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ORIGINAL ARTICLE

Comparison of infection risk between enzalutamide and abiraterone in patients with prostate cancer

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Abstract

Background: Enzalutamide and abiraterone may differ in their immunomodulatory effects, and the prednisone coadministered with abiraterone can be immunosuppressive. This study aimed to compare the risk of different types of infection in patients with prostate cancer receiving enzalutamide or abiraterone in combination with androgen deprivation therapy.

Methods: Patients with prostate cancer receiving enzalutamide or abiraterone in addition to androgen deprivation therapy in Hong Kong between December 1999 to March 2021 were identified in this retrospective cohort study and followed up until September 2021, death, or crossover. Outcomes, including any sepsis, pneumonia, urinary tract infection, cellulitis or skin abscess, central nervous system infections, and tuberculosis, were analyzed as both time-to-event outcomes (multivariable Fine-Gray regression, with mortality considered a competing event) and recurrent-event outcomes (multivariable negative binomial regression).

Results: Altogether, 1582 patients were analyzed (923 abiraterone users; 659 enzalutamide users) with a median follow-up of 10.6 months (interquartile range: 5.3–19.9 months). Compared to abiraterone users, enzalutamide users had lower cumulative incidences of sepsis (adjusted subhazard ratio [SHR] 0.70 [0.53–0.93], $p = .014$), pneumonia (adjusted SHR 0.76 [0.59–0.99], $p = .040$), and cellulitis or skin abscess (adjusted SHR 0.55 [0.39–0.79], $p = .001$), but not urinary tract infection (adjusted SHR 0.91 [0.62–1.35], $p = .643$). Associations between exposure and central nervous system infections and tuberculosis were not assessed because of low event rates. Analyzing the outcomes as recurrent events gave similar results.

Yan Hiu Athena Lee and Jeffrey Shi Kai Chan contributed equally to this work.

Enzalutamide use may be associated with a lower risk of urinary tract infection in patients with diabetes mellitus.

Conclusions: Compared to abiraterone users, enzalutamide users have significantly lower risks of sepsis, pneumonia, cellulitis, or skin abscess.

KEYWORDS
abiraterone, adverse event, androgen receptor signaling inhibitors, antiandrogen, Asian, cohort, enzalutamide, infection, prostate cancer

INTRODUCTION

Prostate cancer (PCa) is one of the leading causes of new cancer cases.[1] In 2020, it became the second most common cancer and the fifth major cause of cancer mortality among males globally.[2] Within the armamentarium of metastatic PCa management strategies, androgen receptor targeting agents, such as abiraterone and enzalutamide, have demonstrated overall survival benefits when added to androgen deprivation therapy (ADT).[3,4]

Both abiraterone and enzalutamide target the androgen receptor signaling pathway. Abiraterone inhibits the CPY17 enzyme, responsible for residual androgen synthesis after ADT.[5] Enzalutamide competitively inhibits androgen receptor binding, nuclear translocation, and downstream transcription.[6] Both abiraterone and enzalutamide confer survival benefits over placebo in not only metastatic castration-resistant prostate cancer (mCRPC),[7] but also metastatic hormone-sensitive prostate cancer.[8]

Although there is evidence supporting the efficacy and safety of both abiraterone and enzalutamide, there is still a lack of high-quality evidence and consensus on the optimal selection of these drugs. A pharmacovigilance analysis of adverse events found that infections accounted for 13% and 9% of fatal adverse events in patients receiving abiraterone and enzalutamide, respectively.[9] However, because of the lack of head-to-head comparison between these two drugs, it remains unknown as to whether the use of any of these drugs associates with more infections than the other. To specifically investigate whether there is any difference in infection risk between abiraterone and enzalutamide subgroups, we conducted this retrospective study, in which we took into account specific types of infection, the time to the events, and such competing events as cancer-related mortality, to minimize bias.

METHODS

Source of data

This retrospective cohort study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. Our data were obtained from the Clinical Data Analysis and Reporting System (CDARS), a population-based electronic health records database. CDARS records demographic information, diagnoses, procedures, and medications for patients receiving care at public health care institutions in Hong Kong. Diagnoses are coded using the International Classification of Diseases, Ninth Revision (ICD-9) codes. The CDARS database is linked to the Hong Kong Death Registry, which is a government registry containing the death records of all citizens. Mortality data, including causes of death, are available from the Death Registry and are encoded using either ICD-9 or ICD-10 codes, depending on the year of death. There were no missing data because of the nature of data source. This system has been widely used by local research teams for conducting epidemiological studies.[10–13]

Study design and population

This study included adult patients, aged 18 years or older, who were diagnosed with PCa and were receiving enzalutamide or abiraterone in addition to ADT in Hong Kong. The study period spanned from December 1, 1999, to March 31, 2021. The diagnosis of PCa was determined using specific ICD-9 codes (Table S1). ADT encompassed surgical ADT (bilateral orchidectomy) and medical ADT (gonadotrophin-releasing hormone agonists and antagonists).

Follow-up and outcomes

All patients included in the study were followed from the date of starting enzalutamide or abiraterone (index date) until September 30, 2021. Patients who switched to the other medication (e.g., initiated on enzalutamide and then switched to abiraterone) were censored at the point of crossover. There was no loss to follow-up because of the nature of the data source. The study focused on outcomes including any sepsis, pneumonia, urinary tract infection (UTI), cellulitis or skin abscess, central nervous system (CNS) infections, and tuberculosis (prevalent in Asia). The ICD-9 codes used for ascertaining these outcomes are listed in Table S1. All of these outcomes were recorded as time-to-event outcomes, as well as recurrent outcomes with multiple episodes, except for tuberculosis, which was analyzed as a time-to-event outcome because of its latent nature.

Statistical analysis

The statistical analyses were detailed in the Supplementary Methods. Associations between the exposure and the risk of CNS infections and tuberculosis were not assessed because of the exceedingly low incidence rates. Associations between the exposure and the cumulative incidence of other outcomes (considered as time-to-event outcomes) were primarily assessed by multivariable Fine-Gray competing risk regression, with mortality as the sole competing event; multivariable adjustments were made for prespecified covariates, including age, the type of ADT, prior myocardial infarction, prior stroke, heart failure, hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, dyslipidemia, prior radical prostatectomy, prior radiotherapy, prior chemotherapy, prior systemic steroid use, baseline antidiabetic use, and the number of recorded episodes of the analyzed event before the index date. The cause-specific cumulative incidences of all assessed outcomes were visualized using Aalen-Johansen curves.[14] As a secondary analysis, associations between the exposure and the incidence of other outcomes (considered as recurrent-event outcomes) were assessed by multivariable negative binomial regression with the follow-up duration as the exposure variable; multivariable adjustments were made for the same prespecified covariates as specified for Fine-Gray competing risk regression given previously.

A prespecified exploratory analysis was conducted to explore the associations between different prednisolone regimens that were coadministered with abiraterone and the risk of the outcomes. Patients were divided into three groups: (1) those who received abiraterone (ABI) with 5 mg of total daily prednisolone (ABI + P5), (2) those who received ABI with 10 mg of total daily prednisolone (ABI + P10), and (3) those who received enzalutamide without any glucocorticoid. These prednisolone regimens were recommended by the pharmaceutical company,[15] and generally followed in daily clinical practice. Notably, 5 mg daily prednisolone is recommended for metastatic hormone-sensitive prostate cancer, whereas 10 mg total daily prednisolone is recommended for mCRPC. Patients who received nonprednisolone prescriptions, prednisolone prescriptions that did not correspond to the previously specified dosages, or enzalutamide with any glucocorticoid were excluded from this exploratory analysis because these prescriptions were likely given for other indications.

In a prespecified sensitivity analysis, inverse probability of treatment weighting (IPTW) was used to minimize imbalances in prespecified covariates (same as previously specified for multivariable Fine-Gray competing risk regression and negative binomial regression) between the enzalutamide and abiraterone groups. Standardized mean difference (SMD) was used to measure covariate balance between groups, with standardized mean difference <0.1 considered to represent acceptable covariate balance.

Two prespecified subgroup analyses were performed, stratifying by age (>70/≤70) and the presence of diabetes mellitus, with pairwise interactions tested.

All p values were two-sided, with $p < .05$ considered statistically significant.

RESULTS

In total, 1582 patients were eligible for this study and were analyzed, including 923 patients in the ABI group and 659 in the enzalutamide group. Of these, 252 (27.3%) in the ABI group and 110 (16.7%) in the enzalutamide group switched between the two arms. The median drug durations were 5.9 months for ABI (interquartile range: 2.5–12.9 months) and 6.4 months for enzalutamide (interquartile range: 2.8–12.0 months), respectively. The patients' baseline characteristics are summarized in Table 1, and the comparison of baseline characteristics before and after IPTW are shown in Table S2. The enzalutamide group had a higher prevalence of diabetes or antidiabetic use at baseline; other baseline characteristics were not substantially different.

Cumulative incidences and incidence rates of outcomes

Over a median follow-up of 10.6 months (interquartile range: 5.3–19.9 months), sepsis occurred in 182 patients (11.5%; 553 [35.0%] competing events [i.e., death without having had the event]), pneumonia in 229 (18.9%; 427 [27.0%] competing events), UTI in 174 (11.0; 855 [54.1%] competing events), cellulitis or skin abscess in 44 (2.8%; 968 [61.2%] competing events), CNS infections in three (0.2%; 1000 [63.2%] competing events), and tuberculosis in two (0.1%; 1002 [63.3%] competing events). When analyzed as recurrent events, the incidence rates of sepsis, pneumonia, and UTIs were the highest (195.4 [95% CI, 161.0–237.2] episodes per 1000 patient-years, 360.9 [290.9–447.8] episodes per 1000 patient-years, and 229.2 [187.2–280.6] episodes per 1000 patient-years, respectively), followed by cellulitis or skin abscess (34.3 [23.7–49.6] episodes per 1000 patient-years) and CNS infections (1.6 [0.7–3.6] episodes per 1000 patient-years). The exposure-specific cumulative incidence rates and incidence rates of each outcome are summarized in Tables S3 and S4, respectively.

Comparison between enzalutamide and abiraterone

Compared to patients who received ABI, patients who received enzalutamide had significantly lower cumulative incidences of sepsis (adjusted subhazard ratio [SHR] 0.70 [0.53–0.93], $p = .014$ [Figure 1A]), pneumonia (SHR 0.76 [0.59–0.99], $p = .040$ [Figure 1B]), and cellulitis or skin abscess (SHR 0.55 [0.39–0.79], $p = .001$ [Figure 1C]), but not UTI (SHR 0.93 [0.64–1.37], $p = .720$ [Figure 1D]).

Similar results were obtained when analyzing the outcomes as recurrent events, with patients who received enzalutamide having significantly lower incidence rate ratios of sepsis (IRR 0.59 [0.42–0.84], $p = .003$), pneumonia (IRR 0.69 [0.50–0.96], $p = .026$), and

TABLE 1 Baseline characteristics of included patients.

	Abiraterone group (*N* = 923)	Enzalutamide group (*N* = 659)
Age, years [interquartile range]	71 [64–77]	73 [66–80]
Type of androgen deprivation therapy, *N* (%)		
Pharmacological only	565 (61.2)	424 (64.3)
Surgical only	201 (21.8)	136 (20.6)
Both pharmacological and surgical	157 (17.0)	99 (15.0)
Hypertension, *N* (%)	291 (31.5)	262 (39.8)
Diabetes mellitus, *N* (%)	124 (13.4)	171 (26.0)
Dyslipidemia, *N* (%)	131 (14.2)	156 (23.7)
Ischemic heart disease, *N* (%)	96 (10.4)	80 (12.1)
Myocardial infarction, *N* (%)	28 (3.0)	30 (4.6)
Stroke, *N* (%)	87 (9.4)	55 (8.4)
Heart failure, *N* (%)	37 (4.0)	30 (4.6)
Chronic kidney disease, *N* (%)	28 (3.0)	19 (2.9)
Atrial fibrillation, *N* (%)	39 (4.2)	35 (3.5)
Chronic liver disease, *N* (%)	10 (1.1)	17 (2.6)
Chronic obstructive pulmonary disease, *N* (%)	28 (3.0)	25 (3.8)
Radical prostatectomy, *N* (%)	131 (14.2)	105 (15.9)
Radiotherapy, *N* (%)	30 (3.3)	11 (1.7)
Chemotherapy, *N* (%)	311 (33.7)	202 (30.7)
Any prior systemic steroid use, *N* (%)	696 (75.4)	469 (71.2)
Antidiabetic use, *N* (%)	166 (18.0)	221 (33.5)

cellulitis or skin abscess (IRR 0.48 [0.25–0.90], $p = .022$), but not UTI (IRR 0.71 [0.48–1.06], $p = .095$).

Subgroup analyses

Prespecified subgroup analysis (Tables 2 and 3) demonstrated that there was a strong association between enzalutamide use and a lower risk of pneumonia in those aged ≤70 years old (SHR 0.52 [0.36–0.76], $p = .001$ and IRR 0.56 [0.37–0.84], $p = .005$), but not in those aged >70 years old (SHR 0.92 [0.66–1.29], $p = .641$ and IRR 0.77 [0.52–1.12], $p = .168$). This interaction was statistically significant ($p_{interaction} = .001$ both when analyzed as a time-to-event outcome and as a recurrent event).

Similarly, there was a strong association between enzalutamide use and a lower risk of cellulitis or skin abscess in those aged ≤70 years (SHR 0.36 [0.25–0.51], $p < .001$ and IRR 0.23 [0.12–0.48], $p < .001$), but not in those aged >70 years (SHR 0.80 [0.47–1.35], $p = .401$ and IRR 0.81 [0.37–1.76], $p = .592$). This interaction was statistically significant in recurrent event analysis ($p_{interaction} = .001$), but not in time-to-event analysis ($p_{interaction} = .101$).

Meanwhile, enzalutamide use was strongly associated with a lower risk of UTI in those with diabetes mellitus (SHR 0.48 [0.24–0.94], $p = .033$ and 0.26 [0.14–0.49], $p < .001$), but not in those without diabetes mellitus (SHR 1.25 [0.84–1.88], $p = .274$ and IRR 1.00 [0.64–1.59], $p = .984$). This interaction was statistically significant in both time-to-event analysis ($p_{interaction} = .018$) and recurrent event analysis ($p_{interaction} < .001$).

The subgroup analyses did not otherwise demonstrate any statistically significant interaction between age or diabetes mellitus and exposure effects. The sensitivity analysis showed consistent results when IPTW was used to balance covariates between treatment groups (Table S5).

Exploratory analysis of prednisolone regimen

After excluding 32 patients from the abiraterone group and 94 patients from the enzalutamide group for prednisolone regimen/glucocorticoid use for other reasons, 565 patients were in the enzalutamide group, 141 were in the ABI + P5 group, and 750 were in the ABI + P10 group. Compared to the ABI + P5 group, those who received ABI + P10 had significantly higher cumulative incidences (Table 4) and incidence rates (Table 5) of sepsis (Figure 2A) and pneumonia (Figure 2B), but not cellulitis or skin abscess (Figure 2C), nor UTI (Figure 2D). There were no significantly different cumulative incidences or incidence rates of any of these four outcomes when compared to the enzalutamide group and the ABI + P5 group.

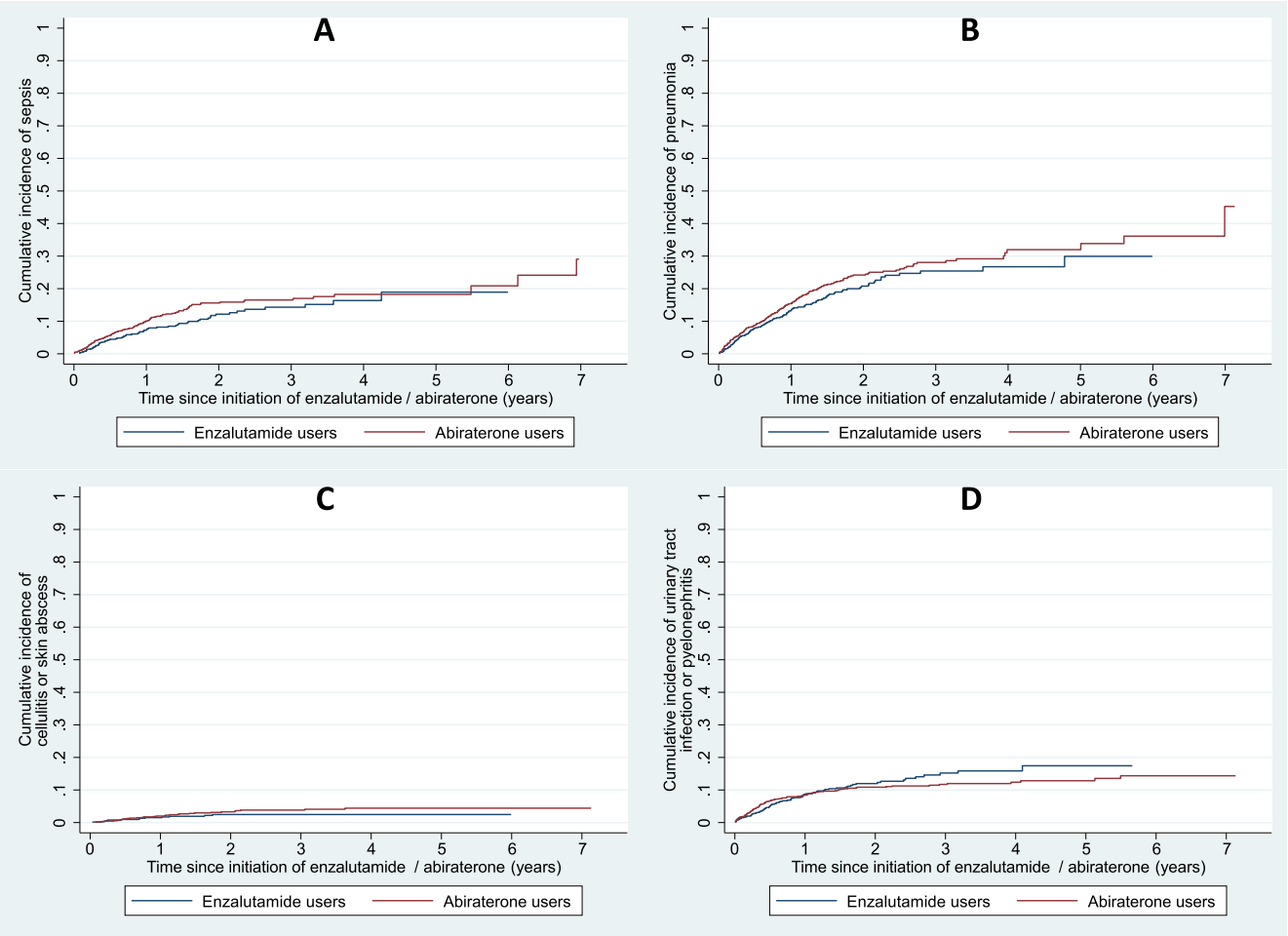

FIGURE 1 Aalen-Johansen cumulative incidence curves of (A) sepsis, (B) pneumonia, (C) cellulitis or skin abscess, and (D) urinary tract infection, stratified by enzalutamide or abiraterone use for the primary analysis.

TABLE 2 Results of subgroup analyses with the outcomes analyzed as time-to-event outcomes using Fine-Gray competing risk regression.

Subgroup		Sepsis	Pneumonia	Urinary tract infection	Cellulitis or skin abscess
Age	>70 y	0.63 [0.43–0.93], $p = .020$	0.92 [0.66–1.29], $p = .641$	0.95 [0.61–1.48], $p = .818$	0.80 [0.47–1.35], $p = .401$
	≤70 y	0.84 [0.54–1.31], $p = .448$	0.52 [0.36–0.76], $p = .001$	0.98 [0.61–1.58], $p = .934$	0.36 [0.25–0.51], $p < .001$
	$p_{interaction}$	.382	.001	.927	.101
Diabetes mellitus	Present	0.52 [0.29–0.93], $p = .029$	0.70 [0.54–0.89], $p = .004$	0.48 [0.24–0.94], $p = .033$	0.69 [0.46–1.05], $p = .085$
	Absent	0.73 [0.48–1.12], $p = .145$	0.79 [0.58–1.09], $p = .154$	1.25 [0.84–1.88], $p = .274$	0.43 [0.19–0.99], $p = .048$
	$p_{interaction}$	.378	.479	.018	.290

Note: All estimates shown are subhazard ratios with the corresponding 95% CIs and with the abiraterone group as reference. All estimates were adjusted for prespecified covariates, including age, the type of androgen deprivation therapy, prior myocardial infarction, prior stroke, heart failure, hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, dyslipidemia, prior radical prostatectomy, prior radiotherapy, prior chemotherapy, prior systemic steroid use, baseline antidiabetic use, and the number of recorded episodes of the analyzed event before the index date.

DISCUSSION

This population-based retrospective cohort study demonstrated that, despite higher diabetes prevalence, the enzalutamide group had significant lower risks of sepsis, pneumonia, and cellulitis or skin abscess, compared to ABI use among patients with PCa receiving ADT.

A previous study by Riekhof et al. in an American cohort found that ABI use was associated with significantly higher incidences of hospitalization for sepsis, pneumonia, and UTI.[16] Although the

TABLE 3 Results of subgroup analyses with the outcomes analyzed as recurrent events using negative binomial regression.

Subgroup		Sepsis	Pneumonia	Urinary tract infection or pyelonephritis	Cellulitis or skin abscess
Age	>70 years	0.59 [0.41–0.85], $p = .005$	0.77 [0.52–1.12], $p = .168$	0.79 [0.43–1.45], $p = .444$	0.81 [0.37–1.76], $p = .592$
	≤70 years	0.64 [0.38–1.07], $p = .086$	0.56 [0.37–0.84], $p = .005$	0.69 [0.40–1.16], $p = .162$	0.23 [0.12–0.48], $p < .001$
	$p_{interaction}$	.815	.001	.727	.001
Diabetes mellitus	Present	0.42 [0.25–0.69], $p = .001$	0.59 [0.48–0.74], $p < .001$	0.26 [0.14–0.49], $p < .001$	0.69 [0.36–1.32], $p = .257$
	Absent	0.67 [0.41–1.08], $p = .101$	0.68 [0.45–1.04], $p = .076$	1.00 [0.64–1.59], $p = .984$	0.39 [0.13–1.13], $p = .081$
	$p_{interaction}$	.087	.662	<.001	.429

Note: All estimates shown were incidence rate ratios with the corresponding 95% CIs and with the abiraterone group as reference. All estimates were adjusted for prespecified covariates, including age, the type of androgen deprivation therapy, prior myocardial infarction, prior stroke, heart failure, hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, dyslipidemia, prior radical prostatectomy, prior radiotherapy, prior chemotherapy, prior systemic steroid use, baseline antidiabetic use, and the number of recorded episodes of the analyzed event before the index date.

TABLE 4 Results of the exploratory analysis, with all outcomes analyzed as time-to-event outcomes using Fine-Gray competing risk regression.

Treatment group	Daily prednisolone dose at treatment initiation (mg)	Sepsis	Pneumonia	Urinary tract infection or pyelonephritis	Cellulitis or skin abscess
Abiraterone	10 ($N = 750$)	1.95 [1.23–3.10], $p = .005$	1.98 [1.17–3.37], $p = .011$	1.38 [0.81–2.34], $p = .236$	2.34 [0.39–14.18], $p = .355$
	5 ($N = 141$)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Enzalutamide	0 ($N = 565$)	1.21 [0.97–1.51], $p = .094$	1.21 [0.71–2.04], $p = .485$	1.08 [0.55–2.13], $p = .827$	1.04 [0.29–3.74], $p = .947$

Note: All estimates shown were subhazard ratios with the corresponding 95% CIs. All estimates were adjusted for prespecified covariates, including age, the type of androgen deprivation therapy, prior myocardial infarction, prior stroke, heart failure, hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, dyslipidemia, prior radical prostatectomy, prior radiotherapy, prior chemotherapy, prior systemic steroid use, baseline antidiabetic use, and the number of recorded episodes of the analyzed event before the index date.

TABLE 5 Results of the exploratory analysis, with all outcomes analyzed as recurrent events using negative binomial regression.

Treatment group	Daily prednisolone dose at treatment initiation (mg)	Sepsis	Pneumonia	Urinary tract infection or pyelonephritis	Cellulitis or skin abscess
Abiraterone	10 ($N = 750$)	3.02 [1.73–5.28], $p < .001$	2.96 [1.61–5.44], $p < .001$	1.59 [0.92–2.74], $p = .096$	3.36 [0.46–24.42], $p = .232$
	5 ($N = 141$)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Enzalutamide	0 ($N = 565$)	1.47 [0.87–2.48], $p = .151$	1.49 [0.84–2.64], $p = .174$	0.89 [0.55–1.45], $p = .634$	1.41 [0.26–7.62], $p = .693$

Note: All estimates shown were incidence rate ratios with the corresponding 95% confidence intervals. All estimates were adjusted for pre-specified covariates, including age, the type of androgen deprivation therapy, prior myocardial infarction, prior stroke, heart failure, hypertension, diabetes mellitus, ischemic heart disease, chronic kidney disease, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, dyslipidemia, prior radical prostatectomy, prior radiotherapy, prior chemotherapy, prior systemic steroid use, baseline antidiabetic use, and the number of recorded episodes of the analyzed event before the index date.

coadministration of glucocorticoids might be intuitively held accountable for the increased sepsis in abiraterone users at first glance, a review by Auchus et al. suggested that steroid side effects increased when the dosage exceeded greater than 20mg /day prednisolone equivalence, and that infection rates were not definitely increased in replacement doses commonly used in mCRPC.[11] Moreover, plasma glucocorticoids levels and individual sensitivity to glucocorticoid may be affected by race and genetic

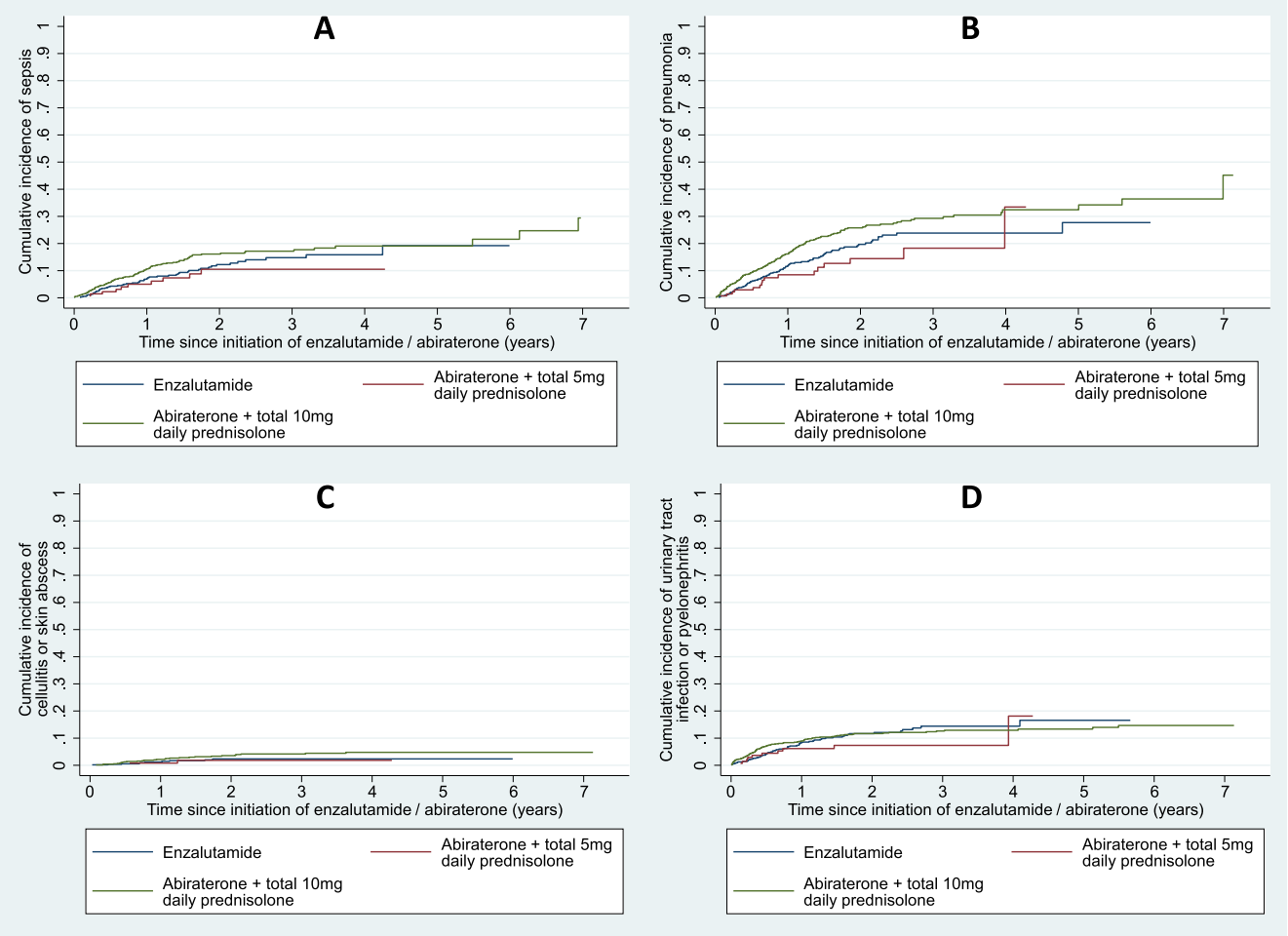

FIGURE 2 Aalen-Johansen cumulative incidence curves of (A) sepsis, (B) pneumonia, (C) cellulitis or skin abscess, and (D) urinary tract infection, stratified by abiraterone/enzalutamide use and prednisolone regimen for the exploratory analysis.

polymorphisms.[17,18] Therefore, the interrelationship between androgen receptor targeting agents (and/or steroid) and infection still remains unclear. Our findings validated these observations in a territory-wide, population-based cohort. Notably, whereas Riekhof et al. found that ABI was associated with increased UTI rates compared to enzalutamide,[16] our cohort did not replicate this finding. However, it should be noted that in patients with metastatic prostate cancer, the risk of UTI is typically multifactorial. For instance, given the advanced stage of PCa in this cohort, the included patients are expected to have certain degrees of voiding dysfunction and bladder outlet obstruction, not to mention those requiring catheterization, all of which may alter the risk of UTI. Meanwhile, data on voiding function and uroflowmetry parameters (e.g., postvoid residual urine volume), were not easily retrievable from CDARS and, hence, not considered in this study.

The effects of enzalutamide and ABI on the immune system in patients with metastatic PCa are incompletely understood. However, emerging evidence suggests that both therapies may possess immunomodulatory properties in advanced PCa. Laboratory evidence indicates that enzalutamide and abiraterone use in patients with mCRPC can activate T cell–mediated immune responses.[19] Increased levels of proinflammatory mediators such as interferon γ, MIP-1α, tumor necrosis factorα and interleukins have been observed in responders to enzalutamide or abiraterone.[19] These findings suggest the potential immune-modulatory roles of steroid, which is commonly coadministered with ABI, on tumor microenvironment and host defense mechanisms against infection. In our subgroup analysis, we observed a significant association between the use of enzalutamide and a reduced risk of UTI among patients with diabetes mellitus. One plausible explanation is that diabetes mellitus is a strong risk factor per se for UTI,[20,21] and the use of prednisolone, a potent immunosuppressant, in these patients with diabetes mellitus may further increase the susceptibility to UTIs. Notably, despite the higher prevalence of diabetes mellitus in the enzalutamide group (26% vs. 13%), a lower incidence of UTI was observed. This finding suggests that there may be a genuine protective effect associated with the use of enzalutamide, independent of the confounding factors. Nevertheless, it remains possible that the observed lower risk of UTIs with enzalutamide was simply the result of glucocorticoid coadministered with abiraterone increasing the risk of UTIs, instead of signifying that enzalutamide has genuine protective effects. Further research in this area is indicated.

The use of ABI suppresses cortisol, with a compensatory increase in adrenocorticotropic hormone. To mitigate mineralocorticoid-related adverse events, the concomitant use of prednisone is recommended.[22] However, concerns regarding the immunosuppressive effects associated with glucocorticoid use, particularly at higher doses, have been raised. At low concentrations, glucocorticoids enhance the function of macrophages in vitro, leading to increased expression of proinflammatory cytokines and chemokines. However, at high concentrations, glucocorticoids act as potent immunosuppressants.[23,24] Numerous observational studies in other conditions have consistently demonstrated an increased risk of severe infections even with the use of low-dose prednisone. An analysis of patients with rheumatoid arthritis in the Safety Assessment in Biologic Therapy study, an American nationwide collaboration, found a significant dose-dependent increase in serious bacterial infections among patients treated with systemic corticosteroids.[25] Similarly, oral corticosteroid use demonstrated a dose-dependent increase in the risk of pneumonia in an asthmatic patient cohort.[26] Furthermore, the duration of therapy is also important, although its association with the risk of infections is less well-defined. A recent study of patients with rheumatoid arthritis found that those who took 5 mg of prednisone daily for the past 7 days had an estimated 3% increase in the odds of serious bacterial infections, which leaped to a 100% increase for those who have been taking the same amount of prednisone for the past 3 years.[27] However, it is crucial to note that when interpreting the impact of glucocorticoids on immune function, careful consideration must be given to the characteristics of the patient population, including factors such as age, frailty, and previous treatment.

In the two landmark studies COU-AA-301[28] and COU-AA-302,[29] the rates of infection were comparable between the group receiving abiraterone (1000 mg) coadministered with prednisolone (5 mg twice daily) and the group receiving prednisone plus placebo. This finding suggests that the use of abiraterone per se does not significantly impact systemic immunomodulation because the infection risk was similar in both treatment groups. Meanwhile, a phase 2 trial found that the use of abiraterone without steroids was feasible in patients with metastatic castration–resistant PCa, but some patients experienced clinically significant adverse events.[30] Therefore, when considering the administration of ABI without prednisone, careful consideration of potential toxicity and close monitoring of patients is warranted. To address mineralocorticoid excess in patients treated with ABI without prednisone, the use of a mineralocorticoid receptor blocker, such as eplerenone, has been investigated. Initially explored in phase I trials for inhibiting peripheral mineralocorticoid excess, eplerenone remains a potential option for mitigating secondary mineralocorticoid excess in clinical practice, particularly for patients who are unwilling to undergo long-term prednisone treatment.[31] Comparisons between prednisone and eplerenone for managing secondary mineralocorticoid excess did not reveal significant differences in terms of hypertension, hypokalemia, or lower extremity edema.[32] With regards to steroid usage in patients with advanced PCa treated with abiraterone, despite the pharmaceutical recommendations of prednisolone 5 mg daily for metastatic hormone-sensitive PCa and altogether 10 mg daily for castration-resistant cases, respectively, there exists heterogeneity in the frequency and dosage of steroids in real-world clinical practice. Although our study did not directly compare the infection profiles of the different antiandrogen therapies, the underlying mechanism suggests these findings may be more broadly applicable. The lower infection risk with enzalutamide compared to abiraterone with prednisone was likely driven by the avoidance of concomitant glucocorticoid use. This mechanism would be expected to extend to other nonsteroidal antiandrogen agents like apalutamide and darolutamide, which also do not require concomitant steroid administration. These findings could be particularly relevant in the context of managing high-volume metastatic castration-sensitive prostate cancer (mCSPC), in which the addition of docetaxel chemotherapy to ABI with prednisone versus with darolutamide may increase the risk of infectious complications. The potential for a lower infection profile with nonsteroidal antiandrogen monotherapy in this setting is an important consideration for clinicians when selecting the optimal treatment approach.

This study used a representative population-based database and had a long follow-up duration, which enhances the likelihood of the results being broadly applicable and reflective of real-world clinical practice. The robustness of the findings was supported by sensitivity analyses using different approaches, which consistently yielded similar results. However, it is important to acknowledge several limitations. First, as an observational study, the presence of residual confounding factors is expected. Second, because all diagnoses were identified using ICD-9 codes as recorded by CDARS, individual data adjudication was not possible. Nonetheless, it is worth noting that the diagnostic codes were input by treating clinicians independent of the study authors, and previous research on CDARS has demonstrated good coding accuracy. Besides, data on duration, dosage, and accumulative exposure to steroid were lacking, for any dose- or time-dependent effects to be established. In addition, cancer staging and castration status are lacking because of the nature of the data. Nonetheless, both drugs are prescribed to patients with castration-resistant prostate cancer, as well as to patients with mCSPC according to local treatment guideline. Therefore, we would not expect a significant difference in terms of the usage of the two drugs in the mCSPC or mCRPC disease stages. Notwithstanding this, further studies with detailed data on disease staging and hormone sensitivity are warranted. Last, several subgroups had limited sample sizes that predisposed to underpowered analyses. Results from the subgroup analyses should therefore be interpreted with caution and seen as hypothesis-generating.

CONCLUSIONS

In patients with prostate cancer receiving ADT, enzalutamide users had a significantly lower risk of sepsis, pneumonia, cellulitis, or skin abscess, but not urinary tract infection when compared to ABI users.

AUTHOR CONTRIBUTIONS

Yan Hiu Athena Lee: Conceptualization; Investigation; Writing - original draft; and Writing - review & editing. **Jeffrey Shi Kai Chan**: Conceptualization; Methodology; Data curation; Investigation; Formal analysis; Writing - original draft; and Writing - review & editing. **Chi Ho Leung**: Methodology; Data curation; and Writing - review & editing. **Alex Qinyang Liu**: Writing - original draft. **Edward Christopher Dee**: Supervision and Writing - review & editing. **Kenrick Ng**: Supervision and Writing - review & editing. **Johnathan Shamash**: Supervision and Writing - review & editing. **Gary Tse**: Supervision and Writing - review & editing. **David Ka Wai Leung**: Supervision; Project administration; Resources; and Writing - review & editing. **Chi Fai Ng**: Writing - review & editing; Project administration; Supervision; and Resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data underlying this study are available on reasonable request to the corresponding authors.

PATIENT CONSENT

The need for patient consent was waived by the Ethics Committee because of the retrospective nature of this study and the use of deidentified data.

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SUPPORTING INFORMATION

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