

## Original Article

# Risk factors for cognitive dysfunction in prostate cancer patients undergoing androgen deprivation therapy: a retrospective study

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**Abstract:** Objective: To evaluate the clinical efficacy of endocrine therapy for prostate cancer and analyze risk factors for treatment-related cognitive dysfunction. Methods: A retrospective study was conducted involving 100 prostate cancer patients receiving endocrine therapy and 100 non-recipients. Quality of life, urinary symptoms, and cognitive function were assessed. Patients were categorized into cognitive dysfunction (n=38) and non-dysfunction (n=62) groups based on post-treatment assessment. Univariate and multivariate analyses were used to identify influencing factors, and a predictive model was developed. Results: The endocrine therapy group showed significantly better quality of life and urinary symptom scores (all  $P < 0.05$ ), though the 5-year survival rate was lower than that of the control group (72.4% vs 82.7%). Cognitive impairment incidence was 38%. Risk factors included older age, lower education, lower Montreal Cognitive Assessment (MoCA) scores, and higher Prostate-Specific Antigen (PSA), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS) scores (all  $P < 0.05$ ). Multivariate analysis confirmed MoCA, age, SAS, and SDS as independent predictors. The predictive model demonstrated high discriminative ability (AUC=0.903). Conclusion: Endocrine therapy improves quality of life and urinary symptoms in prostate cancer patients but is associated with cognitive dysfunction. A model incorporating MoCA, age, and psychological scores effectively predicts cognitive impairment risk, enabling targeted intervention.

**Keywords:** Prostate cancer, endocrine therapy, cognitive dysfunction, predictive model, risk factors

## Introduction

Prostate cancer has emerged as a main threat to men's health globally [1, 2]. Data from international cancer research institutions indicate a marked increase in its incidence over recent decades, particularly in developed nations [3, 4]. Evolving male lifestyles - characterized by rising rates of obesity, sedentary habits, high-fat and high-sugar diets, coupled with the aging of society - have further contributed to its status as a major public health concern [5]. Current clinical management of prostate cancer often involves multimodal therapy. While surgery and radiotherapy remain first-line options for early-stage disease, active endocrine therapy (androgen deprivation therapy, ADT) post-surgery has proven effective in suppressing tumor recur-

rence and improving outcomes, thereby establishing itself as a cornerstone of treatment [6].

However, the benefits of ADT are accompanied by well-documented adverse effects that worsen patients' quality of life. These include osteoporosis, anemia, alterations in sexual characteristics, and metabolic disturbances such as dysglycemia, all of which have been extensively studied [7, 8]. More recently, growing evidence from European and American studies suggests that ADT may also impair cognitive function - affecting memory, executive function, and spatial ability - in patients undergoing long-term treatment [9]. Despite these concerning findings, cognitive side effects remain under-recognized in clinical practice, and relevant studies in Chinese populations are notably scarce. Most

existing research has been conducted in western countries, leaving a critical gap in understanding how these effects manifest in Asian demographic, genetic, and cultural settings. Given these observations, we assessed whether there was a correlation between endocrine therapy for prostate cancer and cognitive function in the region, in order to provide evidence to fill this gap.

### Materials and methods

#### *Case selection*

Data of 100 patients with prostate cancer admitted to our hospital between January 2018 and March 2025 were retrospectively collected. All these patients received endocrine therapy. In addition, 100 cases who did not receive endocrine therapy was selected during the same period as the control group. The control group consisted of patients who did not receive endocrine therapy, and their inclusion and exclusion criteria were the same as those who received endocrine therapy. The study was approved by the ethics committee of MAANSHAN People's Hospital (No: 2025kyll: 20251020).

#### *Inclusion criteria*

1. Patients who completed treatment at our hospital and had postoperative pathologic confirmation of prostate cancer; 2. Age under 80 years; 3. Patients who had received endocrine therapy for at least six months; 4. Patients with complete data.

#### *Exclusion criteria*

1. Patients with radiographically confirmed distant organ metastasis; 2. Patients with recurrent prostate cancer; 3. Patients with a history of psychiatric illness; 4. Patients with significant anxiety or depression; 5. Patients with a history of alcohol dependence.

#### *Treatment*

Both the observation and control groups underwent radical prostatectomy. Under general anesthesia, patients were placed in the Trendelenburg position. After routine disinfection and catheterization, pneumoperitoneum was established in the abdominal wall through a

laparoscopic approach, and the laparoscope and operating instruments were inserted. The retroperitoneum was opened to expose the bilateral seminal vesicles. Careful dissection was performed posteriorly to avoid rectal injury. The bladder neck was dissected anteriorly. The prostate was further dissected, and the prostatic pedicle vessels were clipped and transected. The pelvic fascia and disseminator fascia were further dissected to the prostate apex. The posterior urethra was adequately preserved before the prostate apex was transected. An end-to-end anastomosis of the urethra and bladder neck was performed, and a triple-lumen catheter was placed to adjust the tension of the anastomosis. Pelvic lymph nodes and adipose tissue were also removed. During the operation, the bladder anastomosis was inspected with water injection to ensure leakage. Hemostasis was thoroughly achieved, and the peritoneal and abdominal wall incisions were sutured sequentially to complete the operation. For endocrine therapy, patients received 50 mg of bicalutamide (Zhejiang Hisun Pharmaceutical Co., Ltd., National Medical Approval No. H20073877, 50 mg) orally daily and 3.6 mg of goserelin (AstraZeneca, National Medical Approval No. J20100126, 3.6 mg/vial) via subcutaneous injection monthly.

#### *Data collection*

General patient information, including baseline characteristics, treatment methods, and cognitive dysfunction assessment tools, was obtained through electronic system review. Cognitive dysfunction assessment tools. All subjects completed neuropsychological background tests, including the Montreal Cognitive Assessment (MoCA), the Self-Rating Anxiety Scale, and the Self-Rating Depression Scale. The total score of the MoCA is 30 points, and a total score of less than 26 points is considered to be cognitive impairment [10].

Prostate symptom improvement was assessed before and after treatment using the International Prostate Symptom Score (IPSS), ranging from 0 to 35 points. The higher the score, the more severe the symptoms [11].

Quality of life score: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) scoring scale was used to assess the patient's quality of life [12].

**Table 1.** Comparison of baseline data of patients in the two groups

Group	Endocrine therapy group	No-endocrine therapy	t/ $\chi^2$ value	P-value
Age	58.5±5.8	57.9±5.9	0.716	0.475
BMI	22.3±2.3	22.8±2.4	-1.506	0.134
Course of disease	10.5±2.2	10.8±2.3	-0.943	0.347
Prostate volume	35.2±2.1	34.9±2.0	1.029	0.305
Hypertension	26	22	0.446	0.504
Diabetes	11	9	0.224	0.636
Smoking history	18	15	0.367	0.545
Drinking history	47	54	0.98	0.322

**Table 2.** Comparison of perioperative data between the two groups of patients

Group	Endocrine therapy group	No-endocrine therapy	t/ $\chi^2$ value	P-value
Operation time	181.8±15.8	177.9±16.0	1.785	0.076
Lymph node dissection time	62.3±8.5	63.0±8.3	-0.617	0.538
Intraoperative blood loss	255.6±18.6	260.8±19.0	-1.924	0.056
Pathological margin positive rate	42 (42%)	30 (30%)	3.186	0.074

### Observation indicators

Primary outcome: Changes in quality of life and International Prostate Symptom Score (IPSS) scores before and after treatment in the two groups, as well as the incidence of cognitive impairment in the observation group and its influencing factors.

Secondary outcome measures: Comparison of treatment-related complications and survival rates between the two groups.

### Statistical analysis

Statistical analyses were performed using SPSS 23.0. Continuous variables following a normal distribution were presented as mean  $\pm$  standard deviation and were compared using independent or paired samples t-tests, as appropriate. Categorical variables are expressed as n (%) and were analyzed with the chi-square test. Independent risk factors for cognitive dysfunction were identified through multivariate logistic regression, and a predictive model was constructed and evaluated using receiver operating characteristic (ROC) curve analysis. Survival outcomes were assessed with Kaplan-Meier curves and the log-rank test. A two-sided *P*-value < 0.05 was considered significant.

### Results

#### Comparison of baseline data between the two groups of prostate cancer patients

The two groups were comparable in baseline characteristics including age, BMI, disease duration, prostate volume, and comorbidities (all *P* > 0.05; **Table 1**).

#### Comparison of surgical data between the two groups

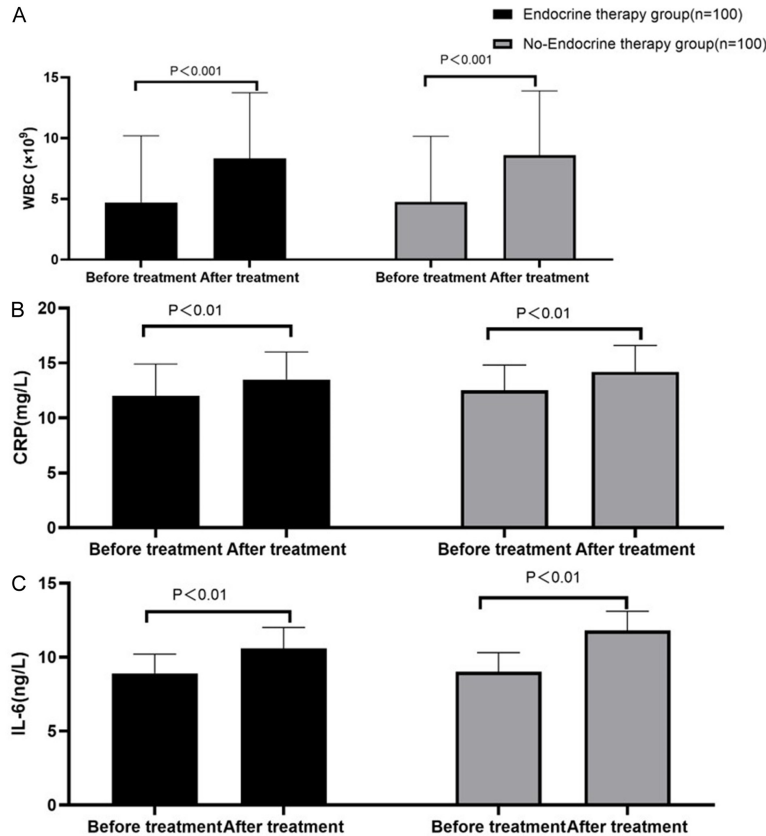
No significant differences were observed between the two groups regarding operation time, lymph node dissection time, intraoperative bleeding, or pathologic margin positive rate (all *P* > 0.05; **Table 2**).

#### Comparison of inflammatory factors between the two groups of patients

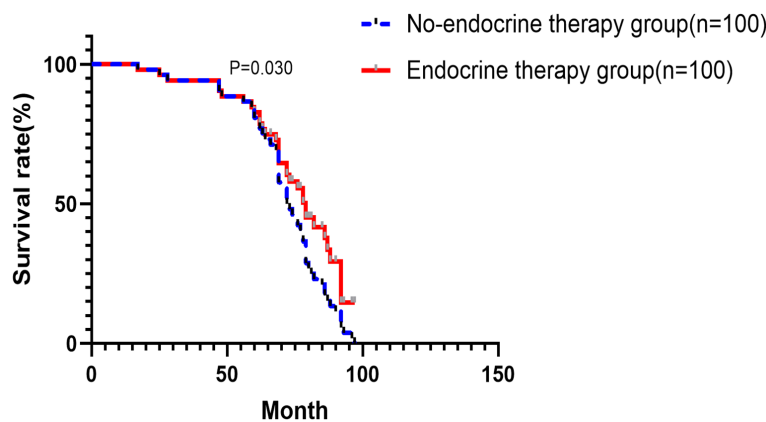
No significant differences in inflammatory factors were found between the two groups before or after treatment (all *P* > 0.05; **Figure 1**).

#### Comparison of survival rates between the two groups of prostate cancer patients

Patients receiving endocrine therapy had a significantly higher 5-year survival rate than those who did not (82.7% vs. 72.4%, *P*=0.030; **Figure 2**).



**Figure 1.** Comparison of inflammatory factors between the two groups before and after treatment. A. Serum leukocyte count; B. Serum IL-6 level; C. Serum CRP level. \*P < 0.05 vs. before treatment.



**Figure 2.** Comparison of survival rates between the two groups of prostate patients.

## Comparison of prostate-related indicators

Before treatment, no significant differences were found in PSA, IPSS, or SF-36 scores between the two groups ( $P > 0.05$ ). After treat-

ment, both groups showed significant improvement in all indicators, with the endocrine therapy group demonstrating superior outcomes compared to the non-endocrine therapy group ( $P < 0.05$ ) (**Figure 3**).

## Incidence of cognitive dysfunction in the endocrine therapy group

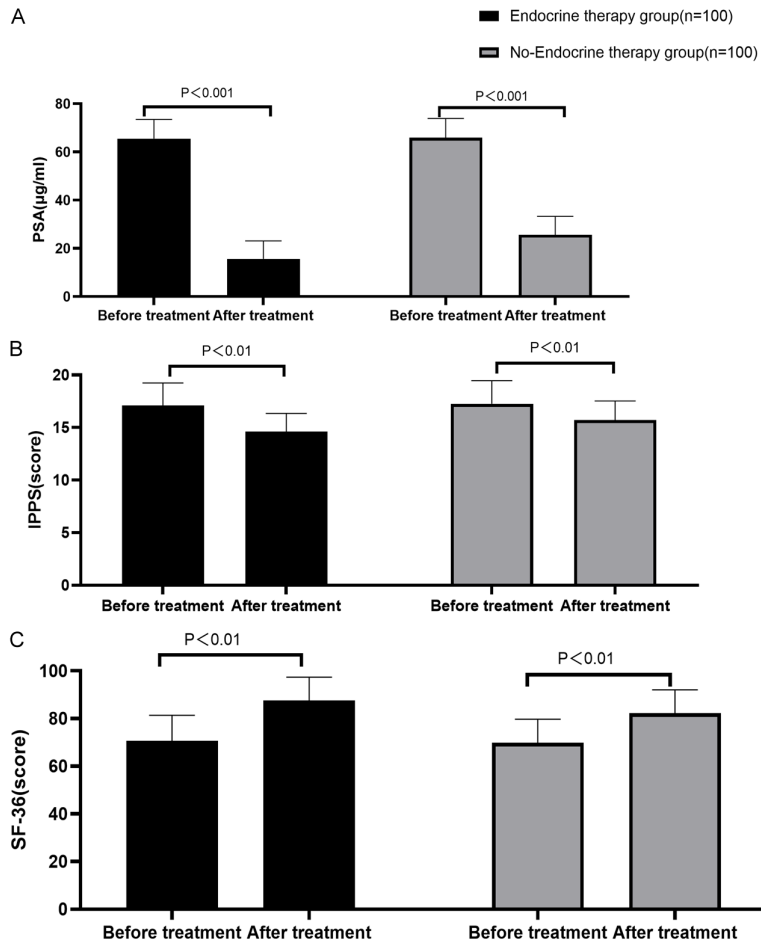
Of the patients receiving endocrine therapy, 38 (38%) developed cognitive dysfunction. No significant differences were observed between the dysfunction and non-dysfunction groups regarding BMI, disease duration, prostate volume, smoking/alcohol history, or comorbidities ( $P > 0.05$ ). However, patients with cognitive dysfunction were significantly older and had higher PSA levels ( $P < 0.05$ ) (**Table 3**).

## Psychological function scores

Patients with cognitive dysfunction had significantly fewer years of education, lower MoCA scores, and higher SAS and SDS scores compared to those without dysfunction (all  $P < 0.05$ ) (**Figure 4**).

## Independent influencing factors for cognitive dysfunction

Multivariate logistic regression identified MoCA score (OR=0.807, 95% CI: 0.724-0.899), age (OR=1.085, 95% CI: 1.032-1.141), years of education (OR=0.882, 95% CI: 0.817-0.953), SAS score (OR=1.110, 95% CI: 1.045-1.179), and SDS score (OR=1.095, 95% CI: 1.028-1.167) as independent influencing factors. Age, SAS, and SDS scores were risk factors, while MoCA score and education years were protective factors (**Tables 4, 5**).



**Figure 3.** Comparison of prostate-related indicators between patients receiving and not receiving endocrine therapy. A. PSA (Prostate-Specific Antigen) levels; B. IPSS (International Prostate Symptom Score) scores; C. SF-36 (Medical Outcomes Study 36-Item Short Form Health Survey) scores.

#### Performance and validation of the predictive model

The predictive model (incorporating MoCA, age, education, SAS, and SDS scores) demonstrated excellent discriminative ability (AUC=0.903, 95% CI: 0.865-0.941). Good model fit was confirmed by the Hosmer-Lemeshow test ( $\chi^2=6.837$ ,  $P=0.728$ ), and calibration analysis showed strong agreement between predicted and observed risks ( $R^2=0.947$ ) (Figure 5).

#### Discussion

Prostate cancer ranks among the most prevalent malignancies in men globally, with incidence markedly increasing with age [13-15]. Adjuvant endocrine therapy following radical prostatectomy can effectively suppress tumor

progression and improve clinical outcomes [16, 17]. While offering survival benefits, endocrine therapy introduces side effects - among which alterations in sexual characteristics have been extensively documented, whereas its impact on cognitive function remains relatively underexplored [18]. Given that cognitive impairment can substantially reduce treatment compliance and thus compromise clinical outcomes, it is clinically significant to evaluate cognitive dysfunction associated with endocrine therapy, identify influencing factors, and establish predictive models to mitigate its incidence and improve prognosis [19-21]. Therefore, systematic investigation into endocrine therapy-related cognitive impairment represents a crucial step toward optimizing comprehensive prostate cancer management while preserving patients' quality of life.

Our findings confirm that post-operative endocrine therapy not only improves survival and prostate-specific markers but

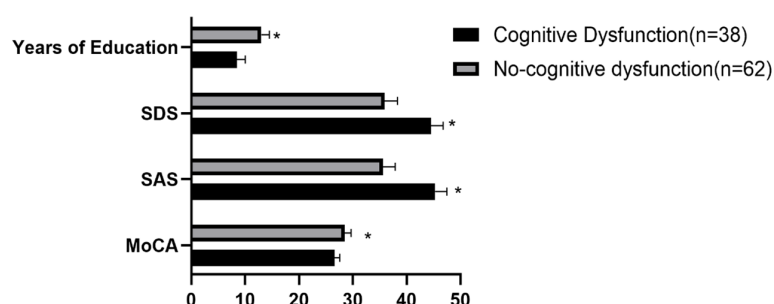
also enhances quality of life, underscoring its therapeutic value. Several mechanisms may underlie these benefits: First, adjuvant endocrine therapy can eliminate minimal residual lesions locally or systemically, thereby reducing recurrence risk. Second, it directly induces apoptosis and inhibits proliferation of hormone-sensitive prostate cancer cells by suppressing androgen levels or blocking receptor binding [22]. Moreover, endocrine therapy may delay the onset of castration-resistant prostate cancer by increasing the sensitivity of metastatic foci to subsequent androgen deprivation. It also modulates tumor-associated immune activity and suppresses angiogenesis, aligning with earlier reports [23, 24]. Additionally, by effectively lowering PSA levels and improving urological symptoms, endocrine therapy alleviates anxiety related to biochemical recurrence and



**Table 3.** Comparison of baseline data between patients with cognitive dysfunction and those without cognitive dysfunction

Group	Cognitive impairment group (n=38)	Group without cognitive impairment (n=62)	t/ $\chi^2$ value	P value
Age	67.4 $\pm$ 5.2	60.5 $\pm$ 5.2	6.459	< 0.001
BMI	22.52 $\pm$ 2.54	23.30 $\pm$ 2.61	-1.551	0.124
Course of disease	11.51 $\pm$ 2.13	11.83 $\pm$ 2.42	-0.649	0.518
Prostate volume	34.83 $\pm$ 2.02	34.44 $\pm$ 2.23	0.923	0.326
Hypertension	11	15	0.964	0.326
Diabetes	5	6	0.003	0.959
Smoking history	5	13	1.499	0.221
Drinking history	13	33	0.003	0.954
PSA levels	65.78 $\pm$ 5.62	60.12 $\pm$ 4.93	5.304	< 0.001

BMI: Body mass index; PSA: Prostate-Specific Antigen.

**Figure 4.** Comparison of baseline education levels and psychological function between patients with and without cognitive impairment. \*P < 0.05 between groups.**Table 4.** Variable assignment

Variable	Copy
Age	Original value
MoCA Scoring	Original value
PSA levels	Original value
Education level	Original value
SAS scoring	Original value
SDS scoring	Original value

MoCA: Montreal Cognitive Assessment; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

reduces symptom-related interference in daily life, thereby promoting quality of life [23, 24]. These multidimensional benefits - spanning from cellular-level tumor control to patient-reported outcomes - collectively validate the integral role of endocrine therapy in the contemporary management of prostate cancer [22-24].

Consistent with prior studies, our results indicate that endocrine therapy is associated with

cognitive impairment, which may be attributed to several pathophysiologic processes [25]. Testosterone can be aromatized into estradiol in the central nervous system, where estrogen supports neuroplasticity, synaptic integrity, and hippocampal function. Androgen deprivation may thus deprive the brain of this protective effect. Furthermore, endocrine therapy can induce insulin resistance, dys-

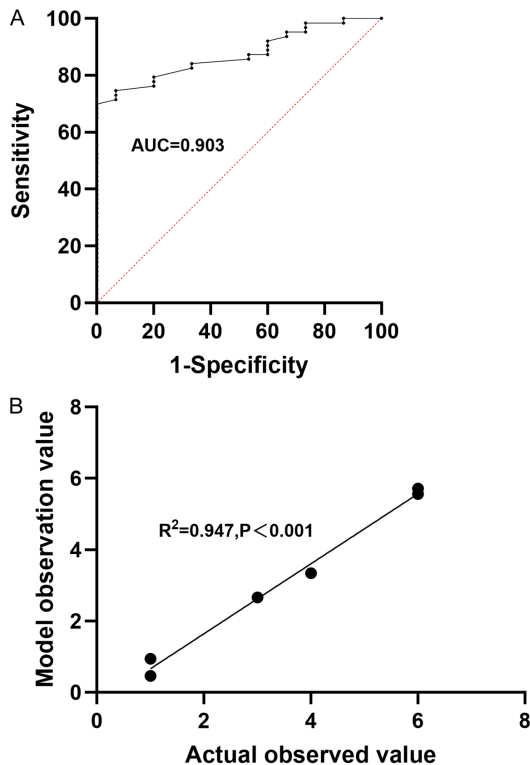
lipidemia, and weight change, contributing to metabolic syndrome and cerebrovascular damage [26]. Altered cerebral perfusion has also been proposed as a mechanism, in line with existing literature [25]. Collectively, these mechanisms - encompassing hormonal, metabolic, and vascular pathways - provide a plausible biological basis for the observed cognitive deficits following endocrine therapy, highlighting the need for integrated clinical management that addresses both oncological and neurocognitive outcomes [25, 26].

Through multivariate analysis, we identified MoCA score, age, education level, SAS, and SDS scores as independent predictors of cognitive dysfunction, and the constructed model demonstrated good performance. These factors reflect the concept of “cognitive reserve”: patients with lower baseline MoCA scores, advanced age, or fewer years of education possess diminished neural resilience. Aging involves natural neuronal decline and reduced synaptic plasticity, while limited education con-

**Table 5.** Multivariate analysis of cognitive dysfunction in the endocrine therapy group

Factor	$\beta$	Wald $\chi^2$	OR	95% CI	P
Age (per 1-year increase)	0.082	10.52	1.085	1.032-1.141	0.001
MoCA score (per 1-point increase)	-0.215	15.89	0.807	0.724-0.899	< 0.001
SAS score (per 1-point increase)	0.104	12.35	1.110	1.045-1.179	< 0.001
SDS score (per 1-point increase)	0.091	8.01	1.095	1.028-1.167	0.005
Years of education (per 1-year increase)	-0.125	11.73	0.882	0.817-0.953	0.001

MoCA: Montreal Cognitive Assessment; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.



**Figure 5.** Development and validation of a predictive model for cognitive dysfunction in patients undergoing endocrine therapy. A: Predictive efficacy of the cognitive dysfunction model in the endocrine therapy group; B: Model calibration plot.

strains the ability to form compensatory neural networks [27]. Low baseline MoCA suggests pre-existing subclinical impairment. In such vulnerable individuals, endocrine therapy may exacerbate central inflammatory responses, perturb cerebral glucose metabolism, and undercut estrogen-mediated hippocampal protection - tipping these patients into overt cognitive decline. Similarly, elevated SAS and SDS scores - reflecting anxiety and depression - can impair attention, executive function, and memory, while chronic activation of the stress axis ele-

vates cortisol, which exerts neurotoxic effects on the hippocampus [28, 29]. Endocrine therapy may worsen mood symptoms, creating a vicious cycle that amplifies cognitive deficits. In summary, the identified predictors delineate a high-risk profile characterized by low cognitive reserve and emotional vulnerability, in whom endocrine therapy may act as a “second hit” that disrupts homeostatic balance and unmasks latent cognitive impairment - highlighting the need for pre-treatment screening and tailored monitoring strategies in this susceptible subgroup.

This study has several limitations. First, its retrospective, single-center design may have introduced selection and information bias. Second, the limited sample size may have affected the generalizability of conclusions. Third, the absence of external validation limited the reliability of the predictive model, warranting further verification. Moreover, the cognitive assessment tool used did not evaluate verbal memory, processing speed, or executive function in detail, restricting insight into domain-specific deficits. Finally, the relatively short follow-up period precluded analysis of long-term cognitive trajectories and their effect on quality of life - a focus for future studies.

In summary, this study reaffirmed the clinical benefits of endocrine therapy in prostate cancer while highlighting its association with cognitive impairment. We identified key risk factors - including baseline cognitive status, age, education, and psychological distress - and developed a well-performing predictive model. These findings underscore the need for integrated cognitive and mental health monitoring in patients undergoing endocrine therapy, facilitating individualized risk assessment and early intervention.

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## Disclosure of conflict of interest

None.

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