N = 6765$; low exposure, $N = 1660$; medium exposure, $N = 655$; high exposure, $N = 345$). The mean age was 71–76 years across cohorts. During the study period, cumulative corticosteroid exposure was associated with a significantly higher risk of developing an infection [high vs. no exposure, adjusted hazard ratio (HR) 2.55; 95% confidence interval (CI) 2.27–2.85; $p < 0.001$ for trend], peptic ulcer (HR 1.91; 95% CI 1.39–2.64; $p < 0.001$), acute cardiovascular events (HR 1.62; 95% CI 1.43–1.83; $p < 0.001$), endocrine disorder (HR 1.61; 95% CI 1.34–1.94; $p < 0.001$), fracture (HR 1.59; 95% CI 1.37–1.86; $p < 0.001$), or mental health condition (HR 1.28; 95% CI 1.06–1.55; $p = 0.014$). Exposure to corticosteroids was associated with a more rapid onset of adverse events.

Conclusion Patients with CRPC receiving corticosteroids had a higher risk of developing a wide range of adverse events than those not receiving them. The increased adverse event risk was observed after accounting, to the extent possible, for patients' overall disease severity.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40264-019-00867-6) contains supplementary material, which is available to authorized users.

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Key Points

This study used claims data to assess the impact of no, low (< 0.5 g), medium (0.5–2.0 g), and high (> 2.0 g) corticosteroid exposure on the risk of developing certain adverse events in men with castration-resistant prostate cancer (CRPC).

We observed that patients with CRPC receiving corticosteroids had a significantly higher risk than those not receiving corticosteroids of developing infections, peptic ulcers, acute cardiovascular events, endocrine disorders, fractures, or mental health conditions.

In addition, the risk of experiencing these adverse events increased with cumulative corticosteroid exposure.

1 Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer-related death for men in the USA [1]. Within 5 years of prostate cancer diagnosis, 10–20% of patients develop castration-resistant prostate cancer (CRPC) [2], defined as prostate cancer that progresses despite the use of surgical or medical castration via androgen-deprivation therapy (ADT) [2, 3]. The prognosis for CRPC is poor, with a median overall survival of < 3 years [4].

Corticosteroids have been used in the management of CRPC for over 3 decades as concomitant and palliative treatment [5–7]. In particular, corticosteroids are commonly used to mitigate the toxic effects of antineoplastic agents (e.g., docetaxel and cabazitaxel) and secondary hormonal therapies (e.g., ketoconazole and abiraterone acetate) [5, 6]. Because of their anti-inflammatory activity, corticosteroids are also used to ameliorate metastasis-related symptoms such as metastatic bone pain [5, 6]. However, corticosteroids have been linked to several toxicities, particularly when used for an extended period of time and/or at high doses [5–8].

In the medical literature, some of the adverse events most commonly reported in corticosteroid-treated patients include osteoporosis, fractures, weight gain, hyperglycemia, diabetes, adrenal suppression, infections, myopathy, insomnia, hypertension, glaucoma, psychiatric disturbances, peptic ulcers, and cardiovascular disease [5, 8–10]. In addition, prolonged exposure to corticosteroids is linked to steroid dependency, wherein abrupt withdrawal can result in severe side effects such as secondary adrenal insufficiency, myalgia, anorexia, nausea, asthenia, and arthralgia [6, 11]. Nevertheless, the long-term outcomes of sustained corticosteroid use has not been investigated in the population of patients with CRPC [5, 6]. Because CRPC is often diagnosed in the seventh decade of life [12] and typically requires years of therapy [3, 5], unwanted adverse events stemming from prolonged corticosteroid exposure may have a particularly negative impact on patients with CRPC, exacerbating existing comorbidities and diminishing quality of life [5, 6]. In recent years, several novel agents that do not require concomitant corticosteroids have been approved in the USA for the treatment of metastatic and/or nonmetastatic CRPC (e.g., sipuleucel-T, apalutamide, and enzalutamide), but the use of corticosteroids in the management of CRPC remains common in clinical practice [6, 7]. Therefore, it is important to better understand the adverse events associated with treatment with corticosteroids among patients with CRPC. To investigate this important issue, we conducted a retrospective study to quantify, for the first time, the association between cumulative corticosteroid exposure and the risk of developing adverse events among patients with CRPC.

2 Methods

2.1 Data Source

Data for this study were obtained from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database (2007–2016). The current manuscript was generated from a larger study, which was designed to address two research objectives; the results of the impact of corticosteroid exposure on healthcare resource utilization have been published elsewhere [13]. Data were fully de-identified and compliant with the Health Insurance Portability and Accountability Act. No institutional review board approval was required.

2.2 Patient Selection and Study Design

To be included in the study, male patients aged ≥ 18 years were required to have at least one medical claim with a diagnosis code for prostate cancer [*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 185 or ICD-10-CM code C61] and a confirmed history of surgical castration (unilateral or bilateral orchiectomy) or medical castration (defined as ≥ 6 months of continuous ADT with luteinizing hormone-releasing hormone agonists or antagonists, including leuprolide, goserelin, triptorelin, histrelin, or degarelix). If patients had claims for both surgical and medical castration, they were recorded as having surgical castration. Additionally, patients were required to have initiated a treatment for either metastatic or nonmetastatic CRPC (Table 1) following surgical or medical castration, which serves as an indicator of progression to castration-resistant disease; the date of CRPC treatment initiation was defined as the index date. Continuous enrollment for ≥ 12 months before and ≥ 3 months after the index date was required. Patients treated with any cytotoxic chemotherapy before the index date were excluded. The use of corticosteroids (betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone) was evaluated during the baseline period, defined as the 12 months before the index date. Doses of different corticosteroids were standardized to equivalent prednisone strengths. Injectable corticosteroid treatments were not included in the analysis because they could not be converted to prednisone-equivalent doses and represented < 1% of corticosteroid use in the current data. Patients with implausible corticosteroid doses (daily prednisone-equivalent dose > 150 mg) were excluded (Fig. 1). The use of nonsteroidal anti-inflammatory drugs was not assessed in the current study. Drugs in the MarketScan databases were captured

Table 1 Baseline characteristics of patients with castration-resistant prostate cancer by cohort

Patient characteristics	No exposure cohort ($n=6765$)	Low exposure cohort (<0.5 g) ($n=1660$)	Medium exposure cohort (0.5–2.0 g) ($n=655$)	High exposure cohort (>2.0 g) ($n=345$)
Age, years	76.0 ± 10.5	73.7 ± 10.8	72.7 ± 10.6	71.0 ± 10.8
Geographical region				
North central	2233 (33.0)	575 (34.6)	205 (31.3)	81 (23.5)
Northeast	1222 (18.1)	269 (16.2)	145 (22.1)	67 (19.4)
South	2087 (30.8)	576 (34.7)	189 (28.9)	132 (38.3)
West	1208 (17.9)	238 (14.3)	115 (17.6)	63 (18.3)
Unknown	15 (0.2)	2 (0.1)	1 (0.2)	2 (0.6)
Insurance type				
Comprehensive	2785 (41.2)	579 (34.9)	202 (30.8)	96 (27.8)
PPO	2785 (41.2)	768 (46.3)	322 (49.2)	167 (48.4)
HMO and other capitated plans	695 (10.3)	168 (10.1)	68 (10.4)	38 (11.0)
Other	500 (7.4)	145 (8.7)	63 (9.6)	44 (12.8)
Medicare supplemental coverage	5430 (80.3)	1214 (73.1)	467 (71.3)	219 (63.5)
Year of index date				
2007–2010	2208 (32.6)	508 (30.6)	207 (31.6)	100 (29.0)
2011–2013	2809 (41.5)	694 (41.8)	283 (43.2)	154 (44.6)
2014–2016	1748 (25.8)	458 (27.6)	165 (25.2)	91 (26.4)
Medical castration treatment received[a]	6616 (97.8)	1617 (97.4)	634 (96.8)	335 (97.1)
CRPC treatments initiated on index date[b]				
Abiraterone	614 (9.1)	397 (23.9)	118 (18.0)	59 (17.1)
Bicalutamide	3888 (57.5)	408 (24.6)	116 (17.7)	34 (9.9)
Cabazitaxel	6 (0.1)	2 (0.1)	1 (0.2)	6 (1.7)
Docetaxel	473 (7.0)	533 (32.1)	268 (40.9)	129 (37.4)
Enzalutamide	410 (6.1)	63 (3.8)	52 (7.9)	59 (17.1)
Flutamide	212 (3.1)	33 (2.0)	9 (1.4)	2 (0.6)
Ketoconazole	550 (8.1)	131 (7.9)	48 (7.3)	29 (8.4)
Nilutamide	226 (3.3)	39 (2.3)	13 (2.0)	9 (2.6)
Radium-223	12 (0.2)	6 (0.4)	6 (0.9)	5 (1.4)
Sipuleucel-T	378 (5.6)	50 (3.0)	24 (3.7)	13 (3.8)
Cumulative CS dose during the baseline period, g	0.0 ± 0.0	0.2 ± 0.1	1.1 ± 0.4	3.4 ± 2.6
Comorbidities during the baseline period, CCI[c]	2.7 ± 1.2	2.9 ± 1.3	3.0 ± 1.3	+3.0 ± 1.4
CS-related conditions				
Cardiovascular disease				
Hypertensive disease	4130 (61.0)	1019 (61.4)	431 (65.8)	200 (58.0)
Ischemic heart disease	1930 (28.5)	507 (30.5)	188 (28.7)	71 (20.6)
Cerebrovascular disease	859 (12.7)	220 (13.3)	82 (12.5)	32 (9.3)
Heart failure	637 (9.4)	170 (10.2)	68 (10.4)	41 (11.9)
Diabetes	1922 (28.4)	431 (26.0)	168 (25.6)	90 (26.1)
Cataracts	1351 (20.0)	314 (18.9)	110 (16.8)	63 (18.3)
Peripheral vascular disease	960 (14.2)	242 (14.6)	89 (13.6)	44 (12.8)
Glaucoma	950 (14.0)	205 (12.3)	89 (13.6)	45 (13.0)
Fractures	480 (7.1)	163 (9.8)	78 (11.9)	42 (12.2)
Osteoporosis	423 (6.3)	106 (6.4)	47 (7.2)	28 (8.1)
Peptic ulcers and related complications	60 (0.9)	12 (0.7)	7 (1.1)	10 (2.9)
Mental health conditions				
Depression	324 (4.8)	108 (6.5)	52 (7.9)	26 (7.5)
Bipolar disorder	21 (0.3)	4 (0.2)	5 (0.8)	1 (0.3)

Table 1 (continued)

Patient characteristics	No exposure cohort ($n=6765$)	Low exposure cohort (<0.5 g) ($n=1660$)	Medium exposure cohort (0.5–2.0 g) ($n=655$)	High exposure cohort (>2.0 g) ($n=345$)
Infections				
Pneumonia	264 (3.9)	117 (7.0)	63 (9.6)	43 (12.5)
Septicemia/bacteremia	127 (1.9)	52 (3.1)	23 (3.5)	23 (6.7)
Endocrine disorders				
Abnormal glucose level	334 (4.9)	90 (5.4)	33 (5.0)	22 (6.4)
Adrenal disorder	51 (0.8)	19 (1.1)	13 (2.0)	8 (2.3)
Abnormal weight gain	26 (0.4)	8 (0.5)	3 (0.5)	1 (0.3)
Prostate cancer-related comorbidities				
Bone metastasis	2158 (31.9)	863 (52.0)	440 (67.2)	262 (75.9)
Urinary tract infection	962 (14.2)	303 (18.3)	112 (17.1)	55 (15.9)
Impotence	373 (5.5)	98 (5.9)	40 (6.1)	18 (5.2)

Data are presented as mean ± standard deviation or *n* (%) unless otherwise indicated

CCI Charlson Comorbidity Index, *CRPC* castration-resistant prostate cancer, *CS* corticosteroid, *HMO* health maintenance organization, *PPO* preferred provider organization

[a]The remaining patients received surgical castration

[b]Combination therapies were included in CRPC treatments initiated at index date and included bicalutamide and ketoconazole, radium-223 and enzalutamide, abiraterone and bicalutamide, and docetaxel and abiraterone

[c]The CCI was modified to exclude prostate cancer and metastatic disease

using the national drug code in prescription claims (identified via a combination of generic names listed in the manuscript and route of administration) and the Healthcare Common Procedure Coding System codes in medical claims.

The study period was defined as the period from the index date to the end of continuous enrollment or data availability, whichever occurred first.

2.3 Study Cohorts

Patients were grouped into four cohorts according to cumulative corticosteroid dose during the baseline period: no corticosteroid exposure, low exposure (cumulative dose < 0.5 g, corresponding to < 1.4 mg/day over 360 days), medium exposure (cumulative dose 0.5–2.0 g, corresponding to 1.4–5.6 mg/day over 360 days), and high exposure (cumulative dose > 2.0 g, corresponding to > 5.6 mg/day over 360 days). Given that the medical literature provides no consensus on how to define low, medium, and high corticosteroid use, the cohorts were selected based on the dose distribution observed in the data to ensure a sufficient sample size for each cohort, as done in other studies, with the consideration that the cut-off values for the cumulative doses had to be easily interpretable [10, 14–16].

2.4 Study Outcomes

Time to adverse event was defined as the number of days from the index date to each of the following adverse events [all ICD-9-CM/ICD-10-CM codes are listed in Table 1 in the Electronic Supplementary Material (ESM)]: fracture, infection (pneumonia, septicemia, or bacteremia), endocrine disorder (adrenal disorder, abnormal weight gain, abnormal glucose level), peptic ulcer and related complications, mental health conditions (bipolar disorder or depression), and acute cardiovascular events (acute myocardial infarction, atrial fibrillation/flutter, heart failure, acute ischemic stroke). These adverse events were selected based on their prevalence and clinical importance in the elderly, according to the medical literature and clinical expert opinion [17–20]. The cumulative incidence of adverse events was assessed 6 and 12 months after the index date.

2.5 Statistical Analyses

Baseline characteristics were described using means, medians, and standard deviations for continuous variables and using counts and proportions for categorical variables.

Time to each adverse event was estimated using Kaplan–Meier analyses and compared using log-rank tests between each corticosteroid exposure cohort (i.e., low, medium, and high) and the no exposure cohort. Patients were followed over the study period until the date of the first

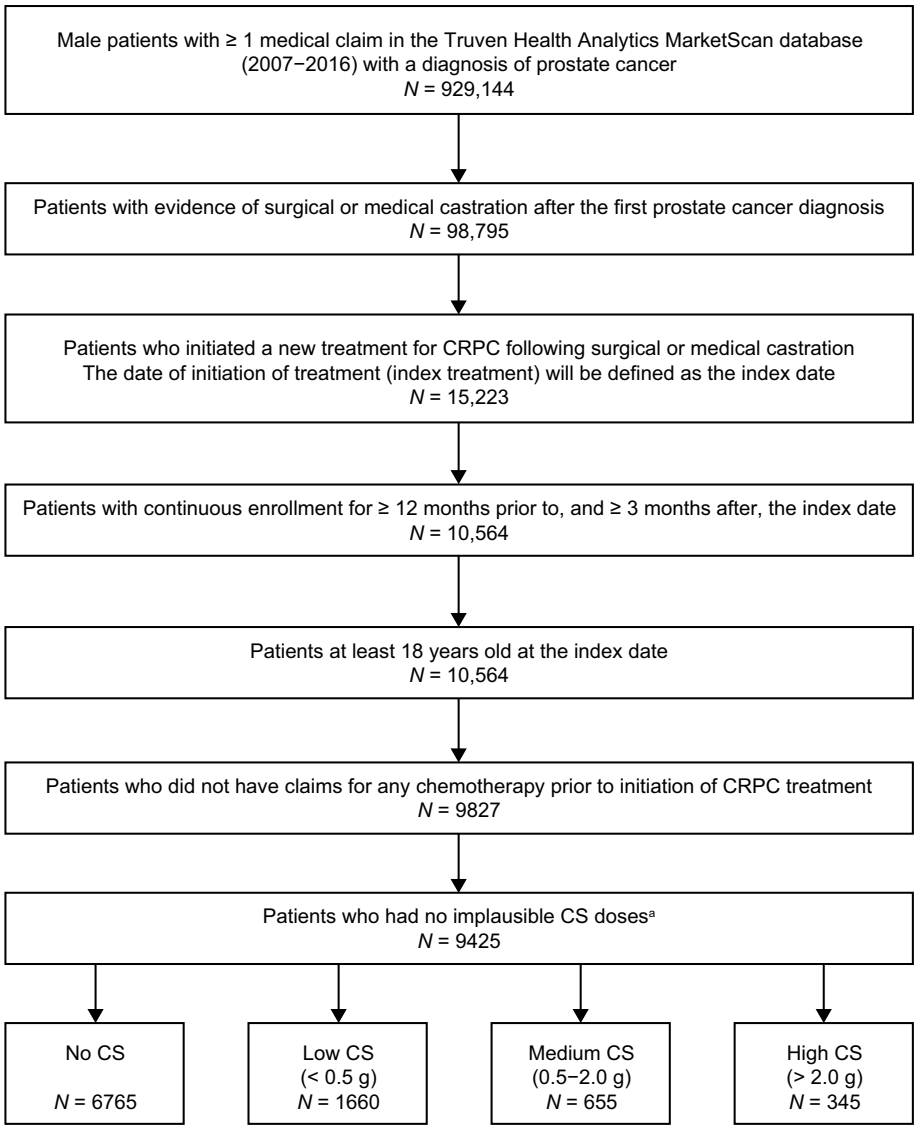

Fig. 1 Sample selection flowchart. *CRPC* castration-resistant prostate cancer, *CS* corticosteroid. [a]CSs identified in the data included betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone

recorded event of interest; data for patients without a specific event over the entire study period were censored at the end of continuous healthcare plan enrollment or data availability, whichever occurred first. For each adverse event, Kaplan–Meier analyses were conducted among patients who did not have that specific event during the baseline period (i.e., only incident cases were assessed). Patient data were restricted to 1 year after the index date in the Kaplan–Meier analyses to ensure relevance of the observed adverse events and baseline cumulative corticosteroid exposure.

Multivariable time-dependent Cox proportional hazard regression models were used to evaluate the association between corticosteroid cohorts and the risk of a particular adverse event, with the no exposure cohort as reference. Both unadjusted and adjusted comparisons were conducted. In the Cox regression analyses, cumulative corticosteroid dose was considered time dependent and was updated after the index date to capture new prescriptions of corticosteroids during the study period until the occurrence of the adverse event or until the end of continuous healthcare plan enrollment or data availability, whichever occurred first. Because both the outcome (adverse events) and the exposure (cumulative corticosteroid dose) continued to be updated after the index date, the Cox regression analysis did not restrict patient data to 1 year after the index date.

Models were adjusted for the following baseline covariates: age, index year, region, presence of bone metastases, Charlson Comorbidity Index (CCI), and presence of adverse events other than the outcome of the given model (i.e., fractures, infections, endocrine disorders, cardiovascular events, peptic ulcers and related complications, and mental health conditions). The *p* values for trend across the low, medium, and high corticosteroid exposure cohorts were calculated for each adverse event.

3 Results

In total, 9425 patients in four cohorts were included in the analysis (Fig. 1): no exposure, $n = 6765$; low exposure, $n = 1660$; medium exposure, $n = 655$; and high exposure, $n = 345$. The relative distribution of patients across cohorts remained similar for each index year.

3.1 Baseline Characteristics

At baseline, on average, patients in the no exposure cohort were older than those in the other three cohorts (means 76.0 vs. 71.0–73.7 years) (Table 1). Across cohorts, the majority of patients had received medical castration (98%), and only 2% had undergone surgical castration. The proportion of patients initiating antiandrogen therapies was higher in the no corticosteroid exposure cohort than in the other three exposure cohorts (70.0 vs. 29.0–32.7%) (Table 1). With respect to baseline comorbidities, patients in the no exposure cohort had lower mean CCI scores than those in the other three exposure cohorts (2.7 vs. 2.9–3.0), and > 70% of patients in each cohort had cardiovascular disease (Table 1). The proportion of patients with bone metastases in the low, medium, and high exposure cohorts (52–76%) was larger than that in the no exposure cohort (32%). A similar pattern was observed for other comorbidities, including fractures, infections, anxiety, depression, adrenal disorder, and urinary tract infections.

3.2 Time to First Adverse Event

During the study period, patients in the low, medium, and high exposure cohorts were 31, 46, and 59% more likely to have a fracture than were patients in the no exposure cohort [low exposure adjusted hazard ratio (HR) 1.31; 95% confidence interval (CI) 1.11–1.55; medium exposure HR 1.46; 95% CI 1.24–1.71; high exposure HR 1.59; 95% CI 1.37–1.86; all $p < 0.001$ for trend] (Fig. 2). A similar trend was observed for infections, with patients in the high exposure cohort being 2.55 times more likely to develop an infection than patients in the no exposure cohort (HR 2.55; 95% CI 2.27–2.85; $p < 0.001$ for trend). Similarly, patients in the medium and high exposure cohorts were 47 and 61% more likely than those in the no exposure cohort to experience an endocrine disorder (medium exposure HR 1.47; 95% CI 1.21–1.78; high exposure HR 1.61; 95% CI 1.34–1.94; all $p < 0.001$ for trend). Patients in the low, medium, and high exposure cohorts were ≥ 37% more likely than those in the no exposure cohort to develop a peptic ulcer and related complications (low exposure HR 1.37; 95% CI 0.96–1.97; medium exposure HR 1.60; 95% CI 1.14–2.25; high exposure HR 1.91; 95% CI 1.39–2.64; all $p < 0.001$ for trend) and ≥ 13% more likely to experience a mental health condition ($p = 0.014$ for trend). The risk of developing acute cardiovascular events was significantly higher for patients in the low, medium, and high corticosteroid exposure cohorts than for patients in the no exposure cohort (low exposure HR 1.32; 95% CI 1.16–1.51; medium exposure HR 1.49; 95% CI 1.31–1.69; high exposure HR 1.62; 95% CI 1.43–1.83; all $p < 0.001$ for trend).

Time to fracture (Fig. 3a) was shorter for patients in the low, medium, and high corticosteroid exposure cohorts than for patients in the no exposure cohort (all log-rank $p < 0.001$). Within 1 year of the index date, 10.3–11.6% of patients in the low, medium, and high exposure cohorts and 7.7% of patients in the no exposure cohort had a fracture. Similarly, time to infection (Fig. 3b) was shorter for patients in the low, medium, and high exposure cohorts than for patients in the no exposure cohort (all log-rank $p < 0.001$). Within 1 year of the index date, 19.6–27.5% of patients in the low, medium, and high exposure cohorts and 13.6% of patients in the no exposure cohort developed an infection.

Time to acute cardiovascular events (Fig. 3c) was shorter for patients in the low, medium, and high exposure cohorts than for patients in the no exposure cohort (log-rank $p = 0.026$, $p = 0.008$, $p = 0.006$, respectively). During the 1-year period after the index date, 18.3–20.1% of patients in the low, medium, and high exposure cohorts and 16.0% of patients in the no exposure cohort experienced an acute cardiovascular event.

Time to endocrine disorder (see Fig. 1 in the ESM) was shorter for patients in the low, medium, and high exposure cohorts than for patients in the no exposure cohort. In addition, 5.9–6.6% of patients in the low, medium, and high exposure cohorts and 5.1% of patients in the no exposure cohort experienced an endocrine disorder during the 1-year period after the index date. Time to peptic ulcers or mental health conditions was not significantly different between cohorts with and without corticosteroid exposure (see Figs. 2 and 3 in the ESM).

4 Discussion

While chronic exposure to corticosteroids has been associated with myriad adverse events in many diseases, its effect on patients with CRPC has not been assessed using real-world evidence [5]. Therefore, it is important to better understand the adverse events that are associated with corticosteroid treatment among patients with CRPC. To evaluate this association, we conducted a retrospective study using administrative claims data to quantify, for the first time, the association between cumulative corticosteroid exposure and the risk of developing a wide range of adverse events in patients with CRPC.

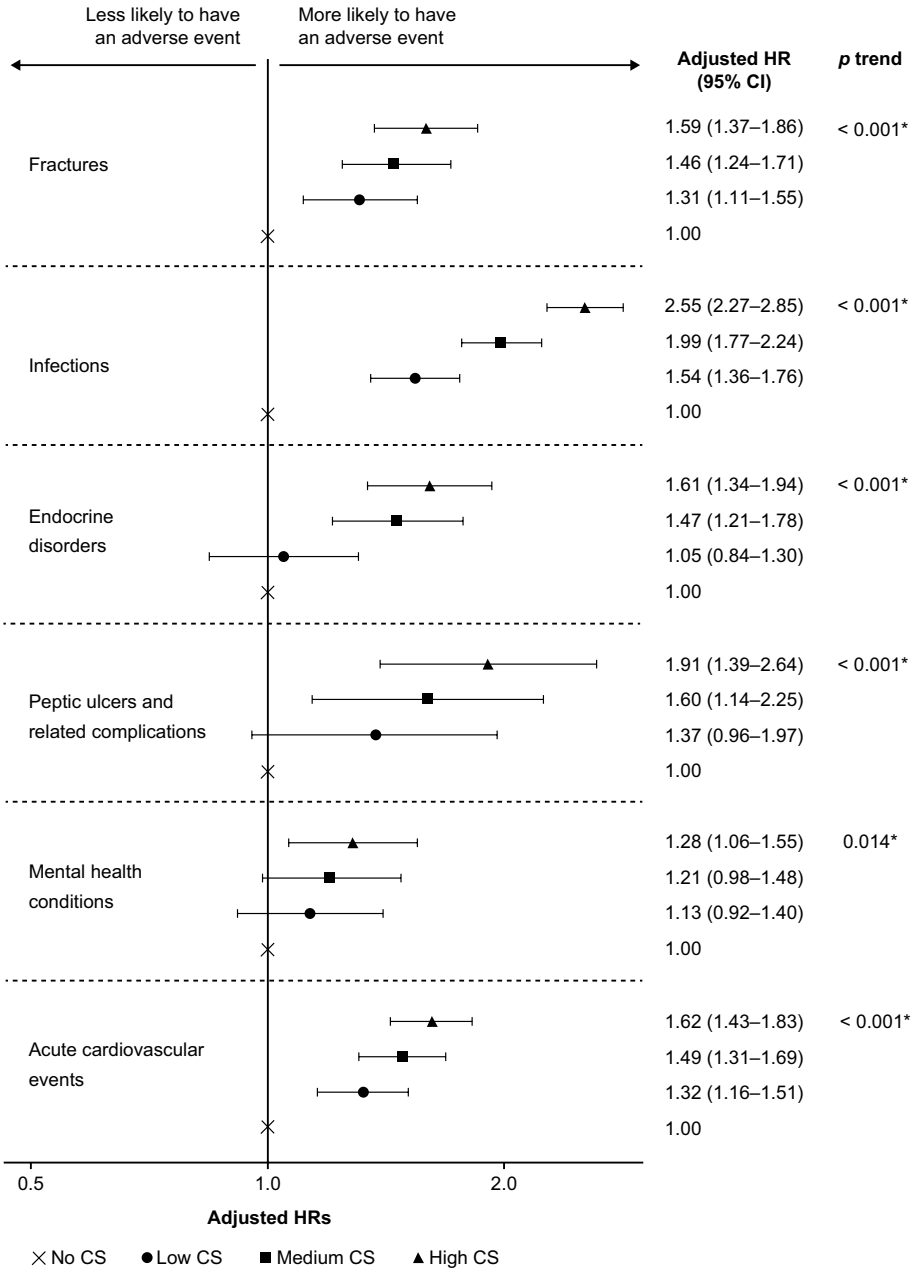

Fig. 2 Risk of developing an adverse event[a,b]. *CCI* Charlson Comorbidity Index, *CI* confidence interval, *CS* corticosteroid, *HR* hazard ratio. *Indicates statistical significance at a level of 0.05. [a]An estimate is statistically significant whenever the CI does not include 1.0 (does not cross the vertical axis). [b]Adjustments were made for the following baseline covariates: age, index year, geographical region, presence of bone metastases, CCI, and presence of adverse events other than the outcome of the given model (i.e., fractures, infections, endocrine disorders, cardiovascular disease, peptic ulcers and related complications, mental health conditions)

The results of this study suggest that patients with CRPC treated with corticosteroids are more likely to develop adverse events than patients with CRPC who do not receive corticosteroids. Some of these adverse events were severe or potentially life threatening and included infections such as pneumonia and septicemia, peptic ulcers, acute cardiovascular events such as acute myocardial infarction and acute ischemic stroke, endocrine disorders, fractures, bipolar disorder, and depression. Importantly, exposure to corticosteroids was generally associated with a more rapid onset of adverse events (particularly fractures, infections, and acute cardiovascular events). The strength of association for the same level of corticosteroid exposure differed across the adverse events (e.g., high corticosteroid exposure was associated with a 2.55-fold risk of developing serious infection compared with a 1.28-fold risk of developing a mental health disorder), we found evidence of a dose–response relationship for all adverse events since the risk of experiencing adverse events increased with cumulative corticosteroid exposure. Notably, even low cumulative exposure to corticosteroids was associated with an increased risk of developing potentially severe adverse events such as fractures, infections, or acute cardiovascular events.

Our results are consistent with those of a previous study in which patients with severe asthma treated with

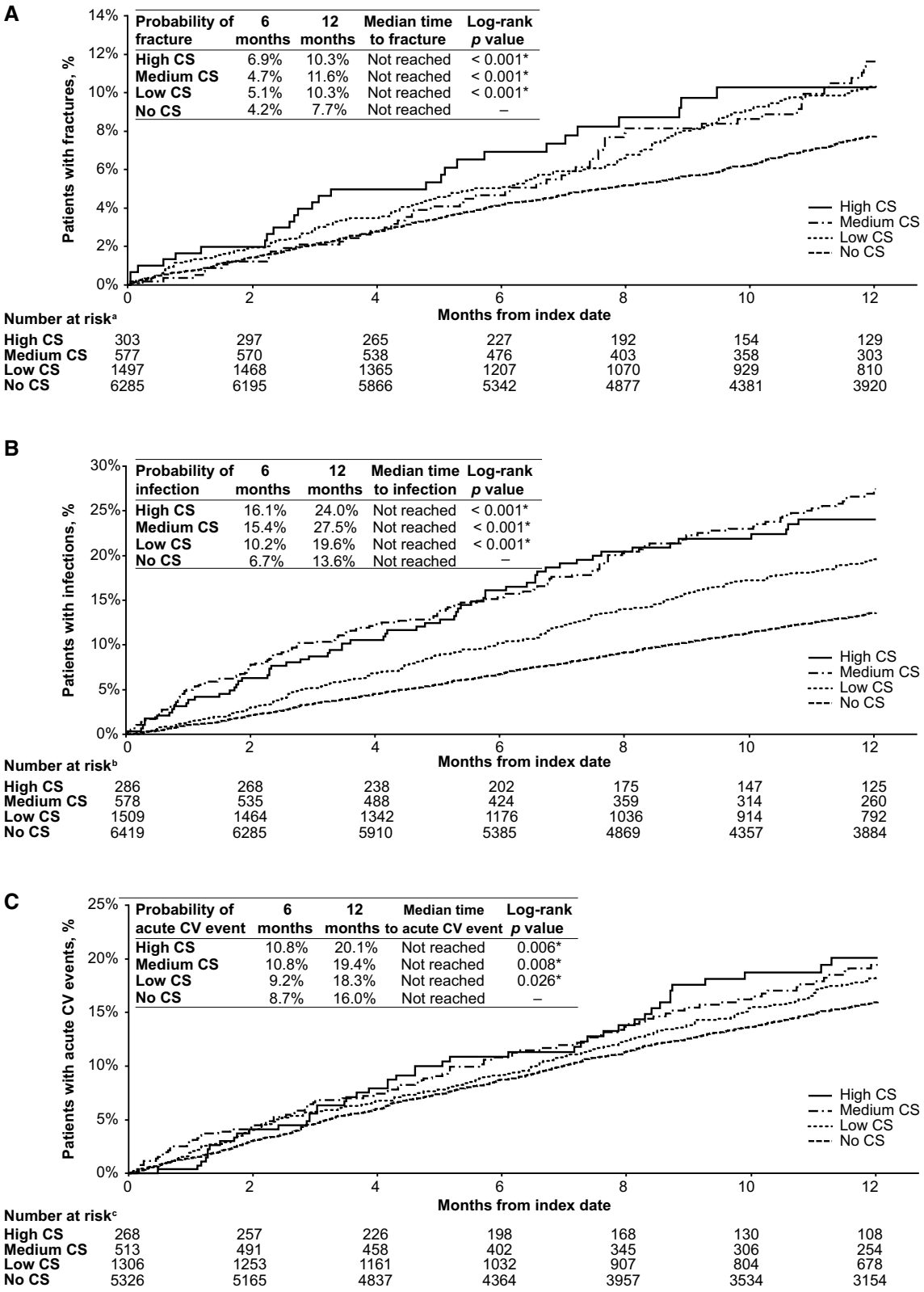

Fig. 3 Time to (**a**) fracture, (**b**) infection, and (**c**) acute CV event. *CS* corticosteroid, *CV* cardiovascular. *Indicates statistical significance at a level of 0.05. [a]763 patients with a fracture event during the baseline period were excluded from this analysis. [b]633 patients with an infection event during the baseline period were excluded from this analysis. [c]2012 patients with an acute CV event during the baseline period were excluded from this analysis

corticosteroids had a significantly higher risk of developing corticosteroid-related adverse events, and that risk increased with exposure to corticosteroids [21]. Some of the corticosteroid-related events were the same as those considered in this study, including fractures, infections (e.g., sepsis, pneumonia), cardiovascular disorders (e.g., myocardial infarction), ulcers, and mental health conditions (e.g., depression and bipolar disorder) [21]. Several other studies involving different diseases (e.g., lupus, rheumatoid arthritis) also found that corticosteroid exposure was associated with an increased risk of a variety of adverse events, including those considered in this study [5, 8–10, 21, 22]. This seems to imply that, regardless of the type of underlying disease, cumulative exposure to corticosteroids is likely to contribute to adverse events that may exacerbate the overall disease burden.

Because most patients are diagnosed with prostate cancer after the age of 65 years [23], corticosteroid-related adverse events may be particularly impactful for patients with CRPC, as they may manifest more frequently or more severely, exacerbate existing comorbidities, or complicate treatment in elderly patients. Indeed, elderly patients have been found to be more susceptible to, among others, fractures, cardiac events, and infections such as pneumonia and sepsis [17–20]. Exposure to corticosteroids may worsen these issues in elderly patients with CRPC.

A previous study among elderly patients with CRPC found that the presence of corticosteroid-sensitive comorbidities was associated with a shorter duration of CRPC treatment [24], suggesting that exposure to corticosteroids may, in the long term, interfere with the management of CRPC. Concerns have also been raised regarding the potential for corticosteroids to promote the growth of prostate cancer in some patients, based on observed mutations of the androgen receptor [7, 25, 26]. Prolonged exposure to corticosteroids may also lead to steroid dependency, and abrupt withdrawal may cause symptoms ranging from severe fatigue to secondary adrenal insufficiency [6, 11, 27].

Corticosteroids have a beneficial role in reducing the toxic effects of antineoplastic agents and secondary hormonal therapy and relieving metastasis-related symptoms [5, 6]. However, this study found an increased incidence of adverse events, some serious or life threatening, in patients with CRPC who were treated with corticosteroids. This association has been reported in other patient populations, but this is the first time it has been quantified in the CRPC population. These results suggest that medically feasible alternatives to corticosteroids in patients with CRPC may result in fewer adverse events, especially considering that most patients with CRPC are elderly and so may have a lower tolerance for the adverse events considered in this study. Future studies on the clinical and economic implications of corticosteroid-related adverse events among patients with CRPC are needed to better inform the decision-making processes of all healthcare stakeholders.

This study should be interpreted within the context of certain limitations. First, since no ICD code for CRPC exists, CRPC was identified in the claims database using proxy measures (i.e., initiation of a CRPC treatment). Although patients were required to have initiated a treatment indicative of CRPC following surgical or medical castration, some of these treatments may also be prescribed in a different setting. For example, bicalutamide and flutamide may be used in the combined androgen blockade (CAB) setting to treat the castration-sensitive disease. Since the purpose of treatment administration is not reported in claims data, the possibility of CAB use could not be excluded. Second, variables such as ethnicity and socioeconomic status were unavailable in the claims database, so we were unable to adjust for these variables. In addition, since the analysis was conducted in a commercially insured population, it may not be generalizable to other patient populations (e.g., publicly insured patients). Third, insurance claims do not capture medical services obtained outside a patient's plan and may not capture the actual drug utilization. Furthermore, the calculated cumulative corticosteroid dose may not capture all corticosteroid use, as injectable corticosteroids could not be assessed because of the inability to convert them into a standardized prednisone-equivalent dose. However, injectable corticosteroids made up $<1\%$ of the corticosteroid pharmacy claims, and their use is not expected to systematically differ across cohorts.

Fourth, because of the observational nature of the study, the possibility of confounding and selection bias cannot be excluded. There may be residual confounding from the characteristics that were not documented in claims data (e.g., baseline disease severity). To the extent possible, we controlled for observed baseline imbalance between the study cohorts, including some proxies of disease severity (e.g., presence of bone metastases and CCI) using multivariable regression modeling. Furthermore, this study focused on quantifying the association between corticosteroid use and selected adverse events and found evidence of a dose–response relationship since the risk of experiencing adverse events increased with cumulative corticosteroid exposure. However, given the observational nature of the study, the possibility of uncontrolled confounding, and that some patients included in this study may have an underlying condition that requires corticosteroids, causal inferences and further interpretations of the observed associations should be made with caution.

Lastly, the relationship between corticosteroid use and adverse events could be confounded by ADT, which is associated with an increased risk for some of the adverse events considered in this study, including fractures, cardiovascular events, and mental health conditions [28–30].

While we could not adjust for potential confounding due to cumulative use of ADT given the current sample selection process, ADT was found to be more frequently used in the no corticosteroid exposure cohort. Therefore, it is unlikely that the observed association between cumulative corticosteroid dose and risk of adverse events is completely driven by cumulative use of ADT. Moreover, corticosteroid exposure was associated with a significantly greater risk, even for adverse events that are less likely to be related to ADT (e.g., infections, endocrine disorders, peptic ulcers, and related complications).

5 Conclusion

This study found that cumulative exposure to corticosteroids in patients with CRPC was associated with a greater risk and more rapid onset of adverse events, including fractures, infections, endocrine disorders, peptic ulcers, mental health conditions, and acute cardiovascular events. The increased adverse event risk was observed after accounting, to the extent possible, for patients' overall disease severity and recognizing the potential for uncontrolled confounding.

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Compliance with Ethical Standards

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Conflict of interest Neil M. Schultz is an employee of Astellas and owns stock in Gilead Sciences and Shire. David F. Penson has served as a consultant for Astellas, Janssen, and Dendreon and has received research funding and travel and accommodation expenses from Astellas and Dendreon. Samuel Wilson is an employee of Astellas and owns stock in Baxter. Yan Song and Hongbo Yang are employees of Analysis Group, Inc., which has received consultancy fees from Astellas. Krishnan Ramaswamy is an employee of, and owns stock in, Pfizer. Benjamin Lowentritt is an employee of Chesapeake Urology and has served as a speaker and consultant for Astellas, Bayer, Dendreon, Janssen, Merck, Pfizer, and UroGen.

Previous presentation A synopsis of the current research was presented in poster format at the 2019 ASCO Genitourinary Cancers Symposium, which took place in San Francisco, CA, USA, 14–16 February 2019.

Availability of data and material The data that support the findings of this study are available from IBM MarketScan Research Databases, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

Ethical approval/informed consent Data were fully de-identified and compliant with the Health Insurance Portability and Accountability Act. No institutional review board approval or informed consent was required for this retrospective study.

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