Clinical Study on Thromboembolic Events in Prostate Cancer Patients Receiving Radiation Therapy With or Without Androgen Deprivation Therapy

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AIM: To investigate the incidence of thromboembolic events (TEs) in prostate cancer (PCa) patients receiving radiation therapy with or without androgen deprivation therapy (ADT).

METHODS: A retrospective analysis was conducted on the clinical data of 125 PCa patients admitted to the Henan Provincial People's Hospital from February 2020 to February 2022. Patients were divided into control and observation groups after baseline matching, with the former consisting of 31 patients receiving radiation therapy alone and the latter constituting 31 patients receiving radiation therapy combined with ADT. The incidence rates of TEs, coagulation function indicators (fibrinogen [FIB], D-dimer [D-D], activated partial thromboplastin time [APTT], prothrombin time [PT]), and thrombotic molecular markers (plasminogen-α2-antiplasmin complex [PIC], thrombomodulin [TM], thrombin-antithrombin [TAT] complex, tissue-type plasminogen activator-inhibitor complex [t-PAIC]) were compared between the two groups.

RESULTS: The incidence of deep vein thrombosis (DVT) in the observation group was significantly higher than in the control group ($p < 0.05$). No cases of pulmonary embolism (PE) or arterial embolism (AE) were reported in either group. After treatment, the observation group showed significantly lower PT and APTT levels and significantly higher levels of FIB, D-D, and all thrombotic molecular markers (TAT, PIC, TM, and t-PAIC) compared to the control group ($p < 0.05$).

CONCLUSIONS: Although ADT provides substantial benefits in controlling PCa progression, it significantly increases the risk of TEs, particularly DVT. Physicians should carefully evaluate the thromboembolic risk before initiating ADT in PCa patients and consider prophylactic anticoagulation strategies for risk mitigation.

Keywords: prostate cancer; radiation therapy; androgen deprivation therapy; thromboembolism

Introduction

Prostate cancer (PCa) is the most common malignant tumor of the male genitourinary system. It progresses slowly and is often asymptomatic in the early stages until tumor growth leads to hematuria or urinary tract obstruction [1,2]. PCa is the most common non-skin malignancy among males in the U.S. and contributes to the second highest incidence among all malignancies affecting males worldwide and the fifth highest mortality rate [3,4]. According to the latest global cancer statistics, there are approximately 1,414,259 new cases of PCa diagnosed in 2020 worldwide, accounting for 3.8% cancer-related deaths [5].

The main treatment modalities for PCa in clinical practice include prostatectomy, radiotherapy, and hormone therapy. Radiotherapy remains a cornerstone of PCa management, particularly for localized or locally advanced disease, as it uses ionizing radiation to kill tumor cells while preserving surrounding tissues. However, PCa is a hormone-dependent malignancy, making androgen deprivation therapy (ADT) a common and effective approach to slow disease progression. ADT works by reducing testosterone levels through medical or surgical castration, thereby inhibiting the proliferation of cancer cells [6–8].

While ADT has proven survival benefits, particularly when combined with radiotherapy, it is also associated with several adverse effects [9]. Common side effects include hot flashes, decreased libido, and osteoporosis [10]. However, more concerning is the emerging reports of thromboembolic events (TEs), including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial embolism (AE), in patients undergoing ADT. Studies such as those by Ehdaie *et al.* [11] and Hong *et al.* [12] have reported that ADT may induce a hypercoagulable state, increasing the risk of TE. Proposed mechanisms include testosterone suppression leading to endothelial dysfunction, increased platelet aggregation, and decreased fibrinolysis [13–15].

Despite the growing body of evidence, the exact relationship between ADT and TEs remains controversial. Some studies suggest a significant association between prolonged ADT use and increased thrombotic risk, while others report no clear link [16,17]. Moreover, patient-specific fac-

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tors such as age, cardiovascular history, and comorbidities may further influence TE risk. Given the increasing use of ADT in PCa treatment, understanding its potential thrombotic complications is critical for optimizing patient care.

This study aims to address this knowledge gap by investigating the incidence of TEs in PCa patients receiving radiotherapy with or without ADT. We hypothesized that patients undergoing ADT in combination with radiotherapy would exhibit a higher incidence of TEs compared to those receiving radiotherapy alone. By identifying risk factors and assessing coagulation markers, this study seeks to provide concrete basis for enabling more personalized risk assessment and facilitating management strategies in clinical practice.

Materials and Methods

General Information

A retrospective analysis was conducted on the clinical data of 125 PCa patients admitted to the Henan Provincial People's Hospital between February 2020 and February 2022. The inclusion and exclusion criteria were applied to ensure the homogeneity of the study cohort. The flowchart of this study is presented in Fig. 1.

To minimize confounding bias and ensure comparability between the two groups, propensity score matching was used to balance baseline characteristics. After matching, 31 cases patients were included in each group.

This study was approved by the Ethics Committee of Henan Provincial People's Hospital (Approval No. 201974) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Since this retrospective study utilized anonymized patient data, the requirement for obtaining informed consent was waived.

The inclusion criteria adopted in this study are as follows: (1) having pathologically confirmed PCa; (2) having complete general information; (3) no distant metastasis; (4) no severe immune deficiency; and (5) no mental illness or consciousness disorders.

Patients with the following conditions were excluded from the study: (1) a history of TEs; (2) concurrent orthopedic diseases; (3) comorbidity with other malignancies; (4) concurrent severe heart, liver, lung, or kidney diseases; and (5) concurrent congenital coagulation disorders.

The malignancy pathologically identified in all included patients was adenocarcinoma of the prostate, which is the most common form of PCa. No patients with rare histological subtypes, such as neuroendocrine carcinoma or sarcomatoid carcinoma, were included in this study. Additionally, tumor grade was assessed using the International Society of Urological Pathology (ISUP) grading system [18].

Study Groups and Treatment Procedures

Patients were divided into two groups: control group and observation group. The subjects in the control group received brachytherapy (BT) alone, while those in the observation group received brachytherapy combined with ADT.

Treatment Protocol for the Control Group

Patients in the control group underwent BT using radioactive seeds. The procedure was performed under transrectal ultrasound (TRUS) guidance to ensure accurate seed placement. The steps included the following:

(1) Prostate immobilization was achieved using a prostate stabilizer connected to the operating table.

(2) A stepper and template system was placed close to the perineum, and a rectal probe was connected to the TRUS device (Model No. BK5000, BK Medical, Herlev, Denmark).

(3) Transrectal ultrasound was performed in the lithotomy position, with transverse prostate images obtained from the base to the apex at 5-mm intervals.

(4) Radioactive seeds, including iodine-125 (^{125}I) or palladium-103 (^{103}Pd), were implanted using a MICK200 particle implantation gun (Computerized Medical Systems, St. Louis, MO, USA).

(5) Post-implantation computed tomography (CT) scans were performed within 30 days to confirm D90, defined as the minimum dose covering 90% of the prostate volume. The median D90 dose was 145 Gy for ^{125}I and 125 Gy for ^{103}Pd.

Treatment Protocol for the Observation Group

In addition to brachytherapy, patients in the observation group underwent ADT therapy. The ADT regimen consisted of the following:

(1) Oral bicalutamide (National Pharmaceutical Standard No. H20073877; Zhejiang Haizheng Pharmaceutical Co., Ltd., Taizhou, China) at a dose of 50 mg once daily, starting from day 1 post-surgery.

(2) Luteinizing hormone-releasing hormone (LHRH) agonist injections initiated one week after surgery to achieve medical castration. Patients received monthly or quarterly injections according to the NCCN Guidelines for Prostate Cancer (Version 2024).

The duration of ADT varied among patients, with a minimum treatment duration of 6 months and a maximum of 24 months, depending on disease progression and physician recommendations.

Outcome Measurements and Observational Indicators

The following outcomes and observational indicators were assessed to evaluate the effects of treatment protocols at two primary time points: before treatment and 6 months after treatment initiation. For patients receiving longer ADT regimens, additional measurements were collected at 12-month and 24-month follow-ups, depending on the individual treatment duration.

(1) Thromboembolic events (TEs). The occurrence of DVT, PE, and AE was recorded for both groups. DVT was

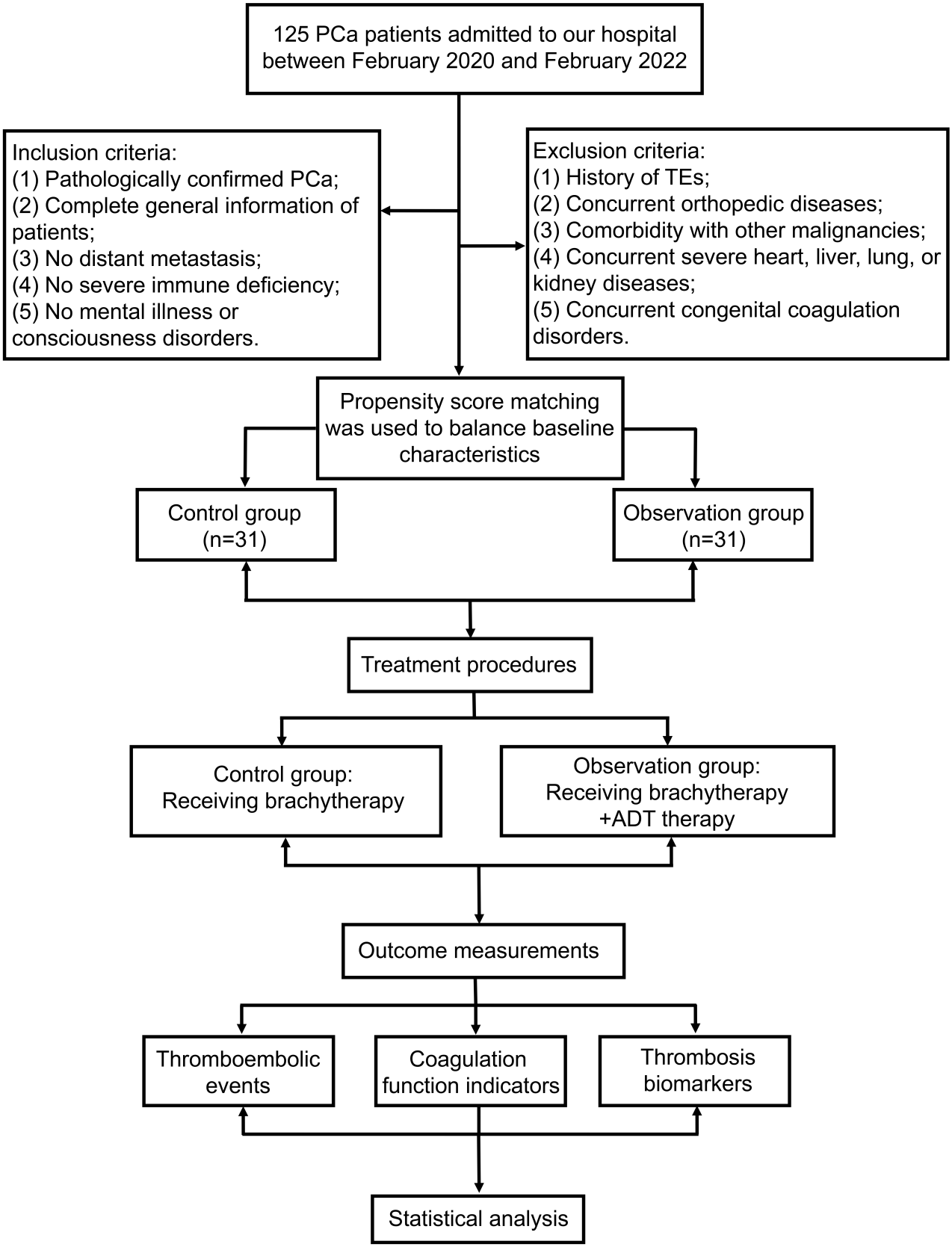

Fig. 1. Flowchart of study design and outcome measurements. PCa, prostate cancer; TEs, thromboembolic events; ADT, androgen deprivation therapy.

diagnosed using compression ultrasonography using a Mindray Resona I9 ultrasound system (No. 20210401, Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). The severity of DVT was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which categorizes adverse events into grade 1 (mild), grade 2 (moderate), and grade 3 (severe) according to clinical symptoms and the extent of venous obstruction [19]. PE was diagnosed using computed tomography pulmonary angiography (CTPA) upon clinical suspicion. CTPA was performed with a Siemens SOMATOM go.Top CT scanner (No. 300521, Siemens Healthineers, Erlangen, Germany). AE was diagnosed based on clinical symptoms such as sudden limb pain, pallor, coldness, and absence of pulse. The timing of TE events was recorded, and implementation of management strategies, including anticoagulation therapy, was documented where applicable.

(2) Coagulation function indicators. Blood samples were collected before treatment and 6 months after treatment. The samples were anticoagulated using 0.109 mol/L sodium citrate solution (1:9 ratio) and processed within 2 h of collection.

Immunoturbidimetric reagent kits were utilized to measure levels of D-dimer (D-D; No. OPBP03, Siemens Healthineers, Erlangen, Germany) and fibrinogen (FIB; No. OQVK11, Siemens Healthineers, Erlangen, Germany) with the aid of a fully automated coagulation analyzer (CA-7000, Siemens Healthineers, Erlangen, Germany). Reagent kits obtained from Siemens Healthineers (Erlangen, Germany) were used to determine prothrombin time (PT; No. OPAT03) and activated partial thromboplastin time (APTT; No. B4224) on the same analyzer. All tests were conducted in adherence to the manufacturer's instructions, with daily quality controls performed to ensure accuracy.

(3) Thrombosis biomarkers. Blood samples were collected before and after treatment and centrifuged at 3000 rpm for 10 min. The following biomarkers were analyzed using a chemiluminescence immunoassay analyzer (FC-302, Guangzhou Wondfo Biotech Co., Ltd., Guangzhou, China): thrombin-antithrombin (TAT) complexes, plasmin-α2-antiplasmin complex (PIC), thrombomodulin (TM), and tissue-type plasminogen activator-inhibitor complex (t-PAIC). The corresponding reagent kits for biomarker detection were provided by Guangzhou Wondfo Biotech Co., Ltd., (Guangzhou, China). All biomarker measurements were conducted following the manufacturer's protocols to ensure consistency and accuracy.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 25.0, IBM, Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test.

For categorical variables, data are expressed as frequencies and percentages. Inter-group comparisons of categorical variables were performed using the chi-square test. When expected frequencies in any cell were less than 5, the corrected chi-square test was used to improve accuracy. For normally distributed continuous variables, data are presented as mean $\pm$ standard deviation (SD), and were analyzed using independent samples *t*-tests.

Propensity score matching was used to minimize baseline differences between the groups, applying a nearest neighbor matching algorithm (1:1 ratio, caliper = 0.02). Eight covariates (age, body mass index [BMI], duration of disease, place of residence, tumor stage, total prostate-specific antigen [tPSA], education level, and tumor grade), which were selected based on their clinical relevance to PCa progression and thromboembolic risk, were included in logistic regression models to calculate propensity scores. All statistical tests were two-tailed, and *p*-values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

Before matching, significant differences were observed between the control group and the observation group in age, disease duration, tPSA, and tumor grade ($p < 0.05$), indicating potential baseline confounding. These baseline differences could potentially introduce bias in the analysis of treatment outcomes. To address this, propensity score matching was applied, resulting in a matched cohort of 31 patients in each group (Table 1).

After matching, the baseline characteristics, including age, place of residence, education level, duration of disease, BMI, tumor stage, tPSA, and tumor grade, were well balanced between the two groups, with no statistically significant differences ($p > 0.05$).

The matching process effectively eliminated the pre-matching differences in age, disease duration, tPSA, and tumor grade, ensuring comparability between the two groups. This balance is crucial for reducing confounding bias and improving the reliability of the analysis of thromboembolic events and coagulation markers.

Comparison of Incidence Rate of Thromboembolic Events

The incidence rates of TEs, including DVT and PE, were analyzed between the observation group and the control group. The results showed that the incidence rate of DVT in the observation group (25.81%) was significantly higher than that in the control group (3.23%). No cases of PE or AE were reported in either group (Table 2).

In the observation group, most DVT cases were classified as grade 2 (moderate) or grade 3 (severe) according to the CTCAE, indicating clinically significant symptoms requiring intervention. These cases were managed primarily with anticoagulation therapy, including low-molecular-weight heparin or direct oral anticoagulants. In contrast, DVT cases in the control group were predominantly grade

Table 1. Comparison of general information between the control and observation groups.

Index		Before matching				After matching			
		Control group (n = 48)	Observation group (n = 77)	χ^2/t	p	Control group (n = 31)	Observation group (n = 31)	χ^2/t	p
Age (years)		62.25 ± 6.23	65.51 ± 6.52	2.7652	0.0066	63.38 ± 6.38	63.89 ± 6.42	0.3137	0.7548
Place of residence (n, %)	Rural areas	25 (52.08)	32 (41.56)	1.3204	0.2505	12 (38.71)	14 (45.16)	0.2650	0.6067
	City	23 (47.92)	45 (58.44)			19 (61.29)	17 (54.84)		
Education level (n, %)	Junior high school and below	12 (25.00)	14 (18.18)	2.7095	0.4386	8 (25.81)	9 (29.03)	1.4112	0.7029
	High school	8 (16.67)	19 (24.68)			6 (19.35)	8 (25.81)		
	College degree	11 (22.92)	23 (29.87)			7 (22.58)	8 (25.81)		
	Bachelor degree or above	17 (35.41)	21 (27.27)			10 (32.26)	6 (19.35)		
Duration of disease (years)		3.52 ± 0.58	3.78 ± 0.69	2.1745	0.0316	3.56 ± 0.35	3.62 ± 0.36	0.6653	0.5084
BMI (kg/m^2)		27.24 ± 2.82	28.17 ± 2.91	1.7584	0.0812	27.83 ± 2.87	27.76 ± 2.83	0.0967	0.9233
Tumor stage (n, %)	T1	13 (27.08)	23 (29.87)	1.1073	0.5749	12 (38.71)	9 (29.03)	0.6943	0.7067
	T2	16 (33.33)	19 (24.68)			8 (25.81)	10 (32.26)		
	T3	19 (39.59)	35 (45.45)			11 (35.48)	12 (38.71)		
tPSA (ng/mL)		12.23 ± 1.25	12.95 ± 1.37	2.9538	0.0038	12.42 ± 1.32	12.39 ± 1.29	0.0905	0.9282
Tumor grade	Grade 1	9 (18.75)	23 (29.87)	6.1458	0.0463	9 (29.03)	11 (35.48)	0.5838	0.7468
	Grade 2	18 (37.50)	14 (18.18)			4 (12.91)	5 (16.13)		
	Grade 3	21 (43.75)	40 (51.95)			18 (58.06)	15 (48.39)		

Abbreviations: BMI, body mass index; tPSA, total prostate-specific antigen.

Table 2. Comparison of incidence rates of thromboembolic events between the control and observation groups.

Group	Deep vein thrombosis	Pulmonary embolism	Arterial embolism	Total thromboembolic events	χ^2	p
Observation group (n = 31)	8 (25.81%)	0 (0.00)	0 (0.00)	8 (25.81%)	4.679	0.031
Control group (n = 31)	1 (3.23%)	0 (0.00)	0 (0.00)	1 (3.23%)		

Note: Data are presented as n (%).

Table 3. Comparison of coagulation function indicators between the control and observation groups.

Group	PT (s)		APTT (s)		FIB (g/L)		D-D (mg/L)	
	BFT	AFT	BFT	AFT	BFT	AFT	BFT	AFT
Observation group (n = 31)	12.62 ± 1.32	11.02 ± 1.02	28.43 ± 1.92	22.63 ± 1.82	3.12 ± 0.26	3.69 ± 0.43	4.52 ± 0.63	7.65 ± 0.92
Control group (n = 31)	12.56 ± 1.22	11.89 ± 1.08	28.58 ± 1.95	23.59 ± 1.78	3.18 ± 0.29	3.45 ± 0.32	4.59 ± 0.65	6.92 ± 0.86
t	0.186	3.261	0.305	2.100	0.858	2.493	0.431	3.227
p	0.853	0.002	0.761	0.040	0.395	0.015	0.668	0.002

Note: Data are expressed as mean ± standard deviation.

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; D-D, D-dimer; BFT, before treatment; AFT, after treatment.

1 (mild), with no severe cases reported. No grade 4 or 5 events were observed in either group.

When considering total incidence of TEs (DVT + PE + AE), the observation group demonstrated a significantly higher incidence compared to the control group ($p < 0.05$). These findings highlight the importance of monitoring and managing thromboembolic risk in patients undergoing ADT, particularly through the use of regular screening and prophylactic anticoagulation in high-risk patients.

Comparison of Coagulation Function Indicators

Before treatment, there was no significant difference in PT, APTT, FIB, and D-D levels between the two groups ($p > 0.05$). After treatment, the observation group showed significant changes in coagulation function indicators compared to the control group (Table 3). Specifically, PT and APTT levels were significantly lower in the observation group, indicating a faster coagulation process, while the FIB and D-D levels were significantly higher, suggesting enhanced coagulation activity and a prothrombotic state ($p < 0.05$).

These results highlighted the prothrombotic effect of ADT, as evidenced by elevated levels of FIB and D-D, indicating heightened thromboembolic risk in the observation group.

Comparison of Thrombotic Molecular Markers

Before treatment, there was no significant difference in thrombotic molecular markers, including TAT, PIC, TM, and t-PAIC, between the two groups ($p > 0.05$). After treatment, the observation group demonstrated significantly higher levels of all thrombotic markers compared to the control group ($p < 0.05$), indicating enhanced coagulation and reduced fibrinolytic activity (Table 4). Specifically, PIC and t-PAIC levels increased more markedly in the observation group, suggesting ongoing fibrinolysis inhibition, while higher TAT levels indicated heightened thrombin generation. These changes reflected a prothrombotic state induced by ADT, further supporting the observed increase in thromboembolic risk.

Discussion

PCa is one of the most common malignancies in older men, with a significant proportion of patients diagnosed at an advanced stage and at risk of developing metastatic complications, including bone metastasis [20,21]. Treatment strategies for PCa often include ADT and radiotherapy, both of which have demonstrated significant benefits in improving overall survival in PCa patients [22–24]. However, ADT is associated with various adverse effects, including metabolic syndrome, cardiovascular complications, and TEs, which necessitate careful risk assessment and monitoring [25]. Malignancies, including PCa, induce a hypercoagulable state that increases the incidence of venous thromboembolism (VTE) in cancer patients. According to Swedish data, the risk of VTE in PCa patients is, on average, 50% higher than in men without PCa [26]. Additionally, ADT has been associated with an increased risk of PE in study [27].

In this study, the incidence of DVT in the observation group (25.81%) was significantly higher than that in the control group (3.23%), while no cases of PE or AE were observed in either group. This finding is consistent with previous research by Ehdaie *et al.* [11] and Hong *et al.* [12], which demonstrated that prolonged exposure to ADT increases the risk of VTE. ADT may promote thrombosis by disrupting the balance of sex hormones, reducing testosterone levels, and inducing a hypercoagulable state through mechanisms such as increased platelet aggregation and decreased fibrinolysis [14,28].

Coagulation function analysis further supported these findings. Patients receiving ADT exhibited elevated levels of FIB and D-D, both of which are markers of enhanced coagulation activity [29]. Elevated D-D levels indicate ongoing

Table 4. Comparison of thrombotic molecular markers between the control and observation groups.

Group	TAT (ng/mL)		PIC (μg/mL)		TM (U/mL)		t-PAIC (ng/mL)	
	BFT	AFT	BFT	AFT	BFT	AFT	BFT	AFT
Observation group (n = 31)	6.88 ± 1.14	8.42 ± 2.21	5.10 ± 1.03	5.99 ± 1.16	7.45 ± 2.14	8.53 ± 2.12	6.32 ± 1.25	7.89 ± 1.36
Control group (n = 31)	6.75 ± 1.12	7.25 ± 2.05	5.24 ± 1.07	5.37 ± 1.12	7.51 ± 2.16	7.38 ± 2.18	6.29 ± 1.23	7.08 ± 1.21
t	0.453	2.161	0.525	2.141	0.110	2.106	0.095	2.477
p	0.652	0.035	0.602	0.036	0.913	0.039	0.924	0.016

Note: Data are expressed as mean ± standard deviation.

Abbreviations: TAT, thrombin-antithrombin; PIC, plasminogen-α2-antiplasmin complex; TM, thrombomodulin; t-PAIC, tissue-type plasminogen activator-inhibitor complex.

fibrinolytic activity and thrombus formation, highlighting the increased thrombotic risk associated with ADT [30]. Additionally, we observed elevated levels of thrombotic molecular markers in the observation group, including TAT, PIC, TM, and t-PAIC. These markers reflect the activation of the coagulation and fibrinolytic systems, endothelial dysfunction, and an increased thrombosis risk, further confirming the prothrombotic state induced by ADT [31,32].

The molecular markers examined in this study play key roles in the coagulation cascade and can provide valuable insights into thromboembolic risk in PCa patients receiving ADT. Higher TAT indicates the activation of thrombin and subsequent coagulation cascade activity [33], while elevated PIC reflects of ongoing fibrinolysis [34]. TM serves as a marker of endothelial dysfunction, which can promote thrombosis by impairing the normal anticoagulant properties of the vascular endothelium [35]. t-PAIC, a marker of fibrinolytic activity, is elevated when fibrinolysis is inhibited [36]. Clinically, these markers can serve as early warning indicators of a hypercoagulable state in patients undergoing ADT, helping clinicians assess thromboembolic risk and adjust treatment plans accordingly. Monitoring these markers during ADT treatment could help prevent serious thrombotic complications and guide timely interventions.

From a mechanistic perspective, testosterone has been shown to play a protective role in cardiovascular health by enhancing fibrinolysis, inhibiting platelet aggregation, and reducing blood viscosity [37,38]. ADT-induced testosterone suppression disrupts these protective effects, leading to increased platelet activation, elevated PAI-1 activity, and decreased fibrinolytic activity, thereby promoting thrombus formation [39]. Our findings were consistent with previous research by Yang *et al*. [40], who reported that decreased serum testosterone levels were associated with an increased 10-year risk of cardiovascular events in younger men. Although no cases of PE or AE were detected in this study, the significantly higher incidence of DVT in the observation group highlights the need for vigilance, especially in patients receiving prolonged ADT. The absence of PE or AE cases may be due to the relatively small sample size and short follow-up period, which is acknowledged as a limitation of this study.

Reducing thrombotic risk in PCa patients undergoing ADT requires a multifaceted approach that includes both pharmacologic and non-pharmacologic interventions. Pharmacologic interventions may involve the use of low-molecular-weight heparin or direct oral anticoagulants in high-risk patients to prevent TEs [41]. Non-pharmacologic strategies should include regular monitoring of coagulation markers (e.g., D-D, FIB) and the use of imaging techniques such as compression ultrasonography to detect early signs of thrombosis [42]. Additionally, lifestyle modifications, such as promoting physical activity, managing weight, and optimizing cardiovascular health, can further reduce thrombotic risk in PCa patients undergoing ADT [43].

Guidelines for clinicians should emphasize the importance of individualized risk assessments before initiating ADT. Patients with pre-existing cardiovascular risk factors or a history of thrombosis should undergo a thorough evaluation, and preventive measures should be considered. Monitoring testosterone levels during ADT and exploring adjunct therapies to mitigate the adverse cardiovascular effects of testosterone suppression may also be beneficial. Future clinical trials should investigate the potential role of direct oral anticoagulants in preventing TEs in PCa patients receiving ADT.

While our study highlights the increased risk of DVT associated with ADT, it has several limitations. First, it is a single-center study with a relatively small sample size, which may limit the generalizability of our findings. Larger, multicenter studies are needed to confirm these results in more diverse populations. Second, the short follow-up period may have limited our ability to detect less common TEs, such as PE and AE. Future studies should incorporate long-term follow-up to capture the full spectrum of thrombotic complications associated with ADT. Third, certain clinically relevant variables, such as cardiovascular disease history and use of anticoagulant medications, were not included in the propensity score matching due to incomplete data. Future research should aim to incorporate a broader range of risk factors to improve the robustness of the matching process. Additionally, our study did not measure serum testosterone levels, limiting our ability to directly link testosterone suppression with thrombotic risk. Including hormonal data in future research could provide

further insights into the mechanisms by which ADT promotes thrombosis and help develop targeted interventions to mitigate thromboembolic risk. Furthermore, this study only included patients with grade 1–3 PCa, yielding findings that have limited applicability to those with higher-grade, more aggressive diseases. Future studies should incorporate a wider range of tumor grades to improve the generalizability of the results and provide a more comprehensive understanding of thromboembolic risks associated with ADT.

Our findings emphasize the importance of monitoring coagulation markers such as D-D and FIB in PCa patients undergoing ADT. Clinicians should carefully evaluate TE risk factors, including age, comorbidities, and baseline coagulation status, when planning ADT. For high-risk patients, prophylactic anticoagulation or regular screening with diagnostic tools such as ultrasound or D-D testing may be considered to mitigate TE risk. Further research is needed to explore the role of direct oral anticoagulants in preventing TEs in this patient population and to assess the long-term cardiovascular impact of ADT-induced testosterone suppression.

Conclusions

While ADT provides substantial benefits in controlling PCa progression, it significantly increases the risk of DVT. This underscores the need for individualized risk assessment and monitoring of TEs during treatment planning. Future research should focus on developing strategies to balance the oncologic benefits of ADT with its potential thrombotic complications, in addition to exploring the role of targeted anticoagulation therapies.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

XJHF: conceptualization, methodology, formal analysis, writing original draft. JZ: formal analysis, data curation; ZQF: conceptualization, data curation, writing, review and editing, project administration, supervision. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Henan Provincial People's Hospital (Approval No. 201974) and conducted in accordance with the principles outlined in the Declaration of Helsinki. Since this retrospective study utilized anonymized patient data, the requirement for obtaining informed consent was waived.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, *et al*. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. The Lancet. Oncology. 2019; 20: 1518–1530. https://doi.org/10.1016/S1470-2045(19)30620-5.

[2] Liu L, Wu F, Ma X, Wang W, Zhang M, Sun Y. The Predictive Value of tPSA, fPSA, fPSA/tPSA Combined with Ultrasound Parameters in Postoperative Gleason Grading of Prostate Cancer. Annali Italiani di Chirurgia. 2024; 95: 1196–1205. https://doi.org/10.62713/aic.3585.

[3] Harryman WL, Hinton JP, Sainz R, Gard JMC, Ryniawec JM, Rogers GC, *et al*. Intermediate risk prostate tumors contain lethal subtypes. Frontiers in Urology. 2025; 4: 1487873.

[4] Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, *et al*. Epidemiology and Prevention of Prostate Cancer. European Urology Oncology. 2021; 4: 877–892. https://doi.org/10.1016/j.euo.2021.09.006.

[5] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a Cancer Journal for Clinicians. 2022; 72: 7–33. https://doi.org/10.3322/caac.21708.

[6] Nandini Devi R, Praveen Kumar Shenoy VP, Ismail I, Avaronnan M. Outcomes and toxicity of oral Fosfestrol in metastatic castration-resistant prostate cancer-a real-world experience. Ecancermedicalscience. 2023; 17: 1589. https://doi.org/10.3332/ecancer.2023.1589.

[7] Zhou L, Song Z, Hu J, Liu L, Hou Y, Zhang X, *et al*. ACSS3 represses prostate cancer progression through downregulating lipid droplet-associated protein PLIN3. Theranostics. 2021; 11: 841–860. https://doi.org/10.7150/thno.49384.

[8] Yu X, Yan J, Li Y, Cheng J, Zheng L, Fu T, *et al*. Inhibition of castration-resistant prostate cancer growth by genistein through suppression of AKR1C3. Food & Nutrition Research. 2023; 67: 10.29219/fnr.v67.9024. https://doi.org/10.29219/fnr.v67.9024.

[9] Forster RB, Engeland A, Kvåle R, Hjellvik V, Bjørge T. Association between medical androgen deprivation therapy and long-term cardiovascular disease and all-cause mortality in nonmetastatic prostate cancer. International Journal of Cancer. 2022; 151: 1109–1119. https://doi.org/10.1002/ijc.34058.

[10] Reyes C, Groshel C, Given R. Androgen Deprivation Therapy. In Trabulsi EJ, Lallas CD, Lizardi-Calvaresi AE (eds.) Chemotherapy and Immunotherapy in Urologic Oncology: A Guide for the Advanced Practice Provider (pp. 77–92). Springer International Publishing: Cham. 2021.

[11] Ehdaie B, Atoria CL, Gupta A, Feifer A, Lowrance WT, Morris MJ, *et al*. Androgen deprivation and thromboembolic events in men with prostate cancer. Cancer. 2012; 118: 3397–3406. https://doi.org/10.1002/cncr.26623.

[12] Hong CS, Chen YC, Ho CH, Hsieh KL, Chen M, Shih JY, *et al*. Association of Gonadotropin-Releasing Hormone Therapies With Venous Thromboembolic Events in Patients With Prostate Cancer: A National Cohort Study. Frontiers in Cardiovascular Medicine. 2022; 9: 794310. https://doi.org/10.3389/fcvm.2022.794310.

[13] Teoh JYC, Tian XY, Wong CYP, Lau CW, Cheng CK, Tang VWL, *et al*. Endothelial dysfunction after androgen deprivation therapy and the possible underlying mechanisms. The Prostate. 2022; 82: 13–25. https://doi.org/10.1002/pros.24244.

[14] Beitzen-Heineke A, Wise DR, Berger JS. Thrombo-inflammation linking androgen suppression with cardiovascular risk in patients with prostate cancer. Cardio-oncology (London, England). 2024; 10: 87. https://doi.org/10.1186/s40959-024-00278-2.

[15] Cintra AR, Linhares BL, Da Rocha EL, Monteiro MMF, Da Trindade KM, Lopes MSR, *et al*. (134) Early Impact of Androgen Deprivation Therapy on Endothelial Function and Metabolic Parameters in Prostate Cancer Patients: A Prospective Study. The Journal of Sexual Medicine. 2024; 21: qdae002. 122.

[16] Nead KT, Boldbaatar N, Yang DD, Sinha S, Nguyen PL. Association of Androgen Deprivation Therapy and Thromboembolic Events: A Systematic Review and Meta-analysis. Urology. 2018; 114: 155–162. https://doi.org/10.1016/j.urology.2017.11.055.

[17] Deka R, Simpson DR, Panizzon MS, Hauger RL, Riviere P, Nalawade V, *et al*. Stroke and thromboembolic events in men with prostate cancer treated with definitive radiation therapy with or without androgen deprivation therapy. Prostate Cancer and Prostatic Diseases. 2019; 22: 600–608. https://doi.org/10.1038/s41391-019-0150-5.

[18] Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer - An ISUP consensus on contemporary grading. APMIS: Acta Pathologica, Microbiologica, et Immunologica Scandinavica. 2016; 124: 433–435. https://doi.org/10.1111/apm.12533.

[19] Eapen RS, Buteau JP, Jackson P, Mitchell C, Oon SF, Alghazo O, *et al*. Administering [(177)Lu]Lu-PSMA-617 Prior to Radical Prostatectomy in Men with High-risk Localised Prostate Cancer (LuTectomy): A Single-centre, Single-arm, Phase 1/2 Study. European urology. 2024; 85: 217–226.

[20] Wang J, Ding C, Lu Y. Reversal effect and mechanism of Beauvericin B on the invasion of prostate cancer cells induced by androgen deprivation. Chinese Journal of Pathophysiology. 2023; 39: 1408–1414. (In Chinese)

[21] Tian H, Zhang Y, Ren J, Wang C, Mou R, Li X, *et al*. Developing a Core Outcome Set for Assessing Clinical Safety Outcomes of Prostate Cancer in Clinical Trials of Traditional Chinese Medicine: Protocol for a Mixed Methods Study. JMIR Research Protocols. 2023; 12: e46794. https://doi.org/10.2196/46794.

[22] Hajdenberg J. ACP Journal Club. Adding radiotherapy to endocrine therapy improved survival in locally advanced prostate cancer. Annals of Internal Medicine. 2009; 150: JC6–6. https://doi.org/10.7326/0003-4819-150-12-200906160-02006.

[23] Imamura J, Ganguly S, Muskara A, Liao RS, Nguyen JK, Weight C, *et al*. Lineage plasticity and treatment resistance in prostate cancer: the intersection of genetics, epigenetics, and evolution. Frontiers in Endocrinology. 2023; 14: 1191311. https://doi.org/10.3389/fendo.2023.1191311.

[24] Zeng S, Guan G, Qin Q, Xie H, Meng Y, Zhao Q. Efficacy and Prognostic Factors of Androgen Deprivation Therapy Combined with Radiation Therapy for Prostate Cancer. Evidence-based Complementary and Alternative Medicine: ECAM. 2021; 2021: 2237069. https://doi.org/10.1155/2021/2237069.

[25] Reiss AB, Vasalani S, Albert J, Drewes W, Li K, Srivastava A, *et al*. The Effect of Androgen Deprivation Therapy on the Cardiovascular System in Advanced Prostate Cancer. Medicina (Kaunas, Lithuania). 2024; 60: 1727. https://doi.org/10.3390/medicina60111727.

[26] Balabanova Y, Farahmand B, Garmo H, Stattin P, Brobert G. Risk of venous thromboembolism in men with prostate cancer compared with men in the general population: a nationwide population-based cohort study in Sweden. BMJ Open. 2022; 12: e055485. https://doi.org/10.1136/bmjopen-2021-055485.

[27] Guo Z, Huang Y, Gong L, Gan S, Chan FL, Gu C, *et al*. Association of androgen deprivation therapy with thromboembolic events in patients with prostate cancer: a systematic review and meta-analysis. Prostate Cancer and Prostatic Diseases. 2018; 21: 451–460. https://doi.org/10.1038/s41391-018-0059-4.

[28] Akakura K, Suzuki H, Ichikawa T, Fujimoto H, Maeda O, Usami M, *et al*. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. Japanese Journal of Clinical Oncology. 2006; 36: 789–793. https://doi.org/10.1093/jjco/hyl115.

[29] Guo J, Gao Y, Gong Z, Dong P, Mao Y, Li F, *et al*. Plasma D-Dimer Level Correlates with Age, Metastasis, Recurrence, Tumor-Node-Metastasis Classification (TNM), and Treatment of Non-Small-Cell Lung Cancer (NSCLC) Patients. BioMed Research International. 2021; 2021: 9623571. https://doi.org/10.1155/2021/9623571.

[30] Nam KW, Kwon HM, Lee YS. Clinical significance of D-dimer levels during acute period in ischemic stroke. Thrombosis Journal. 2023; 21: 55. https://doi.org/10.1186/s12959-023-00496-1.

[31] Muniyan S, Xi L, Datta K, Das A, Teply BA, Batra SK, *et al*. Cardiovascular risks and toxicity - The Achilles heel of androgen deprivation therapy in prostate cancer patients. Biochimica et Biophysica Acta. Reviews on Cancer. 2020; 1874: 188383. https://doi.org/10.1016/j.bbcan.2020.188383.

[32] Zhou K, Zhang J, Zheng ZR, Zhou YZ, Zhou X, Wang LD, *et al*. Diagnostic and Prognostic Value of TAT, PIC, TM, and t-PAIC in Malignant Tumor Patients With Venous Thrombosis. Clinical and Applied Thrombosis/hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2020; 26: 1076029620971041. https://doi.org/10.1177/1076029620971041.

[33] Song P, Xie J, Li W, Zhang X, Sun Z, You C. Effect of plasma thrombin-antithrombin complex on ischemic stroke: a systematic review and meta-analysis. Systematic Reviews. 2023; 12: 17. https://doi.org/10.1186/s13643-023-02174-9.

[34] Chen Q, Shou W, Wu W, Wang G, Cui W. Performance evaluation of thrombomodulin, thrombin-antithrombin complex, plasmin-α2-antiplasmin complex, and t-PA: PAI-1 complex. Journal of Clinical Laboratory Analysis. 2019; 33: e22913. https://doi.org/10.1002/jcla.22913.

[35] Suzuki K. Thrombomodulin: A key regulator of intravascular blood coagulation, fibrinolysis, and inflammation, and a treatment for disseminated intravascular coagulation. Proceedings of the Japan Academy. Series B, Physical and Biological Sciences. 2025; 101: 75–97. https://doi.org/10.2183/pjab.101.006.

[36] Feng YF, Su MY, Xu HX, Zhang SZ, Ma YF, Chen HP. Plasma tissue plasminogen activator-inhibitor complex levels in acute myocardial infarction patients: an observational study. BMC Cardiovascular Disorders. 2024; 24: 722. https://doi.org/10.1186/s12872-024-04406-9.

[37] Elagizi A, Köhler TS, Lavie CJ. Testosterone and Cardiovascular Health. Mayo Clinic Proceedings. 2018; 93: 83–100. https://doi.org/10.1016/j.mayocp.2017.11.006.

[38] Alhawiti NM, Alqahtani SA. Chronic testosterone administration improves cardiac contractility and has a beneficial effect on the haemostatic system by enhancing fibrinolytic activity and inducing hypocoagulation in healthy rats. Archives of Physiology and Biochemistry. 2019; 125: 311–320. https://doi.org/10.1080/13813455.2018.1458244.

[39] Morrow GB, Whyte CS, Mutch NJ. Functional plasminogen activator inhibitor 1 is retained on the activated platelet membrane following platelet activation. Haematologica. 2020; 105: 2824–2833.

https://doi.org/10.3324/haematol.2019.230367.

[40] Yang HH, Tu SK, Chen HH, Hung CL, Kuo CW, Tsan YT, *et al*. Testosterone Level Reduction Increases the 10-Year Risk of Cardiovascular Diseases: A Retrospective Cohort Study in a Taiwanese Young Male Population. Frontiers in Cardiovascular Medicine. 2022; 9: 869251. https://doi.org/10.3389/fcvm.2022.869251.

[41] Zhou H, Chen TT, Ye LL, Ma JJ, Zhang JH. Efficacy and safety of direct oral anticoagulants versus low-molecular-weight heparin for thromboprophylaxis after cancer surgery: a systematic review and meta-analysis. World Journal of Surgical Oncology. 2024; 22: 69. https://doi.org/10.1186/s12957-024-03341-5.

[42] Zheng F, Chen X, Huang J, Lin C. Study on risk factors of preoperative deep vein thrombosis in patients with lower limb fractures and construction and validation of risk prediction nomogram model. BMC Surgery. 2024; 24: 408. https://doi.org/10.1186/s12893-024-02718-3.

[43] Edmunds K, Tuffaha H, Scuffham P, Galvão DA, Newton RU. The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer. 2020; 28: 5661–5671. https://doi.org/10.1007/s00520-020-05637-0.