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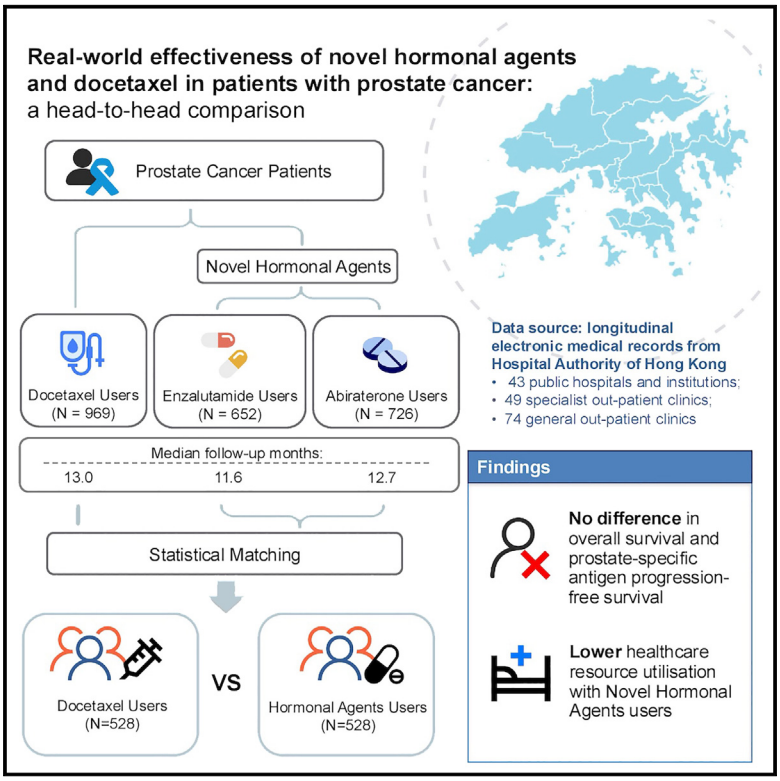
Real-world effectiveness of novel hormonal agents and docetaxel in patients with prostate cancer: A head-to-head comparison

Graphical abstract



Highlights

- Novel hormonal agents and docetaxel show comparable clinical effectiveness
- Novel hormonal agents exhibit significantly reduced health resource utilisation
- Novel hormonal agents are potentially cost-effective in managing prostate cancer

Authors

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In brief

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Real-world effectiveness of novel hormonal agents and docetaxel in patients with prostate cancer: A head-to-head comparison

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SUMMARY

Next-generation hormonal-targeted therapies for advanced prostate cancer are widely used. We aimed to evaluate the effectiveness and health resource utilization (HRU) of novel hormonal agents (NHAs) compared to chemotherapy in a real-world context. After propensity score matching, survival analysis revealed no significant difference in overall survival between the individuals treated with NHAs and those treated with docetaxel (hazard ratio [HR]: 1.00, 95% confidence interval [CI]: 0.89–1.11) in the cohort of 1,056 patients. Similar results were observed for prostate-specific antigen (PSA) progression-free survival (HR: 1.02, 95% CI: 0.91–1.14) and PSA response rate (72% [95% CI: 68–76%] for NHAs vs. 76% [95% CI: 72–80%] for docetaxel, $p > 0.05$). Additionally, patients treated with NHAs had a significantly lower annual HRU during follow up. These findings indicate comparable effectiveness between NHAs and chemotherapy, with a more favorable HRU profile for NHA-treated patients, suggesting potential cost-effectiveness of NHAs.

INTRODUCTION

Prostate cancer (PCa) is the most common urological malignant tumor with a significant impact on global health. In 2020, PCa emerged as the second most frequently diagnosed cancer among men worldwide, accounting for 14.1% of all new cancer cases in males.[1] PCa is also a leading cause of cancer-related deaths, with 375,304 deaths annually worldwide, positioning it as the fifth most common cause of cancer-related mortality in men.[1] The increasing incidence of PCa poses challenges to healthcare systems, with implications for resource allocation, and affects patients' life expectancy. As an androgen-dependent cancer, the epidemiology and pathogenesis of PCa are intimately linked to androgen levels, with testosterone playing a pivotal role in both the incidence and progression of the disease.[2,3] Androgen deprivation therapy (ADT), which includes surgical castration and antiandrogen medications, is the standard treatment for PCa.[4–6] ADT effectively delays disease progression by attenuating androgenic stimulation. However, the majority of patients eventually develop resistance to ADT within 2–3 years, leading to castration-resistant prostate cancer (CRPC).[7,8]

On the landscape of advanced PCa, particularly non-metastatic CRPC (nmCRPC), metastatic hormonal-sensitive prostate cancer (mHSPC), and metastatic CRPC (mCRPC), taxanes and androgen receptor (AR) signaling inhibitors have significantly improved patient survival.[9,10] Enzalutamide and abiraterone represent a class of second-generation AR inhibitors that have been particularly effective in targeting the AR signaling pathway. Enzalutamide impedes the nuclear translocation of the AR, disrupt AR-DNA binding, and inhibits coactivator recruitment.[7,11–13] The large-scale phase III randomized controlled trials (RCTs) have demonstrated the efficacy of enzalutamide used in combination with ADT to extend survival, compared with ADT alone.[14–17] Abiraterone, on the other hand, inhibits androgen biosynthesis to effectively reduce androgen levels.[18–20] Phase III RCTs have shown that combining abiraterone acetate with ADT improves overall survival compared with ADT alone.[21–23]

The use of enzalutamide and abiraterone as adjunct therapies for advanced PCa is well established in various treatment guidelines.[10,24] However, due to the substantial cost differences and the ongoing uncertainty regarding cost-effectiveness, physicians often face difficult decisions when managing patients

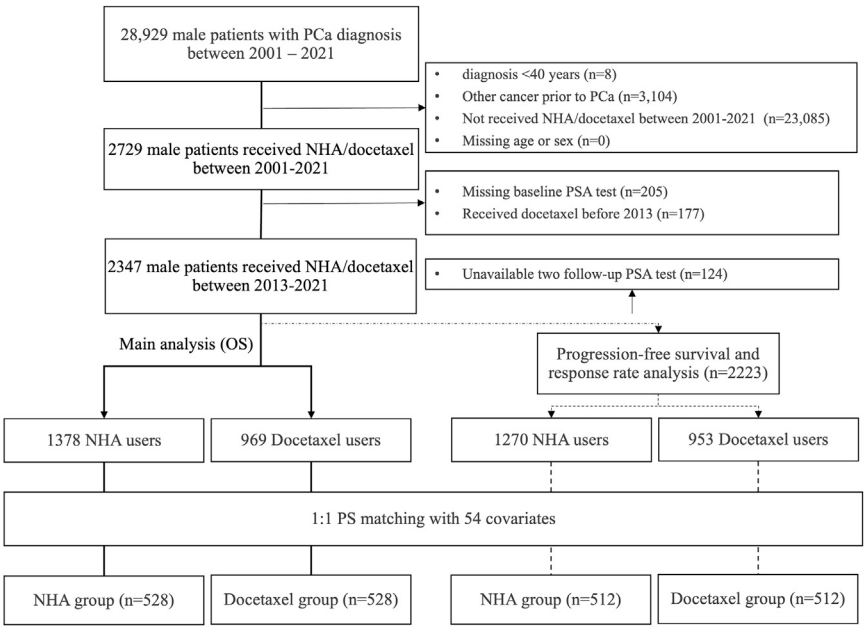

Figure 1. Patient identification flow

NHA, novel hormonal agent; PCa, prostate cancer; PSA, prostate-specific antigen; OS, overall survival; PS, propensity score.

who have progressed after first-line ADT or those diagnosed at advanced stages (22). The challenge lies in choosing between docetaxel and novel hormonal agents (NHAs), which can carry high out-of-pocket costs for patients.

Despite the clinical importance, direct comparisons of treatment effectiveness between NHAs and other therapeutic modalities for PCa remain underreported in the literature.[25] Existing literature frequently underscores the need for rigorous head-to-head comparative research to guide the selection of adjunct therapies in the management of advanced PCa, including mHSPC, nmCRPC, and mCRPC.[6,25–28] In this study, we aim to use territory-wide electronic medical records (EMRs) data to compare the effectiveness and healthcare resource utilization (HRU) of NHAs versus chemotherapy among patients with mHSPC, nmCRPC, and mCRPC, thereby contributing to informed treatment choices and clinical decisions for PCa.

RESULTS

Cohort characteristics

The cohort identification flow is illustrated in Figure 1. Between 1 January 2001 and 31 December 2021, our retrospective cohort study identified 28,929 patients diagnosed with PCa. Of these, 2,347 individuals (8.11%) met the inclusion criteria and had received NHA or docetaxel treatments. The initial treatment regimens included 969 patients receiving docetaxel, 726 patients receiving abiraterone, and 652 patients receiving enzalutamide. The median follow-up time was 12.95 months, 12.75 months, 11.62 months; and the mean age of initial PCa diagnosis was 65.7 years, 74.93 years, and 73.48 years for the docetaxel, abiraterone, and enzalutamide groups, respectively (Table S2).

Before PS matching, the mean age at the time of treatment initiation was 67.30 years in the docetaxel group and 77.36 years in the NHA group. After PS matching, the standardized mean differences (SMD) for all covariates fell below the 0.1 threshold, indicating a well-balanced comparison between the two groups (Table S3). After excluding patients with incomplete baseline PSA data, the final matched analysis included 1,056 patients, with an equal number from each comparison group (n = 528 for each).

Comparable overall survival

Accounting for censoring, the overall 5-year survival rate was 0.18 (95% confidence interval [CI] 0.14 to 0.23) in the whole population, and the median survival time was 538 days. At the end of the study, with a maximum follow-up time of 3,533 days, the overall survival (OS) probability was 0.16 (95% CI: 0.12–0.21) in the whole population. In the flexible parametric survival model, NHAs did not demonstrate a statistically significant improvement in OS compared to docetaxel, with a hazard ratio (HR) of 1.00 (95% CI: 0.89–1.11, Figure 2A).

In the sensitivity analysis, excluding patients dying within 30 days of treatment initiation, the results were similar to the main analysis, yielding an HR of 0.903 (95% CI: 0.803–1.01). The application of inverse probability of treatment weighting (IPTW) produced an HR of 1.02 (95% CI: 0.88–1.19), while the use of inverse probability of censoring weighting (IPCW) resulted in an HR of 0.88 (95% CI: 0.67–1.15). These findings substantiate the robustness of the primary analysis (Table S4).

Subgroup comparisons revealed no significant OS advantage for either abiraterone (HR 1.00, 95% CI: 0.87–1.13) or enzalutamide (HR 0.92, 95% CI: 0.78–1.08) when compared with docetaxel (Figure 2B). Additionally, NHAs did not show a significant OS benefit in either patients aged <75 years (HR 0.94, 95% CI: 0.82–1.06) or patients aged ≥75 years (HR 0.78, 95% CI: 0.59–1.01) at the time of drug dispensing (Figure 2C). In the mHSPC cohort (n = 1436), after accounting for censoring, the overall 5-year survival rate was 0.13 (95% CI: 0.09–0.18) for the matched cohort (n = 600), with a median survival time of 468 days. In the flexible parametric survival model, the use of NHAs was associated with slightly worse overall survival compared to docetaxel, with a HR of 1.18 (95% CI: 1.03–1.35) (Figure S1).

Comparable 50% PSA response rate and progression-free survival

Accounting for censoring, the overall 5-year PSA-progression-free survival was 0.20 (95% CI: 0.16–0.25) in the whole population. At the study's completion, with a maximum follow-up time

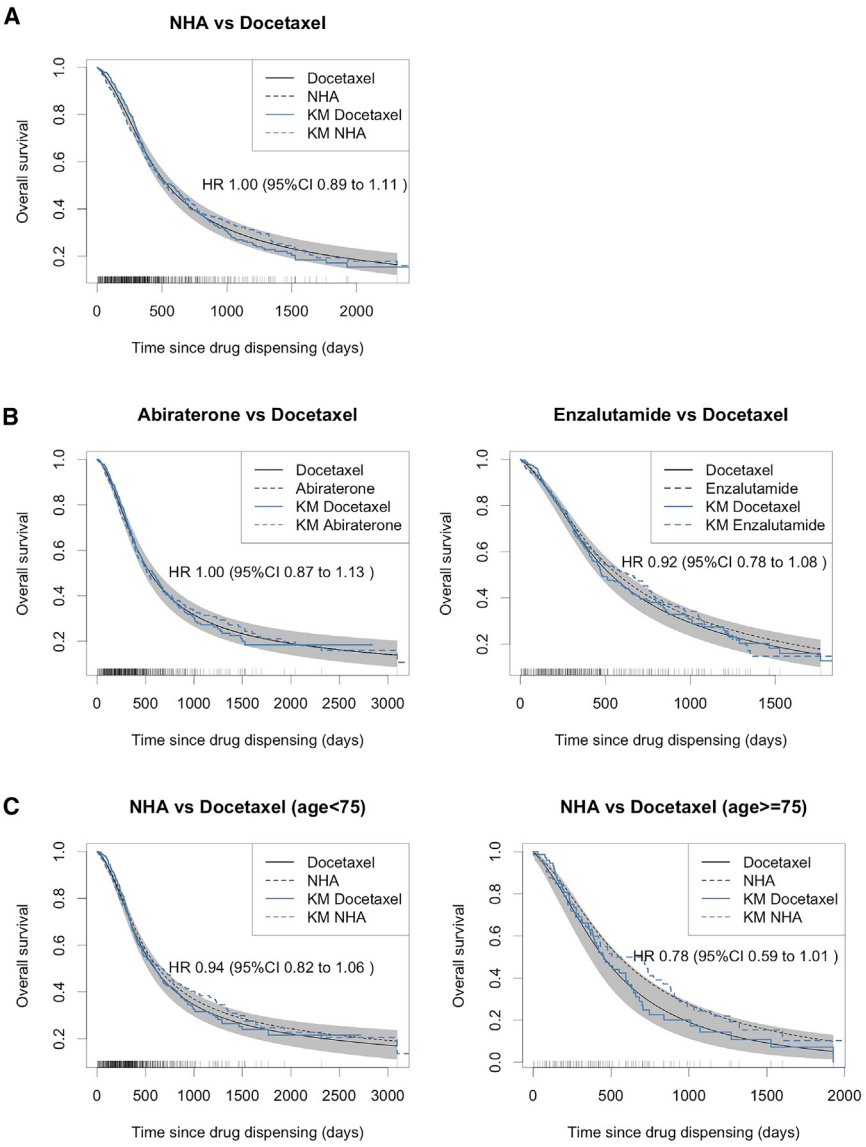

Figure 2. Overall survival comparison between novel hormonal agents and docetaxel

(A) Overall comparison.

(B) Subgroup comparison by NHA types.

(C) Subgroup comparison by age of diagnosis.

NHA, novel hormonal agent; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.

of 3,342 days, the PSA progression-free survival probability was 0.09 (95% CI: 0.02–0.35) in the whole population. The 50% PSA response rates were 0.72 (95% CI 0.68 to 0.76) in the NHA group and 0.76 (95% CI 0.72 to 0.80) in the docetaxel group, with no statistically significant difference between the two groups (chi-squared test, $p = 0.51$). Although NHAs showed relatively lower 50% PSA response rates across all subgroups, the differences did not reach statistical significance (Table 1).

Furthermore, NHAs did not show a statistically significant improvement in PSA-PFS, with an HR of 1.02 (95% CI: 0.91–1.14) (Figure 3A). The observation was consistent among all subgroup comparisons.

Improved health resource utilization

Patients treated with NHAs showed significantly lower healthcare resource usage compared to the docetaxel group. This was evident across various services, including inpatient, outpatient, and emergency department utilization (Figure 4). Specifically, the median annual inpatient admissions numbered 1.31 (interquartile range [IQR]: 0–4.96) for the NHA group, markedly lower than the 9.30 (IQR: 5.28–13.83) observed for the docetaxel group. Outpatient visits also followed this trend, with the NHA group registering a median of 17.64 (IQR: 12.74–24.00) annually, compared to 25.36 (IQR: 17.39–39.12) for the docetaxel cohort. The hospital length of stay mirrored these findings, with the NHA group exhibiting a median length of stay of 1.86 days (IQR: 0–13.88), in contrast to 12.35 days (IQR: 6.50–23.95) for the docetaxel group. Finally, emergency department admission was lower in the NHA group, with a median of 0.21 (IQR: 0–2.08) annually, against 0.98 (IQR: 0–2.54) in the docetaxel group. When separating the two NHAs, both abiraterone and enzalutamide showed reduced healthcare resource utilization across all four categories. Stratified by age, the NHA group consistently showed significantly lower use of healthcare services in all settings compared to the docetaxel group. The reduced HRU consumption was also observed in the mHSPC cohort. After excluding HRU consumption during the first six months for both the NHA and docetaxel groups, the significantly reduced annualized HRU effects in the NHA group remained evident (Figure S2).

DISCUSSION

Clinical guidelines have widely acknowledged the advantages of combining ADT with either NHAs or docetaxel for advanced PCa.[9,10,24] The comparative effectiveness and treatment sequencing of NHAs have been well documented, with enzalutamide generally associated with better clinical outcomes—including improved OS, delayed disease progression, and better disease response—compared to abiraterone.[29–32] However, enzalutamide is also linked to higher rates of adverse events, such as fatigue.[33] Despite these findings, there remains no clear consensus in the literature regarding the relative effectiveness of NHAs versus widely adopted chemotherapies like docetaxel,

Table 1. 50% Prostate-specific antigen response rate (proportion with 95% confidence interval)

Group	NHA	Docetaxel	*p* value of chi-squared test
NHA vs. Docetaxel	0.72 (95% CI 0.68 to 0.76)	0.76 (95% CI 0.72 to 0.80)	>0.05
Abiraterone vs. Docetaxel	0.72 (95% CI 0.67 to 0.77)	0.77 (95% CI 0.72 to 0.81)	>0.05
Enzaluatmide vs. Docetaxel	0.72 (95% CI 0.66 to 0.77)	0.71 (95% CI 0.65 to 0.77)	>0.05
NHA vs. Docetaxel (<75)	0.74 (95% CI 0.55 to 0.87)	0.68 (95% CI 0.49 to 0.83)	>0.05
NHA vs. Docetaxel (≥75)	0.74 (95% CI 0.69 to 0.78)	0.75 (95% CI 0.71 to 0.79)	>0.05

NHA, novel hormonal agent.

especially when assessed through real-world evidence.[28,34] For regions like Hong Kong, such evidence is crucial to inform clinical recommendations for managing patients who have progressed after first-line ADT.[6,35] To the best of our knowledge, this is the first study to employ territory-wide, population-based data to provide direct comparative evidence between adjunctive treatment modalities—specifically, docetaxel, abiraterone, and enzalutamide—and their respective efficacies and impacts on HRU. Our results indicate that patients treated with NHAs experience comparable OS and PSA-PFS to those treated with docetaxel, yet they require less frequent use of healthcare resources.

Initial data from a direct head-to-head RCT comparing abiraterone ($n = 377$) with docetaxel ($n = 189$) in patients with metastatic hormone-naive prostate cancer (PCa) demonstrated no significant difference in OS.[36] Supporting this finding, real-world evidence from a smaller Japanese cohort also indicated comparable OS when comparing abiraterone ($n = 172$) to docetaxel ($n = 86$).[34] Our study corroborates these observations by employing a more extensive 10-year longitudinal dataset from multiple centers in Hong Kong and utilizing PS techniques to mitigate the impact of differences in baseline characteristics, selection biases and informative censoring. Relative to evidence obtained from RCTs, our study benefits from including cohorts with complex baseline characteristics, making it more representative of real-world clinical settings and further substantiating its conclusions. We also observed a comparable PSA progression-free survival in the head-to-head comparison between NHAs and docetaxel. We selected PSA progression-free survival as the study endpoint in preference to radiographic PFS due to the heterogeneity in imaging schedules and modalities across the multicentre cohort. In contrast, PSA measurements were standardized across various healthcare facilities, thus ensuring uniformity of the data.

For enzalutamide, the direct comparative evidence against docetaxel remains inexplicit.[6,25] An indirect comparison from a network meta-analysis of RCT suggested an HR of 0.79 (95% CI: 0.64–0.97) for OS, with a low certainty of evidence due to heterogeneity of studies.[25] Our head-to-head comparison showed no significant difference in OS but improved PSA-PFS for patients treated with enzalutamide versus docetaxel. Compared with network meta-analysis, our cohort study employed direct comparison, which could better assist clinical decisions. Although variations in PSA testing frequency could potentially bias these results, we observed no substantial differences in 50% PSA response rates between NHAs and docetaxel, in line with previous studies.[34]

This investigation elucidates the notable disparities in HRU between patients treated with NHAs and those receiving docetaxel, especially inpatient and outpatient services. The cohort receiving docetaxel showed increased inpatient admissions, higher consumption of outpatient services, and an extended average inpatient stay—indicating a more substantial overall burden on the healthcare system. Within the health economic perspective, the cost-effectiveness of new next-generation hormonal-targeted therapies remains a topic of debate. Docetaxel, when used as an adjunct in the treatment of metastatic castration-sensitive prostate cancer (mCSPC), has long been considered the most cost-effective strategy.[37–39] However, recent cost-effectiveness analyses have shown that NHAs adjunct therapy can also be a high-value healthcare option, particularly when accounting for long-term follow up, reduced drug costs, and the differential costs of second-line treatments.[40–42] Our findings suggest that NHAs not only offer comparable or superior clinical benefits in terms of OS, PSA progression free survival, and PSA response rates, but also result in significantly lower overall HRU when juxtaposed with docetaxel treatment. The reduction in HRU observed with NHAs could be attributed to differences in the way these treatments are administered. Docetaxel is typically prescribed in ambulatory wards, requiring patients to be admitted to inpatient wards multiple times for intravenous drug administration. In contrast, NHAs are oral medications prescribed in outpatient clinics, meaning that patients receiving NHA therapy often require fewer follow-up admissions. Based on our estimation using publicly available charges of public hospital services in Hong Kong, the NHA-treated PCa is anticipated to be associated with an average reduction of HK$ 25,013 (approximately USD 3,218) of health service cost per year in matched groups.

In this study, we incorporated HRU data to evaluate the health system burden associated with treatment. To our knowledge, this is the first study comparatively evaluating HRU between patients treated with docetaxel and those treated with NHAs. Among studies reporting on HRU for individual treatments, a study based on the US Veterans Health Administration (VHA) database reported an annual of 30.1–34.3 all-cause outpatient visits for patients on NHAs,[43] which is higher than the 17.64 visits observed in our study. Similarly, a US PharMetrics database study reported an annual rate of 32.3–38.8 clinician visits for patients receiving docetaxel, which is closer to the 25.36 visits seen in our cohort.[44] These insights highlight the imperative for healthcare systems to refine oncology care pathways and foster rigorous prostate cancer cost-effectiveness analysis to mitigate health resource demands.

Limitations of the study

Our current study has several limitations. Firstly, the analysis of the effectiveness and HRU between NHAs and docetaxel are constrained by the absence of detailed dosage information in

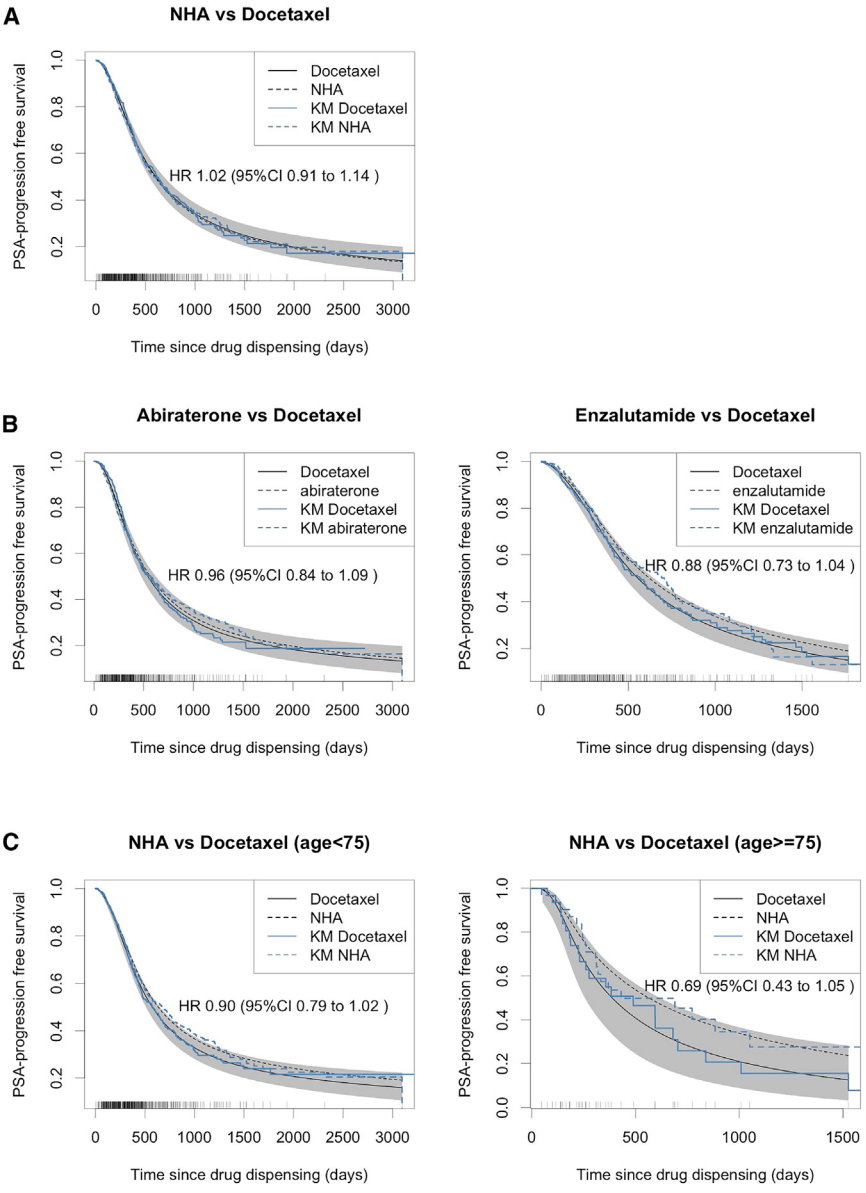

Figure 3. Prostate-specific antigen progression-free survival of novel hormonal agents and docetaxel

NHA, novel hormonal agent; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.

the prescription records of our database, as well as indeterminate patient actual usage. This necessitated the assumption that all patients received a standard prescribed dosage in a head-to-head comparison. Secondly, our study did not account for all emerging treatments for prostate cancer. Androgen-targeted therapies, such as nilutamide, apalutamide, and darolutamide, which were not registered in Hong Kong until after 2020, are underrepresented in our data. To address this limitation, we matched patients based on their existing medication history, specifically whether they had received common treatments that could potentially confound treatment assignment and health outcomes, including surgical castration and first-line ADT. Thirdly, a notable limitation of the EMR database we used is the lack of baseline imaging records and cancer staging information, as well as the inability to accurately identify the duration of first-line treatment. Given that NHAs and docetaxel are not reimbursed for the initial stages of prostate cancer, and considering their high costs, we assume that both treatments were predominantly dispensed for patients with advanced stages of prostate cancer who were concurrently receiving first-line ADT, consistent with clinical guidelines[9,24,45] and local consensus.[6,35] However, we acknowledge that the comparison cohort could include a mix of patients with different disease settings, such as nmCRPC, mHSPC and mCRPC. Also, we fully acknowledge the pathology disparities in different disease settings. To minimize discrepancies related to disease progression between treatment groups, we employed baseline matching on key factors, including the most recent PSA levels within one month, to mitigate this variability. We also conducted a subgroup analysis within the mHSPC cohort, identified using biochemical markers. However, due to the lack of imaging information, the identification of mHSPC in this study may be inconsistent with clinical practice. Additionally, given the relatively stringent PSA-based definition of CRPC used,[9] the mHSPC cohort may include patients with clinical or radiographical progression to mCRPC. Therefore, the findings related to the mHSPC cohort should be interpreted with caution. Fourthly, as is common in observational studies, unmeasured confounders cannot be fully controlled due to the lack of individual-level data, such as family history, body weight, and socio-economic status. Although we employed PS matching with a 0.1 caliper, residual confounding may still exist, highlighting the inherent limitations of PS matching as a substitute for randomization. To mitigate these methodological limitations, we implemented multiple alternative statistical approaches in sensitivity analyses, including IPTW and IPCW.

Conclusion

This study demonstrated that patients who were treated with NHAs achieved outcomes comparable to those treated with docetaxel in terms of OS, PSA-PFS, and PSA response rate. Additionally, NHAs were associated with lower annual HRU during follow-up. The clinical and health economic implications of these

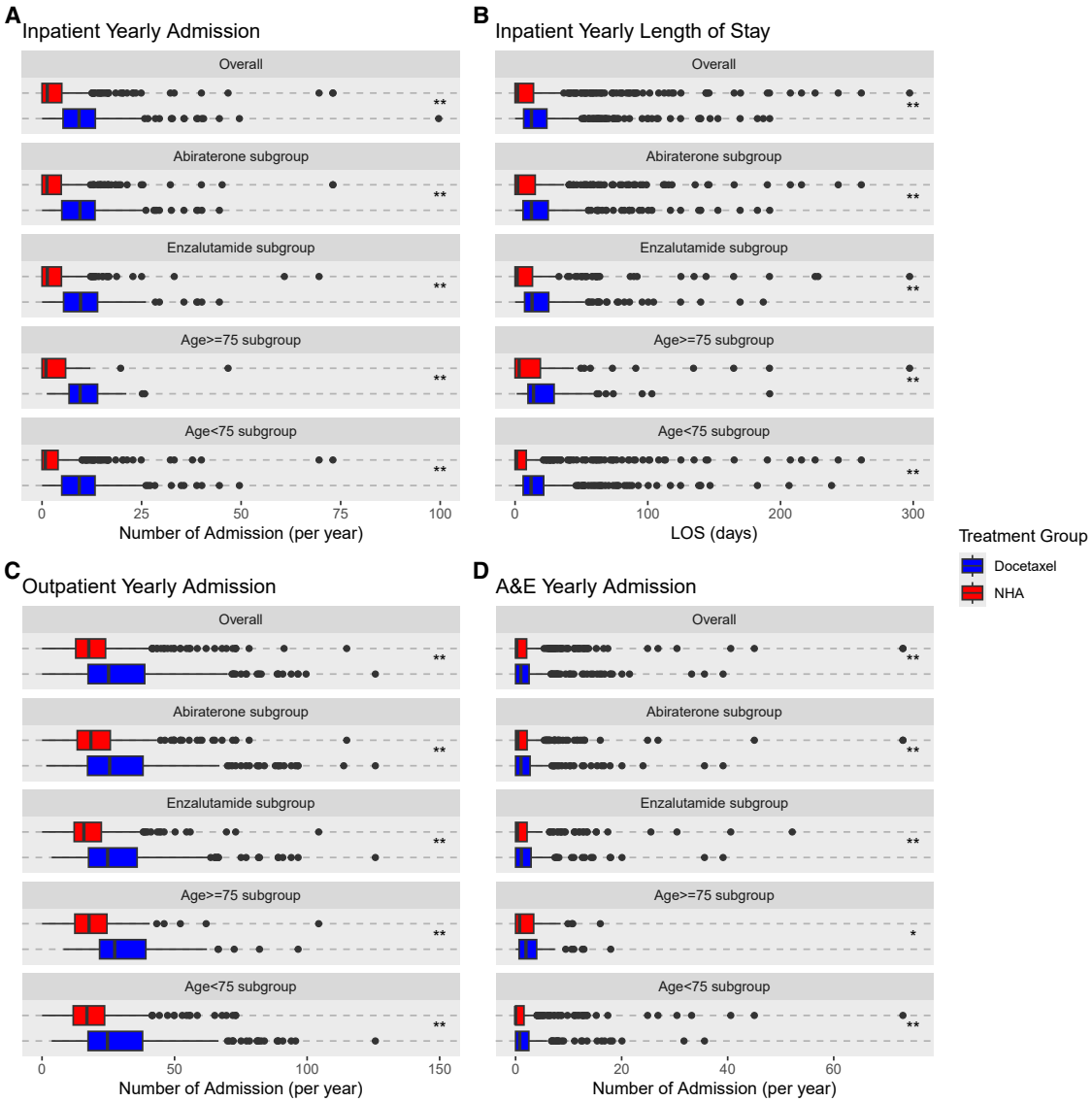

Figure 4. Health resource utilization of novel hormonal agents and docetaxel

* for p value <0.05; ** for p value <0.01.

NHA, novel hormonal agent; A&E, accident and emergency; LOS, length of stay.

findings warrant further consideration, particularly given the real-world evidence suggesting equivalent health outcomes and the potential cost-effectiveness of NHAs.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Dr Xue Li (Email: sxueli@hku.hk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- We are unable to directly share the data used in this study since the data custodian, the Hong Kong Hospital Authority who manages the Clinical Data Analysis and Reporting System (CDARS), has not given permission. However, CDARS data can be accessed via the Hospital Authority Data Sharing Portal for research purpose. The relevant information can be found online (https://www3.ha.org.hk/data).
- All analysis R code is open at https://github.com/STONE-117/NHA-vs-Docetaxel, also available from Zenodo (https://doi.org/10.5281/zenodo.15004285).
- Any additional information required to the analysis reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Y.J., data analysis, visualization, writing-original draft, and writing-review and editing; I.H., writing-review, clinical advice, and study design; C.W., writing-review, clinical advice, and study design; T.L. and J.W., cross-checking and writing-review; R.N. and S.W.K.S, writing-review and clinical advice; Y.W. and Y.C., writing-review; E.W.C., writing-review, administration, and technical support; X.L., conceptualization, supervision, methodology, study design, writing-review, data acquisition, and funding acquisition; all authors have read and approved the final manuscript.

DECLARATION OF INTERESTS

Outside the submitted work: X.L. received research grants or contracts from the Health and Medical Research Fund (HMRF Main Scheme, HMRF Fellowship Scheme, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR); she is also the former non-executive director of ADAMS Limited Hong Kong; commission grants from Hospital Authority of Hong Kong, internal funding from the University of Hong Kong; consultancy fees from Merck Sharp & Dohme, Pfizer and Open Health and The Office of Health Economics; and honoraria for associate editorship from Nature Springer. E.W.C. reports grants from the Health Bureau (Hong Kong), the Research Grants Council (RGC, Hong Kong), National Natural Science Fund of China, Bayer, AstraZeneca, Novartis, RGA Reinsurance Company, Pfizer, Narcotics Division of the Security Bureau of HKSAR; Consulting fee from Pfizer, Novartis, and AstraZeneca; honorarium from Hospital Authority (Hong Kong), Pfizer outside the submitted work.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Code for statistical analysis (R)	This work	https://doi.org/10.5281/zenodo.15004285
R verison 4.2.2	The R Foundation	https://www.R-project.org/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design and participants

We conducted a territory-wide, retrospective cohort study by EMRs sourced from the Hong Kong Hospital Authority (HA), which oversees all public hospitals, specialist, and general outpatient clinics in Hong Kong (HK). The HA delivers complimentary public healthcare services to the entirety of the HK's populace, exceeding 7.3 million individuals, mainly Asian descent, and is responsible for roughly 80% of all hospital admissions within the region.[46]

Our study population consisted of male patients diagnosed with PCa, identified by the International Classification of Diseases (ICD)-9 code 185, between 1 January 2001 and 31 December 2021. We included individuals who were prescribed any of the following treatments: docetaxel, enzalutamide, or abiraterone from 1 January 2013 to 31 December 2021. This period corresponds to when NHAs and docetaxel were simultaneously recommended for advanced-stage PCa in Hong Kong. In local practice, concurrent treatment with ADT with NHAs or docetaxel is standard practice for nmCRPC, mHSPC and mCRPC, in line with guidance by the European Association of Urology and the American Society of Clinical Oncology Provisional Clinical Opinion recommending ADT maintenance after castration-resistance progression.[9,45] Therefore, no additional measures were applied to identify simultaneous ADT use.

Patients were excluded from the study if they were under 40 years of age at the time of PCa diagnosis or had documented pre-existing malignancies other than prostate cancer (ICD-9 codes: 140–209, 230–239). Data collection included diagnostic records, mortality data, medication prescriptions, procedural interventions, prostate-specific antigen (PSA) test results, and hospitalization records. An up to 13-year observation period prior to treatment initiation and a minimum observation period of one year after treatment initiation was ensured for all patients. Patients with missing baseline PSA within the last month prior to the first administration of NHA or docetaxel were excluded. Personal information on race or ancestry was unavailable in Hong Kong's electronic medical records.

Ethics statement

Given the completely de-identified nature of the EMR data utilised from the HA database, patient consent was deemed unnecessary for this study. The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB reference number: UW 22-279). The authors confirm that the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Target population

For PCa patients who received NHAs or docetaxel, we extracted associated EMRs from the HA, detailing both baseline characteristics and follow-up data. EMRs were linked using internal unique de-identified reference keys to ensure the integrity and continuity of patient records. Treatment groups were delineated by the initial administration of NHAs or docetaxel, with the date of first exposure as the index date to commence follow-up. This follow-up started from the index date until the occurrence of any of the following events: the patient's death, transition to another treatment of NHAs or docetaxel, or study end date as 31 December 2022, whichever occurred earliest. Since NHAs and docetaxel accounted for the majority of local prescriptions for next-generation hormonal-targeted therapies and chemotherapies, treatments outside abiraterone, enzalutamide, and docetaxel—as well as therapies beyond these categories, including immunotherapies—were not considered in this study.

METHOD DETAILS

The primary endpoint for our effectiveness analysis was overall survival (OS), defined as the duration from treatment initiation to death from any cause. Secondary outcomes were 50% PSA response rate, PSA-progression-free survival (PSA-PFS) and annualised HRU during the follow-up period. The 50% PSA response rate was defined as the proportion of patients who experienced a reduction of 50% or more in their PSA levels from baseline, with this decrease confirmed by a subsequent PSA evaluation at least four weeks later.[18] This metric serves as an indicator of biochemical response to therapy in patients with prostate cancer. PSA-PFS was defined as the interval from treatment initiation to the point of PSA progression or death from any cause.[18] PSA progression was

characterised in alignment with criteria established by a phase III multinational RCT – for patients who did not experience a decrease in PSA levels, progression was defined as an elevation of 25% above baseline, coupled with an absolute increase of at least 5 ng/mL; for those whose PSA levels decreased without satisfying response criteria (PSA $\leq$50% of baseline), progression was marked by a 25% rise with an absolute increase of a minimum 5 ng/mL from the nadir; and for cases where PSA levels had diminished by at least 50%, progression was defined as a 50% augmentation from the nadir with an absolute increase of a minimum of 5 ng/mL.[18] For PSA response and PSA progression analysis, patients with less than two PSA tests in follow-up were excluded.

All-cause healthcare resource utilisation was annualised according to the individual's follow-up time. HRU captured all healthcare services used during the follow-up period, quantified as the number of hospitalisation episodes or inpatient days per patient-year. HRU was disaggregated into 14 service categories, reflecting the diversity of care settings: from outpatient, inpatient and emergency service settings as categorised by the Hong Kong Hospital Authority's fees and charges framework.[47]

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analysis

To mitigate confounding effects and ensure comparability between treatment cohorts, we employed propensity score (PS) matching. The PS was generated using logistic regression models, which were designed to predict the probability of patients receiving docetaxel in comparison to NHAs, based on 53 demographic and clinical factors including age at drug dispensing, clinical history, recent one-month PSA level, and prostatectomy history (Table S1). Following PS calculation, the 1:1 nearest-neighbour matching without replacement was utilised to pair patients treated with docetaxel to a counterpart receiving enzalutamide or abiraterone, applying a calliper width of 0.1. The balance between the matched cohorts was appraised using the standardised mean difference (SMD), with values exceeding 0.1 being a sign of significant imbalance.

To model OS and PSA-PFS, we implemented flexible parametric survival models based on preliminary data analysis that indicated non-linearity in the hazard function. Flexible parametric survival models are adept at capturing the complex survival distributions often encountered in clinical and medical research and are particularly beneficial for addressing delayed treatment effects in oncological studies.[48] Analyses were stratified by age and type of NHA. The PSA response rate of each group was compared using a Chi-squared test. For HRU comparison, we conducted two-sample Wilcoxon rank-sum tests for significance testing.

Subgroup and sensitivity analyses

We performed subgroup analyses for both primary and secondary outcomes. In the NHA subgrouping, we analysed the usage of abiraterone or enzalutamide separately. In addition, we stratified the patients into age-based subgroups according to their age at drug dispensing, categorising them as either younger than 75 years, or 75 years and older. We rematched the cohort with PS for all subgroup analyses.

In clinical practice, the specific disease setting (nmCRPC, mHSPC or mCRPC) is important for treatment decisions. Due to the nature of our dataset, these settings could not be unequivocally distinguished based on the available data. However, we also conducted an additional analysis on mHSPC patients who were classified as being at the metastatic stage but had not yet progressed to CRPC. Patients were identified as having progressed to CRPC if they recorded a testosterone level below 1.7 nmol/L, along with three consecutive PSA rises (at least one week apart), resulting in two 50% increases over the PSA nadir and a PSA level exceeding 2 ng/mL.[9] The remaining subgroups, consisting of nmCRPC (N=47) and mCRPC patients (N=145), were deemed too small to generate meaningful results and were therefore excluded from further analysis.

To test the robustness of findings from the main analysis, we conducted four sensitivity analyses: First, we excluded patients who died or switched to another treatment within 30 days of drug dispensing. This was done to account for the prolonged survival characteristic of prostate cancer and the potential delayed effects of treatment; Second, we applied inverse probability of treatment weighting (IPTW) as an alternative method to propensity score (PS) matching to account for all subjects.[49] The same covariates used in the PS analysis (Table S1) were incorporated, and the analysis was conducted using the R package 'ipw'. The detailed procedures for IPTW were described by van der Wal and Geskus[50]; Third, we constructed inverse probability of censoring weighting (IPCW) to adjust for non-random censoring due to treatment switching.[51] In this method, uncensored observations were up-weighted to represent censored observations with similar characteristics. The stabilised probability of not being censored was estimated using a Cox model with the same covariates as the PS analysis. Detailed protocols for IPCW were described by Willems and Fiocco.[52] Lastly, to account for the potential short-term, high-intensity HRU associated with different treatment modalities, we conducted an additional analysis focusing on long-term HRU. This was achieved by excluding health resource consumption within the first six months following drug prescription.

All statistical analyses were conducted using R software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), and cross-checked by three independent investigators (Jiao Y, Li T and Wang J).