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Association of 5α-reductase inhibitor prescription with immunotherapy efficacy in metastatic renal cell carcinoma: a multicenter retrospective analysis

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of metastatic renal cell carcinoma (mRCC), but response rates remain heterogeneous, and reliable predictive biomarkers are lacking. Recent studies suggest that androgen receptor (AR) signaling plays a role in regulating $CD8^+$ T-cell function, implying that 5α-reductase inhibitors (5-ARIs), which lower androgen activity, could enhance antitumor immunity and improve clinical outcomes in patients receiving immunotherapy. This study retrospectively investigates the impact of a history of 5-ARI use (≥12 months) on the efficacy of ICIs in mRCC.

Methods We conducted a multicenter retrospective cohort study of 185 patients with mRCC who received ICIs. Patients were stratified based on their history of 5-ARI use. Baseline characteristics included age, body mass index, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group, programmed death-ligand 1 (PD-L1) expression levels, tumor stage, and metastasis sites. The primary endpoints were progression-free survival (PFS) and overall survival (OS), analyzed using Cox proportional hazards models. Secondary endpoints included objective response rate (ORR) and disease control rate (DCR). Key immunological insights were gained through single-cell RNA sequencing analysis of tumor samples.

Results Patients with a history of 5-ARI use demonstrated improved ORR (59.8% vs 39.8%, p=0.0075) and DCR (87.0% vs 78.7%, p=0.1747) compared with those without. The median PFS and OS were significantly longer in the 5-ARI group, with HRs of 0.64 (95% CI: 0.47 to 0.86, p=0.0085) for PFS and 0.65 (95% CI: 0.47 to 0.90, p=0.0271) for OS. Subgroup analysis further indicated enhanced ICI efficacy with 5-ARI use across age, IMDC risk scores, and PD-L1 expression levels. Single-cell RNA sequencing analysis revealed that 5-ARI treated patients exhibited a reduced presence of regulatory T cells and CD8 T-cell exhaustion (CD8 Tex), and lower programmed cell death protein-1 expression in CD8 Tex cells, suggesting an immunologically favorable modification of the tumor.

Conclusion A history of 5-ARI use is associated with improved responses to ICI therapy in mRCC, potentially through AR-related modulation of $CD8^+$ T-cell activity and favorable alterations in the immune microenvironment. These findings support further investigation into androgen-targeted approaches as adjunctive strategies in immunotherapy for RCC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Androgen receptor (AR) signaling may influence $CD8^+$ T-cell function and immune responses.

WHAT THIS STUDY ADDS

⇒ 5α-reductase inhibitor (5-ARI) use is associated with improved immune checkpoint inhibitor (ICI) efficacy, including better survival outcomes and reduced T-cell exhaustion, suggesting immune modulation via AR inhibition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ 5-ARIs could serve as adjunctive agents to enhance ICI therapy, warranting further research in androgen-targeted immunotherapy strategies.

INTRODUCTION

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, and its metastatic form (mRCC) carries a poor prognosis, especially in advanced stages.[1–3] The introduction of immune checkpoint inhibitors (ICIs) has marked a major advance in the management of mRCC, as these therapies leverage the host's immune system to target and destroy cancer cells.[4–6] Despite these developments, only a subset of patients with mRCC respond favorably to ICIs, and treatment outcomes remain highly variable.[7] This variability underscores the need to identify factors that may predict or enhance response to ICIs, thereby improving patient selection and optimizing therapeutic efficacy.

Sex-based differences in immune function and cancer outcomes are increasingly

recognized in oncology.[8 9] Epidemiological data suggest that men generally exhibit higher RCC incidence and mortality compared with women.[10] Emerging evidence points to androgen receptor (AR) signaling as a contributing factor to these disparities. The AR pathway plays a central role in modulating immune cell activity, particularly $CD8^+$ T cells, which are essential for antitumor immunity.[11] AR activation is known to impair $CD8^+$ T-cell functionality, reducing their stem-like properties and limiting their antitumor potential. Thus, strategies that inhibit androgen activity may enhance T cell-mediated immunity in RCC.

5α-reductase inhibitors (5-ARIs), which inhibit the conversion of testosterone to the more potent androgen dihydrotestosterone (DHT), are widely prescribed for benign prostatic hyperplasia. By reducing DHT levels, 5-ARIs effectively decrease AR activation.[12] Given the role of AR in immune regulation, there is a biological rationale to hypothesize that prior use of 5-ARIs could impact response to ICIs by improving $CD8^+$ T-cell functionality. However, the effect of 5-ARI use history on the efficacy of ICIs in mRCC has not been thoroughly investigated.

In this retrospective, multicenter cohort study, we examined the impact of a history of 5-ARI use on ICI treatment outcomes in patients with mRCC. We hypothesized that patients with a history of 5-ARI use (≥12 months) would exhibit improved clinical outcomes, including longer progression-free survival (PFS), overall survival (OS), and higher objective response rates (ORR) and disease control rates (DCR), as compared with those without 5-ARI exposure. Additionally, we conducted single-cell RNA sequencing analysis of tumor samples to provide a detailed understanding of the immunological landscape altered by 5-ARI use, elucidating how these changes correlate with the improved clinical outcomes observed. By evaluating these associations, we aimed to offer new insights into the potential utility of modulating the androgen pathway as an adjunctive strategy in enhancing immunotherapy efficacy in RCC.

METHODS

Data sources and study population

This multicenter retrospective cohort study was conducted using de-identified electronic health record (EHR) data from participating institutions (Nanfang Hospital; Sun Yat-sen Memorial Hospital; Peking University People's Hospital) specializing in oncology and urology. Eligible patients had a confirmed diagnosis of mRCC and received treatment with ICIs as part of their clinical care. The study period spanned from January 2015 to December 2020, allowing for adequate follow-up time for assessing long-term survival outcomes. Patients were stratified into two groups: those with a documented history of continuous 5-ARI use for at least 12 months prior to ICI initiation, and those without any prior 5-ARI exposure. Patients with incomplete records or who had received systemic therapies other than ICIs and 5-ARIs were excluded from the study to ensure data consistency and accuracy. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and in line with the STROCSS(Strengthening the Reporting of Cohort Studies in Surgery) criteria.[13 14]

Exposure, outcomes, and covariates

The primary exposure was a pre-ICI 5-ARI use history, defined as at least 12 consecutive months of 5-ARI prescriptions before starting ICI therapy. To minimize reverse causation, patients with recent 5-ARI prescriptions within 3 months before the cohort entry date (ICI initiation) were excluded to ensure that 5-ARI use preceded cancer progression and ICI treatment decisions. Treatment duration was calculated by summing the supply days for all filled 5-ARI prescriptions, excluding short-term interruptions (up to 30 days).

The primary endpoints were PFS and OS. PFS was measured from the date of ICI initiation to the first documented progression event or death, whichever occurred first. OS was defined as the time from ICI initiation to death from any cause. Secondary endpoints included the ORR, defined as the proportion of patients achieving complete response (CR) or partial response (PR), and the DCR, encompassing CR, PR, and stable disease, as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1.

Data collection and covariates

Data were collected from EHRs at participating institutions, with standardized protocols for gathering comprehensive, de-identified information on eligible male patients with mRCC who received ICIs as part of their treatment. Data extraction was performed by trained personnel with access to institutional EHR systems, ensuring consistent data retrieval across sites. Each data point was reviewed by an independent team member for accuracy and completeness.

The collected data included: (1) Demographic information: age at ICI initiation and body mass index (BMI) were recorded for each patient to assess baseline characteristics that could influence ICI efficacy. (2) Clinical characteristics: variables such as Eastern Cooperative Oncology Group (ECOG) performance status, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score (low, intermediate, high),[15] tumor stage at diagnosis, and programmed death-ligand 1 (PD-L1) expression levels were collected to provide a detailed profile of disease severity and treatment context. (3) Treatment history: Detailed treatment information, including 5-ARI use, was documented. 5-ARI exposure was defined by at least two filled prescriptions over a continuous 12-month period prior to ICI initiation, excluding prescriptions issued within 3 months before starting ICI therapy. Additionally, data on the type of ICI administered (eg, pembrolizumab, nivolumab, or combination therapies), ICI treatment duration, and response to treatment were recorded. (4) Outcome variables:

Table 1 Baseline characteristics of 185 patients with clear renal cell carcinoma

Characteristics	Patients, n (%)		P value
	ICIs+5-ARI	ICIs	
Age, median (IQR)	56 (51–65)	58 (50–63)	0.8839
BMI at diagnosis (kg/m^2), mean (95% CI)	23.45 (21.74 to 24.89)	23.23 (22.36 to 23.93)	0.6654
GFR (mL/min), mean (95% CI)	92.90 (88.93 to 96.87)	91.19 (87.44 to 94.93)	0.5419
PD-L1 expression, n			0.9865
Negative (<1%)	27 (35.1)	38 (35.2)	
Positive (≥1%)	50 (64.9)	70 (64.8)	
cT-stage, n			0.9125
T1-2	18 (23.4)	26 (24.1)	
T3-4	59 (76.6)	82 (75.9)	
cN-stage, n			
N0	47 (61.0)	74 (68.5)	0.2918
N1	30 (39.0)	34 (31.5)	
cM-stage, n	77 (100.0)	85 (100.0)	–
M0	0 (0)	0 (0)	
M1	77 (100.0)	108 (100.0)	
Number of distant metastases, n			0.6616
1	25 (32.5)	42 (38.9)	
2–5	30 (39.0)	39 (36.1)	
>5	22 (28.5)	27 (25.0)	

5-ARI, 5α-reductase inhibitor; BMI, body mass index; GFR, glomerular filtration rate; ICI, immune checkpoint inhibitor.

primary endpoints included PFS and OS, calculated from the date of ICI initiation to the date of documented disease progression or death. Secondary endpoints, such as ORR and DCR, were based on follow-up assessments, with response categorized per RECIST V.1.1.[16]

All collected data were securely stored in a centralized database, with quality control procedures to verify data accuracy and resolve any discrepancies between source records and database entries. Data collection adhered to institutional and ethical guidelines, ensuring confidentiality and data integrity throughout the process (online supplemental figure S3).

Subgroup and sensitivity analysis

To explore the effect of 5-ARI use across various patient subgroups, we conducted stratified analyses based on age (<60 vs ≥60 years), IMDC risk group, PD-L1 expression level (low vs high), and specific metastatic sites (eg, lung, liver, bone). Sensitivity analyses were performed to assess the robustness of the results by excluding patients with intermittent 5-ARI use and by varying the definition of continuous use (eg, extending the minimum duration of 5-ARI exposure to 18 months).

Single-cell RNA sequencing and data analysis

The study protocol was approved by the Sun Yat-sen University Ethics Committee for Research Involving Human Subjects (Approval No.SYSKY-2025-097-01), and all patients provided written informed consent.

Tumor tissue collection and single-cell preparation

Fresh tumor tissues were obtained from patients with mRCC undergoing surgical resection. Patients were categorized based on their prior treatment with 5-ARI. Tissues were promptly processed post-resection to minimize RNA degradation. The tissues were dissociated using the Tumor Dissociation Kit (Miltenyi Biotec) according to the manufacturer's protocols, which employs a combination of enzymatic and mechanical methods to ensure a high yield of viable single cells.

Single-cell RNA sequencing

Single cells were suspended in a buffer solution and loaded onto a 10x Genomics Chromium Controller to generate single-cell gel beads in emulsion. The barcoded libraries were prepared using the Chromium Single Cell 3' Library and Gel Bead Kit v3, enabling capture of 3' end polyadenylated messenger RNA transcripts for digital gene expression profiling. Sequencing was performed on an Illumina NovaSeq 6000 with a sequencing depth aiming for at least 50,000 reads per cell.

Quality control and data processing

The Cell Ranger software suite (10x Genomics) was used for demultiplexing, barcode processing, and gene count

Table 2 Clinical characteristics and treatment regimens among patients

Characteristics	Patients, n (%)		P value
	ICIs+5-ARI	ICIs	
5-ARI			–
Finasteride	58 (75.3)	–	
Dutasteride	19 (24.7)	–	
ICIs			0.9087
Pembrolizumab	2 (2.6)	3 (2.8)	
Nivolumab	1 (1.3)	2 (1.9)	
Pembrolizuma+axitinib	43 (55.8)	65 (60.1)	
Nivolumab+ipilimumab	31 (40.3)	38 (35.2)	
IMDC risk			0.8576
Low	19 (24.7)	30 (27.8)	
Intermediate	48 (62.3)	66 (61.1)	
High	10 (13.0)	12 (11.1)	
Prior treatment history			0.8691
None	70 (90.9)	95 (88.0)	
Surgery	2 (2.6)	5 (4.6)	
Radiotherapy	0 (0)	0 (0)	
TKIs	5 (6.5)	8 (7.4)	

5-ARI, 5α-reductase inhibitor; ICIs, immune checkpoint inhibitors; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; TKIs, tyrosine kinase inhibitors.

quantification from raw sequencing data. Quality control was stringently performed to filter out cells with less than 200 detected genes, more than 10% mitochondrial-derived transcripts, or signs of multiple nuclei (suggestive of doublets). The Seurat package was then used for further data normalization, variable gene identification, and scaling.

Dimensionality reduction and clustering analysis

Normalized data underwent principal component analysis to identify principal components that captured the most significant variance and potential batch effects. Cells were subsequently projected onto two-dimensional space using t-distributed stochastic neighbor embedding (t-SNE) for visualization. Clusters were identified through a shared nearest neighbor modularity optimization-based clustering algorithm.

Phenotypic annotation and differential expression analysis

Cells were annotated by comparing expression patterns to known markers of renal cancer immune cell types and tumor cells. Differential expression analysis between 5-ARI-treated and control groups was performed using the MAST framework, which accounts for cellular detection rate in single-cell transcriptomics data. Significantly differentially expressed genes were used to infer functional impacts of 5-ARI treatment via pathway enrichment analysis involving KEGG(Kyoto Encyclopedia of Genes and Genomes) and Reactome databases.

Immune checkpoint analysis

Focus was placed on the expression of the programmed cell death protein-1 (PD-1) checkpoint protein, a critical modulator in immune response, across identified cell clusters. Expression levels of PD-1 were quantitatively assessed in both 5-ARI-treated and control groups. This analysis specifically measured the expression of PD-1 protein, not a panel of genes associated with PD-1 signaling. By comparing immune profiles, we aimed to evaluate the immunomodulatory impact of 5-ARI in the context of tumor immunity.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics between the 5-ARI and non-5-ARI groups. Differences in categorical variables (eg, gender, ECOG performance status) were evaluated using χ^2 or Fisher's exact tests, and continuous variables (eg, age, BMI) were compared using t-tests or Mann-Whitney U tests, as appropriate. Missing data were handled with complete case analysis, excluding any patients with incomplete records for primary covariates or outcomes. Kaplan-Meier survival analysis was performed to generate PFS and OS curves for each group, and the log-rank test was used to

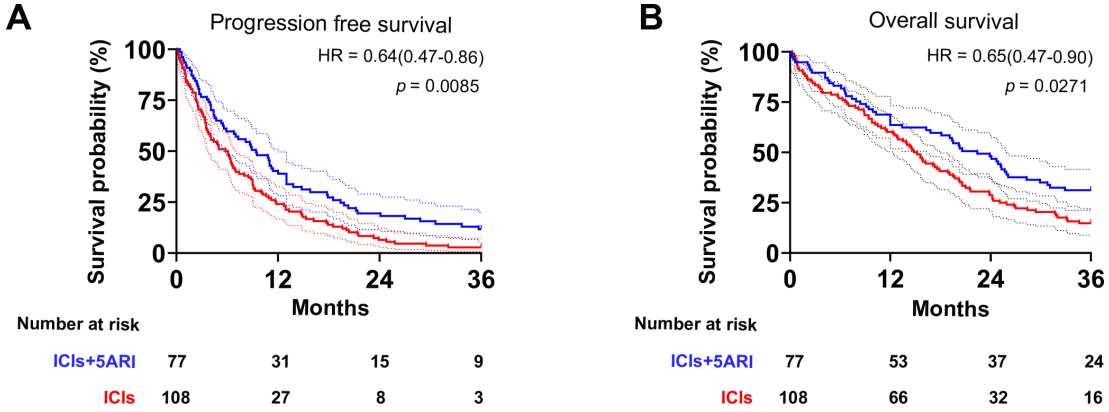

Figure 1 Kaplan-Meier plots of progression-free survival (A) and overall survival (B) for patients treated with ICIs with and without 5α-reductase inhibitor use history. ICI, immune checkpoint inhibitor; 5-ARI, 5α-reductase inhibitors.

Table 3 Comparison of treatment efficacy outcomes in patients receiving ICIs with or without 5-ARI

Covariate	Patients, n (%)		P value
	ICIs+5-ARI	ICIs	
RECIST			0.0353
CR	15 (19.5)	11 (10.2)	
PR	31 (40.3)	32 (29.6)	
SD	21 (27.3)	42 (38.9)	
PD	10 (12.9)	23 (21.3)	
ORR	46 (59.8)	43 (39.8)	0.0075
DCR	67 (87.0)	85 (78.7)	0.1747
PFS			
6-month PFS rate	47 (61.0)	54 (50.0)	0.0087
1-year PFS rate	31 (40.1)	27 (25.0)	0.0364
OS			
1-year OS rate	56 (72.7)	66 (61.1)	0.1003
3-year OS rate	24 (31.2)	16 (15.0)	0.0271
Time to response median (IQR)	2.80 (1.90–3.95)	4.05 (3.30–4.80)	<0.001
Duration of response median (IQR)	7.50 (1.50–18.0)	1.8 (0–7.43)	<0.001
Surgical conversion rate	7 (9.1)	2 (1.9)	0.0241

5-ARI, 5α-reductase inhibitor ; CR, complete response; DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

compare survival distributions. Multivariable Cox proportional hazards models were employed to estimate HRs and 95% CIs for PFS and OS, adjusting for key covariates, including age, gender, BMI, ECOG performance status, IMDC risk group, PD-L1 expression, tumor stage, metastasis sites, and ICI treatment regimen. The proportional hazards assumption was assessed using Schoenfeld residuals. ORR and DCR were compared between groups using χ^2 or Fisher's exact test, with $p<0.05$ considered statistically significant.

To account for potential confounding factors and ensure covariate balance between groups, we used propensity score matching (PSM). Patients with and without 5-ARI use were matched on baseline characteristics with a caliper width of 0.02, using nearest neighbor matching. Covariate balance after matching was assessed with standardized mean differences, with values <0.10 indicating acceptable balance. All statistical analyses were conducted using GraphPad Prism V.10.2.2 and R V.4.1.1 (R Foundation for Statistical Computing). The study protocol adhered to the principles outlined in the Declaration of Helsinki.[17]

Table 4 Comparison of adverse event severity and performance status in patients receiving ICIs with or without 5-ARI

Covariate	Patients, n (%)		P value
	ICIs+5-ARI	ICIs	
CTCAE			0.9210
Grade I	31 (40.3)	46 (42.5)	
Grade II	23 (29.9)	31 (28.4)	
Grade III	9 (11.7)	11 (10.2)	
Grade IV	0	0	
Grade V	0	0	
ECOG median (IQR)	2 (1–3)	2 (1–3)	0.6689
KPS median (IQR)	80 (70–90)	75 (65–85)	0.9528

5-ARI, 5α-reductase inhibitors; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors; KPS, Karnofsky performance status.

Ethics approval

Ethical approval for this study was obtained from the institutional review boards (IRBs) of each participating institution. Given the retrospective design, informed consent was waived by the IRBs as per institutional and national guidelines. Data were anonymized before analysis to ensure patient privacy and confidentiality.

RESULTS

Study cohort and baseline characteristics

From January 2015 to December 2020, a total of 185 patients with mRCC undergoing ICIs treatment were included in this retrospective analysis. Patients were

Table 5 Multivariable Cox regression analysis for predictors of overall survival

Covariate	HR, 95% CI		P value
5-ARI use			
Yes	0.78	0.63 to 0.96	0.023
No (reference)	1.00	–	–
IMDC risk group			
Low	0.55	0.42 to 0.72	<0.001
Intermediate	0.85	0.68 to 1.06	0.1528
High (reference)	1.00	–	–
Treatment regimen			
Pembrolizumab	0.89	0.70 to 1.12	0.3226
Nivolumab	0.92	0.73 to 1.16	0.4526
Combination therapies	0.75	0.60 to 0.95	0.012
BMI (per unit increase)	0.98	0.95 to 1.01	0.1895
Metastasis site			
Lung	1.12	0.90 to 1.40	0.3052
Liver	1.35	1.10 to 1.65	0.003
Bone	1.20	0.98 to 1.47	0.072

5-ARI, 5α-reductase inhibitor; BMI, body mass index; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

stratified into two groups based on their history of 5-ARI use: 77 patients had a history of 5-ARI use, while 108 did not. Before PSM, there were significant differences in baseline characteristics such as age and previous treatments. Following PSM, the cohorts were well-matched with no significant differences in age, BMI, glomerular filtration rate, PD-L1 expression, and tumor staging, ensuring comparability for outcome analysis (standardized mean differences <0.10 for all compared variables) (table 1).

Treatment regimens and 5-ARI usage

The treatment regimen distribution showed that a significant portion of patients in the 5-ARI group were treated with either finasteride (75.3%) or dutasteride (24.7%). ICIs used included pembrolizumab, nivolumab, and combination therapies with axitinib or ipilimumab, with no significant difference in the distribution of these treatments between the groups. The IMDC risk categories were similarly distributed, affirming the methodological robustness of the study's comparative analysis (table 2).

Efficacy outcomes

The efficacy outcomes showed differences between the groups. The ORR was 59.8% in the 5-ARI group versus 39.8% in the non-5-ARI group (p=0.0075). The DCR was also higher in the 5-ARI group (87.0% vs 78.7%), though the difference was not statistically significant (p=0.1747). PFS at 6 months was significantly better in the 5-ARI group (61.0% vs 50.0%, p=0.0087). The 1-year OS rates showed a trend toward improvement in the 5-ARI group (72.7% vs 61.1%, p=0.1003), but statistical significance was not reached. However, the 3-year OS rate was significantly higher in the 5-ARI group (31.2% vs 15.0%, p=0.0271). Kaplan-Meier survival curves illustrate a significant extension in both median PFS and OS times in the 5-ARI group compared with the non-5-ARI group (figure 1). The survival probabilities over the study period highlight sustained benefits of 5-ARI, with notable divergences in the curves suggesting a durable impact of 5-ARI on disease progression and survival. These results suggest that 5-ARI use may enhance the clinical benefits of ICIs in mRCC treatment (table 3).

Adverse events and safety profile

The safety profile analysis based on the Common Terminology Criteria for Adverse Events indicated that there were no significant increases in the occurrence of Grade III or higher adverse events across the groups, suggesting that 5-ARI use does not exacerbate the toxicity profile of ICIs (table 4).

Multivariable Cox regression analysis

The multivariable Cox regression analysis, adjusting for factors such as IMDC risk group and specific ICI regimens, demonstrated that 5-ARI use was associated with a reduced risk of mortality (HR=0.78, 95% CI: 0.63 to 0.96, p=0.023). This analysis confirms the survival advantage of 5-ARI use in this patient population, underscoring its potential protective role against cancer progression (table 5).

Subgroup and sensitivity analysis

Subgroup analysis highlighted that the benefits of 5-ARI were particularly pronounced in patients under 60 years of age and those with positive PD-L1 expression, indicating potential interactions between 5-ARI use and immune status. These findings were supported by sensitivity analyses, which also showed consistent benefits across various patient subgroups, reinforcing the robustness of the primary outcomes (table 6).

Single-cell RNA sequencing analysis insights

We performed single-cell RNA sequencing on fresh tumor specimens from patients with mRCC and compared the results between the 5-ARI-exposed and non-exposed groups. Complementary to the clinical findings, our single-cell RNA sequencing analysis (online supplemental figures S1–S3 and table S1) provided deeper insights into the cellular mechanisms potentially underlying the observed clinical benefits. The t-SNE plots (figure 2A–C) revealed distinct clustering of immune cell types, with notable differences in immune cell compositions between the 5-ARI treated and control groups. Notably, the control group exhibited elevated levels of regulatory T cells (Tregs) and CD8 T-cell exhaustion (CD8 Tex) compared with the 5-ARI group, as depicted in the t-SNE plots (figure 2C,E). Furthermore, PD-1 expression was markedly higher in CD8 Tex cells within the control

Table 6 Subgroup analysis of immunotherapy efficacy stratified by 5α-reductase inhibitor usage in patients with metastatic renal cell carcinoma

Subgroup	5-ARI use	ORR	Median PFS months	Median OS Months	P value
Age					
<60 years	Yes	45.2	9.5	24.0	0.042
	No	38.6	7.8	19.5	
≥60 years	Yes	42.8	8.9	22.0	0.1223
	No	36.5	6.8	18.0	
PD-L1 expression					
Negative (<1%)	Yes	42.0	8.2	20.0	0.0745
	No	35.5	6.9	18.5	
Positive (≥1%)	Yes	50.0	9.7	25.5	0.0212
	No	43.5	8.0	22.5	
IMDC score					
Low	Yes	58.7	12.5	30.2	0.008
	No	50.0	9.8	25.6	
Intermediate	Yes	41.2	8.0	21.5	0.10
	No	36.5	6.5	17.4	
High	Yes	30.5	5.5	15.0	0.23
	No	28.0	5.2	14.3	
Number of distant metastases, n					
1	Yes	50.0	10.0	26.0	0.032
	No	42.0	8.5	22.0	
2–5	Yes	44.5	9.2	24.5	0.0625
	No	38.7	7.5	21.0	
>5	Yes	40.0	8.0	20.0	0.1058
	No	33.5	6.5	17.5	

5-ARI, 5α-reductase inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1 ; PFS, progression-free survival.

group, suggesting a mechanism for the reduced efficacy of ICIs observed in these patients (figure 2F,G).

DISCUSSION

This retrospective cohort study represents an innovative analysis examining the association between the history of 5-ARI use and the efficacy of ICIs in mRCC. We demonstrated that a history of 5-ARI use is associated with significantly improved outcomes, including enhanced PFS and OS rates. These findings suggest that 5-ARIs may exert beneficial effects beyond their traditional use, potentially delaying cancer progression and enhancing the response to ICIs. Such results indicate a possible preventive role against aggressive cancer phenotypes, which could partly explain the observed reductions in mortality rates among the treated population.

To mitigate potential confounders and ensure comparability between groups, PSM was used to balance diverse baseline characteristics across the cohorts. This method is critical in observational studies where randomized controlled trials (RCTs) are not feasible, and it helps in emulating the conditions of an RCT, thus enhancing the reliability of the conclusions drawn from observational data. Our application of PSM has allowed us to establish a robust model that highlights the potential influence of 5-ARIs on treatment outcomes in mRCC, supporting its utility in pharmacovigilance and therapeutic optimization.

Our findings align with emerging literature that suggests a modulatory role of androgen deprivation therapies in cancer treatment,[18 19] particularly regarding their immunomodulatory effects.[9 20 21] Similar studies have observed lower rates of surgical interventions and systemic progression in cancers treated with androgen-targeting strategies.[22 23] However, unlike previous studies that did not control for other risk factors, our analysis provides a clearer association by adjusting for these variables, offering a more direct understanding of 5-ARI's impact.

The mechanism behind the improved outcomes with 5-ARI use could involve the modulation of AR signaling

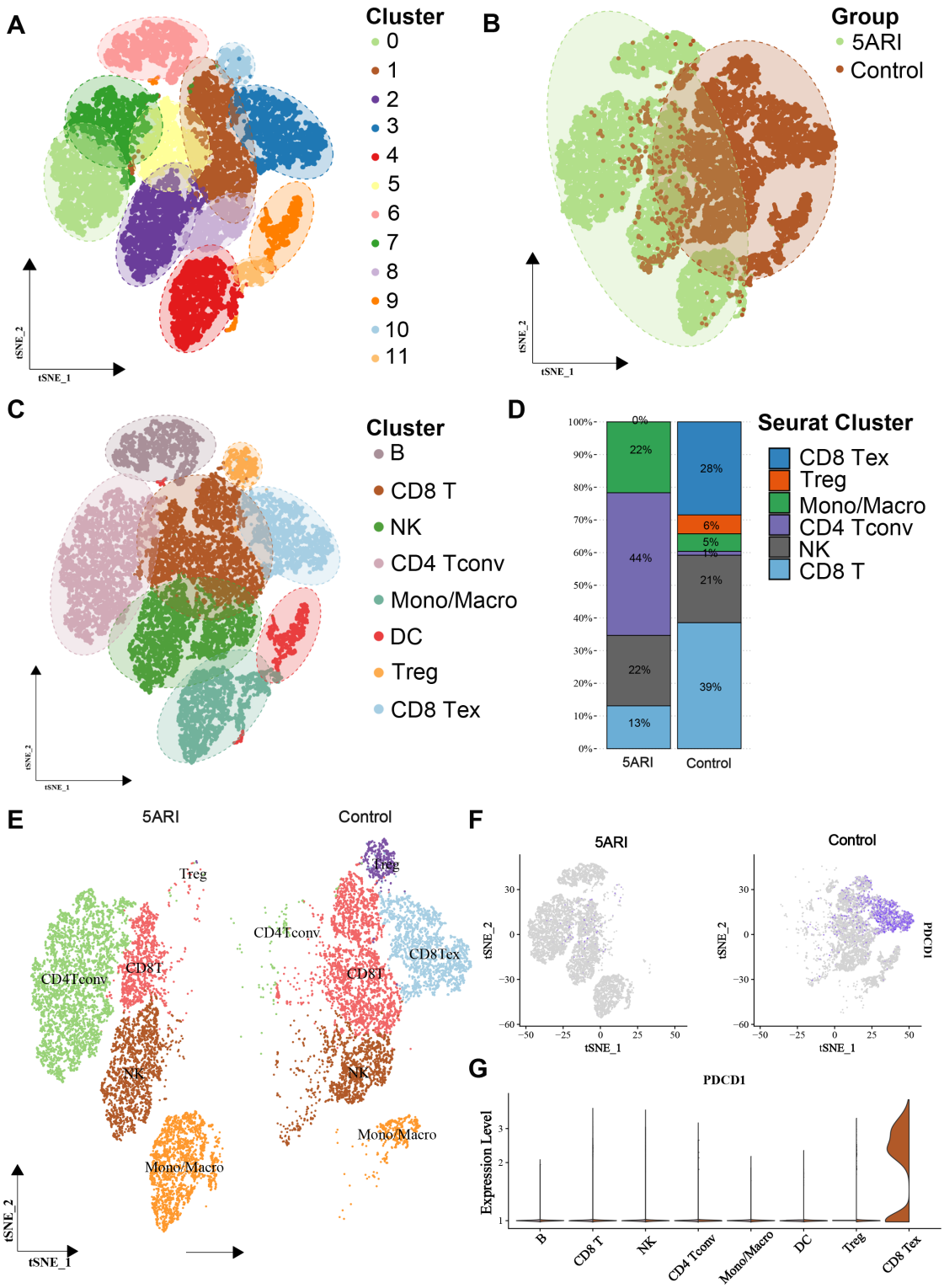

Figure 2 Single-cell RNA sequencing analysis of patients with renal cancer with and without 5-ARI usage history. (A) t-SNE visualization of all identified cell clusters from patients with renal cancer, with each cluster color-coded for distinct cell identities. (B) t-SNE representation highlighting cell distributions from patients with a history of 5-ARI use (green) and controls without 5-ARI use (orange), demonstrating differential clustering patterns. (C) t-SNE plot categorizing cells by immune phenotype, including CD8 T cells, CD8 T-cell exhaustion (CD8 Tex), NK cells, B cells, monocytes/macrophages (Mono/Macro), dendritic cells (DC), conventional CD4 T cells (CD4 Tconv), and regulatory T cells (Treg). (D) Proportion of immune cell subsets in patients with and without 5-ARI treatment, displayed in a bar chart to elucidate variations in immune cell composition. (E) Side-by-side t-SNE plots for 5-ARI-treated and control groups, detailed by immune cell type distribution. (F) t-SNE plots showing PD-1 expression in immune cells from both 5-ARI-treated and control groups. (G) Violin plot detailing PD-1 expression across various immune cells. NK, natural killer; PD-1, programmed cell death protein-1; t-SNE, t-distributed stochastic neighbor embedding; 5-ARI, 5α-reductase inhibitors.

pathways known to affect tumor microenvironment, immune escape, and cancer cell survival.[24 25] In vitro and in vivo studies suggest that AR signaling influences various aspects of cellular proliferation and immune regulation.[26–28] By inhibiting this pathway, 5-ARIs may enhance the immune system's ability to recognize and destroy cancer cells, thereby synergizing with ICIs. This hypothesis is further supported by our single-cell RNA sequencing analysis, which revealed a reduced presence of immunosuppressive cells (Tregs and exhausted $CD8^+$ T cells) in the 5-ARI group, along with altered PD-1 expression patterns, suggesting an immunologically favorable tumor microenvironment for ICIs efficacy.

Limitations and directions for future research

While our study provides significant insights, it is not without limitations. The retrospective design and the reliance on existing medical records limit the ability to capture all potential confounders and biases inherent in such data. Furthermore, the generalizability of our findings is constrained by the demographic homogeneity of our cohort, primarily consisting of patients from a single ethnic background. Future studies should aim to replicate these findings in a prospective, multicenter trial involving a more diverse patient population to validate the potential universal applicability of 5-ARIs in mRCC treated with ICIs.

CONCLUSION

In conclusion, our findings demonstrate that a history of 5-ARI use enhances the efficacy of ICIs in advanced RCC, suggesting a role for 5-ARIs in optimizing immunotherapy outcomes. The modifications in the tumor microenvironment, characterized by reduced immunosuppressive populations and altered PD-1 expression as revealed by single-cell RNA sequencing, underpin these clinical benefits. These insights justify further exploration of 5-ARIs as a potential adjunctive treatment in oncology, encouraging prospective studies to validate and refine this therapeutic strategy.

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Contributors BC, JW, and KC conceptualized and designed the study, formulated the research goals, and outlined the overall research strategy. WL, JY, WS, LY, and WH were responsible for the acquisition of data, managing the data (including quality control), and performing the initial analyses. CM, ZL, and BS provided essential tools and reagents for the study, assisted in interpreting the data, and contributed to the methodology by refining the analytical techniques. BC led the bioinformatics analysis, interpreted complex data, and integrated results into the broader context of the study. PW, HH, and QW oversaw the literature review, ensuring a comprehensive understanding of the topic and relevance to current research. They also played a significant role in revising the manuscript critically for important intellectual content and overseeing the manuscript preparation, including final editing and proofreading. PW is the guarantor of the study. All authors have reviewed and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval for this study was obtained from the institutional review boards (IRBs) of each participating institution. Given the retrospective design, informed consent was waived by the IRBs as per institutional and national guidelines. Data were anonymized before analysis to ensure patient privacy and confidentiality. Single-cell RNA Sequencing and Data Analysis: The study protocol was approved by the Sun Yat-sen University Ethics Committee for Research Involving Human Subjects (Approval No. SYSKY-2025-097-01), and all patients provided written informed consent.

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