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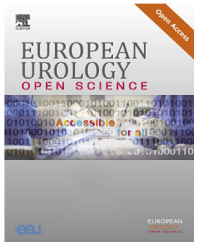

European Association of Urology

Prostate Cancer

Treatment-related Hypertension as a Prognostic Factor for De Novo Metastatic Hormone-sensitive Prostate Cancer: A Retrospective Real-world Evidence Study

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Abstract

Background and objective: Hypertension (HTN) has been linked to an elevated risk of prostate cancer (PC) development and poorer prognosis in localized cases, and is a common side effect of hormonal PC treatments. However, its relationship with the prognosis of metastatic PC is still unclear. We assessed the prognostic role of treatment-related HTN in patients with de novo metastatic hormone-sensitive PC (mHSPC) undergoing androgen deprivation therapy (ADT) alone or in combination with docetaxel or androgen receptor pathway inhibitors (ARPIs).

Methods: Our retrospective analysis included 100 patients with de novo mHSPC treated with ADT, ADT + docetaxel, or ADT + ARPI between 2014 and 2021. Data on clinical variables, antihypertensive drugs, and blood pressure were collected from treatment initiation to 7 mo from ADT start. HTN development within 7 mo from hormonal treatment initiation was graded according to the Common Toxicity Criteria for Adverse Events version 5.0, and Cox analyses were performed for time to castration resistance (TTCR) and overall survival (OS).

Key findings and limitations: In the overall population, grade (G) 2–3 HTN development within 7 mo from hormonal treatment initiation was associated with improved TTCR and OS at both univariate (TTCR: 19.8 vs 7.9 mo, hazard ratio [HR]: 0.35, 95% confidence interval [CI]: 0.20–0.63, $p < 0.001$; OS: 42 vs 18.4 mo, HR: 0.48, 95% CI: 0.26–0.87, $p = 0.017$) and multivariate (TTCR: HR: 0.41, 95% CI: 0.18–0.91, $p = 0.029$; OS: HR: 0.42, 95% CI: 0.18–0.97, $p = 0.042$) analyses. A

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subgroup analysis of the ADT + ARPI–treated population revealed 7-mo treatment-related G2–3 HTN to be an independent positive prognostic factor in terms of both TTCR and OS multivariate survival analyses (HR: 0.30, 95% CI: 0.09–0.95, $p = 0.040$, and HR: 0.12, 95% CI: 0.02–0.57, $p = 0.008$, respectively).

Conclusions and clinical implications: The early development or worsening of HTN under hormonal treatment may be associated with longer TTCR and OS in de novo mHSPC patients. Larger studies are needed to validate these findings and explore the potential underlying mechanisms.

Patient summary: In this report, we examined the outcomes of patients with metastatic hormone-sensitive prostate cancer and their correlation with hypertension toxicities. We found that patients who developed clinically significant blood pressure toxicity early in oncological treatment experienced longer survival.

1. Introduction

Prostate cancer (PC) is the second most commonly diagnosed solid tumor among men [1]. Despite the good prognosis generally associated with localized forms of PC, only 32% of patients with metastatic PC are alive 5 yr after the diagnosis [2]. Among these patients, those with a diagnosis of de novo metastatic disease have a worse prognosis [3].

Several factors may contribute to patients' prognosis or predict treatment response, and research is currently very active on these essential domains.

The microenvironment of PC is characterized by a complex interplay of multiple entities [4]. Previous studies showed that the autonomic nervous system (ANS) contributes to PC development and progression via different mediators [5]. Specifically, peripheral fibers of the sympathetic nervous system (SNS) can promote primary tumor growth. In contrast, the SNS seems to become less relevant in the later stages of PC, when the activation of the parasympathetic nervous system (PNS) can promote metastasis development and further cancer progression [6].

Furthermore, the renin-angiotensin system (RAS) has been found to be active within the tumor microenvironment and to influence cancer cell growth and metabolism [7,8]. Dysregulation of local RAS has been suggested to increase PC progression and metastasis [9].

Activation of the ANS and RAS can manifest through various phenomena, including variation in blood pressure (BP) [10].

Several factors can influence the development of hypertension (HTN) in patients with PC undergoing systemic treatment. HTN development is a frequent side effect of both androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs). These drugs represent part of the current standard of care for metastatic PC [11]. While a recent meta-analysis [12] indicates that roughly two-thirds of metastatic PC patients treated with ARPIs experience clinically relevant HTN as a treatment-related toxicity, with enzalutamide treatment exhibiting the highest incidence, in a cohort of 56 230 men with advanced PC [13], those treated with abiraterone were at a higher risk of developing adverse events related to diabetes, HTN, or cardiovascular diseases than those treated with enzalutamide.

Finally, a substantial portion of PC patients are receiving treatment with antihypertensive medications before starting oncological therapy, potentially influencing both the development of HTN and the survival outcomes. Two retrospective single-center studies [14,15], conducted in patients with metastatic castration-resistant PC (mCRPC) treated with ADT and abiraterone acetate or enzalutamide, suggested that in those with pre-existing HTN, treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) concomitant to ARPIs correlated with superior survival outcomes.

Moreover, the use of antihypertensive β-blocker drugs has been suggested to be associated with a lowered risk of PC incidence [16] and biochemical recurrence after radical treatment for high-risk localized PC [17].

Despite these insights, there remains a scarcity of data concerning the relationship between HTN and outcomes in metastatic PC, and a significant gap persists in understanding the correlation between the emergence of treatment-related side effects in metastatic PC and patients' response, disease progression, and OS.

This study addresses this knowledge gap by comprehensively assessing, for the first time, the relationship between the development of treatment-related HTN in patients undergoing treatment for mHSPC and their key survival outcomes.

2. Patients and methods

The analysis of this real-world evidence study has been reported in accordance to the European Society for Medical Oncology (ESMO) Guidance for Reporting Oncology real-World Evidence (ESMO-GROW) recommendations [18].

2.1. Methods

This is a single-center retrospective study analyzing the data extracted from electronic medical records of patients who consecutively presented with de novo metastatic hormone-sensitive PC (mHSPC) and initiated first-line ther-

apy at the Oncology Institute of Southern Switzerland between the years 2014 and 2021.

Every patient either signed an informed consent for data collection or was deceased at the time of data analysis. The study was in the scope of a retrospective data collection protocol approved by the local ethics committee, and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We included patients with de novo metastatic PC who received first-line treatment with either ADT monotherapy or ADT in association with docetaxel or an ARPI, with available data on BP measurement and/or antihypertensive drug at diagnosis and/or antihypertensive drug introduced within 7 mo from treatment start. The detailed inclusion and exclusion criteria can be found in the Supplementary material.

2.2. Clinical measurements and variable definitions

Several demographic and clinical parameters were gathered to account for potential factors influencing time to castration resistance (TTCR) and overall survival (OS) in the multivariate (MV) Cox analysis, as shown in the Supplementary material.

Hypertensive toxicity was defined according to the Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE v5.0). In this classification system, grade (G) 1 HTN is defined as a systolic BP of 120–139 mmHg or a diastolic BP of 80–89 mmHg. Since values below these thresholds are not specified, we grouped them under the definition of G0 HTN.

"HTN_T2_AE" is a categorical variable that distinguishes patients experiencing G $\geq$1 HTN toxicity, compared with G0, within 7 mo ± 28 d from treatment initiation. This measurement is based solely on BP readings and does not consider the introduction of antihypertensive medications or changes in BP values. The grouping (G0 vs G1 or higher) was chosen to better explore the contribution of lower BP values (G0), which could reflect the presence of frail patients and potentially introduce a bias.

"HTN_T2_CTCAEv5.0" represented a categorical variable distinguishing patients experiencing mild or severe forms (G $\geq$2) versus either no or nonsignificant HTN toxicities (ie, G0/G1) within 7 mo ± 28 d from treatment initiation, accounting for both antihypertensive drug introduction and BP changes. Within the study, we grouped G0 and G1 HTN together, as neither represents clinically significant HTN.

A comprehensive description of the HTN variables and BP measurement procedures is provided in the Supplementary material and Supplementary Figure 1.

2.3. Study endpoints

Our primary objectives were to compare, in the overall population, TTCR and OS between patients who, within 7 mo from hormonal treatment initiation, did or did not:

1. Introduce novel antihypertensive medications
2. Develop HTN_T2_AE
3. Develop HTN_T2_CTCAEv5.0

The secondary objective was to examine these outcomes in the subgroup treated with ADT + ARPI.

The decision to assess toxicity within 7 mo from treatment initiation was based on the proven reliability of the same time point in assessing treatment response and prognosis for mHSPC patients, as demonstrated by the well-established use of prostate-specific antigen (PSA) measurements at 7 mo as a validated surrogate marker [19,20].

The employed definitions of TTCR and OS [21,22] are provided in the Supplementary material.

Exploratory analyses were performed to investigate the activity of the SNS and PNS, systemic inflammation, and RAS (Supplementary material).

Data extraction is described in the Supplementary material.

2.4. Statistical analyses

We employed Pearson's chi-square test to examine associations between categorical variables, comparing patients with HTN G 2–3 versus G 0–1, as defined by "HTN_T2_CTCAEv5.0. The association between HTN and OS or TTCR was depicted using Kaplan-Meier survival curves, and group comparisons were made using the log-rank test. Patients without a documented event were censored at their last follow-up. All statistical comparisons were made with two-tailed tests.

We performed univariate (UV) analyses using Cox proportional hazard models, incorporating HTN variables and baseline clinical characteristics (eg, 7-mo PSA and disease volume). Variables showing significance ($p < 0.10$) in UV analyses were included in the MV Cox model, along with significant HTN variables. To address the immortal time bias, we conducted landmark analyses at 6 and 7 mo from the start of treatment for both TTCR and OS.

In the ARPI-treated subgroup, we performed UV Cox analyses for TTCR and OS only for variables significant ($p < 0.10$) in the overall population. Those remaining significant were included in MV Cox analyses.

The results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs). All statistical analyses were carried out using Jamovi software version 2.4.11. The detailed statistical procedure is provided in the Supplementary material.

3. Results

3.1. Study population characteristics

The ESMO-GROW flowchart for real-world evidence studies in oncology is presented in the Supplementary material. During the inclusion period (April 2014–December 2021), a total of 276 consecutive patients with mHSPC were screened. Among them, 100 patients met the inclusion criteria. Table 1 presents the baseline demographics of patients at the time of treatment initiation (T0), distinguishing between those treated with ARPI and those who were not. The overall median TTCR was 11.2 mo (95% CI: 10.1–14.2; range: 2–60.9), and the median OS was 34 mo (95% CI: 26.7–43; range: 4.3–87.5). Within the study population, 46% of patients were on antihypertensive medication at T0,

Table 1 – Patient baseline demographics in ARPI-treated versus not ARPI-treated patients

Prognostic variable	All patients (%; *n* = 100)	ARPI-free regimen (*n* = 72; 72.0%)	ARPI treated (*n* = 28; 28.0%)	*p* value
Age (yr), median (IQR)	77 (min: 50 to max: 94)	80 (68, 84)	75 (67, 79)	0.080[a]
Age (yr)—categorical, *n* (%)				0.67[b]
<70	29 (29)	20 (27.8)	9 (22.1)	
≥70	71 (71)	52 (72.2)	19 (67.9)	
First-line docetaxel, *n* (%)				0.03[b]
0	89 (89)	61 (84.7)	28 (100)	
1	11 (11)	11 (15,3)	0 (0)	
First-line ARPI drug, *n* (%)				<0.01[b]
Abiraterone	17 (17)		17 (60.7)	
Enzalutamide	8 (8)		8 (28.6)	
Apalutamide	3 (3)		3 (10.7)	
Number of antihypertensive drugs at oncological treatment start, *n* (%)				0.88[b]
0	54 (54)	43 (59.7)	11 (39.2)	
1	19 (19)	11 (15.2)	8 (28.5)	
>1	27 (27)	18 (11.1)	9 (31.1)	
Number of antihypertensive drugs introduced after oncological treatment start, *n* (%)				0.15[b]
0	66 (66)	47 (65.2)	19 (67.8)	
1	21 (21)	16 (22.2)	5 (17.8)	
2	13 (13)	9 (12.5)	4 (14.2)	
Gleason score, *n* (%)				0.11[b]
7	10 (10)	8 (11.1)	2 (7.1)	
8	13 (13)	9 (12.5)	4 (14.3)	
9	38 (38)	24 (33.3)	14 (50)	
10	11 (11)	7 (9.7)	4 (14.3)	
NA	28 (28)	24 (33.3)	4 (14.3)	
ISUP grade, *n* (%)				0.37[b]
<5	23 (23)	17 (23.6)	6 (21.4)	
5	49 (49)	31 (43)	18 (64.3)	
NA	28 (28)	24 (33.3)	4 (14.3)	
CHAARTED criteria, *n* (%)				0.34[b]
Low volume	47 (47)	36 (50)	11 (39)	
High volume	53 (53)	36 (50)	17 (61)	
7-mo PSA level (ng/ml), *n* (%)				0.05[b]
<0.2	15 (15)	7 (9.7)	8 (28.6)	
0.2–4.0	29 (29)	21 (29.1)	8 (28.6)	
>4	56 (56)	44 (61.1)	12 (42.9)	
HTN T0 AE, *n* (%)				0.80[b]
G0/G1	26 (26)	17 (23.6)	9 (32)	
G2/G3	38 (38)	26 (36.1)	12 (43)	
NA	36(36)	29 (40.3)	7 (25)	
HTN T2 CTCAE V5.0, *n* (%)				0.28[b]
G0/G1	27 (27)	16 (22.2)	11 (39.28)	
G2/G3	36 (36)	26 (36.1)	10 (35.7)	
NA	37 (37)	30 (41.6)	7 (25%)	
TTCR (d), median (95% CI)	11.2 (10.1–14.2)	11.7 (10.2–16.3)	7.6 (4.9–15.6)	0.196[c]
TTCR censored patients, *n* (%)	3 (3)	3 (4.2)	0 (0)	
Follow up for TTCR censored (mo), median (95% CI)	NA (51.5–NA)	NA (51.5–NA)	NA	
OS (mo), median (95% CI)	34 (26.7–43)	35.3 (27.1–44.9)	28.5 (18.2–not reached)	0.612[c]
OS censored patients, *n* (%)	26 (26%)	16 (22.2)	10 (35.7)	
Follow up for OS censored (mo), median (95% CI)	72.5 (60.9–90.9)	72.5 (60.9–not reached)	80.5 (59.9–not reached)	

ARPI = androgen receptor pathway inhibitor; CI = confidence interval; CTCAE = Common Toxicity Criteria for Adverse Events; G = grade; HTN = hypertension; HTN T0 AE = hypertension toxicity grading at T0 (before treatment start) according to CTCAE v5.0 cutoff criteria for HTN toxicities (without accounting for treatment intervention); HTN T2 CTCAE V5.0 = worst hypertension toxicity graded adverse event from T0 to T2 (7 mo from treatment start) according to CTCAE v5.0 for HTN toxicities (accounting also for treatment intervention and pressure variations); IQR = interquartile range; ISUP = International Society of Urological Pathology; NA = not available; OS = overall survival; PSA = prostate-specific antigen; TTCR = time from first-line start to castration resistance development.

[a] Wilcoxon test.

[b] Pearson test.

[c] Log rank test.

and 32% introduced at least one new antihypertensive medication within 7 mo of beginning oncological treatment.

Furthermore, in the patient cohort, 63% had available data on BP records and antihypertensive drugs at both T0 and within 7 mo from treatment start, enabling precise estimation of CTCAE v5.0 HTN toxicities (HTN_T2_CTCAEv5.0). Table 2 illustrates the comparison between patients experiencing G2–3 HTN_T2_CTCAEv5.0 toxicities within 7 mo

from treatment start and those who did not. A substantial proportion of patients experiencing HTN G2/G3 (72.2%, $p = 0.012$) were found not to be on antihypertensive drugs at the time of diagnosis, in stark contrast to those with G0/G1 (33%) HTN toxicity. The two groups of patients (those who developed and those who did not develop significant HTN toxicities) did not significantly differ in terms of the percentage of patients receiving docetaxel or an ARPI.

3.2. Impact of early-onset treatment-related HTN on survival outcomes

In the overall population, evaluating HTN_T2_AE (which did not account for the introduction of antihypertensive medications or BP changes), we found no statistically significant differences between patients experiencing G $\geq$1 versus G0 HTN in a UV Cox analysis for both TTCR (HR: 0.72, $p = 0.344$) and OS (HR: 0.52, $p = 0.108$; Supplementary Tables 1 and 2).

In the patient cohort providing comprehensive BP and antihypertensive treatment data (HTN_T2_CTCAEv5.0 cohort), we assessed the prognostic impact of HTN_T2_CTCAEv5.0, which also accounted for the introduction of antihypertensive drugs and BP changes within the first 7 mo of treatment.

HTN_T2_CTCAEv5.0 was an independent positive prognostic factor for both TTCR and OS. This significance persisted in the Cox MV analysis for both the overall population and the subgroup treated with ARPIs.

The effects of HTN_T2_CTCAEv5.0 on patients' TTCR and OS in the overall population and results from UV and MV Cox analyses are presented in Table 3, and Supplementary Tables 3 and 4. The median TTCR for patients with G2/G3 HTN toxicity was 11.6 mo (95% CI: 8.8–26.9) compared with 6.33 mo (95% CI: 4.9–10.3) for patients with G0/G1 HTN toxicity. Patients with G2/G3 HTN also had longer median OS of 28.5 mo (95% CI: 24.5–44.9) than patients with G0/G1 HTN (OS 18.5 mo; 95% CI: 13.1–39.5). Early treatment-related HTN was a significant prognostic factor in both the UV and the MV Cox analysis for both TTCR (HR: 0.35, 95% CI: 0.20–0.63, $p < 0.001$, and HR: 0.41, 95% CI: 0.18–0.91, $p = 0.029$, respectively) and OS (HR: 0.48, 95% CI: 0.26–0.87, $p = 0.017$, and HR: 0.42, 95% CI: 0.18–0.97, $p = 0.042$, respectively). To address the immortal time bias, we conducted a landmark analysis at 7 mo from the start of treatment, which confirmed the consistency of our findings for both TTCR (HR: 0.39, 95% CI: 0.18–0.85, $p = 0.018$) and OS (HR: 0.47, 95% CI: 0.25–0.87, $p = 0.016$), as shown in Supplementary Table 5.

Within the ARPI-treated subpopulation, Cox analysis exploring the effect of HTN_T2_CTCAEv5.0 on patient outcomes is shown in Table 3, and Supplementary Tables 6 and 7. Early treatment-related HTN toxicity was a significant prognostic factor in both the UV and the MV Cox analysis for both TTCR (UV: HR: 0.39, 95% CI: 0.14–1.04, $p = 0.052$; MV: HR: 0.30, 95% CI: 0.09–0.95, $p = 0.040$) and OS (UV: HR: 0.31, 95% CI: 0.10–0.99, $p = 0.043$; MV: HR: 0.12, 95% CI: 0.02–0.57, $p = 0.008$).

Kaplan-Meier curves describing TTCR and OS in patients experiencing G2–3 HTN (red line) versus G0–1 HTN (blue line) are shown in Figures 1 and 2, and Supplementary Figure 2.

3.3. Effect of diastolic/systolic changes and antihypertensive therapy on survival outcomes

In the UV Cox analysis, a positive correlation with OS was observed for higher systolic and diastolic BP values at 7 mo from treatment initiation ($p = 0.035$ and $p = 0.078$, respectively; Supplementary Table 8) and in patients with an increased BP (both systolic and diastolic) after 7 mo compared with the time of treatment initiation (>10 mmHg change; systolic, $p = 0.038$; diastolic, $p = 0.086$), as shown in Supplementary Table 2. However, statistical significance was not reached in the MV analyses.

The administration of antihypertensive treatments, whether initiated before or within 7 mo of oncological treatment, did not show a correlation with TTCR or OS. This lack of association persisted even when specifically examining patients treated with ACE inhibitors or ARBs (Supplementary Tables 9 and 10).

3.4. Quality Assessment

The quality and completeness of the real-world data analysis was evaluated considering the ESMO-GROW guidance and self-reported informative score (Supplementary Table 11).

4. Discussion

To the best of our knowledge, this is the first study that explores the predictive and prognostic roles of treatment-related HTN during hormonal treatments in patients with de novo mHSPC.

In our analysis, we found that the development of clinically significant HTN (ie, G2–3 based on CTCAE v5.0) within 7 mo from oncological treatment initiation for mHSPC predicted longer TTCR and was an independent prognostic factor for OS with statistically significant and clinically relevant effect size in both the UV and the MV analysis, in the overall population and among patients treated with ADT plus an ARPI.

We did not detect any significant differences in terms of well-known prognostic factors between the group of patients experiencing G2–3 HTN and those who did not experience it.

We further observed a trend toward longer survival in patients with higher BP values or with an increase of >10 mmHg in either systolic or diastolic BP at 7 mo from treatment start. However, statistical significance was not reached in the MV analysis.

In our analysis, the development of G2–3 HTN within 7 mo of treatment initiation did not correlate with a statistically significant increase in PSA suppression (<0.2 ng/ml) at 7 mo. However, its prognostic value for both TTCR and OS remained significant in the MV Cox analysis even after adjusting for 7-mo PSA levels. This finding strengthens the evidence in support of an independent prognostic role for treatment-related HTN, providing additional information

Table 2 – Patient baseline demographics by HTN toxicity (HTN T2 CTCAE V5.0)

Prognostic variable	All patients (%; *n* = 63)	G0/1 HTN AE patients (*n* = 27; 42.9%)	G2/3 HTN AE patients (*n* = 36; 57.1%)	*p* value
Age (yr), median (range)	77 (min: 50 to max: 94)	80.0 (74–84)	76.0 (63.0–82.2)	0.16[a]
Age (yr)—categorical, *n* (%)				0.23[b]
<70	19 (30.2)	6 (22.2)	13 (36.1)	
≥70	44 (69.8)	21 (77.8)	23 (63.9)	
First-line ARPI, *n* (%)				0.28[b]
ARPI-free regimen	42 (66.7)	16 (59.3)	26 (72.2)	
ARPI treated	21 (33.3)	11 (40.7)	10 (27.8)	
First-line docetaxel, *n* (%)				0.66[b]
0	55 (87.3)	23 (85.2)	32 (88.9)	
1	8 (12.7)	4 (14.8)	4 (11.1)	
First-line ARPI drug, *n* (%)				0.69[b]
Abiraterone	12 (19)	6 (22.2)	6 (16.6)	
Enzalutamide	6 (9.5)	3 (11.1)	3 (8.3)	
Apalutamide	3 (4.7)	2 (7.4)	1 (2.7)	
Number of antihypertensive drugs at oncological treatment start, *n* (%)				0.01[b]
0	35 (55.6)	9 (33.3)	26 (72.2)	
1	15 (23.8)	9 (33.3)	6 (16.6)	
>1	13 (20.6)	9 (33.3)	4 (11.1)	
Introduction of antihypertensive drugs after oncological treatment start, *n* (%)				<0.01[b]
0	30 (47.6)	27 (100)	3 (8.3)	
1	33 (52.4)	0 (0)	33 (91.7)	
Gleason score, *n* (%)				0.21[b]
7	7 (11.1)	3 (11.1)	4 (11.1)	
8	7 (11.1)	1 (3.8)	6 (16.7)	
9	25 (39.7)	10 (37)	15 (41.2)	
10	9 (14.3)	6 (22.2)	3 (8.3)	
NA	15 (23.8)	7 (26)	8 (22.2)	
ISUP grade, *n* (%)				0.24[b]
<5	14 (22.2)	4 (15)	10 (27.8)	
5	34 (54)	16 (59)	18 (50)	
NA	15 (23.8)	7 (26)	8 (22.2)	
CHAARTED criteria, *n* (%)				0.38[b]
Low volume	32 (50.8)	12 (44.4)	20 (55.6)	
High volume	31 (49.2)	15 (55.6)	16 (44.4)	
7-mo PSA level (ng/ml), *n* (%)				0.88[b]
<0.2	10 (16)	4 (14.8)	6 (16.7)	
0.2–4.0	18 (29)	7 (26)	11 (31)	
>4	35 (56)	16 (59)	19 (53)	
TTCR (mo), median (95% CI)	9.3 (7.6–12.2)	6.33 (4.9–10.3)	11.6 (8.8–26.9)	<0.001[c]
TTCR censored patients, *n* (%)	3 (4.8)	1 (3.7)	2 (5.6)	
Follow-up for TTCR censored (mo), median (95% CI)	NA (51.5–NA)	NA (13.6–NA)	NA (51.5–NA)	
OS (mo), median (95% CI)	28.5 (24.5–44.9)	18.5 (13.1–39.5)	42 (26.1–65)	0.017[c]
OS censored patients, *n* (%)	18 (28.6)	7 (26)	11 (30.6)	
Follow-up for OS censored (mo), median (95% CI)	72.5 (50.4–not reached)	50.4 (31.8–not reached)	75 (55.8–not reached)	

ARPI = androgen receptor pathway inhibitor; CI = confidence interval; CTCAE = Common Toxicity Criteria for Adverse Events; G = grade; HTN = hypertension; HTN T2 CTCAE V5.0 = worst hypertension toxicity graded adverse event from T0 to T2 (7 mo from treatment start) according to CTCAE v5.0 for HTN toxicities (accounting also for treatment intervention and pressure variations); ISUP = International Society of Urological Pathology; NA = not available; OS = overall survival; PSA = prostate-specific antigen; TTCR = time from first-line start to castration resistance development.

[a] Wilcoxon test.

[b] Pearson test.

[c] Log rank test.

for prognostic stratification of patients undergoing hormonal treatment, beyond PSA suppression.

The incidence of HTN in mHSPC observed in our study is comparable with the findings of a recent network meta-analysis on the topic [12].

ARPIs are known to cause several cardiovascular side effects, including HTN as one of the most frequent ones [12,23], and their administration in association with ADT showed a significant survival benefit for patients with mHSPC compared with those with ADT monotherapy [22].

Our patient cohort demonstrates comparable survival outcomes to those observed in larger real-world studies of patients with de novo mHSPC during a similar time period [24–26].

Within our cohort, no significant differences were observed in terms of G2–3 HTN rate or survival outcomes (TTCR or OS) when comparing patients treated with ADT plus an ARPI with those receiving ADT alone or in combination with docetaxel. On one side, this could be attributed to the study's relatively modest sample size. However, there

Table 3 – Univariate and multivariate Cox proportional hazard models for TTCR and OS

Prognostic variable	Levels	Univariate analysis HR (95% CI), *p* value	Multivariate analysis HR (95% CI), *p* value
Univariate and multivariate Cox proportional hazard models for TTCR in overall population			
HTN T2 CTCAE V5.0	G0–1	–	–
	G2–3	0.35 (0.20–0.63), $p < 0.001$*	0.41 (0.18–0.91), $p = 0.029$**
Univariate and multivariate Cox proportional hazard models for OS in overall population			
HTN T2 CTCAE V5.0	G0–1	–	–
	G2–3	0.48 (0.26–0.87), $p = 0.017$*	0.42 (0.18–0.97), $p = 0.042$**
Univariate and multivariate Cox proportional hazard models for TTCR in ARPI-treated population			
HTN T2 CTCAE V5.0	G0–1	–	–
	G2–3	0.39 (0.14–1.04), $p = 0.052$*	0.30 (0.09–0.95), $p = 0.040$**
Univariate and multivariate Cox proportional hazard models for OS in ARPI-treated population			
HTN T2 CTCAE V5.0	G0–1	–	–
	G2–3	0.31 (0.10–0.99), $p = 0.043$*	0.12 (0.02–0.57), $p = 0.008$**

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CI = confidence interval; CTCAE = Common Toxicity Criteria for Adverse Events; G = grade; HR = hazard ratio; HTN = hypertension; HTN T2 CTCAE V5.0 = worst hypertension toxicity graded adverse event from T0 to T2 (7 mo from treatment start) according to CTCAE v5.0 for HTN toxicities (accounting also for treatment intervention and pressure variations); ISUP = International Society of Urological Pathology; OS = overall survival; MV = multivariate; PSA = prostate-specific antigen; TTCR = time from first-line start to castration resistance development.
Prognostic variables retained clinically significant a priori (see methods) or statistically significant (*$p \leq 0.10$) as identified from the univariate survival models were included in the multivariate model as covariates together with HTN (HTN T2 CTCAE V5.0).
The *p* value in parenthesis indicates the significance of a variable with more than two categories.
MV model in overall population included the following: age, first line ARPI, antihypertensive drugs at diagnosis, CHAARTED criteria, ISUP grade, PSA level at 7 mo from ADT start, and HTN T2 CTCAE V5.0.
MV model in ARPI-treated population included the following: ARPI type, anti-HTN drugs at diagnosis, PSA level at 7 mo from ADT start, and HTN T2 CTCAE V5.0.
Prognostic variables included in the multivariable model were retained statistically significant if **$p \leq 0.05$.

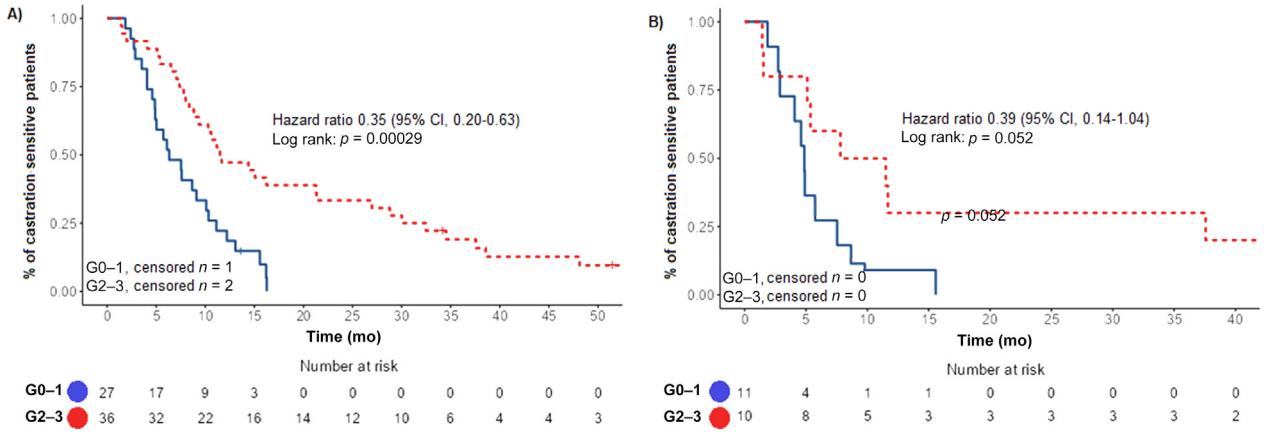

Fig. 1 – Time to castration resistance (TTCR) by hypertension grading at 7 mo from treatment start in the (A) overall population and (B) ARPI-treated population. Kaplan-Meier curves are resulting from the univariate analysis. ARPI = androgen receptor pathway inhibitor; CI = confidence interval.

was a significant baseline imbalance in disease aggressiveness between the ARPI and ADT ± docetaxel treatment groups. The ARPI group had a higher proportion of patients with high-risk PC features, including a greater percentage of cases with International Society of Urological Pathology G >5 (64.3% vs 43.0%) and CHAARTED high-volume disease (61.0% vs 50.0), which may partially explain the observed differences in outcomes between the two groups. Moreover, a recent study by Schoen et al [27] based on extensive US national registries revealed that in patients over 70 yr old with de novo mHSPC, median survival has improved only modestly in recent decades, even with the advent of more potent combination therapies, when compared with their younger counterparts. In our study, where 71% of patients were over 70 yr, survival outcomes align closely with those reported in national registries for this specific elderly population with de novo mHSPC.

It is important to acknowledge that the comparison among treatment groups was not part of our study's endpoints. Moreover, the two groups defined by the development of G2–3 HTN toxicities were well balanced in terms of the treatment received for mHSPC. Finally, first-line ARPI administration was considered in MV analyses for both TTCR and OS in the total population, and a subgroup analysis limited to the ARPI-treated population confirmed a strong association between early HTN and survival outcomes.

Side effect development during oncological treatment for aggressive cancer has been associated with prolonged survival in various other cancers and settings [28,29]. When looking specifically at HTN, its development as a side effect of oncological treatments has been associated with improved survival outcomes in different cohorts [30,31].

On one side, such findings, as well as those from our study, might be explained by individual patients' differences in pharmacokinetics [32], as those with reduced drug metabolism may exhibit heightened drug activity, fostering a higher risk of side effect development but also potentially

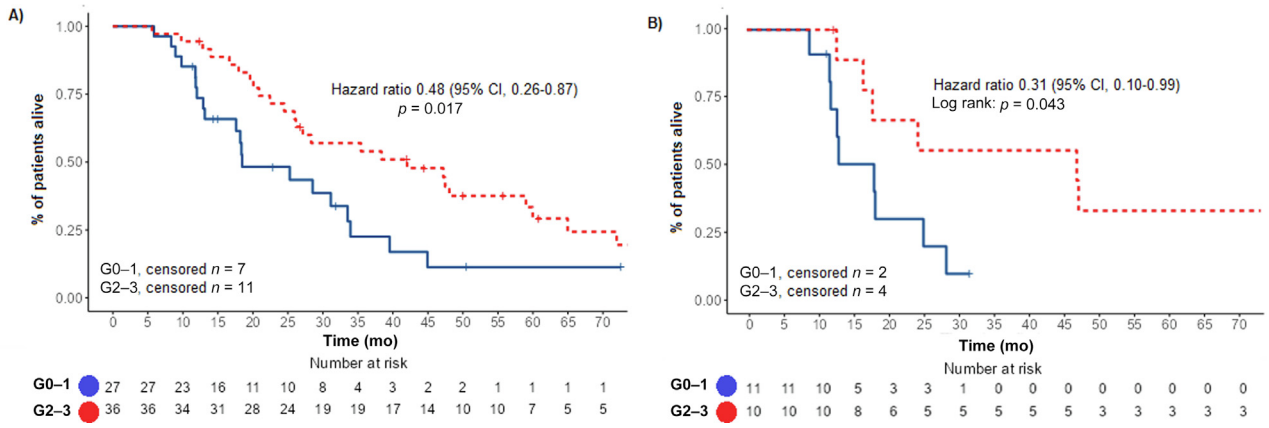

Fig. 2 – Overall survival (OS) by hypertension grading at 7 mo from treatment start in the (A) overall population and (B) ARPI-treated population. Kaplan-Meier curves are resulting from the univariate analysis. ARPI = androgen receptor pathway inhibitor; CI = confidence interval.

showing greater efficacy against cancer. In the PC context, drug dosing is uniform for all mHSPC patients and the activity of ADT is monitored regularly through testosterone blood level measurements. In our exploratory analysis, we found no differences in testosterone levels between the two groups and no association between testosterone levels and survival outcomes. Moreover, our findings were consistent in the overall population independently from first-line ARPI exposure, suggesting the aforementioned interpretation to be less convincing in this context.

Alternative explanations could involve the specific activity of the drug employed for PC treatment, which might induce both HTN toxicity and cancer inhibition through the same mechanism. This could involve an effect on the RAS activity, which impacts PC development and progression, as shown by previous studies [9]. When considering PC treatments, abiraterone acetate inhibits androgen biosynthesis by targeting steroid 17-hydroxylase/17,20-lyase, thereby inducing a decrease in cortisol levels [33]. Meanwhile, ADT can cause endothelial dysfunction [34], possibly impacting nitric oxide production and BP control [35]. It is worth noting that cytokine release also plays an essential role in the genesis of HTN [36], possibly linking cardiovascular toxicity with tumor-related systemic inflammation.

In mHSPC, an alternative explanation relies on interesting preclinical and clinical evidence of nerve fibers constituting a significant component within the PC microenvironment while potentially also playing a major role in its development and progression [4]. In 2013, Magnon et al [6] outlined a PC progression scheme where SNS activation controls initial tumor engraftment, giving way to PNS dominance, which guides the final stages of the disease.

In clinical studies, HTN has been linked to a higher risk of PC development and localized PC progression, and the use of β-blockers has shown an inverse correlation with these outcomes [16,17].

Furthermore, a positive impact of ACE inhibitors and ARBs has been observed on survival outcomes and recurrence among cancer patients [37], including those with genitourinary malignancies [38]. Two studies demonstrated that patients with mCRPC receiving ACE inhibitors or ARBs for HTN at the initiation of ARPI treatment had prolonged survival outcomes compared with those not receiving these medications [14,15].

In our study, conducted in the mHSPC setting, both the prior use and the introduction of antihypertensive medications did not emerge as significantly predictive factors for TTCR or OS. This lack of association persisted even when specifically considering the use of ACE inhibitors or ARBs. The substantial differences in patient demographics, disease stage, and treatment allocation between our study population and those mentioned previously may account for the discrepancies in results. Additionally, the small sample size and retrospective design of all studies involved, including ours, make it difficult to draw definitive conclusions and may prevent the detection of smaller effects of ACE inhibitors or ARBs.

Our observations collectively suggest that, in de novo mHSPC, the early development of HTN under hormonal treatments translates into improved cancer control.

We argue that HTN development during PC treatment may represent not only an adverse effect of the therapeutic regimen, but also a manifestation of diverse biological processes and systemic factors capable of exerting influence on the progression of PC.

Larger studies are needed to further validate HTN toxicity as an independent prognostic factor, while translational research could contribute to a deeper understanding of the complex interplay between PC treatment, HTN-associated systems, and PC cell biology, as well as their impact on the clinical outcomes of PC patients.

4.1. *Limitations and future perspectives*

The main limitations of our study include its retrospective single-center nature, relatively small sample size, and treatment heterogeneity. Moreover, the reported toxicity data were limited to what was recorded during oncological outpatient visits.

To mitigate these issues, we conducted a multivariable analysis considering prognostically relevant clinical vari-

ables and performed subgroup analyses only for variables that reached statistical significance in the overall population. Additionally, HTN_T2_CTCAEv5.0 accounted for the introduction of antihypertensive medication, which was the determining factor in classifying 91.7% of patients with G2–3 HTN toxicity. This approach reduces the bias associated with relying solely on BP readings, which can be influenced by the location and circumstances of their acquisition.

Finally, in our analyses, we did not account for all patient comorbidities, which may limit the generalizability of our findings; however, we attempted to mitigate this bias by including only patients with an Eastern Cooperative Oncology Group performance status of 0–1 and by accounting for pre-existing HTN and patient age.

We underscore the need for larger datasets to validate and extend the insights gained from our study.

5. Conclusions

Our findings reveal, for the first time, that the development of HTN toxicity can be an independent prognostic factor for longer TTCR and OS in de novo mHSPC patients undergoing hormonal treatments. Our results, despite their retrospective nature and the small sample size, should be regarded as hypothesis generating and encouraging for further similar research on larger, multicenter datasets.

Author contributions: Ricardo Pereira Mestre had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Salfi, Pedrani, Merler, Castelo-Branco, Pereira Mestre.
Critical revision of the manuscript for important intellectual content: Merler, Urechie, Testi, Castelo-Branco, Tortola, Turco, Vogl, Gabutti, Gillessen, Pereira Mestre.
Statistical analysis: Pedrani, Ruinelli, Colombo.
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Appendix A. Supplementary data

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