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Feasibility of androgen receptor pathway inhibitors in prostate cancer: impact of comorbidities, age, and concomitant medication use-a multicenter cohort study

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ABSTRACT

Aims: Androgen receptor pathway inhibitors (ARPIs) have improved outcomes in advanced prostate cancer. Still, evidence regarding their feasibility in older patients with comorbidities and multiple concomitant medications remains limited, as such populations are often underrepresented in clinical trials.

Methods: This multicenter, retrospective cohort study included 538 prostate cancer patients diagnosed between January 2021 and November 2023 across seven centers in Turkiye. Demographic, clinical, pathological, and treatment data were extracted from institutional records. Patients were stratified by treatment type [androgen deprivation therapy (ADT), androgen receptor pathway inhibitor (ARPI), chemotherapy (CT)] and by the number of medications used (≥ three vs. <3). The primary outcome was overall survival (OS); secondary outcomes included follow-up duration, tumor grade, and metastatic distribution.

Results: The mean age at diagnosis was 70.3 years, and 59.5% of patients had comorbidities. Concomitant medication use of three or more drugs, was observed in 34.4%. Metastatic disease was present in 82.3% of cases, most commonly involving the bone (62.8%). ARPI therapy was administered to 72.7% of patients, ADT alone to 18.6%, and CT to 8.7%. Patients receiving ARPIs had higher comorbidity and concomitant medication rates and more frequent metastases than those receiving ADT. Still, they achieved significantly longer median follow-up (901 vs. 470 days, p<0.001) and prolonged OS. Patients with concomitant medication use of three or more drugs also showed a longer follow-up (1081 vs. 573 days, p<0.001), lower mortality (32.4% vs. 47.3%, p=0.001), and a higher proportion of grade 1 tumors compared with patients using fewer than three medications.

Conclusion: In this large real-world cohort, ARPIs were found to be feasible and effective, even in elderly, comorbid, and medication use of three or more patients, supporting their use beyond traditional trial populations.

Keywords: Prostate cancer, ARPI, comorbidity, medication, real-world study

INTRODUCTION

Prostate cancer remains one of the most common malignancies among men worldwide, with incidence and mortality increasing with advancing age, mainly due to global demographic shifts. Older patients (≥65 years) represent a large proportion of prostate cancer diagnoses, and age is a well-established prognostic factor influencing both disease presentation and treatment outcomes.[1,2] As life expectancy increases, so too does the burden of comorbidities and the use of multiple concurrent medications in this population.[3,4]

The use of multiple concurrent medications is highly prevalent among elderly cancer patients, with prevalence estimates varying depending on the definition and population studied, but frequently exceeding 50%.[5,6] In prostate cancer specifically, comorbid conditions such as cardiovascular disease, diabetes, and chronic kidney disease are common and are known to affect survival independently of cancer-specific factors adversely.[7,8]

Novel androgen receptor pathway inhibitors (ARPIs), which target androgen receptor signaling, have significantly advanced the treatment of advanced prostate cancer. Randomized controlled trials have demonstrated survival advantages over androgen deprivation therapy (ADT) alone, with manageable toxicity profiles, even in older patients.[9,10] However, patients with high comorbidity burden and those

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receiving multiple medications are often underrepresented in clinical trials, underscoring the importance of real-world safety and effectiveness data in these subgroups for clinical decision-making.[11]

This study aims to address this gap by evaluating the feasibility, safety, and effectiveness of ARPI therapy in older prostate cancer patients with high comorbidity burden and use of multiple concurrent medications. We compared these patients with those using fewer medications or receiving alternative therapies [ADT or chemotherapy (CT)] with respect to metastatic burden, tumor grade, treatment type, follow-up duration, and survival outcomes.

METHODS

Ethics

The study was carried out with the permission of the Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 19.08.2024, Decision No: 2024/262). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

This multicenter, retrospective observational study included 538 patients diagnosed with prostate cancer between January 2021 and November 2023 from 7 participating centers in Turkiye. Eligible patients were adults (≥18 years) with histopathologically confirmed prostate cancer and complete baseline data available in institutional records. Patients who initiated systemic therapy in the metastatic hormone-sensitive (mHSPC) setting were included. Patients with incomplete clinical information, missing follow-up data, or concurrent malignancies were excluded from the analysis.

Data Collection

This multicenter, retrospective observational study included 538 patients diagnosed with prostate cancer between January 2021 and November 2023 from 7 participating centers in Turkiye. Eligible patients were adults (≥18 years) with histopathologically confirmed prostate cancer and complete baseline data available in institutional records. Demographic variables (age at diagnosis, family history), clinical characteristics (comorbidity status, medication use), tumor-related parameters (histological grade, metastatic stage at diagnosis), and treatment-related data [ADT, novel androgen receptor pathway inhibitor (ARPI) therapy, CT, and local treatments such as surgery or radiotherapy] were obtained from electronic data systems and manually recorded patient files. Medication use was evaluated by the number of concomitant medications at baseline, and pa-tients were stratified according to a threshold of ≥3 medications.

Outcomes and Follow-Up

The primary aim of the study was to evaluate the real-world feasibility and treatment patterns of ARPIs, ADT, and CT in older and comorbid patients with metastatic prostate cancer. Outcomes were analyzed descriptively to characterize patient distribution by age, comorbidity, tumor grade, medication use, and treatment type. Overall survival (OS), defined as the time from diagnosis to death from any cause, was assessed as a secondary endpoint to provide contextual information and to explore how baseline factors such as comorbidity burden and the number of concomitant medications might influence patient outcomes. Mortality events were verified through hospital records and the national death registry, and the median follow-up duration was recorded for the entire cohort.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean±standard deviation (SD), while those without normal distribution were presented as median [interquartile range (IQR)]. For comparisons between two independent groups, the independent t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. For comparisons among three or more groups, the ANOVA test was used for normally distributed variables, with Bonferroni correction applied for post-hoc analyses when significant differences were observed. For non-normally distributed continuous variables, the Kruskal-Wallis test was applied, followed by appropriate post-hoc tests (e.g., Mann-Whitney U test). Chi-square test and Fisher's exact test were used for categorical variables. Survival analyses were conducted using the Kaplan-Meier method, with comparisons between groups performed using the Log-Rank test. Kaplan-Meier curves were generated to illustrate OS stratified by treatment type and medication use. To evaluate the independent effects of key clinical factors on OS, a multivariable Cox proportional hazards regression analysis was performed. Covariates included age at diagnosis, comorbidities, tumor grade, presence of metastasis, treatment type, and medication use (defined as use of three or more medications). Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 538 patients diagnosed with prostate cancer were included in this multicenter study, conducted across seven centers between January 2021 and November 2023. The mean age at diagnosis was 70.3±10.9 years. A positive family history of prostate cancer was reported in 3.9% of patients. Comorbid conditions were observed in 59.5% of the cohort, the most common being hypertension (46.5%), followed by coronary artery disease (21.4%), diabetes mellitus (19.9%), chronic obstructive pulmonary disease (COPD, 3.2%), and chronic kidney disease (CKD, 1.3%). Regarding medication use, 34.4% of patients were taking three or more concomitant medications, while 65.6% were taking fewer than three (**Table 1**).

Histological grade and metastatic stage were available for the majority of patients. Before therapy, 50.2% had grade 1 tumors, 25.1% had grade 2, and 24.7% had grade 3. Local treatment was administered to 26% of patients, with 13.6% receiving radiotherapy and 12.5% undergoing surgery (**Table 1**).

Table 1. Demographic, clinical, and treatment characteristics of prostate cancer patients

Characteristic	Patients (n=538)
Age at diagnosis (years), mean±SD	70.26±10.89
Family history	21 (3.9%)
Comorbidities	320 (59.5%)
Hypertension	250 (46.5%)
Coronary artery disease	115 (21.4%)
Diabetes	107 (19.9%)
COPD	17 (3.2%)
Chronic kidney disease	7 (1.3%)
Medication use	
≥3 medications	185 (34.4%)
<3 medications	353 (65.6%)
Grade before therapy	
1	270 (50.2%)
2	135 (25.1%)
3	133 (24.7%)
Local treatment type	140 (26%)
Radiotherapy	73 (13.6%)
Operation	67 (12.5%)
Metastatic sites	443 (82.3%)
Bone metastasis	338 (62.8%)
Lung metastasis	57 (10.6%)
Liver metastasis	21 (3.9%)
Nonregional lymph nodes	180 (33.5%)
Treatment type	
Only ADT	100 (18.6%)
ARPI	391 (72.7%)
Only chemotherapy	47 (8.7%)
Follow-up period (days), median (IQR)	667 (243.50-1655.55)
Exitus (death)	227 (42.2%)
Time from diagnosis to exitus (days), median (IQR)	772 (191-1629)

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, ECOG: Eastern cooperative oncology group, IQR: Interquartile range, ADT: Androgen deprivation therapy, ARPI: Androgen receptor pathway inhibitors

Metastatic disease was identified in 82.3% of patients. The most common sites were bone (62.8%), followed by non-regional lymph nodes (33.5%), lung (10.6%), and liver (3.9%) (Table 1).

Regarding systemic treatment, 18.6% of patients received ADT alone, 72.7% received novel ARPI therapy in combination with ADT, and 8.7% received CT in combination with ADT (Table 1).

The median follow-up duration was 667 days (IQR, 243.5-1655.6). During follow-up, 227 patients (42.2%) died. The median time from diagnosis to death was 772 days (IQR, 191-1629) (Table 1).

When comparing patients who died during follow-up (n=227) with those who survived (n=311), no significant difference in mean age at diagnosis was observed (70.3±8.6 vs. 70.3±12.3 years, p=0.987). A positive family history of prostate cancer was slightly more common among deceased patients (5.7% vs. 2.6%), but this did not reach statistical significance (p=0.062). The overall prevalence of comorbidities was comparable between groups (62.1% vs. 57.6%, p=0.288), with no significant differences in hypertension or coronary artery disease rates. However, diabetes mellitus was significantly more frequent among deceased patients compared with survivors (24.2% vs. 16.7%, p=0.031). No significant differences in the prevalence of COPD or CKD were observed between groups (Table 2).

Table 2. Comparison of demographic, clinical, and treatment characteristics between patients with and without exitus

Characteristic	Exitus (n=227)	No exitus (n=311)	p
Age at diagnosis (years), mean±SD	70.27±8.61	70.26±12.31	0.987[a]
Family history	13 (5.7%)	8 (2.6%)	0.062[b]
Comorbidities	141 (62.1%)	179 (57.6%)	0.288[b]
Hypertension	111 (48.9%)	139 (44.7%)	0.334[b]
CAD	49 (21.6%)	66 (21.2%)	0.919[b]
Diabetes	55 (24.2%)	52 (16.7%)	0.031[b,*]
COPD	5 (2.2%)	12 (3.9%)	0.278[b]
CKD	1 (0.4%)	6 (1.9%)	0.248[c]
Medication use			0.001[b,*]
≥3 medications	60 (26.4%)	125 (40.2%)	
<3 medications	167 (73.6%)	186 (59.8%)	
Grade before therapy			0.011[b,*]
1	103 (45.4%)	167 (53.7%)	
2	53 (23.3%)	82 (26.4%)	
3	71 (31.3%)[k]	62 (19.9%)	
Local treatment type	60 (26.4%)	80 (25.7%)	0.853[b]
Radiotherapy[¥]	27 (45%)	46 (57.5%)	0.143[b]
Operation[¥]	33 (55%)	34 (42.5%)	
Metastatic sites	202 (89%)	241 (77.5%)	0.001[b,*]
Bone metastasis	157 (69.2%)	181 (58.2%)	0.009[b,*]
Lung metastasis	24 (10.6%)	33 (10.6%)	0.989[b]
Liver metastasis	8 (3.5%)	13 (4.2%)	0.689[b]
Nonregional LN	67 (29.5%)	113 (36.3%)	0.098[b]
Treatment type			<0.001[b,*]
Only ADT	9 (4%)	91 (29.3%)[k]	
ADT with ARPI	184 (81.1%)[l]	207 (66.6%)	
ADT with chemotherapy	34 (15%)[m]	13 (4.2%)	
Follow-up period (days), median (IQR)	772 (191-1629)	620 (290-1732)	0.519[d]

SD: Standard deviation, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, LN: Lymph nodes, ADT: Androgen deprivation therapy, IQR: Interquartile range, ARPI: Androgen receptor pathway inhibitors
a: Independent T test; b: Chi-square test; c: Fisher's exact test; d: Mann-Whitney U test. k,l,m: Letters indicate statistically significant differences between groups. [¥]: This symbol is used to indicate that the percentages represent the distribution of patients according to their local treatment type categories. *: Statistically significant (p<0.05)

Importantly, patients who died were significantly less likely to be using three or more medications compared with survivors (26.4% vs. 40.2%, p=0.001), suggesting a potential inverse association between the use of three or more drugs

and OS (Table 2). This observation may reflect closer medical monitoring and more comprehensive management of comorbidities among survivors, rather than a direct protective effect of higher medication use.

Regarding tumor grade before therapy, a significantly higher proportion of deceased patients had grade 3 disease compared with survivors (31.3% vs. 19.9%, p=0.011), whereas grade 1 tumors were more common among survivors (53.7% vs. 45.4%). Local treatment rates were similar between groups (26.4% vs. 25.7%, p=0.853). Among patients who underwent local treatment, radiotherapy was more frequently administered to survivors (57.5% vs. 45.0%), while surgery was more common among deceased patients (55.0% vs. 42.5%); however, these differences did not reach statistical significance (Table 2).

Metastatic disease at diagnosis was significantly more frequent among deceased patients compared with survivors (89.0% vs. 77.5%, p=0.001), with bone metastases being particularly more prevalent in the deceased group (69.2% vs. 58.2%, p=0.009). No significant differences in the frequency of lung, liver, or nonregional lymph node metastases were observed between groups (Table 2).

Treatment distribution differed significantly between groups (p<0.001). Deceased patients were more likely to have received ARPI therapy (81.1% vs. 66.6%) or CT (15.0% vs. 4.2%). In contrast, ADT was administered more frequently alone to survivors (29.3% vs. 4.0%). The median follow-up duration was slightly longer among deceased patients (772 days; IQR, 191-1629) compared with survivors (620 days; IQR, 290-1732), although this difference did not reach statistical significance (p=0.519) (Table 2).

When patients were stratified by treatment type, significant differences emerged across several clinical and demographic variables. Patients receiving ADT alone were significantly older at diagnosis compared with those in the ARPI group (73.7±15.7 vs. 69.4±9.0 years, p=0.002). A positive family history of prostate cancer was most frequent in the CT group (12.8%) and least frequent in the ARPI group (2.6%, p=0.013). Although the overall prevalence of comorbidities did not differ significantly across treatment groups (p=0.253), patients in the ARPI group exhibited significantly higher rates of hypertension (52.4%), coronary artery disease (25.8%), and diabetes mellitus (23.5%) compared with the other groups (all p<0.001). Chronic kidney disease was most common in the ADT group (4.0%, p=0.042).

Regarding medication use, patients in the ARPI group had the highest proportion of patients using three or more medications (43.7%), which was significantly higher than in the ADT (14.0%) and CT (0%) groups (p<0.001). Notably, all patients in the CT group were taking fewer than three medications. This pattern may reflect differences in comorbidity burden, treatment intensity, or patient selection across groups (Table 3).

Table 3. Comparison of demographic, clinical, and treatment characteristics by treatment type in prostate cancer patients

Characteristic	Only ADT (n=100)	ARPI (n=391)	CT (n=47)	p
Age at diagnosis (years), mean±SD	73.69±15.73[k]	69.41±9.03[k]	70.11±11.38	0.002[b,*]
Family history	5 (5%)	10 (2.6%)	6 (12.8%)[k]	0.013[b,*]
Comorbidities	54 (54%)	241 (61.6%)	25 (53.2%)	0.253[b]
Hypertension	28 (28%)	205 (52.4%)[k]	17 (36.2%)	<0.001[b,*]
CAD	9 (9%)	101 (25.8%)[k]	5 (10.6%)	<0.001[b,*]
Diabetes	10 (10%)	92 (23.5%)[k]	5 (10.6%)	0.001[b,*]
COPD	5 (2 %)	10 (2.6%)	2 (4.3%)	0.448[b]
CKD	4 (4%)[k]	2 (0.5%)	1 (2.1%)	0.042[b,*]
Medication use				<0.001[b,*]
≥3 medications	14 (14%)	171 (43.7%)[k]	0 (0%)	
<3 medications	86 (86%)	220 (56.3%)	47 (100%)[l]	
Grade before therapy				<0.001[b,*]
1	37 (37%)	225 (57.5%)[k]	8 (17%)	
2	27 (27%)	106 (27.1%)	2 (4.3%)[l]	
3	36 (36%)	60 (15.3%)	37 (78.7%)[m]	
Local treatment type	20 (20%)	112 (28.6%)	8 (17%)	0.063[b]
Radiotherapy[¥]	17 (85%)[k]	55 (49.1%)	1 (12.5%)	<0.001[b,*]
Operation[¥]	3 (15%)	57 (50.9%)	7 (87.5%)[l]	
Metastatic sites	32 (32%)	375 (95.9%)[k]	36 (76.6%)	<0.001[b,*]
Bone metastasis	20 (20%)	293 (74.9%)[k]	25 (53.2%)	<0.001[b,*]
Lung metastasis	2 (2%)	54 (13.8%)[k]	1 (2.1%)	<0.001[b,*]
Liver metastasis	3 (3%)	16 (4.1%)	2 (4.3%)	0.866[b]
Nonregional LN	6 (6%)	166 (42.5%)[k]	8 (17%)	<0.001[b,*]
Follow-up period (days), median (IQR)	470 (245-730)[k,l]	901 (281-2146)[k,m]	261 (100-683)[l,m]	<0.001[c,*]
Exitus (death)	9 (9%)	184 (47.1%)	34 (72.3%)[k]	<0.001[b,*]
Time from diagnosis to exitus (days), median (IQR)	403 (207.50-7339)	990.50 (220-1826.75)	175 (90.50-405.25)[k]	<0.001[c,*]

ADT: Androgen deprivation therapy, ARPI: Androgen receptor pathway inhibitors, CT: Chemotherapy, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, LN: Lymph nodes, IQR: Interquartile range, a: ANOVA test (post hoc: Bonferroni test); b: Chi-square test; c: Kruskal-Wallis test. k,l,m: Letters indicate statistically significant differences between groups. [¥]: This symbol is used to indicate that the percentages represent the distribution of patients according to their local treatment type categories. *: Statistically significant (p<0.05)

The distribution of tumor grades also varied significantly by treatment group. Grade 1 disease was most prevalent in the ARPI group (57.5%), whereas grade 3 tumors predominated in the CT group (78.7%) and, to a lesser extent, in the ADT group (36.0%, p<0.001). Local treatment was most frequently administered in the ARPI group (28.6%), although this difference did not reach statistical significance (p=0.063). Among patients undergoing local treatment, radiotherapy was most commonly delivered in the ADT group (85.0%), whereas surgery was more frequent in the CT group (87.5%, p<0.001) (Table 3).

Metastatic disease at diagnosis was significantly more frequent in the ARPI (95.9%) and CT (76.6%) groups than in the ADT group (32.0%; p<0.001). Bone metastases were most common in the ARPI group (74.9%), and nonregional lymph node involvement was also significantly higher in this group (42.5%, p<0.001). Lung metastases were relatively uncommon in the ADT and CT groups but were observed in 13.8% of ARPI patients (p<0.001). No significant differences in the prevalence of liver metastases were observed across groups (Table 3).

The median follow-up duration was significantly longer in the ARPI group (901 days; IQR, 281-2146) than in the ADT (470 days; IQR, 245-730) and CT (261 days; IQR, 100-683) groups (p<0.001). Mortality was highest in the CT group (72.3%), followed by the ARPI (47.1%) and ADT (9.0%) groups (p<0.001). Furthermore, the median time from diagnosis to death was significantly shorter in the CT group (175 days; IQR, 90.5-405.3) than in the ARPI (990.5 days; IQR, 220-1826.8) and ADT (403 days; IQR, 207.5-7339) groups (p<0.001) (Table 3).

When patients were stratified by ARPI treatment type-Abiraterone (n=133) versus Enzalutamide (n=258)-most clinical and demographic characteristics were comparable between the two groups, with only a few statistically significant differences observed (Table 4). There was no significant difference in mean age at diagnosis (68.51±9.59 vs. 69.87±8.71 years, p=0.160). Similarly, family history of prostate cancer was uncommon in both groups (1.5% vs. 3.1%, p=0.505). The overall prevalence of comorbidities was similar (59.4% vs. 62.8%, p=0.513), with no differences in hypertension (50.4% vs. 53.5%, p=0.559), coronary artery disease (26.3% vs. 25.6%, p=0.875), chronic obstructive pulmonary disease (1.5% vs. 3.1%, p=0.505), or chronic kidney disease (0.8% vs. 0.4%, p=1.000). However, diabetes was significantly more prevalent in the Enzalutamide group (26.7% vs. 17.3%, p=0.037).

Tumor grade distributions before therapy were not significantly different (p=0.356). Grade 1 tumors were slightly more common in the Abiraterone group (62.4% vs. 55%), while grade 3 tumors showed a comparable distribution (14.3% vs. 15.9%).

The vast majority of patients had metastatic disease at baseline, with no difference between groups (96.2% vs. 95.7%, p=0.812). Patterns of metastatic spread were also similar: bone metastasis (75.2% vs. 74.8%, p=0.934), lung metastasis (13.5% vs. 14.0%, p=0.909), liver metastasis (3.0% vs. 4.7%, p=0.437), and nonregional lymph node involvement (42.1% vs. 42.6%, p=0.920).

Table 4. Comparison of clinical and demographic features by ARPI type

Characteristic	Abiraterone (n=133)	Enzalutamide (n=258)	p
Age at diagnosis (years), mean±SD	68.51±9.59	69.87±8.71	0.160[a]
Family history	2 (1.5%)	8 (3.1%)	0.505[b]
Comorbidities	79 (59.4%)	162 (62.8%)	0.513[c]
Hypertension	67 (50.4%)	138 (53.5%)	0.559[c]
CAD	35 (26.3%)	66 (25.6%)	0.875[c]
Diabetes	23 (17.3%)	69 (26.7%)	0.037[c,*]
COPD	2 (1.5%)	8 (3.1%)	0.505[b]
CKD	1 (0.8%)	1 (0.4%)	1.000[b]
Grade before therapy			0.356[c]
1	83 (62.4%)	142 (55%)	
2	31 (23.3%)	75 (29.1%)	
3	19 (14.3%)	41 (15.9%)	
Metastatic sites	128 (96.2%)	247 (95.7%)	0.812[c]
Bone metastasis	100 (75.2%)	193 (74.8%)	0.934[c]
Lung metastasis	18 (13.5%)	36 (14%)	0.909[c]
Liver metastasis	4 (3%)	12 (4.7%)	0.437[c]
Nonregional LN	56 (42.1%)	110 (42.6%)	0.920[c]
Follow-up period (days), median (IQR)	765 (284.50-1780.50)	998.50 (280.50-2296.25)	0.213[d]
Exitus (death)	52 (39.1%)	132 (51.2%)	0.024[c,*]
Time from diagnosis to exitus (days), median (IQR)	643.50 (179.50-1678)	1016 (237-2128)	0.213[d]

ARPI: Androgen receptor pathway inhibitors, SD: Standard deviation, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, LN: Lymph nodes, IQR: Interquartile range
a: Independent T test, b: Fisher's exact test, c: Chi-square test, d: Mann-Whitney U test. *: Statistically significant (p<0.05)

Median follow-up was longer in the Enzalutamide group (998.5 vs. 765 days), although this did not reach statistical significance (p=0.213). Mortality, however, was significantly higher among patients treated with Enzalutamide (51.2% vs. 39.1%, p=0.024). Despite this, the median time from diagnosis to death was not statistically different between groups (1016 vs. 643.5 days, p=0.213), although numerically longer in the Enzalutamide cohort.

When patients were stratified by medication use (≥three medications, n=185; <3 medications, n=353), significant differences were observed in several clinical and demographic characteristics (Table 3). There was no significant difference in mean age at diagnosis between the groups (69.9±10.6 vs. 70.5±11.1 years, p=0.590). A positive family history of prostate cancer was significantly less frequent among patients taking ≥3 medications (1.6% vs. 2.6%, p=0.048).

Tumor grade distribution differed significantly between groups; grade 1 tumors were more prevalent among patients using ≥3 medications (65.4% vs. 42.2%), whereas grade 3 tumors were more common in those using <3 medications (34.8% vs. 5.4%, p<0.001). The prevalence of comorbidities was markedly higher in the ≥3 medications group (80.5% vs. 48.4%, p<0.001). Specifically, hypertension (71.9% vs. 33.1%), coronary artery disease (41.1% vs. 11.0%), and diabetes mellitus (35.1% vs. 11.9%) were all significantly more common in the ≥3 medications group (all p<0.001). No significant differences were observed for COPD or chronic kidney dis-ease.

Metastatic disease was significantly more frequent in the ≥3 medications group compared with the <3 medications group (93.5% vs. 76.5%, p<0.001). Patients in the ≥three medications group also had higher rates of bone metastasis (73.5% vs. 57.2%), lung metastasis (16.8% vs. 7.4%), and nonregional lymph node involvement (44.9% vs. 27.5%) (p<0.001, p<0.001, and p=0.001, respectively).

Regarding treatment type, the majority of patients using ≥3 medications received andro-gen receptor pathway inhibitor (ARPI) therapy (92.4%), while only 7.6% received ADT alone. In contrast, among patients using <3 medications, 24.4% received ADT alone and 13.3% re-ceived CT (p<0.001).

The median follow-up duration was significantly longer in the ≥3 medications group compared with the <3 Medications group (1081 vs. 573 days, p<0.001). Mortality was lower among patients taking ≥3 medications (32.4% vs. 47.3%, p=0.001), and the median time from diagnosis to death was significantly prolonged (1254.5 vs. 565 days, p=0.001).

In summary, patients on multiple medications exhibited a higher burden of comorbidities and more advanced metastatic disease but were more likely to have lower tumor grade, experienced longer follow-up, and demonstrated better survival outcomes. These findings suggest that use of three or more medications is common among patients with complex clinical profiles and that treatment and monitoring strategies may need to be tailored to this subgroup (Table 5).

A multivariable Cox proportional hazards regression analysis was conducted to evaluate factors associated with OS (Table 6). The overall model was statistically significant (p<0.001). Older age at diagnosis was independently associated with worse survival, with each additional year increasing the hazard of death by 2.1% (HR=1.021, 95% CI: 1.009-1.034, p=0.001). Tumor grade was significantly associated with survival. Compared to grade 1, patients with grade 2 had a significantly lower hazard of death (HR=0.386, 95% CI: 0.269-0.554, p<0.001), while those with grade 3 had a significantly higher hazard of death (HR=3.757, 95% CI: 2.543-5.551, p<0.001). Medication use of three or more was associated with a nearly two-fold increased hazard of death (HR=1.906, 95% CI: 1.360-2.672, p<0.001). Diabetes mellitus was associated with a 43% reduction in the hazard of death (HR=0.573, 95% CI: 0.405-0.809, p=0.002). Presence of metastasis was associated with a significantly increased hazard of death (HR=2.201, 95% CI: 1.288-3.761, p=0.004). Comorbidity status and bone metastasis were not significantly associated with OS in the adjusted model (p>0.05).

Kaplan-Meier survival analysis demonstrated significant differences in survival times among prostate cancer patients according to treatment type (p<0.001, log-rank test) (Table 7, Figure 1). Patients treated with ADT combined with novel ARPI had the longest mean (2848.8 days) and median (2233 days) survival times. In contrast, patients receiving only CT had the shortest survival times, with a mean of 655.1 days and a median of 277 days. Patients treated with ADT alone had intermediate survival. These results suggest that combining ADT with ARPI may provide a significant survival benefit compared to other treatment modalities.

Table 5. Comparison of clinical and demographic features by medication use

Characteristic	≥3 medications (n=185)	<3 medications (n=353)	p
Age at diagnosis (years), mean±SD	69.91±10.59	70.45±11.06	0.590[a]
Family history	3 (1.6%)	18 (2.6%)	0.048[b,*]
Comorbidities	149 (80.5%)	171 (48.4%)	<0.001[b,*]
Hypertension	133 (71.9%)	117 (33.1%)	<0.001[b,*]
CAD	76 (41.1%)	39 (11%)	<0.001[b,*]
Diabetes	65 (35.1%)	42 (11.9%)	<0.001[b,*]
COPD	5 (2.7%)	12 (3.4%)	0.661[b]
CKD	4 (2.2%)	3 (0.8%)	0.240[c]
Grade before therapy			<0.001[b,*]
1	121 (65.4%)[k]	149 (42.2%)	
2	54 (29.2%)	81 (22.9%)	
3	10 (5.4%)	132 (34.8%)[l]	
Local treatment type	54 (29.2%)	86 (24.4%)	0.226[b]
Radiotherapy[¥]	26 (48.1%)	47 (54.7%)	0.453[b]
Operation[¥]	28 (51.9%)	39 (45.3%)	
Metastatic sites	173 (93.5%)	270 (76.5%)	<0.001[b,*]
Bone metastasis	136 (73.5%)	202 (57.2%)	<0.001[b,*]
Lung metastasis	31 (16.8%)	26 (7.4%)	0.001[b,*]
Liver metastasis	6 (3.2%)	15 (4.2%)	0.567[b]
Nonregional LN	83 (44.9%)	97 (27.5%)	<0.001[b,*]
Treatment type			<0.001[b,*]
Only ADT	14 (7.6%)	86 (24.4%)[k]	
ADT with ARPI	171 (92.4%)[l]	220 (62.3%)	
ADT with chemotherapy	0 (0%)	47 (13.3%)[m]	
Follow-up period (days), Median (IQR)	1081 (368.50-2278.50)	573 (218.50-1228.50)	<0.001[d,*]
Exitus (death)	60 (32.4%)	167 (47.3%)	0.001[b,*]
Time from diagnosis to exitus (days), median (IQR)	1254.50 (576.75-2209.50)	565 (156-1402)	0.001[d,*]

SD: Standard deviation, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, LN: Lymph nodes, ADT: Androgen deprivation therapy, ARPI: Androgen receptor pathway inhibitors, IQR: Interquartile range
a: Independent T test, b: Chi-square test, c: Fisher's exact test, d: Mann-Whitney U test. k,l,m: Letters indicate statistically significant differences between groups. [¥]: This symbol is used to indicate that the percentages represent the distribution of patients according to their local treatment type categories. *: Statistically significant (p<0.05)

Table 6. Multivariable cox proportional hazards regression analysis of factors associated with overall survival

Variable	p	HR [Exp (B)]	95% CI for HR
Age at diagnosis (years)	0.001*	1.021	(1.009-1.034)
Grade before therapy (ref: grade 1)			
Grade 2	0.001*	0.386	(0.269-0.554)
Grade 3	0.001*	3.757	(2.543-5.551)
Medication use (≥3 vs. <3 meds)	<0.001*	1.906	(1.360-2.672)
Comorbidity (yes vs. no)	0.511	0.901	(0.660-1.230)
Diabetes (yes vs. no)	0.002*	0.573	(0.405-0.809)
Metastasis presence (yes vs. no)	0.004*	2.201	(1.288-3.761)
Bone metastasis (yes vs. no)	0.904	1.021	(0.732-1.424)
Treatment type (ref: ADT alone)			
ADT+chemotherapy	<0.001*	6.754	(3.221-14.162)
ADT+ARPI	<0.001*	5.703	(2.665-12.201)

HR: Hazard ratio, CI: Confidence interval, ADT: Androgen deprivation therapy, ARPI: Androgen receptor pathway inhibitor, *: Statistically significant (p<0.05)

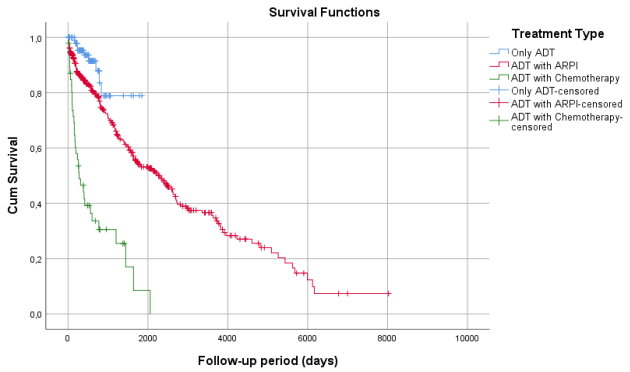


Figure 1. Kaplan-Meier survival curves by treatment type in prostate cancer patients

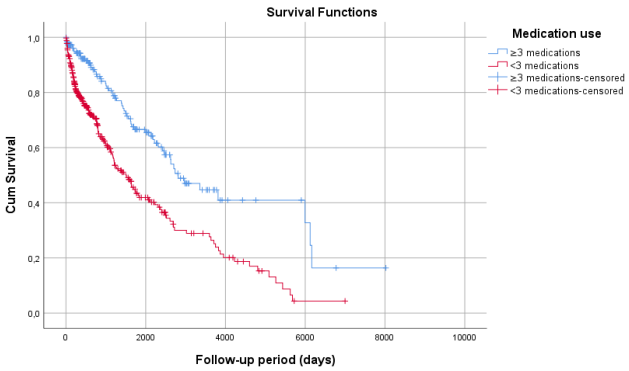


Figure 2. Kaplan-Meier survival curves by medication use in prostate cancer patients

Kaplan-Meier survival analysis revealed a statistically significant difference in survival times between prostate cancer patients based on medication use (p<0.001, log-rank test) (Table 7, Figure 2). Patients taking three or more medications had a significantly longer mean survival time (3834.8 days; 95% CI: 3167.9-4501.7) and median survival time (2814.0 days; 95% CI: 2099.4-3528.6) compared to those using fewer than three medications, who had a mean survival time of 2195.8 days (95% CI: 1879.9-2511.8) and median survival time of 1510.0 days (95% CI: 1195.1-1824.9). These findings suggest that patients using three or more medications may experience better OS, potentially reflecting differences in patient management or underlying health status.

DISCUSSION

In this multicenter, real-world cohort, we demonstrated that patients with a higher comorbidity burden and concomitant medications (≥three medications) more frequently presented with metastatic disease and had a higher preva-lence of bone, lung, and nonregional lymph node metastases. Despite this heavier disease bur-den, these patients were more likely to receive ARPI therapy rather than chemotherapy or ADT alone and, importantly, achieved longer follow-up, prolonged survival, and lower mortality compared with those taking fewer medications. These findings suggest that ARPIs can be safely and effectively used even in older, more comorbid populations, supporting their feasibility beyond the confines of clinical trial eligibility.[12]

The association between concomitant medications and improved survival outcomes in our cohort likely reflects in highly comorbid patients, potentially allowing for greater treat-ment exposure and greater benefit from ARPI therapy.[15]

The preferential use of ARPIs over chemotherapy in patients with concomitant medications is consistent with recent real-world evidence demonstrating that these agents are generally well tolerated, even in frail, elderly, and multimorbid patients.[16,17] They provide a practical and less toxic alternative to chemotherapy, which may be poorly tolerated in this population due to an increased risk of hematologic and infectious complications.[18]

In our real-world cohort comparing Abiraterone (AA) and Enzalutamide (ENZ), baseline clinicodemographic features were broadly similar, with two notable signals: (i) a higher prevalence of diabetes in the ENZ group and (ii) higher crude mortality in ENZ despite comparable disease characteristics and follow-up distribution. Randomized trials establishing the efficacy of each agent in earlier disease settings (ENZAMET for mHSPC and LATITUDE for high-risk mHSPC) demonstrate clear OS benefits versus ADT alone, supporting the oncologic validity of both strategies.[19,20] However, head-to-head comparative evidence has primarily been derived from observational data. Multiple extensive real-world studies-including a Medicare analysis and nationwide cohorts-tend to show equal or modestly better OS with ENZ versus AA in 1 L mCRPC, particularly among older and comorbid patients.[21,22]

In contrast, our higher crude mortality in the ENZ arm likely reflects treatment selection patterns rather than intrinsic drug-related differences. In routine oncology practice in Turkiye, frailer or diabetic patients are more frequently prescribed ENZ

Table 7. Kaplan-Meier survival analysis by treatment type and medication use in prostate cancer patients

Group	Subgroup	Mean survival time (days)	95% CI	Median survival time (days)	95% CI
Treatment type	Only ADT	1582.3	1413.2-1751.4	-	-
	ADT with ARPI	2848.8	2497.3-3200.3	2233.0	1718.4-2747.6
	ADT with chemotherapy	655.1	433.1-877.0	277.0	91.0-463.0
	Overall	2742.7	2411.9-3073.5	2110.0	1679.5-2540.5
	Log-rank test: p<0.001 *				
Medication use	≥3 medications	3834.8	3167.9-4501.7	2814.0	2099.4-3528.6
	<3 medications	2195.8	1879.9-2511.8	1510.0	1195.1-1824.9
	Overall	2742.7	2411.9-3073.5	2110.0	1679.5-2540.5
	Log-rank test: p<0.001 *				

CI: Confidence interval, ADT: Androgen deprivation therapy, ARPI: Androgen receptor pathway inhibitor, *: Statistically significant (p<0.05)

because Abiraterone requires concomitant corticosteroid use, which may worsen glycemic control or be contraindicated in these individuals. This clinical preference may have enriched the ENZ group for patients with higher baseline comorbidity, leading to apparent mortality differences. Such patterns are consistent with international real-world observations, though additional multicenter data from Turkish practice are needed to clarify these selection dynamics.[21,22]

The imbalance in diabetes in our data (higher in ENZ) likely reflects treatment selection rather than a drug-induced signal. Abiraterone is given with chronic low-dose corticosteroids, which carry well-known risks of dysglycemia; consistent with this, the EVADE study found a higher risk of new-onset or worsening type 2 diabetes mellitus with AA vs ENZ in mCRPC, despite shorter treatment duration on AA.[23] Case reports and pharmacovigilance also document severe hyperglycemia with AA+prednisone.[24] Thus, clinicians may avoid AA in patients with existing diabetes or poor glycemic control, enriching ENZ arms for baseline diabetes-exactly the pattern we observed. This selection dynamic underscores the importance of adjusting for metabolic comorbidities and steroid exposure when comparing outcomes across ARPIs.[23,24] Finally, cardiovascular-metabolic safety profiles may further influence real-world outcomes. Comparative observational work suggests differential risks of major adverse cardiovascular events across ARPIs, with several datasets indicating greater cardiometabolic liability with steroid-bearing AA versus ENZ. However, findings vary and are sensitive to confounding and analytic choices.[21,25] Given the broadly similar disease burden across treatment arms, future Turkish real-world analyses should incorporate cause-specific mortality, competing risk models, and detailed comorbidity adjustments to determine whether the observed mortality difference reflects drug effect or patient selection. Prospective registry-based designs with standardized clinical data collection would help address this question more robustly.

Clinically, our findings support considering ARPIs as a first-line systemic therapy option for older patients with high comorbidity burden and multiple drug use, provided that close monitoring and multidisciplinary care are ensured. Individualized treatment plans, medication reconciliation, and proactive management of comorbidities may optimize outcomes and minimize toxicity risks. Importantly, these findings should be interpreted with caution, as they may reflect confounding by indication rather than intrinsic treatment effects. Physicians are to prescribe certain ARPIs to patients who are more closely monitored, have better baseline health status, or possess specific comorbidities that influence treatment choice. Therefore, the observed survival differences may stem from patient selection and closer clinical follow-up rather than the pharmacologic superiority of one agent over another.

Strengths of this study include its multicenter design, relatively large sample size, and comprehensive evaluation of clinical, pathological, and treatment parameters in a real-world setting. Importantly, this analysis addresses a population underrepresented in randomized clinical trials, thereby providing practical insights into everyday oncology practice.

Limitations

This study has several limitations. First, the retrospective, feasibility-focused design may introduce selection bias and preclude causal inference; however, this approach was appropriate for capturing real-world treatment applicability in older, comorbid patients. Second, detailed data on specific drug classes, potential drug-drug interactions, and treatment-related toxicities were not uniformly available, limiting the ability to perform a thorough safety analysis. In addition, data on treatment-related toxicities and quality-of-life outcomes were not consistently collected across centers, particularly among patients receiving multiple concomitant medications. These parameters were therefore not included in the analysis but represent important areas for future research. Third, the severity of comorbidities was not stratified, and specific clinical parameters, such as ECOG performance status, PSA levels, and Gleason score, were inconsistently recorded across centers. However, given that the study's primary aim was to evaluate treatment feasibility rather than prognostic outcomes, these variables were not expected to affect the main findings. Finally, the inclusion of patients from seven centers improves generalizability but may have introduced variability in documentation and follow-up procedures. Additionally, progression-free survival and treatment duration were not analyzed, as the study was not designed to assess treatment efficacy. Future prospective and controlled studies with standardized data collection are warranted to validate and expand upon these findings.

CONCLUSION

In this multicenter, real-world study, we demonstrated that ARPI therapy is feasible and well-tolerated, even in patients with advanced age, a high comorbidity burden, and concomitant medication use. Despite presenting with a higher metastatic burden, these patients achieved longer follow-up, prolonged survival, and lower mortality compared with those on fewer medications or alternative treatments. Our findings support considering ARPIs as a preferred systemic therapy option over chemotherapy or ADT alone in this complex subgroup, provided that close clinical monitoring and multidisciplinary care are implemented. Future prospective studies are warranted to validate these results and to explore quality-of-life and toxicity outcomes in similar high-risk populations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 19.08.2024, Decision No: 2024/262).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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