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Urology Research

Focus and Scope

Urology Research publishes peer-reviewed research articles across basic, translational, and clinical Urology medicine. The Journal covers all aspects of Urology medicine (full listing below) with an emphasis on studies that challenge the status quo of treatments and practices in Urology care or facilitate the translation of scientific advances into the clinic as new therapies or diagnostic tools.

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The Impact of Combined Traditional Chinese Medicine and Finasteride on the Morphology of the Posterior Urethra in Patients with Benign Prostatic Hyperplasia

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Abstract: *Objective:* This study aims to evaluate the effects of a six-month treatment combining traditional Chinese medicine derived from oilseed rape pollen with finasteride on the mean curvature of the prostatic urethra (UMCP), urethral length of the prostate (ULP), thickness of the prostate and bladder neck (TPBN), testosterone/estradiol ratio (T/E), and International Prostate Symptom Score (IPSS) in patients with benign prostatic hyperplasia (BPH). The goal is to determine whether the oilseed rape pollen preparation enhances the alleviation of urinary obstruction symptoms. *Methods:* Sixty-two patients with urinary obstruction due to prostatic hyperplasia, who met the study's inclusion criteria and were treated at Tongxiang Municipal Hospital of Traditional Chinese Medicine, were selected. They were randomly divided into two groups: one receiving the oilseed rape pollen preparation in combination with finasteride and the other receiving finasteride alone. Relevant indicators were measured and recorded at baseline and six months after treatment. Data were analyzed using appropriate statistical methods. *Results:* The combined therapy with oilseed rape pollen did not significantly reduce the mean curvature of the prostatic urethra but effectively delayed its further increase. Patients in the experimental group showed a greater increase in urethral length compared to the control group. Additionally, the thickening of the prostate and bladder neck was significantly inhibited in the experimental group. Both groups exhibited a significant increase in T/E, with no notable difference between them. IPSS scores improved significantly in both groups, with a more pronounced reduction in the experimental group. *Conclusion:* The combination of oilseed rape pollen-based traditional Chinese medicine and finasteride for BPH treatment can help improve posterior prostatic urethral morphology, regulate hormone levels, and enhance symptom relief. This combined approach provides notable benefits for patients with BPH.

Keywords: Benign prostatic hyperplasia; Urethral morphology; Oilseed rape pollen preparation

Online publication: April 2, 2025

1. Introduction

Benign prostatic hyperplasia (BPH) is a common and frequently occurring disease that affects the quality of life of elderly men and the final dignity of terminal patients in the context of the increasingly serious aging population in China ^[1]. BPH is a disease with extremely complex pathological mechanisms. The currently known pathological mechanisms include sex hormones, polypeptide growth factors, inflammatory signal transduction, apoptosis, oxidative stress, and smooth muscle, and their mechanisms in the pathogenesis have not been fully elucidated ^[2]. Literature indicates that sex hormones and their receptors, as well as oxidative stress, play important roles in the pathogenesis of BPH ^[3-5] and are currently important keys to clinical drug treatment. Among them, the representative Western medicine is 5 α -reductase inhibitor, and the representative Chinese medicine is oilseed rape pollen preparation. Their common goal is to control the continued proliferation of the gland to improve the disease prognosis. Currently, the main treatment methods for improving urination symptoms in BPH patients are drug therapy and transurethral surgery. Some patients cannot undergo surgical treatment due to advanced age, bedridden status, or multiple underlying diseases and can only solve urination problems through bladder fistulization. This method changes the natural urination path, causes great pain, and affects patients' self-esteem. Therefore, it is crucial to select effective drug treatment to improve prognosis as early and quickly as possible.

2. Materials and methods

2.1. Clinical data

We selected 62 patients for follow-up observation from those with benign prostatic hyperplasia who visited Tongxiang Traditional Chinese Medicine Hospital from January 2022 to February 2023, based on the inclusion and exclusion criteria designed for the experiment.

Inclusion criteria: (a) $Q_{\max} \leq 15$ ml/s in both measurements when urine volume is ≥ 200 ml; (b) IPSS score ≥ 20 (severe); (c) Prostate-specific antigen (PSA) < 10 ng/ml, and those with PSA between 4–10 ng/ml have been diagnosed with BPH by prostate biopsy 10 weeks later; (d) Patients and their families explicitly refuse surgery and request medical treatment.

Exclusion criteria: (a) Patients with PSA between 4–10 ng/ml but cannot rule out prostate cancer; (b) Presence of other conditions that affect the detection of testosterone, estradiol, PSA, and other indicators; (c) Patients with contraindications for MRI examination; (d) Patients who develop acute urinary retention and urgently need other treatment methods; (e) Recurrence after prostate hyperplasia surgery; (f) Diseases caused by various reasons such as urethral stenosis, bladder, bladder neck, etc., that affect the interpretation of results; (g) Patients who have used other Chinese medicine preparations before enrollment; (h) Patients who are randomly included in the experimental group and indicate that they cannot adhere to Chinese medicine treatment for six months.

Withdrawal criteria: (a) Patients who experience adverse drug reactions, develop other serious diseases during medication, and need to withdraw from the experiment; (b) Patients who change the treatment plan, refuse to take, or miss multiple administrations of the treatment drug; (c) Patients who request to terminate the experiment or are lost to follow-up and automatically withdrawn.

2.2. Experimental methods

The control group received treatment with 5 α -reductase inhibitor finasteride for BPH. The experimental group received combined therapy with a representative Chinese herbal medicine, oilseed rape pollen preparation, on the basis of the control group's treatment. Patients were randomly assigned to the two groups using a random number

table. This experimental design strictly followed the ethical review requirements of the ethics committee.

The control group received oral administration of 5 α -reductase inhibitor finasteride at a dose of 5 mg once daily. The experimental group received additional oral administration of oilseed rape pollen preparation at a dose of 2 g three times daily on the basis of the control group's treatment. The treatment duration was six months for both groups.

2.3. Observation and follow-up indicators

This study innovatively observed three types of indicators: morphological changes in the prostatic urethra (including the mean curvature of the prostatic urethra [UMCP], urethral length of the prostate [ULP], thickness of the prostate and bladder neck [TPBN]), changes in testosterone/estradiol levels (T/E), and improvement in urinary symptoms assessed using the International Prostate Symptom Score (IPSS). These indicators reflected the effects of combined therapy on prostate stromal cell proliferation, androgen/estrogen balance, and symptom improvement, respectively.

Among these indicators, the thickness of the prostate at the bladder neck was measured as a line segment representing the anteroposterior diameter of the prostate at the bladder neck on MRI images in the sagittal plane of the urethral bladder entrance axis. The urethral length of the prostate was defined as the length from the bladder urethral opening to the tip of the prostate on MRI images in the sagittal plane of the urethral axis. The urethral mean curvature of the prostate was calculated as the ratio of the angle between the tangents at both ends of the prostatic urethra to the arc length of the urethra. Morphological indicators were observed for changes after six months of treatment.

2.4. Statistical methods

Data were processed and charted using GraphPad Prism9 statistical software. All measurement data passed the normality test. One-way ANOVA was used for statistical analysis, with a significance level of $\alpha = 0.05$. A *P*-value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Morphological changes in the prostatic urethra

There was no significant difference in the average UMCP between the experimental group and the control group at the beginning of the experiment. The curvature in the experimental group remained at the initial level after six months of treatment. The curvature in the control group increased at the end of the experiment compared to the beginning, and that of the experimental group at six months, with *P*-values of 0.0053 and 0.0033, respectively, indicating significant differences. There was no significant difference in the ULP between the experimental group and the control group at the beginning of the experiment. The experimental group showed a slight increase in ULP after six months of medication compared to the beginning ($P = 0.0390$), while the control group showed no significant difference. There was no significant difference in the TPBN between the experimental group and the control group at the beginning of the experiment. The TPBN in the experimental group remained stable after six months of medication. The control group showed a significant increase in this value ($P = 0.0004$), resulting in a significant difference from the experimental group after six months ($P < 0.0001$) (**Table 1**) (**Figures 1 to 3**).

3.2. Changes in androgen/estrogen levels

Testosterone/estradiol levels were consistent and showed no significant difference between the experimental group and the control group at the beginning of the experiment. Both groups showed significant increases in T/E levels before and after the experiment, with mean differences of -53.15 and -45.41, respectively, and *P*-values less than 0.0001. There was no significant difference in the results between the experimental group and the control group after six months of medication (Table 1) (Figure 4).

3.3. Improvement in urination symptoms indicated by the International Prostate Symptom Score (IPSS)

The experimental group and the control group maintained good consistency in IPSS at the beginning of the experiment. Both groups showed significant improvement in IPSS within the group at the end of the experiment (*P* < 0.0001), and the improvement in IPSS in the experimental group was significantly better than that in the control group (*P* = 0.0011) (Table 1) (Figure 5).

Table 1. One-way ANOVA results of the efficacy of finasteride alone or combined with oilseed rape pollen in the treatment of BPH

	UMCP		ULP		TPBN		T/E		IPSS	
	Mean diff.	<i>P</i>	Mean diff.	<i>P</i>	Mean diff.	<i>P</i>	Mean diff.	<i>P</i>	Mean diff.	<i>P</i>
Experimental group before vs six months after treatment	0.1219	0.1756	-8.109	0.0390	4.593	0.0516	-53.15	< 0.0001	13.42	< 0.0001
Control group before vs six months after treatment	-0.1883	0.0053	4.137	0.9614	-7.161	0.0004	-45.41	< 0.0001	11.26	< 0.0001
Experimental group vs control group before treatment	0.1140	0.2475	-1.342	> 0.9999	0.2948	> 0.9999	-8.732	> 0.9999	-0.2258	> 0.9999
Experimental group vs control group six months after treatment	-0.1962	0.0033	10.90	0.0018	-11.46	< 0.0001	-0.9903	> 0.9999	-2.387	0.0011

4. Discussion and conclusion

Based on the analysis of the results in this study, it is concluded that the combination therapy of finasteride and traditional Chinese medicine with oilseed rape pollen as the main ingredient can relieve obstructive urination symptoms faster than monotherapy in the treatment of BPH.

Combination therapy more effectively preserves the morphology of the prostatic urethra without significant changes. In the finasteride monotherapy group, the curvature of the prostatic urethra continued to increase, and the thickness of the prostate-bladder junction also showed progressive thickening. Although combination therapy did not demonstrate a significant advantage in terms of hormonal level changes, it provided a clear benefit in improving IPSS scores, which reflect symptom relief. According to the fundamental principles of fluid dynamics, when fluid passes through a channel with greater curvature, resistance is significantly higher compared to a channel with less curvature. In this study, the combination therapy group exhibited a delayed progression of prostatic urethral curvature compared to the monotherapy group, which may be a key morphological factor

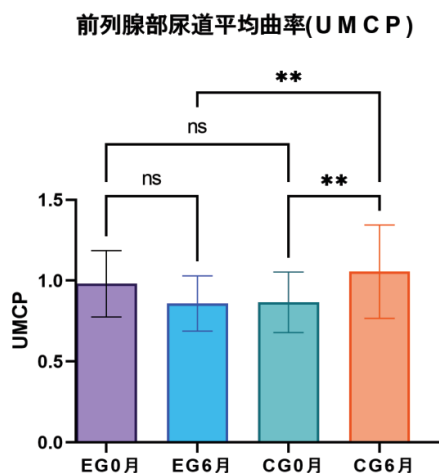


Figure 1. UMCP before and after six months of treatment in the experimental group (EG) and the control group (CG)

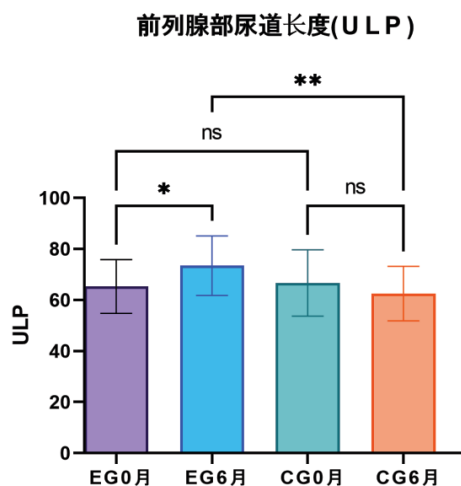


Figure 2. ULP before and after six months of treatment in the experimental group (EG) and the control group (CG)

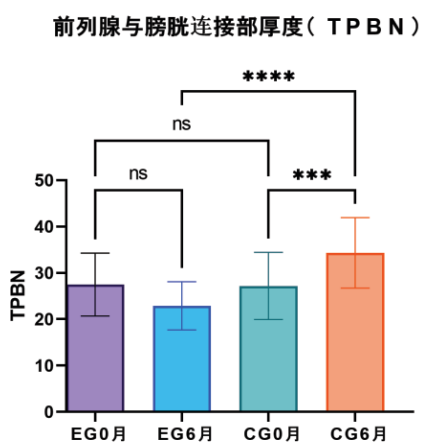


Figure 3. TPBN before and after six months of treatment in the experimental group (EG) and the control group (CG)

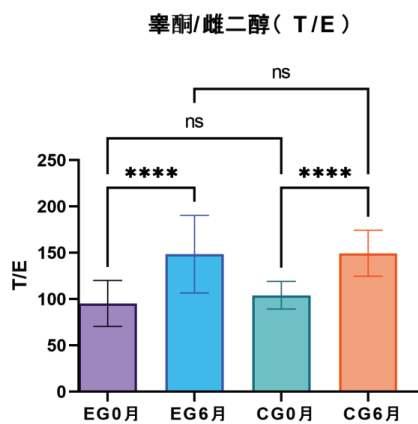


Figure 4. T/E before and after six months of treatment in the experimental group (EG) and the control group (CG)

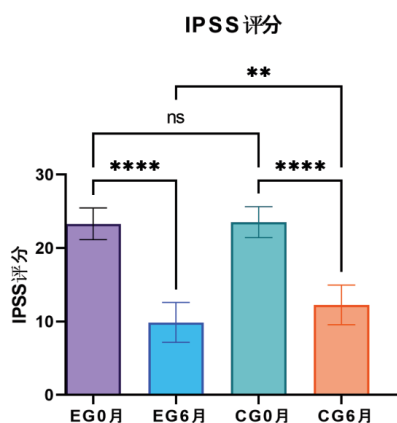


Figure 5. IPSS before and after six months of treatment in the experimental group (EG) and the control group (CG)

contributing to the improvement or stabilization of urination difficulty symptoms. Additionally, regarding the thickness of the prostate-bladder junction, the combination therapy group demonstrated the ability to stabilize prostate morphology and prevent further progression, whereas the monotherapy group continued to show thickening at the bladder entrance.

This study selected prostate thickness at the bladder-prostate junction as an indicator of urine flow obstruction. During the trial, it was observed that some patients with severe urination difficulties exhibited significant enlargement of the anterior lobe of the prostate, even protruding above the internal urethral orifice, resembling a dam obstructing the urethral opening. Others displayed pronounced hyperplasia of the posterior lobe, which pushed the urethra forward from behind the internal urethral orifice or blocked the urethral opening in a similar manner. These morphological changes appeared to exacerbate urination difficulties. Since measuring only the thickness of the anterior or posterior lobe or the extent of protrusion into the bladder would not provide a comprehensive assessment, this study instead examined prostate thickness at the urethral orifice to reflect the overall progression of prostate hyperplasia. The experimental results aligned with observed changes in urethral curvature and IPSS scores, suggesting that this indicator holds potential for further investigation in subsequent observational studies.

Another morphological indicator selected in this experiment is the length of the prostatic urethra. According to the general principles of fluid dynamics, the longer a fluid travels, the greater the resistance it encounters, leading to increased velocity loss. However, experimental results indicate that combination therapy actually prolonged the prostatic urethral length, whereas the monotherapy group better preserved the original local urethral length. Upon further discussion, we found that morphological indicators such as total urethral length, minimum urethral width, and the length and number of stenotic segments have a greater impact on urine flow than the velocity loss associated with prostatic urethral length. The total urethral length may be unrelated to, or even inversely correlated with, changes in prostatic urethral length. Additionally, the urethra is a muscular tube, with the spongy segment being particularly variable. Its thickness and length are challenging to measure accurately, and the velocity loss caused by urethral length may be negligible compared to other obstructive factors. Rather than analyzing every individual fluid dynamics factor separately, it may be more practical to focus on significant and easily measurable physical parameters that can effectively explain real-world phenomena.

This experiment also recorded changes in the testosterone-to-estradiol (T/E) ratio. The data indicated that although both testosterone and estradiol levels decreased, estrogen declined at a faster rate, leading to an increase in the T/E ratio. No significant difference in efficacy was observed between the experimental and control groups in this regard. This indicator was selected because, while individual hormone baselines vary significantly, their ratios tend to remain relatively stable. Existing research has demonstrated that androgens are the primary drivers of prostatic acinar hyperplasia, with most estrogens being converted from testosterone or androstenedione. Finasteride acts as an enzyme inhibitor in the metabolic pathway that converts testosterone into the more potent dihydrotestosterone (DHT). By reducing DHT levels in both the bloodstream and the prostate, finasteride helps slow the progression of hyperplasia. It is well established that finasteride does not affect circulating estradiol levels. Short-term use of the drug can increase testosterone levels in the prostate without disrupting the pituitary-testicular axis.

The Chinese herbal medicine oilseed rape pollen extract contains long-chain fatty acids, flavonoids, alkaloids, and cerebrosides—compounds known for their effectiveness in combating BPH^[6-8]. Among these, flavonoid extracts are the primary active substances responsible for the antioxidant properties of oilseed rape pollen, while

long-chain fatty acids exhibit significant activity in hormone regulation and anti-inflammatory effects ^[9,10]. Additionally, oilseed rape pollen polysaccharides exert antitumor effects by increasing the expression of IL-2 and TNF- α mRNA in the body ^[11]. Some discrepancies were observed between the hormonal changes recorded in this experiment and established theories. We speculate that clinical tests may not precisely measure circulating and tissue levels of DHT, testosterone (T), estradiol (E), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and other hormones related to the gonadal axis as accurately as laboratory-based analyses. A comprehensive assessment of hormonal fluctuations across various stages of the gonadal axis is necessary to accurately determine the positive or negative feedback effects of these drugs and to elucidate their pharmacological mechanisms convincingly.

Finally, both the experimental and control groups showed significant improvements in IPSS, with high patient satisfaction reported for both treatments. The combined medication group outperformed the control group, demonstrating that combination therapy can more effectively and rapidly alleviate urinary discomfort. This approach offers hope for continued conservative treatment in patients with severe obstruction who are ineligible for surgery. By alleviating the distress associated with bladder fistulization, it also enhances patients' quality of life.

Finally, after discussion, this experiment identified certain deficiencies in research indicators, providing a valuable foundation for more detailed studies on the relationship between posterior urethral morphology and urinary tract obstruction. The findings highlight the need for further research to exclude physical variables related to fluid mechanics, which are complex, highly variable, difficult to measure accurately, and influenced by multiple interfering factors in the human body. Additionally, the study should account for functional and molecular biological factors, such as bladder contractility, the gonadal hormone axis, and target organ hormone concentrations, as they may impact experimental results. Moreover, the small sample size limits the ability to fully capture the true pharmacological effects. Therefore, further research should incorporate regular observations on a smaller scale to refine and expand the research indicators.

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Disclosure statement

The authors declare no conflict of interest

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Evaluation of the Application Value of Combined Detection of BTA, BTA stat, NMP22, and Survivin in the Diagnosis of Urothelial Carcinoma

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Abstract: *Objective:* To explore the diagnostic value of combined detection of bladder tumor antigen (BTA), bladder tumor antigen-associated test (BTA stat), nuclear matrix protein 22 (NMP22), and survivin in urothelial carcinoma. *Methods:* Sixty patients with urothelial carcinoma admitted from January 2024 to January 2025 were selected as the observation group for this study, and 60 healthy individuals were selected as the control group. BTA, BTA stat, NMP22, and survivin tests were performed on both groups, respectively. The test results were analyzed to evaluate the diagnostic value of combined detection. *Results:* The levels of BTA, BTA stat, NMP22, and survivin in the observation group were higher than those in the control group ($P < 0.05$). The specificity, sensitivity, and accuracy of combined detection of BTA, BTA stat, NMP22, and survivin were higher than those of single detection methods ($P < 0.05$). There were significant differences in the positive rates of BTA, BTA stat, NMP22, and survivin among patients with different tumor diameters, tumor numbers, pathological grades, clinical stages, and lymph node metastasis status ($P < 0.05$). *Conclusion:* In the diagnosis of urothelial carcinoma, the combined detection of BTA, BTA stat, NMP22, and survivin has high diagnostic value and can be promoted and applied in clinical diagnosis.

Keywords: BTA; BTA stat; NMP22; Survivin; Urothelial carcinoma

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1. Introduction

Bladder urothelial carcinoma, as a malignant tumor, is relatively common in the urinary system. Early symptomatic treatment can timely inhibit tumor progression, reduce patient mortality, and effectively extend the patient's life cycle. Currently, there is no clear conclusion on the specific pathogenesis of urothelial carcinoma, and it is generally believed to be closely related to the genomic stability of the bladder mucosal epithelium. Cystoscopy is the gold standard for diagnosing urothelial carcinoma, which can provide patients with accurate diagnosis

results. However, this method is an invasive examination that may induce urinary tract infections during testing, and some patients have relatively low acceptance, which limits its clinical application. Although urine exfoliative cytology does not cause trauma to patients during the examination, its sensitivity is related to tumor grading. If the patient has a poorly differentiated tumor, the diagnostic sensitivity is relatively poor, and it is easily affected by other lesions, resulting in certain interference with the final diagnosis. Therefore, a more scientific diagnostic method is needed to provide timely and effective treatment for patients. Bladder tumor antigen (BTA), bladder tumor antigen-associated test (BTA stat), nuclear matrix protein 22 (NMP22), and survivin are all tumor markers for diagnosing urothelial carcinoma, and there are relatively few clinical reports on the effect of their combined detection. Based on this, this article mainly explores the application value of combined detection of BTA, BTA stat, NMP22, and survivin in the diagnosis of urothelial carcinoma.

2. Materials and methods

2.1. General information

60 cases of urothelial carcinoma treated from January 2024 to January 2025 were selected for the study, and 60 healthy individuals who underwent physical examination during the same period were selected as controls. The patients and healthy individuals were assigned to the observation group and the control group, respectively. The control group had a male-to-female ratio of 34:26, with ages ranging from 38 to 76 years old, and an average age of 57.28 ± 7.31 years old. The observation group had a male-to-female ratio of 36:24, with ages ranging from 39 to 75 years old, and an average age of 57.26 ± 7.29 years old. There was no significant difference in general information between the two groups ($P > 0.05$). Inclusion criteria: (1) The observation group was diagnosed with urothelial carcinoma by pathological examination; (2) None of them had immune system diseases or blood system diseases; (3) The clinical data of the two groups were recorded in detail and preserved intact; (4) The key points of this experiment were fully informed to the enrolled personnel, and informed consent forms were signed. Exclusion criteria: (1) History of other tumors; (2) Acute cardio-cerebrovascular diseases; (3) No urine samples were collected for examination; (4) Those who withdrew due to personal factors and had missing data.

2.2. Methods

After enrollment, 100 ml of the first clean urine in the morning was collected from the subjects. The urine was centrifuged at 1000 r/min for 15 minutes, and the supernatant was taken for testing. BTA detection: The level of BTA in urine was detected by enzyme-linked immunosorbent assay. The detection instrument was an automatic multi-functional microplate reader^[1-3], and the detection operation needed to be carried out step by step according to the requirements of the kit instructions. BTA stat detection: The immune chromatographic assay kit was used for detection. Five drops of fresh urine were dropped into the BTA stat test paper sample addition hole using a sterile dropper. When the urine flowed through the detection area, if there was a bladder tumor-related antigen in the urine sample, it would promote the formation of antigen conjugates. After 5 minutes, a red band appeared in the test area, which was positive. If no red band appeared, it was negative. If this red band was not observed in the control area, it meant that the rapid kit was faulty. NMP22 detection: Enzyme-linked immunosorbent assay was used for detection, using anti-NMP22-digoxin conjugate and digoxin-horseradish peroxidase display system, enzyme-linked 490 nm wavelength measurement and calculation, and drawing a straight-line regression graph

to calculate the antigen concentration of the urine sample. Survivin detection: Detected by streptomycin avidin-peroxidase method, subject to the requirements of the instruction manual. Survivin was selected as a ready-to-use rabbit anti-human polyclonal antibody. The sections were dewaxed, hydrated, and soaked in 3% hydrogen peroxide-microwave-methanol at room temperature for 10 minutes to inactivate hydrogen peroxide enzyme activity. Microwave antigen was continuously repaired for 20 minutes, with a pH of 7.6, and EDTA antigen repair solution was used as the repair solution. After being cooled to room temperature, the primary antibody was added and incubated in a wet box at 4°C overnight. On the second day, the samples were washed three times with TBS, followed by the addition of a biotin-labeled secondary antibody and incubation at room temperature for 10 minutes. Horseradish peroxidase-labeled streptavidin was then added and incubated at room temperature for another 10 minutes. DAB color development was performed for 2 minutes, followed by hematoxylin counterstaining for 2 minutes. The samples were then dehydrated, rendered transparent, sealed, and observed under a microscope. To avoid affecting the staining quality, each section should use positive tissue as a positive control, and use phosphate buffered saline instead of the primary antibody as a negative control. The test results were reviewed by two pathologists with rich experience in reading films using a double-blind method. If there was a disagreement, the results would be discussed and negotiated. The final result was that the cell nucleus or cytoplasm appeared brown, which could be judged as positive.

2.3. Observation indicators

The levels of BTA, BTA stat, NMP22, and survivin were compared between the two groups to analyze the diagnostic value of single and combined detection of BTA, BTA stat, NMP22, and survivin for urothelial carcinoma. The positive rates of BTA, BTA stat, NMP22, and survivin in patients with different clinical features were also compared.

2.4. Statistical methods

SPSS 26.0 was used to process the research data, and *t*-test and chi-square test were used to measure the data (mean \pm standard deviation [SD]) and count data (%). When the research result was $P < 0.05$, it indicated that the research was statistically significant.

3. Results

3.1. Comparison of BTA, BTA stat, NMP22, and survivin levels between the two groups

There were significant differences in the levels of BTA, BTA stat, NMP22, and survivin between the two groups ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of BTA, BTA stat, NMP22, and survivin between the two groups (mean \pm SD)

Group	BTA (ng·mL ⁻¹)	BTA stat (ng·mL ⁻¹)	NMP22 (U·mL ⁻¹)	Survivin (%)
Observation group (<i>n</i> = 60)	23.16 \pm 8.81	26.37 \pm 5.53	5.02 \pm 1.78	22.32 \pm 2.39
Control group (<i>n</i> = 60)	9.82 \pm 5.26	18.21 \pm 4.46	2.16 \pm 0.91	13.58 \pm 1.25
<i>t</i> value	10.070	8.897	11.082	25.101
<i>P</i> value	< 0.001	< 0.001	< 0.001	< 0.001

3.2. Comparison of diagnostic effectiveness of BTA, BTA stat, NMP22, and survivin for urothelial carcinoma

Significant differences ($P < 0.05$) were observed in sensitivity, specificity, and accuracy between combined detection and single detection. See **Table 2**.

Table 2. Diagnostic effectiveness of BTA, BTA stat, NMP22, survivin, and combined detection for urothelial carcinoma [n (%)]

Group	Sensitivity	Specificity	Accuracy
BTA	83.33% (50/60)	78.33% (47/60)	81.67% (49/60)
BTA stat	85.00% (51/60)	76.67% (46/60)	80.00% (48/60)
NMP22	86.67% (52/60)	80.00% (48/60)	83.33% (50/60)
Survivin	86.67% (52/60)	81.67% (49/60)	85.00% (51/60)
Combined detection	98.33% (59/60)	95.00% (57/60)	98.33%(59/60)
χ^2 value ₁	0.063/0.261/0.261/8.107	0.048/0.051/0.208/7.212	0.054/0.058/0.240/9.259
P value ₁	0.803/0.609/0.609/0.004	0.827/0.822/0.648/0.007	0.817/0.810/0.624/0.002
χ^2 value ₂	0.069/0.069/6.982	0.196/0.455/8.292	0.223/0.520/10.439
P value ₂	0.794/0.794/0.008	0.658/0.500/0.004	0.637/0.471/0.001
χ^2 value ₃	0.000/5.886	0.054/6.171	0.063/8.107
P value ₃	1.000/0.015	0.817/0.013	0.803/0.004
χ^2 value ₄	5.886	5.175	6.982
P value ₄	0.015	0.023	0.008

Note: χ^2_1 tests the comparison between BTA and BTA stat, NMP22, survivin, and combined detection; χ^2_2 tests the comparison between BTA stat and NMP22, survivin, and combined detection; χ^2_3 tests the comparison between NMP22 and survivin, and combined detection; χ^2_4 tests the comparison between survivin and combined detection.

3.3. Comparing the positive rates of BTA, BTA stat, NMP22, and survivin among patients with different clinical characteristics

There were significant differences in the positive rates of BTA, BTA stat, NMP22, and survivin among patients with different tumor diameters, tumor numbers, pathological grades, clinical stages, and the presence or absence of lymph node metastasis ($P < 0.05$). See **Table 3** for details.

Table 3. Comparison of positive rates of BTA, BTA stat, NMP22, and survivin among patients [n (%), $n = 60$]

Group	Number of cases	BTA			BTA stat			NMP22			Survivin		
		Positive rate	χ^2	P	Positive rate	χ^2	P	Positive rate	χ^2	P	Positive rate	χ^2	P
Age (years)			0.024	0.876		0.184	0.668		0.156	0.693		0.203	0.887
< 60	29	72.41% (21)			75.86% (22)			72.41% (21)			75.86% (22)		
≥ 60	31	74.19% (23)			70.97% (22)			67.74% (21)			77.42% (24)		
Gender (cases)			0.074	0.785		0.016	0.898		0.278	0.598		0.196	0.658
Male	36	80.56% (29)			77.78% (28)			77.78% (28)			83.33% (30)		
Female	24	83.33% (20)			79.17% (19)			83.33% (20)			87.50% (21)		
Tumor diameter (cm)			5.432	0.020		4.705	0.030		4.271	0.039		4.812	0.028
< 3	29	65.52% (19)			58.62% (17)			68.97% (20)			72.41% (21)		
≥ 3	31	90.32% (28)			83.87% (26)			90.32% (28)			93.55% (29)		
Tumor number			4.973	0.026		4.877	0.027		4.184	0.041		5.939	0.015
Single	27	59.26% (16)			55.56% (15)			70.37% (19)			70.37 % (19)		
Multiple	33	84.85% (28)			81.82% (27)			90.91% (30)			93.9% (31)		
Pathological grade			5.001	0.025		4.242	0.039		5.001	0.025		4.434	0.035
Low	26	57.69% (15)			53.85% (14)			57.69% (15)			61.53% (16)		
High	34	82.35% (28)			76.47% (26)			82.35% (28)			85.29% (29)		
Clinical stage			5.284	0.022		5.180	0.023		5.143	0.023		6.655	0.010
T ₁ ~T ₂	25	52.00% (13)			56.00% (14)			60.00% (15)			60.00% (15)		
T ₃ ~T ₄	35	80.00% (28)			82.86% (29)			85.71% (30)			88.57% (31)		
Lymph node metastasis			4.106	0.043		5.000	0.025		4.261	0.039		8.298	0.004
Yes	20	75.00% (15)			80.00% (16)			90.00% (18)			100.00% (20)		
No	40	47.50% (19)			50.00% (20)			65.00% (26)			67.50% (27)		

4. Discussion

Bladder urothelial carcinoma is a malignant tumor with a high incidence in the clinical urinary system. With the advent of an aging society, the incidence and death toll of urothelial carcinoma continues to increase ^[4]. Therefore, timely and accurate screening and treatment are needed. Currently, clinical practices mainly adopt methods such as urinary exfoliative cytology, cystoscopy, and ultrasonography for diagnosis. However, due to various factors, the implementation effects of the above diagnostic methods are relatively mediocre. Moreover, some patients cannot accept certain examinations due to tolerability and examination costs, necessitating the search for more ideal diagnostic markers ^[5]. In recent years, various tumor markers have been widely used in the diagnosis of urothelial carcinoma. However, the sensitivity and accuracy of single detection still cannot achieve the desired goals, making combined detection and diagnosis a hot spot of clinical attention ^[6].

BTA, a hydrolytic fragment formed during the development of urothelial carcinoma, is mainly related to the degradation of the basement membrane of urothelial cells. It can affect the complement activation pathway, protect the tumor from immune attack, and promote tumor growth ^[7]. An increase in BTA levels in urine indicates the possibility of urothelial carcinoma ^[8]. BTA can diagnose superficial and small bladder tumors. However, if patients have received treatment for bladder cancer or have urinary system infections, it may cause false-positive results in clinical testing, which restricts its application ^[9]. BTA stat, as the second-generation bladder tumor antigen reagent, can be detected using monoclonal antibodies. It can bind to complement C3b and inhibit the formation of the membrane attack complex, laying the foundation for tumor growth ^[10]. NMP22, a cellular structural protein, plays a role in DNA replication and transcription, improving cell proliferation activity. In healthy individuals, its expression level is relatively low. The malignant transformation of urothelial mucosa, accelerates the proliferation and apoptosis of urothelial cells, promoting the massive release of NMP22 into the urine ^[11]. Thus, significantly elevated NMP22 levels can be detected in the urine of patients with urothelial carcinoma ^[12]. Survivin, a member of the apoptosis-inhibiting protein family, can regulate the cell cycle and inhibit apoptosis. Survivin is highly expressed in multiple tumor tissues, appearing only in the testes, thymus, and secretory uterus in normal tissues ^[13,14]. Analyzing the detection results of the two groups, the levels of BTA, BTA stat, NMP22, and survivin in the observation group were higher than those in the healthy controls, suggesting an association between the expression levels of these markers and the occurrence of urothelial carcinoma. They can be used for the diagnosis of urothelial carcinoma. Meanwhile, comparing single and combined detections of BTA, BTA stat, NMP22, and survivin in patients with urothelial carcinoma revealed that the diagnostic efficacy of combined detection was superior to single detection. This indicates the relatively high value of combined detection of BTA, BTA stat, NMP22, and survivin in the diagnosis of urothelial carcinoma. Different tumor markers have varying diagnostic advantages. Single tumor marker detection can lead to missed diagnosis or misdiagnosis, affecting the accuracy of the final diagnosis. Combined detection facilitates complementary advantages and provides more assistance for patient diagnosis and treatment ^[15].

After analyzing the positive rates of BTA, BTA stat, NMP22, and survivin in patients with urothelial carcinoma with different clinical features, it was found that tumor diameter, number of tumors, pathological grade, clinical stage, and the presence of lymph node metastasis all significantly affect the positive rates of these markers. However, age and gender do not have a significant impact on the positive rates. These results suggest that BTA, BTA stat, NMP22, and survivin all play a role in the occurrence and development of urothelial carcinoma. Changes in their levels can be used to assess the severity of the patient's condition and understand disease progression and treatment directions. Therefore, these markers can serve as important indicators for diagnosing and treating

patients ^[16]. Patients with a tumor diameter of $\geq 3\text{cm}$, multiple tumors, high pathological grade, clinical stage T3–T4, and lymph node metastasis have higher levels of these tumor markers. This is mainly because the positive rates of BTA and BTA stat increase with the pathological grade of urothelial carcinoma. By understanding the positive rates of BTA and BTA stat, the pathological grade of the patient can be judged ^[17]. NMP22 remains highly sensitive in tumors with low pathological grades and clinical stages. As the tumor size increases, the number of tumors increases, and the staging rises, the positive rate of NMP22 also increases. Therefore, NMP22 can not only be used for early diagnosis of urothelial carcinoma but also to analyze the prognosis of patients based on changes in its expression level ^[18]. The positive expression rate of survivin is closely related to the pathological grade, staging, and lymph node metastasis of urothelial carcinoma. The positive expression of survivin can be detected early in cellular malignancy, and its overexpression can disrupt the balance between cell proliferation and apoptosis, playing an important role in the early stages of tumor development. Additionally, survivin can protect growth factors, induce the formation of new blood vessels in tumor tissue, and provide a favorable environment for tumor growth and invasion, thereby promoting tumor development ^[19]. Overall, the high positive expression rates of BTA, BTA stat, NMP22, and survivin promote the malignant transformation of urothelial carcinoma, and their abnormal expression is closely related to the clinicopathological features of urothelial carcinoma patients. This allows for better patient identification, and combined detection can improve diagnostic sensitivity and ensure diagnostic efficacy ^[20].

5. Conclusion

In summary, the combined detection of BTA, BTA stat, NMP22, and survivin has definite application value in the diagnosis of urothelial carcinoma patients. It can provide an important reference for patient condition evaluation and is recommended for active use in the diagnosis and treatment of urothelial carcinoma.

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Exploring the Adverse Reactions and Risk Factors of Toripalimab in the Treatment of Urothelial Carcinoma

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Abstract: *Objective:* This study aims to investigate the adverse reactions and risk factors associated with toripalimab in the treatment of urothelial carcinoma. *Methods:* The clinical data of 63 patients with urothelial carcinoma who received toripalimab treatment in our hospital from June 2021 to January 2025 were retrospectively analyzed. Patient data, including baseline characteristics (age, gender, Eastern Cooperative Oncology Group [(ECOG) score, comorbidities), treatment history (chemotherapy, radiotherapy), and adverse reactions, were selected through the hospital's electronic medical record system. *Results:* Among the 63 patients, 49 (77.78%) experienced toripalimab-related adverse reactions, with skin rash occurring most frequently. Univariate analysis showed that age, comorbidities such as hypertension, diabetes, and bronchial asthma, as well as the use of combined radiotherapy and chemotherapy, were significantly associated with toripalimab-related adverse reactions (all $P < 0.05$). Multivariate logistic regression analysis revealed that combined chemotherapy was an independent risk factor for toripalimab-related adverse reactions ($P < 0.05$). *Conclusion:* Immune-related adverse reactions observed during toripalimab treatment for urothelial carcinoma include skin rash, elevated transaminase levels, abnormal renal function, anemia, etc. Factors influencing these reactions include age, underlying diseases, and combined radiotherapy and chemotherapy, among which combined chemotherapy is an independent risk factor for adverse reactions. When using toripalimab in clinical practice, it is essential to follow the approved indications on the label, monitor patients for adverse reactions during treatment, and intervene effectively to ensure patient safety.

Keywords: Toripalimab; Urothelial carcinoma; Risk factors; Logistic regression analysis; Adverse reactions

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1. Introduction

Urothelial carcinoma, including bladder cancer, renal pelvis cancer, ureteral cancer, and urethral cancer, is one of the common malignancies of the urinary system. Its incidence and mortality rates have been increasing year by year.

According to the latest domestic research statistics, the incidence of urothelial carcinoma ranks 13th among all cancer patients, making it a significant public health issue ^[1]. In recent years, immunotherapy, primarily focused on immune checkpoint inhibitors, has brought new hope for the treatment of urothelial carcinoma. This therapeutic approach can effectively activate anti-tumor immunity and reduce the immune escape rate of tumors ^[2], offering hope to patients. Toripalimab is China's first domestically produced programmed death receptor-1 (PD-1) monoclonal antibody drug approved for market. By disrupting the immunosuppressive effects of the PD-1 signaling pathway, it restores T cell function, targets tumor cells, and regulates autoimmunity. The emergence of toripalimab has improved the treatment effectiveness of cancer patients to a certain extent, prolonged their survival time, and enhanced their quality of life ^[3,4]. However, there is limited research on its adverse reactions in practical applications. Therefore, this study adopts a retrospective approach to analyze the adverse reactions and risk factors of toripalimab in treating urothelial carcinoma, aiming to provide a reliable theoretical foundation for clinical medication administration.

2. Materials and methods

2.1. General information

A retrospective analysis was conducted on the clinical data of 63 patients with urothelial carcinoma who received toripalimab treatment in our hospital from June 2021 to January 2025. Inclusion criteria: (1) Aged between 18 and 85 years old; (2) Patients were diagnosed with locally advanced/metastatic urothelial carcinoma after cytological or histological examination ^[5]; (3) All were treated with toripalimab (240 mg of toripalimab intravenously every two weeks); (4) Good function of important organs; (5) At least one measurable target lesion. Exclusion criteria: (1) Incomplete clinical data collection; (2) Combined with other types of bladder cancer besides urothelial carcinoma; (3) Previously received other types of PD-1 or PD-L1 drugs for treatment; (4) Suffering from severe underlying diseases; (5) Having toxic reactions caused by drugs other than toripalimab.

2.2. Data collection

Patient data, including basic information (age, gender, Eastern Cooperative Oncology Group [ECOG] score, comorbidities), treatment history (chemotherapy, radiotherapy), and adverse reactions, were selected through the hospital's electronic medical record system. The occurrence of adverse reactions includes the number of cases, types, severity, etc.

2.3. Criteria for determining adverse events

Based on the Common Terminology Criteria for Adverse Events (CTCAE), toripalimab-related adverse events were classified and graded as follows:

- (1) Grade 1 (mild): asymptomatic or mild symptoms; observed only during clinical or diagnostic examinations; no treatment required.
- (2) Grade 2 (moderate): requiring local or non-invasive therapy; age-related instrumental activities of daily living are limited.
- (3) Grade 3 (severe): medically significant but not immediately life-threatening; requiring hospitalization or prolongation of hospitalization; disabling; limiting self-care.
- (4) Grade 4 (life-threatening consequences): requiring urgent intervention.
- (5) Grade 5: death related to adverse events ^[6,7].

2.4. Statistical analysis

SPSS 26.0 statistical software was used for data processing in this study. The count data involved were expressed as (*n*, %), and chi-square test analysis was performed. Logistic regression analysis was used to identify influencing factors. When $P < 0.05$, it indicated that the data had statistically significant differences.

3. Results

3.1. Incidence and types of toripalimab-related adverse events

Among the 63 patients, 49 patients (77.78%) experienced toripalimab-related adverse events, with a total of 60 occurrences. Grade 1 and 2 adverse events occurred 56 times, accounting for 93.33%, while Grade 3 and above adverse events occurred 4 times, accounting for 6.67%. The specific data are shown in **Table 1**:

Table 1. Incidence and types of toripalimab-related adverse events (*n*, %)

Types of adverse reactions	Severity level	Frequency of occurrence	Incidence rate (%)
Rash	Grade 1	15	25.00
Elevated transaminase levels	Grade 1	11	18.33
Abnormal renal function	Grade 2	7	11.67
Anemia	Grade 2	9	15.00
Neutropenia	Grade 1	5	8.33
Thrombocytopenia	Grade 1	4	6.67
Loss of appetite	Grade 1	4	6.67
Blood clot formation	Grade 2	1	1.67
Muscle weakness	Grade 3	2	3.33
Interstitial pneumonia	Grade 3	2	3.33
Total		60	100.00

3.2. Univariate analysis of toripalimab-related adverse events

Univariate analysis showed that age, comorbidities such as hypertension, diabetes, bronchial asthma, and combined radiotherapy and chemotherapy were the main factors associated with toripalimab-related adverse events (all $P < 0.05$). However, gender, primary tumor location, ECOG score, and comorbid chronic bronchitis were not significantly associated with adverse events (all $P > 0.05$). Specific data are presented in **Table 2**:

Table 2. Univariate analysis of toripalimab-related adverse events (*n*, %)

Factors		Group without adverse reactions (<i>n</i> = 14)	Group with adverse reactions (<i>n</i> =49)	χ^2 -value	<i>P</i> -value
Age	> 65	10	19	4.673	0.031
	≤ 65	4	30		
Gender	Male	6	26	0.454	0.501
	Female	8	23		

Table 2 (Continued)

Factors		Group without adverse reactions (<i>n</i> = 14)	Group with adverse reactions (<i>n</i> =49)	χ^2 -value	<i>P</i> -value
Location of the primary tumor	Bladder cancer	9	31	0.828	0.843
	Renal pelvis cancer	3	13		
	Ureteral cancer	2	4		
	Others	0	1		
ECOG score	0 points	7	29	0.284	0.594
	1 point	7	20		
Hypertension	Combined	3	30	6.914	0.009
	Not combined	11	19		
Diabetes mellitus	Combined	5	34	5.236	0.022
	Not combined	9	15		
Chronic bronchitis	Combined	10	21	3.556	0.059
	Not combined	4	28		
Bronchial asthma	Combined	2	26	6.631	0.010
	Not combined	12	23		
Combined radiotherapy	Combined therapy	4	31	5.308	0.021
	Not combined therapy	10	18		
Combined chemotherapy	Combined therapy	5	33	5.998	0.014
	Not combined therapy	9	16		

3.3. Multivariate logistic regression analysis of toripalimab-related adverse reactions

Using the occurrence of adverse reactions as the dependent variable (occurred = 1, did not occur = 0), and with age, comorbid hypertension, diabetes, bronchial asthma, as well as combined radiotherapy and chemotherapy as independent variables, values were assigned (**Table 3**). The results of the multivariate logistic regression analysis showed that combined chemotherapy is an independent risk factor for toripalimab-related adverse reactions ($P < 0.05$), as shown in **Table 4**.

Table 3. Independent variable assignment table

Independent variables	Value assignment
Age	65 years old = 1, ≤ 65 years old = 0
Comorbid hypertension	With comorbidity = 1, without comorbidity = 0
Comorbid diabetes	With comorbidity = 1, without comorbidity = 0
Comorbid bronchial asthma	With comorbidity = 1, without comorbidity = 0
Combined radiotherapy	Combined = 1, not combined = 0
Combined chemotherapy	Combined = 1, not combined = 0

Table 4. Multivariate logistic regression analysis of toripalimab-related adverse reactions

Related factors	β -value	SE	Wald χ^2 -value	P-value	OR-value	95% CI
Age	0.051	0.694	0.005	0.941	1.053	(0.271, 4.104)
Comorbid hypertension	0.149	0.776	0.037	0.848	1.161	(0.254, 5.315)
Comorbid diabetes	1.153	0.802	2.066	0.151	0.316	(0.066, 1.521)
Comorbid bronchial asthma	0.211	0.702	0.091	0.763	1.235	(0.312, 4.891)
Combined radiotherapy	0.696	0.777	0.803	0.370	0.498	(0.109, 2.286)
Combined chemotherapy	2.351	1.106	4.517	0.034	1.095	(0.011, 0.833)

4. Discussion

Urothelial carcinoma is a common malignancy of the urinary system with poor prognosis and high recurrence and metastasis rates^[8]. Although radiotherapy, chemotherapy, and other means are currently used clinically to treat patients with unresectable advanced urothelial carcinoma, which can improve the prognosis of patients to some extent, the long-term survival rate is still at a low level, and further treatment options need to be explored.

Currently, PD-1/PD-L1 immune checkpoint inhibitors have achieved good results in studies on lung cancer, liver cancer, etc.^[9], providing new ideas for the treatment of malignant tumors. Toripalimab is a recombinant humanized anti-PD-1 monoclonal antibody injection with a unique dual mechanism of action. It not only binds to PD-1 to block its binding to PD-L1, significantly increasing its killing effect on tumors but also induces endocytosis of PD-1, further improving the T-cell response to antigenic stimulation and controlling tumor development^[10]. However, there are few studies on the safety of toripalimab. Therefore, this study focuses on the adverse reactions of toripalimab in clinical treatment and uses retrospective analysis to explore the influencing factors of toripalimab-related adverse reactions. The results showed that among 63 patients, 49 experienced toripalimab-related adverse reactions (77.78%), with rash occurring most frequently. As a common adverse reaction, rash may be closely related to increased PD-1 expression levels in skin tissue and T-cell activation, which is consistent with the typical toxicity profile of PD-1 inhibitors. Therefore, when using toripalimab for clinical treatment, attention should be paid to rash prevention measures and strengthened monitoring^[11].

Univariate analysis showed that age, comorbid hypertension, comorbid diabetes, comorbid bronchial asthma, and combined radiotherapy and chemotherapy are the main factors for toripalimab-related adverse reactions ($P < 0.05$ for all). The reason may be that elderly patients often experience immune senescence, and the body itself exhibits T-cell dysfunction, which may lead to immunotherapy-induced toxicity. In patients with metabolic diseases, insulin resistance and vascular endothelial injury alter the metabolism and migration ability of immune cells in the body. Respiratory diseases such as asthma may affect the immune microenvironment due to Th2 immune deviation, intensifying toxic reactions^[12]. Additionally, multivariate logistic regression analysis showed that combined chemotherapy is an independent risk factor for toripalimab-related adverse reactions ($P < 0.05$). Chemotherapy drugs such as cisplatin and gemcitabine can damage the mucosal barrier and induce cell damage, releasing autoantigens. These drugs may produce a synergistic immunostimulatory effect with toripalimab, further leading to toxicity superposition^[13]. In summary, when using toripalimab for clinical treatment, it is important to follow the approved indications on the package insert, closely monitor patients for adverse reactions during

treatment, and intervene effectively once they are detected to ensure patient safety.

5. Conclusion

In conclusion, the immune-related adverse reactions observed during the treatment of urothelial carcinoma with toripalimab include rash, elevated transaminase levels, abnormal kidney function, anemia, etc. Analysis shows that age, underlying diseases, and combined radiotherapy and chemotherapy are influencing factors, with combined chemotherapy being an independent risk factor for adverse reactions. However, this study has some limitations. For example, the small sample size may cause data deviation, and the adverse reaction grading and correlation with dosage are not clear, limiting the assessment of toxicity severity. Future research will further optimize the study protocol to provide a strong theoretical foundation for the safety study of toripalimab in the treatment of urothelial carcinoma.

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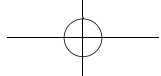
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