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Prostate Cancer

Real-world Evidence on Baseline Characteristics and Treatment in Metastatic Hormone-sensitive Prostate Cancer: Findings from the PIONEER 2.0 Big Data Investigation Group

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Abstract

Background and objective: As first-line therapies for metastatic hormone-sensitive prostate cancer (mHSPC) expand, real-world insights into the baseline characteristics and treatment patterns of mHSPC patients are critical. This study characterises baseline patient profiles and treatment patterns in a multinational real-world cohort from the PIONEER 2.0 Big Data Investigation Group.

Methods: This longitudinal observational study utilised health records, insurance claims, and cancer registries from eight European and North American databases. Men diagnosed with mHSPC between January 2016 and December 2020 were included. First-line regimes were classified into four cohorts: (1) androgen deprivation therapy (ADT) monotherapy, (2) ADT + chemotherapy, (3) ADT + androgen receptor pathway inhibitors (ARPIs), and (4) ADT + ARPI + chemotherapy. Baseline characteristics were analysed across treatment groups, and treatment patterns were evaluated over time.

Key findings and limitations: A total of 69 680 mHSPC patients were identified across eight databases, of whom 71% presented with synchronous mHSPC. The median age ranged from 70 to 79 yr, and the most prevalent comorbidities were arterial hypertension peaking at 71% (OPTUM ADT monotherapy), obesity (up to 46%), and diabetes mellitus (up to 32%). Patients aged 70–79 yr were most often treated with ADT monotherapy or ADT + ARPI, whereas those aged 60–69 yr more frequently received ADT + chemotherapy or ADT + ARPI + chemotherapy. From 2016 through 2020, the adoption of ARPI-based combinations rose steadily, use of ADT + chemotherapy declined, and ADT monotherapy remained stable.

Conclusions and clinical implications: In this expansive real-world analysis of nearly 70 000 mHSPC patients, age and comorbidity burden emerged as the primary determinants of frontline therapy, alongside a clear shift towards the increased use of ADT + ARPI regimes from 2016 to 2020. Embedding these real-world insights into clinical guidelines and decision-making can enhance treatment personalisation, accelerate adoption of evidence-backed combinations, and ultimately enhance mHSPC patient outcomes.

Patient summary: In this study of nearly 70 000 men with metastatic hormone-sensitive prostate cancer, doctors' treatment decisions were influenced strongly by patients' age and other health issues, highlighting a growing preference for combination therapies. The findings highlight the importance of real-world evidence, which captures diverse, often under-represented, patients to complement clinical trials and guide more inclusive, evidence-based care.

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1. Introduction

Metastatic hormone-sensitive prostate cancer (mHSPC) denotes a stage in the progression of prostate cancer, in which systemic therapy plays a central role in disease management. In recent years, the treatment landscape has evolved with increasing adoption of combination therapies, including androgen deprivation therapy (ADT) with chemotherapy, and new androgen receptor pathway inhibitors (ARPIs), as well as triplet regimes. While clinical trials have established the efficacy of these regimens, real-world treatment patterns are influenced by a range of factors beyond the controlled settings of randomised controlled trials (RCTs) [1–3].

RCTs remain the gold standard for evaluating treatment efficacy, but their inclusion criteria often limit generalisability to broader patient populations. Many mHSPC RCTs exclude patients with significant comorbidities, advanced

age, or prior cardiovascular disease, or those receiving anti-coagulation therapy. Furthermore, patients from under-represented regions or health care systems with variable treatment access are often omitted, restricting trial applicability to routine practice. Consequently, real-world evidence (RWE) is critically needed to complement RCT data and provide insights into treatment decision-making across diverse clinical settings [4].

Previous studies suggest that treatment selection in mHSPC hinges on a complex interplay of patient factors such as age, comorbidities, disease burden, and symptoms [5,6]. Although clinical guidelines and decision frameworks document these considerations, their translation into real-world treatment choices remains unclear. Additionally, physician preferences, structures of health care systems, and access to novel therapies may further shape prescribing patterns. A comprehensive understanding of how these patient characteristics and external factors drive

real-world clinical practice is lacking and warrants further investigation.

Integration of RCT findings with RWE is essential for a holistic view of treatment efficacy and safety, ensuring that clinical guidelines address the full spectrum of patients encountered in daily practice. The PIONEER+ Big Data Investigation Group, an international investigation group led by the European Association of Urology (EAU), seeks to bridge this gap by leveraging real-world data (RWD) in prostate cancer. This study analyses a large mHSPC cohort to characterise baseline patient profiles and frontline treatment choices in routine practice.

2. Methods

2.1. Study design and data sources

This observational study was conducted within the PIONEER+ Big Data Investigation Group, an initiative of the EAU data initiatives. It leveraged harmonised electronic health records (EHRs), insurance claims data, primary care databases, and cancer registries from multiple European and North American sources. All datasets were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) to ensure standardised data integration and analysis across diverse health care settings.

The study protocol, an open-access publication, details the methodology, data sources, and analytical framework [7]. A custom *R* characterisation package, developed by PIONEER members using Observational Health Data Sciences and Informatics (OHDSI) tools, extracted distributions for index year (year of diagnosis), age groups, baseline comorbidities, treatments, and treatment switches.

This study is designed as a longitudinal observational cohort study, tracking patient characteristics and treatment patterns in men diagnosed with mHSPC between January 2016 and December 2020. This timeframe balanced contemporary treatment patterns in the management of mHSPC with sufficient follow-up to assess longitudinal treatment trajectories while preserving data completeness and consistency across contributing sources.

Data were drawn from eight networks of observational EHR datasets standardised to the OMOP-CDM: the Clinical Practice Research Datalink (CPRD) AURUM and IQVIA ambulatory electronic medical records (EMRs), the Netherlands Cancer Registry (NCR) and IQVIA US Oncology EMRs, and the IBM MarketScan, IQVIA US OPENCLAIMS, US OPTUM, and IQVIA PharMetricsPlus health insurance claims databases (all reported in [Supplementary Table 1](#)). Each custodian used deidentified data, classifying the analysis as non-human subjects research waiving the need for informed consent. In compliance with the General Data Protection Regulations (GDPR), no identifiable information is shared, and all data are aggregated with a minimum cell count of five patients.

2.2. Cohort definitions and inclusion criteria

Two mHSPC subcohorts were defined based on metastatic disease presentation: the synchronous mHSPC subcohort includes patients with metastatic disease at the time of

initial prostate cancer diagnosis, and the metachronous mHSPC subcohort includes patients who progress to metastatic disease after an initial diagnosis of localised prostate cancer. These classifications are then applied to each individual treatment cohort.

Patients were included in the analysis if they met all the following criteria: adult males (≥ 18 yr) diagnosed with mHSPC, at least one recorded prostate cancer diagnosis (ICD-10: C61) between 183 d before and 30 d after the first metastasis diagnosis, no prior diagnosis of any primary malignancy (except nonmelanoma skin cancer), at least 365 d of recorded health care data before mHSPC diagnosis, and no history of ADT within 6 mo before diagnosis unless administered as part of localised treatment.

Patients were classified into treatment-initiated cohorts based on their first systemic therapy—ADT monotherapy, ADT + chemotherapy, ADT + ARPI, or ADT + ARPI + chemotherapy, and all had to have metastatic prostate cancer diagnosis as defined above.

The treatment start date was defined as the first recorded prescription or administration of systemic therapy within 183 d after mHSPC diagnosis.

2.3. Baseline characteristics and treatment profiles

Baseline characteristics, which included demographics (age at diagnosis, reported as mean and age group distribution) and comorbidities (arterial hypertension, diabetes mellitus, obesity, asthma, and chronic obstructive pulmonary disease [COPD]), were analysed across treatment cohorts.

2.4. Descriptive statistics and statistical analysis

Continuous variables are reported as means with standard deviations and 95% confidence intervals (CIs), and categorical variables are reported as frequencies and proportions with Wald's 95% CIs. A time-to-event analysis were performed using the Kaplan-Meier method. All analyses were conducted in *R* statistical software (R Foundation for Statistical Computing, Vienna, Austria). The open-source *R* package used in this study is publicly available on GitHub (<https://github.com/bdemeulder/PIONEERmetastaticTreatment>), and cohort characterisation follows the methods described by Schuemie et al [8]. All the results described in this paper are available at <https://pioneer-shiny.hzdr.de/app/PioneerMetastaticTreatmentExplorer2>.

2.5. Data governance and ethical considerations

This study was conducted in compliance with GDPR and institutional review board guidelines. No patient-identifiable information was accessed; only deidentified aggregated statistics were shared under a federated data model, with raw patient-level data retained by each federated data model and each data custodian.

3. Results

Across eight databases, we identified a total of 69 680 patients who received treatment for mHSPC. The number of patients in each cohort and database are shown in [Table 1](#).

Table 1 – Number of treated mHSPC patients by cohort and data source

Cohort	AMBEMR	CPRD	MarketScan	NCR	ONCO	OPENCLAIMS	OPTUM	PharmetricsPlus
mHSPC treated (total)	1593	708	2554	9094	1619	40 190	6306	7616
mHSPC treated (synchronous)	761	620	1588	8784	916	27 695	3915	5261
mHSPC treated (metachronous)	17	9	94			1147	140	191
ADT only treated	1083	684	1543	4995	845	29 539	4369	5108
ADT + ARPI treated	481	24	553	268	496	6290	1291	1139
ADT + chemotherapy treated	15		375	3804	208	3809	545	1173
ADT + ARPI + chemotherapy treated	14		83	27	70	552	101	196

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CPRD = Clinical Practice Research Datalink; mHSPC = metastatic hormone sensitive prostate cancer; NCR = the Netherlands Cancer Registry.

These sources include EMR data from the USA (AMBEMR and ONCO), US claims data (OPENCLAIMS, OPTUM, MarketScan, and IQVIA PharmetricsPlus), UK primary care EMR data (CPRD), and the NCR. Among these men, 49 540 (71%) presented as having synchronous mHSPC and 1598 (2%) with metachronous mHSPC; the remaining 18 542 (27%) men were unclassified.

Across all databases, treated and synchronous mHSPC patients were most frequently in the 70–79-yr age group (range 38–54%; Fig. 1). In contrast, in MarketScan and PharmetricsPlus, the 60–69-yr age group predominated (range 41–43%). Among metachronous mHSPC patients, the age group of 60–69 yr was also most common (range of 41–58%) in MarketScan, OPENCLAIMS, and PharmetricsPlus (Fig. 1).

In patients aged 70–79 yr, ADT monotherapy was the most common regimen in claims datasets, reaching 78% in OPENCLAIMS. The use of ADT + ARPI was peaked at 30% in ONCO and 27% in AMBEMR. Chemotherapy-based regimens declined with age in all datasets except the NCR, where ADT + chemotherapy use remained high at 45%. Triplet therapy (ADT + ARPI + chemotherapy) was rare, peaking

at 9% in ONCO in patients aged <60 yr and dropping to 2% in those aged ≥80 yr. All treatment combinations were least common in patients <60 or ≥80 yr of age (Fig. 2 and Supplementary Table 1).

Patients with synchronous and metachronous mHSPC had high comorbidity rates. The most prevalent comorbidities across all databases were arterial hypertension (up to 71%), obesity (up to 46%), type 2 diabetes mellitus (up to 32%), and asthma or COPD (up to 21%; Fig. 3). Comorbidity distributions were consistent across treatment modalities. ADT monotherapy and ADT + ARPI cohorts had the highest proportion of arterial hypertension (up to 71% and 70%, respectively), whereas ADT + ARPI + chemotherapy and ADT + chemotherapy cohorts had lower rates (up to 54% and 60%, respectively; Supplementary Table 2).

An analysis of index year distribution from 2016 to 2020 was roughly uniform (~20%/yr) across all datasets, with minor year-to-year variation (Supplementary Fig. 1). Over the same period, the use of ADT monotherapy remained relatively stable with a slight downward trend, ADT + ARPI use increased steadily, and ADT + chemotherapy use declined across all databases (Fig. 4 and Supplementary Table 3).

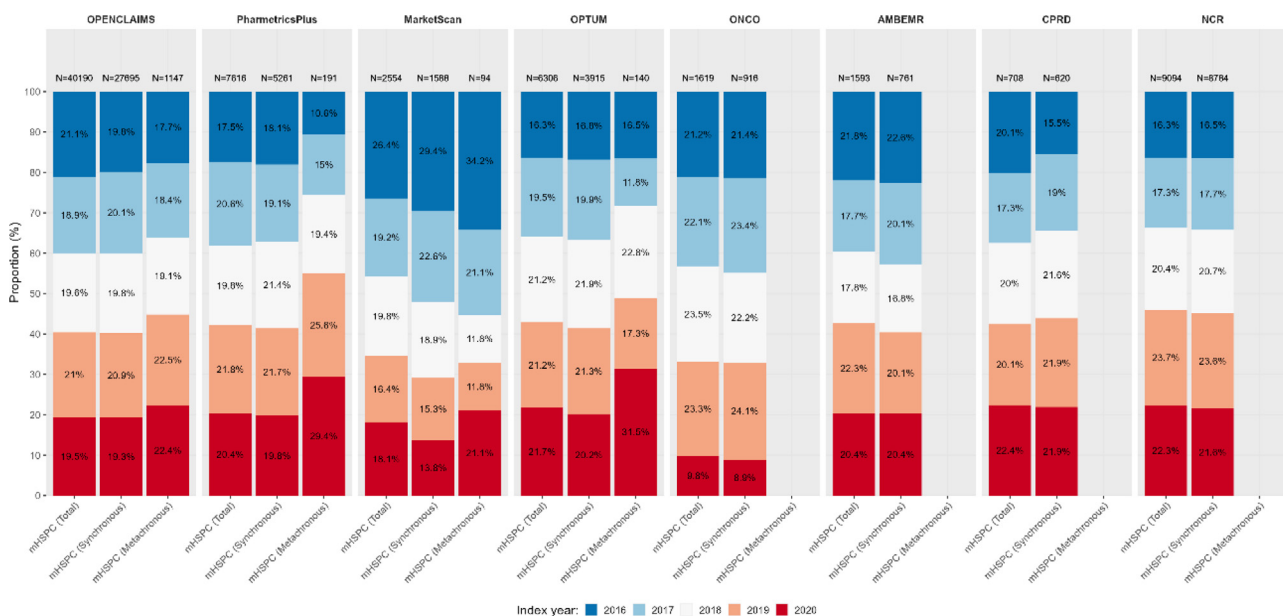


Fig. 1 – Age distribution by metastatic presentation (total vs synchronous vs metachronous mHSPC) across eight data sources. CPRD = Clinical Practice Research Datalink; mHSPC = metastatic hormone-sensitive prostate cancer; NCR = the Netherlands Cancer Registry.

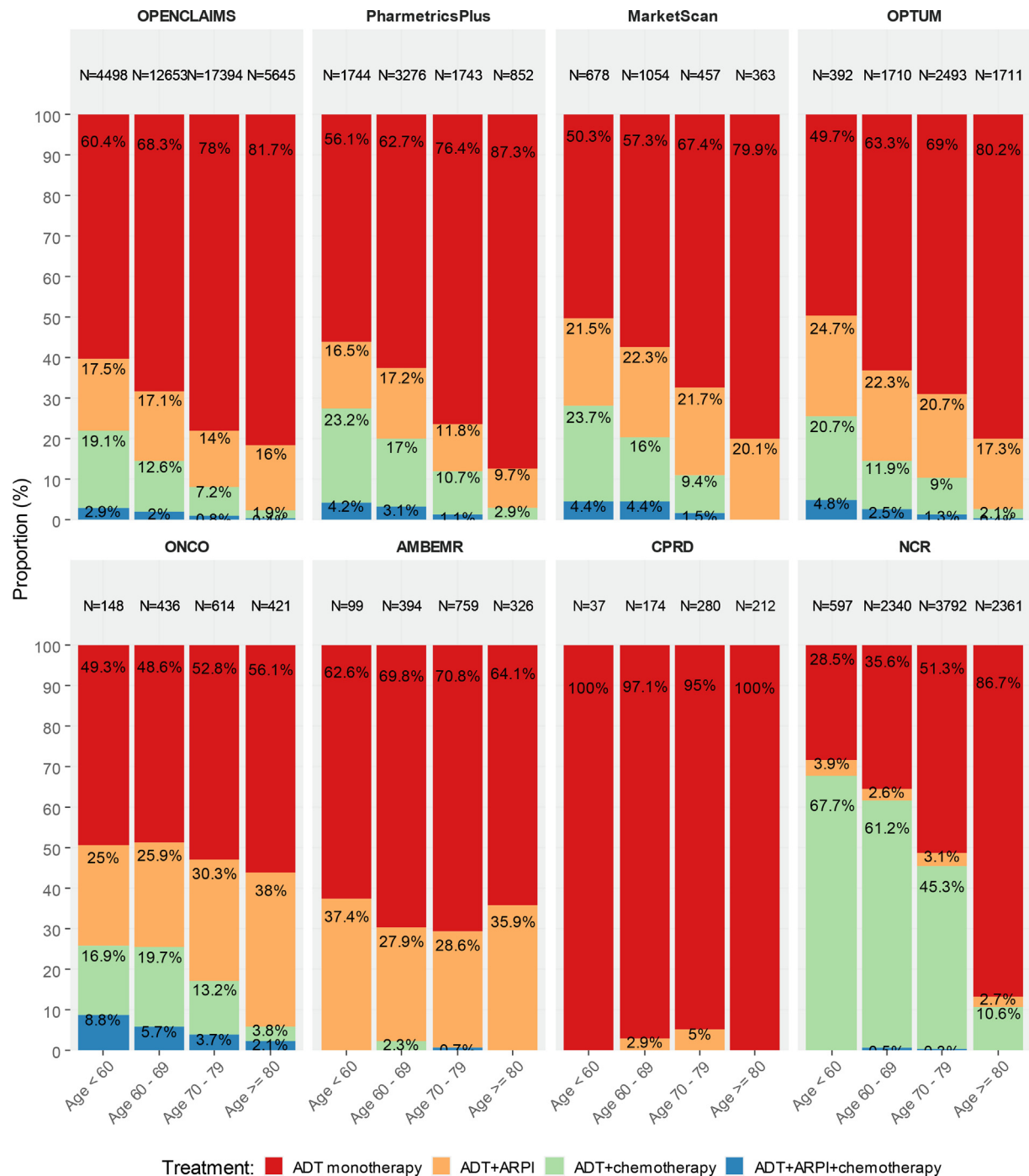


Fig. 2 – Age distribution by first-line regimen in mHSPC patients (ADT only, ADT + ARPI, ADT + chemotherapy, and ADT + ARPI + chemotherapy) across data sources. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitors; CPRD = Clinical Practice Research Datalink; mHSPC=metastatic hormone-sensitive prostate cancer; NCR = the Netherlands Cancer Registry.

4. Discussion

This study provides a comprehensive real-world analysis of baseline characteristics and treatment patterns of mHSPC patients using data from European and North American databases. Among 69 680 patients identified, 49 540 (71%) had synchronous mHSPC and 1598 (2%) had metachronous mHSPC; the remaining 27% were unclassified. The most treated age group was 70–79 yr, although in some US claims

datasets, the 60–69 yr age group was predominant. Treatment patterns varied by age: ADT monotherapy peaked at 78% in OPENCLAIMS, and ADT + ARPI being most common in older patients reached 30% in ONCO and 29% in AMBERMR among 70–79 yr olds; conversely, chemotherapy-based regimes declined with advancing age across most sources, except in the NCR where ADT + chemotherapy remained above 45% in 70–79 yr olds. Combined intensified regimes (ADT + chemotherapy and

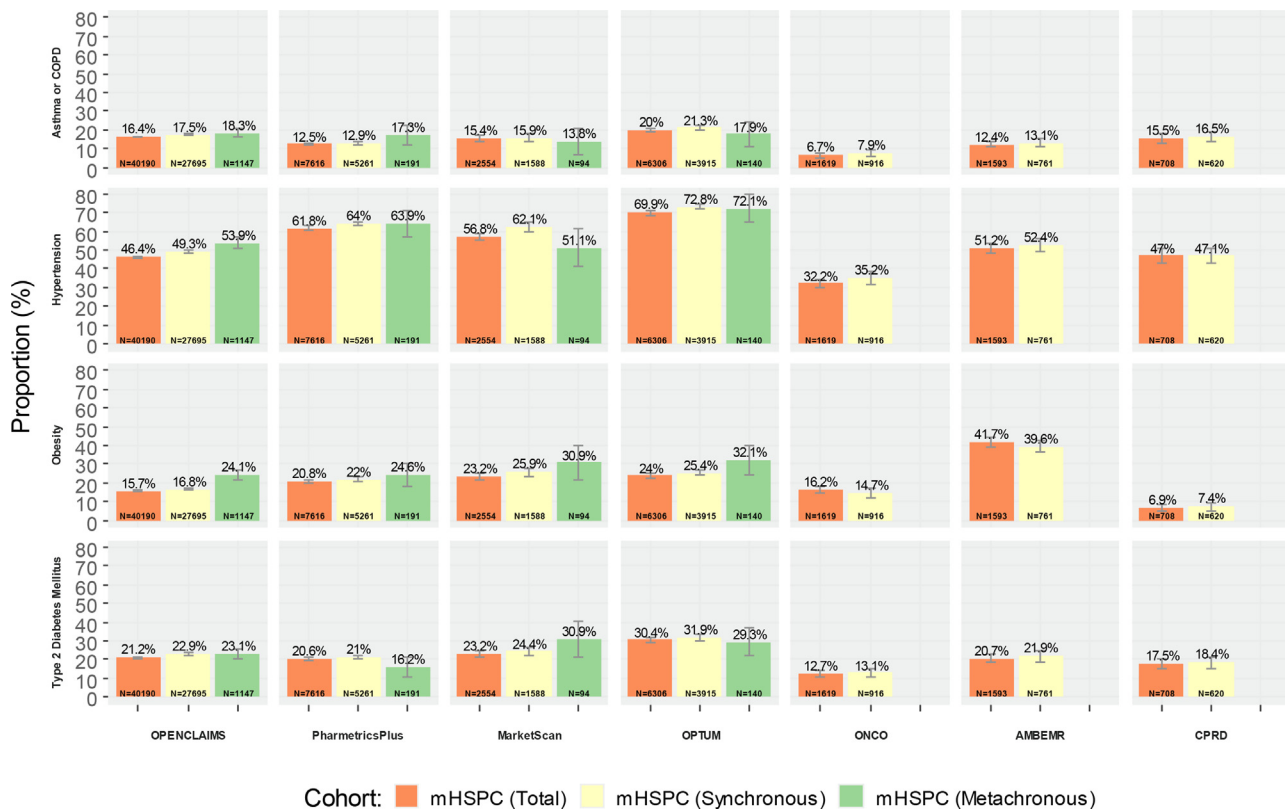


Fig. 3 – Baseline comorbidity prevalence (hypertension, obesity, diabetes, and asthma/COPD) in mHSPC patients by treatment cohort across data sources. COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; mHSPC = metastatic hormone-sensitive prostate cancer.

triplet therapy) dropped with age from ~24% in patients aged <60 yr to under 3% in those aged ≥80 yr within claims datasets. Hypertension (up to 70%), obesity (up to 42%), and diabetes (up to 32%) were the most prevalent comorbidities.

Over time, the use of ADT + ARPI has increased, while the use of ADT + chemotherapy declined. These findings highlight the influence of age and comorbidities on treatment selection, and reinforce the need for RWE to guide equitable and optimised treatment strategies in mHSPC.

Age plays a role in the selection of systemic therapy in mHSPC. In our study, ADT monotherapy and ADT + ARPI were used most frequently in older patients (70–79 yr), whereas combination chemotherapy-based therapies were more common in younger men (60–69 yr). This suggests that clinicians weigh chronological age and fitness when tailoring therapy. Raval et al [9] reported a median age of 65 yr in their US claims cohort versus 70–79 yr in ours, underscoring how age, comorbidities, and health care systems share prescribing patterns. As treatment intensification becomes standard practice, ensuring equitable access and individualised patient selection is essential, warranting further research into long-term outcomes and toxicity management in diverse populations [10–12].

The LATITUDE and STAMPEDE trials demonstrated survival benefit with ADT intensification using ARPIs [13,14], but RWD suggest that uptake in elderly patients remains heterogeneous, likely due to concerns over cardiovascular toxicity and tolerability [9,15–17]. Future studies should focus on mitigating toxicity and refining patient selection

to extend the benefits of intensified therapy to older and comorbid men.

While our findings confirm that age influences systemic treatment selection, we acknowledge that additional confounding factors also contribute to treatment variation. Disease burden (eg, low vs high volume), performance status, and comorbidities are critical eligibility determinants for intensified regimens, but these clinical details were available inconsistently across datasets. Furthermore, the health care setting and provider speciality may affect treatment access. These patient- and system-level biases highlight the complexity of real-world treatment decision-making and underscore the need for more granular data and qualitative research to better clarify disparities in care.

Our cohort included a high proportion of older patients, most commonly aged 70–79 yr, which contrasts with many pivotal trials that report a younger median age. For example, Helstrom et al [18] found median ages of 64–68 yr in recent mHSPC trials, with relatively few patients being ≥75 yr old. This gap in trial representativeness reinforces the value of real-world studies to assessing the generalisability of efficacy and tolerability in older, comorbid populations. The cardiovascular risk associated with ARPIs has become a growing concern in advanced prostate cancer management. Matsukawa et al [19] demonstrated that ARPI use significantly increases the risk of cardiac disorders, including heart failure, ischaemic heart disease, and atrial fibrillation. Interestingly, in our data, we observed a high prevalence of arterial hypertension and diabetes among

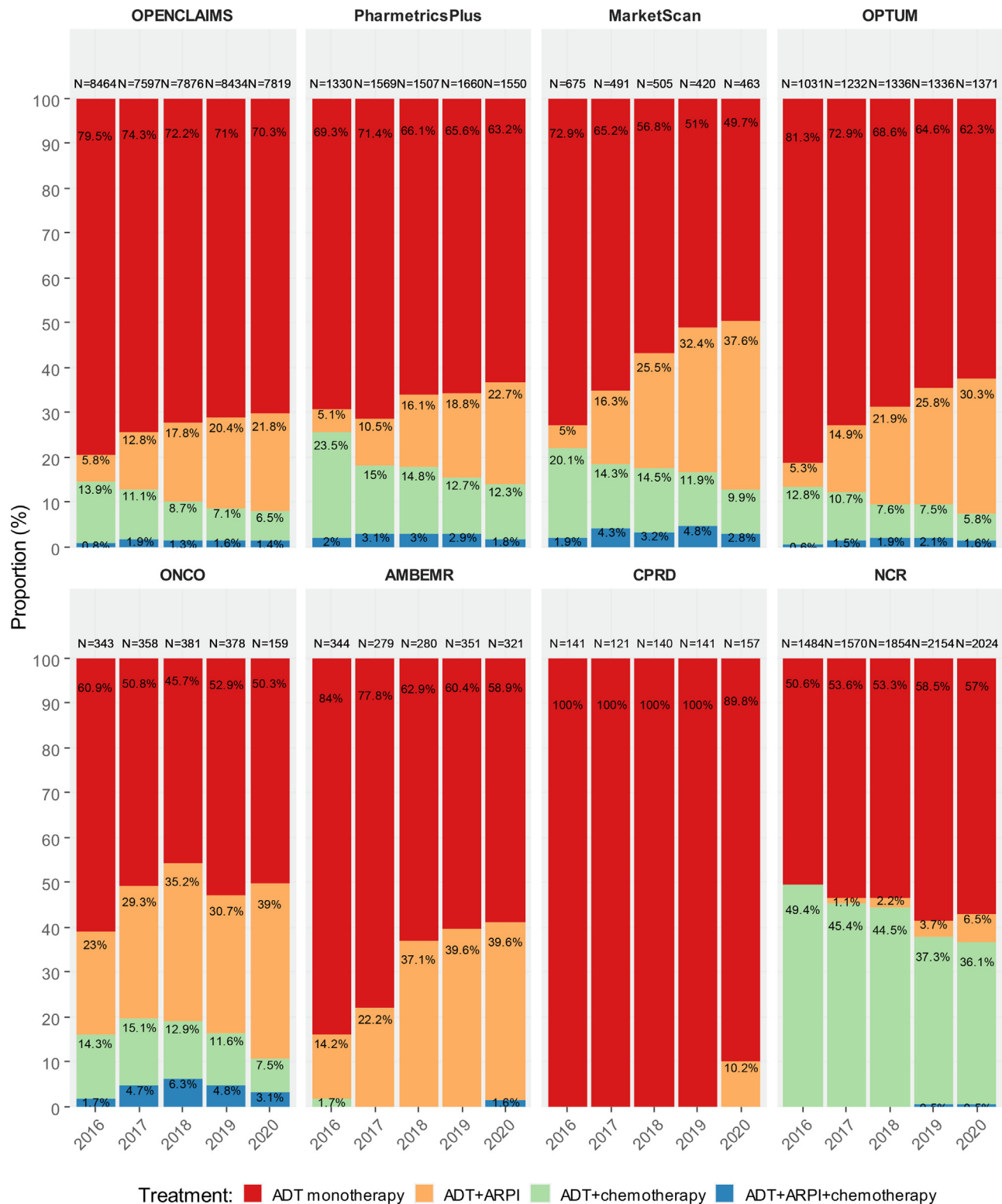


Fig. 4 – Temporal trends (2016–2020) in cohort size and first-line regimens for mHSPC across data sources. ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitors; CPRD = Clinical Practice Research Datalink; mHSPC = metastatic hormone-sensitive prostate cancer; NCR = the Netherlands Cancer Registry.

patients receiving ADT + ARPI. This paradox suggests that, despite known cardiovascular risks, clinicians may still favour ARPI-based regimens due to their proven oncological benefit, especially when alternatives appear less effective or

inappropriate. Prescribing decisions likely reflect a balance of disease aggressiveness, patient preferences, and the availability of cardioprotective strategies. On-going trials such as PEACE-6 are evaluating the feasibility and safety

of systemic therapy intensification in frail or comorbid patients, which will be critical in guiding treatment for this growing population and underscores the importance of tailoring therapy to disease characteristics, patient fitness, and comorbidity burden.

The prescribing patterns in our study—a stable use of ADT monotherapy, increasing ADT + ARPI uptake, and declining ADT + chemotherapy use—reflect broader real-world patterns. A recent systematic review of RWE from multiple countries reported a progressive shift towards ADT + ARPI intensification and away from chemotherapy use, particularly in North America and Europe. Despite guideline recommendations, ADT monotherapy remains common, especially among older patients and those managed by urologists rather than oncologists [20]. This aligns with our findings that older and comorbid men were less likely to receive intensified therapy, reflecting concerns over tolerability, toxicity, and physician preferences. The rise in ADT + ARPI use in recent years corresponds with better drug accessibility, expanded regulatory approvals, and robust trial evidence favouring ARPI-based intensification over chemotherapy. However, geographic variations persist, with Asia reporting lower ADT intensification rates than Western countries, likely due to differences in health care infrastructure, reimbursement policies, and cultural attitudes towards chemotherapy. These observations underscore the importance of addressing barriers to treatment intensification to ensure equitable access to life-prolonging therapies [9,21].

Of note, a subset of patients in our cohort received triplet therapy (ADT + ARPI + chemotherapy). The growing adoption of triplet therapy in real-world settings may reflect early clinical uptake following positive signals from trials such as ARASENS and PEACE-1 [22–24]. Local guideline variations, clinician judgement in high-volume or fit patients, and health system preferences likely also contribute. In our data, men aged 60–69 yr were most likely to receive triplet therapy, which may indicate greater physician confidence in tolerability for younger patients. However, the lack of consistent, uniform recommendations and reimbursement criteria raises concerns about practice heterogeneity and potential off-label use. Prospective observational studies and registry-based analyses should therefore evaluate real-world triplet outcomes, including survival benefits, quality of life, and toxicity profiles, to inform best practices.

A key strength of this study is its size and scope: to our knowledge, it represents the largest multinational real-world cohort to date examining mHSPC treatment patterns and baseline characteristics. By harmonising data across US claims sources, European EMRs, primary care databases, and cancer registries, we achieved a comprehensive, generalisable view of prescribing behaviour across diverse health care systems. The federated data model preserves patient privacy while enabling standardised cross-country comparisons and mitigating single-centre or single-country biases. Importantly, unlike many prior real-world analyses, we incorporated detailed baseline comorbidity profiles, shedding light on how patient health status influences treatment intensification.

Nonetheless, several limitations merit discussion. As an observational study, our findings are subject to residual confounding and selection bias: treatment decisions were at the discretion of clinicians rather than randomised. Heterogeneity in data capture, owing to differences in coding practices, completeness of records, and health care access, may influence cross-database comparability. Crucial clinical variables, such as tumour volume, disease burden, performance status, and patient-reported outcomes, were recorded inconsistently, limiting our ability to adjust fully for disease burden. We also lacked long-term follow-up data, precluding analyses of adherence, late-onset toxicities, and overall survival outcomes beyond initial treatment selection. Lastly, evolving guideline recommendations, drug approvals, and reimbursement changes over the study period may have driven some prescribing shifts independently of clinical choice.

Despite these limitations, our real-world insights can help optimise treatment selection, address disparities in care, and guide future investigations into long-term outcomes and toxicity management in mHSPC patients. As additional RWD emerge, research should aim to refine patient selection criteria for combination therapy beyond age and comorbidities, evaluate the long-term safety of ARPIs in elderly and comorbid populations, and quantify how health care system factors affect prescribing patterns. Integration of artificial intelligence-driven risk prediction models may enhance personalised treatment approaches further, matching each patient with the optimal treatment at the right time [25–27]. In Europe, the Optimal Treatment for Patients with Solid Tumors in Europe Through artificial intelligence (OPTIMA) project is a promising example: by leveraging a centralised data network and artificial intelligence-powered analytics, OPTIMA aims to produce dynamic, transparent real-time clinical decisions support tools based on comprehensive, evidence-based insights that enhance shared decision-making and ensure rapid translation of evidence into practice [28].

5. Conclusions

This study constitutes one of the largest real-world analyses of mHSPC treatment patterns, offering insights into how age, comorbidities, and the evolving therapeutic landscape drive clinical decision-making. It reveals a clear shift towards ARPI-based intensification, selective reduction in chemotherapy use, and enduring disparities in treatment selection linked to patient characteristics. Robust RWE is critical for bridging the gap between clinical trial efficacy and everyday clinical practice, paving the way for more equitable, personalised, and evidence-based treatment strategies for men with mHSPC.

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Critical revision of the manuscript for important intellectual content: Gomez Rivas, Kraft, Evans-Axelsson, Beyer, Liu, Steinbeisser, Gandaglia, Rajwa, Kasivisvanathan, Omar, Sierra, Briganti, Gacci, Willemse, Cornford, Abbott, N'Dow.

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Supervision: Gomez Rivas.

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Appendix A. Supplementary data

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