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Original Article

Comparison of neoadjuvant chemotherapy and combined chemotherapy with immunotherapy for muscle-invasive bladder cancer: a propensity score-matched analysis

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Abstract: Objective: To evaluate the efficacy and safety of neoadjuvant chemotherapy (NAC) compared to NAC combined with immune checkpoint inhibitors (ICI) in patients with muscle-invasive bladder cancer (MIBC). Propensity score matching (PSM) was employed to assess the impact of these two treatment regimens on the pathological complete response rate (pCR) and overall survival (OS). Methods: A retrospective analysis was conducted on 320 MIBC patients treated at the Cancer Hospital affiliated to Sun Yat-sen University Gansu Hospital between January 2017 and June 2022. Patients were categorized into the NAC group (n=194) and the NAC+ICI group (n=126) based on their treatment regimens. After PSM, 154 patients were included, with 77 in each group. Baseline characteristics, clinical efficacy, and prognosis were analyzed using various statistical methods. Results: Before PSM, significant differences were observed between the groups in baseline characteristics, including tumor diameter, tumor number, and adjuvant treatment (all P<0.05). After PSM, these differences were no longer statistically significant (all P>0.05). The NAC+ICI group demonstrated a significantly higher pCR rate both before and after PSM (both P<0.001). Similarly, pathological downstaging rates were higher in the NAC+ICI group before and after PSM (both P<0.001). However, there was no significant difference in disease control rates between the two groups before (P=0.057) and after PSM (P=0.240). Logistic regression analysis identified the treatment regimen (before PSM: P<0.001, OR=0.161; after PSM: P<0.001, OR=0.141) and complications (before PSM: P=0.005, OR=2.339; after PSM: P=0.019, OR=2.753) as independent risk factors for pCR. Cox regression analysis revealed that age (before PSM: P<0.001, HR=1.059; after PSM: P=0.011, HR=1.066), pretreatment T stage (before PSM: P<0.001, HR=2.342; after PSM: P<0.001, HR=3.244), tumor diameter (before PSM: P=0.005, HR=1.810; after PSM: P=0.025, HR=2.077), and treatment outcome (before PSM: P<0.001, HR=1.722; after PSM: P=0.020, HR=1.444) were independent prognostic factors for OS. Conclusion: NAC combined with ICI significantly improves pCR and pathological downstaging rates in MIBC patients. Independent prognostic factors affecting OS include age, pretreatment T stage, tumor diameter, and treatment outcome.

Keywords: Neoadjuvant chemotherapy, chemotherapy combined with immunotherapy, muscle-invasive bladder cancer, propensity score matching analysis

Introduction

Bladder cancer is a prevalent malignancy worldwide, with over 570,000 new cases and approximately 210,000 deaths reported in 2020 [1]. Urothelial carcinoma (UC) is the most common type, accounting for over 90% of all bladder cancer cases [2]. Among these, about 25% are classified as muscle-invasive bladder cancer (MIBC), a highly aggressive but chemotherapy-sensitive tumor [3]. In China, the incidence of bladder cancer has been increasing, surpassing the global average due to factors such as population aging, urbanization, industrialization, and rising smoking rates [4, 5]. Consequently, effective control and treatment

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of bladder cancer, particularly MIBC, have become focal points in clinical research and public health policy.

For MIBC patients who can tolerate platinum-based chemotherapy, the current standard treatment involves neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) [5]. The primary goals of NAC are to reduce tumor burden before surgery, minimize the risk of micrometastasis, and enhance both surgical completeness and long-term survival [6]. A 2016 meta-analysis, comprising 3,285 MIBC patients from 15 randomized clinical trials, showed that cisplatin-based NAC increases the 5-year overall survival rate by 8% (from 45% to 53%), solidifying its status as the standard treatment [7]. Achieving a pathological complete response (pCR) after NAC is associated with significantly improved long-term survival outcomes [8]. While pathological downstaging has been linked to better survival in MIBC patients [9], pCR is regarded as a more robust clinical endpoint because it eliminates discrepancies between clinical and pathological staging, reducing diagnostic and treatment uncertainties [10].

Despite its advantages, only about 40% of MIBC patients achieve pT0N0M0 or pCR after NAC, leaving a substantial proportion with residual or progressing tumors [11, 12]. For these non-responders, chemotherapy's toxic side effects and delays in radical surgery may adversely affect prognosis. Thus, identifying effective methods to predict NAC response is crucial for improving treatment outcomes [13].

With the growing adoption of immune checkpoint inhibitors (ICI) in cancer therapy, the combination of NAC and ICI has garnered attention [14]. However, comparative studies evaluating the two regimens remain limited, and high-quality clinical evidence is scarce. This study systematically compares the efficacy and safety of NAC versus NAC combined with ICI in MIBC patients using propensity score matching (PSM). By analyzing the impact of these two regimens on pCR and overall survival (OS) and identifying independent risk factors influencing treatment outcomes, this research aims to guide clinicians in developing tailored treatment strategies that maximize therapeutic benefits while minimizing unnecessary risks.

Methods and materials

Clinical data

This study retrospectively analyzed MIBC patients treated at the Cancer Hospital affiliated with Sun Yat-sen University Gansu Hospital between January 2017 and June 2022. Inclusion criteria: (1) MIBC confirmed through preoperative biopsy, imaging studies, transurethral cystoscopy, and postoperative pathology, with clinical staging classified as T2 to T4, N0/N+, M0 [15]; (2) receipt of NAC; (3) absence of distant organ metastasis; (4) availability of complete clinical and follow-up data. Exclusion criteria: (1) concurrent malignancies; (2) severe heart, lung, or cerebrovascular diseases; (3) prior preoperative radiotherapy; (4) fewer than three NAC cycles; (5) an expected survival of less than 90 days. Based on these criteria, 320 eligible cases were identified, comprising 194 patients in the NAC group and 126 in the NAC+ICI group. Ethical approval was obtained from the Ethics Committee of Cancer Hospital affiliated with Sun Yat-sen University Gansu Hospital.

Treatment regimen

Patients in the NAC group received the GC regimen (gemcitabine combined with cisplatin), with each cycle lasting 21 days. The regimen included gemcitabine 1000 mg/m^2 administered intravenously on day 1 and 8, and cisplatin 70 mg/m^2 administered intravenously on day 2. The NAC+ICI group received the same GC regimen combined with an immune checkpoint inhibitor (ICI). ICIs included tislelizumab 200 mg, pembrolizumab 200 mg, or toripalimab 3 mg/kg, administered intravenously on day 1 of each 21-day cycle. Radical cystectomy and pelvic lymph node dissection (RC-PLND) were performed within 4 to 8 weeks after neoadjuvant therapy. For female patients, hysterectomy and bilateral salpingo-oophorectomy were also conducted during surgery [16]. Thirty-two cases required conversion to open surgery during the procedure.

Data collection

Clinical data were collected from surgical records, electronic medical records, and outpatient follow-ups. Variables included gender, smoking and alcohol history, and medical histo-

ries (e.g., diabetes, hypertension). Tumor characteristics, such as pre-treatment T and N stages (T2, T3, T4; N0, N+), tumor diameter (≥3 cm or <3 cm), number (single or multiple), histologic grade (high-grade or low-grade), and hydronephrosis, were recorded. Surgical approach (robot-assisted, laparoscopic, or open surgery) and urinary diversion type (orthotopic neobladder or ileal conduit) were noted. Histologic type was classified as urothelial carcinoma or other types. Data on positive lymph node percentage (0, 1-25%, >25%), positive surgical margins, and complications were also included. Additional clinical indicators, such as age, BMI (kg/m^2), hemoglobin (Hb, g/L), platelet count (PLT, ×10^9/L), lymphocyte count (LYM, ×10^9/L), albumin (ALB, g/L), and the number of lymph nodes cleared, were meticulously documented.

PSM

PSM was employed to control for baseline differences between the NAC and NAC+ICI groups. A caliper of 0.02 was used to ensure high comparability between matched patients. The "optimal" matching method was applied with no replacement (replace = FALSE) and optimization enabled (optim = TRUE) to enhance precision [17]. This method aimed to minimize confounding factors, allowing for a more accurate evaluation of the efficacy and safety of the two regimens. After PSM, 154 matched patients were included, with 77 in each group.

Clinical efficacy evaluation

Clinical efficacy after chemotherapy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [18]. The evaluation criteria were as follows: Complete response (CR): Disappearance of all target lesions for at least 4 weeks, with no new lesions. Partial response (PR): At least a 30% reduction in the sum of the longest diameters of target lesions, with no new lesions. Stable disease (SD): Changes insufficient to qualify as PR or progressive disease (PD). Progressive disease (PD): At least a 20% increase in the sum of the longest diameters of target lesions or the appearance of new lesions.

Pathological complete response (pCR) was defined as the absence of any residual tumor cells (ypT0N0M0) in pathological examination after radical cystectomy. Pathological downstaging referred to a reduction in tumor stage post-neoadjuvant therapy compared to pre-treatment. Disease control (DC), encompassing CR, PR, and SD, was defined as the proportion of patients with non-progressive disease.

Follow-up

Patients were followed up until June 2024. Follow-up intervals were scheduled based on the time since surgery: every 3 months during the first year, every 4 months in the second year, and every 6 months from the third year onward. Assessments included regular physical examinations and imaging studies (e.g., CT or MRI). Overall survival (OS) was defined as the duration from surgery to death from any cause.

Outcome measures

Primary outcomes: Logistic regression analysis was used to identify independent risk factors for pCR before and after PSM. Cox regression analysis identified independent prognostic factors affecting OS before and after PSM.

Secondary outcomes: Baseline data differences before and after PSM were analyzed. Density plots and Q-Q plots were used to visualize propensity score distributions. The clinical efficacy of the two groups was evaluated before and after PSM.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) and compared using the Student's t-test or Mann-Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages, analyzed using the Chi-square test or Fisher's exact test. PSM was performed using a caliper width of 0.02 and nearest-neighbor matching without replacement. Covariate balance after matching was assessed using standardized mean differences. Logistic regression analyses identified independent risk factors influencing pCR before and after PSM. Cox proportional hazards models identified independent prognostic factors for OS. Kaplan-Meier survival curves were generated and compared using the log-rank

Table 1. Comparison of baseline characteristics of patients before PSM

Variable	Total	NAC Group (n=194)	NAC+ICI Group (n=126)	Statistic	*P* Value
Gender					
Male	264	163	101	χ^2=0.789	0.374
Female	56	31	25		
Smoking history					
Yes	169	97	72	χ^2=1.564	0.211
No	151	97	54		
History of alcoholism					
Yes	22	12	10	χ^2=0.366	0.545
No	298	182	116		
History of diabetes					
Yes	35	25	10	χ^2=1.921	0.166
No	285	169	116		
History of hypertension					
Yes	52	33	19	χ^2=0.209	0.647
No	268	161	107		
Pre treatment T stage					
T2	173	111	62	χ^2=1.974	0.373
T3	92	52	40		
T4	55	31	24		
Pre treatment N stage					
N0	258	155	103	χ^2=0.167	0.683
N+	62	39	23		
Tumor diameter					
≥3 cm	166	113	53	χ^2=8.014	0.005
<3 cm	154	81	73		
Tumor number					
Single	153	103	50	χ^2=5.505	0.019
Multiple	167	91	76		
Histologic grade					
High-grade	305	184	121	χ^2=0.241	0.624
Low-grade	15	10	5		
Hydronephrosis					
Yes	219	140	79	χ^2=3.169	0.075
No	101	54	47		
Adjuvant Treatment					
Yes	228	165	63	χ^2=45.816	<0.001
No	92	29	63		
Surgical Approach					
Robot-assisted surgery	251	155	96	χ^2=1.684	0.431
Laparoscopic surgery	37	23	14		
Open surgery	32	16	16		
Urinary Flow Diversion Approach					
Orthotopic neobladder	119	62	57	χ^2=5.767	0.016
Ileal conduit	201	132	69		
Histologic type					
Urothelial carcinoma	253	159	94	χ^2=2.38	0.114
Other	67	35	32		
Percentage of positive lymph nodes					
0	258	164	94	χ^2=5.26	0.067
45316	32	14	18		
>25	30	16	14		

Positive margins					
Yes	300	178	122	χ^2=3.355	0.067
No	20	16	4		
Complications					
Yes	191	120	71	χ^2=0.963	0.327
No	129	74	55		
Age (years)	55.00 [51.00, 60.00]	54.00 [47.00, 59.00]	55.00 [52.00, 60.00]	t=4.93	0.045
BMI (kg/m^2)	23.19±2.77	23.01±2.76	23.47±2.77	t=1.463	0.145
Hb (g/L)	124.37±21.43	121.96±21.53	128.09±20.82	t=2.538	0.012
PTL (×10^9/L)	268.83±73.83	265.48±75.23	273.99±71.60	t=1.018	0.31
LYM (×10^9/L)	1.58±0.56	1.54±0.54	1.65±0.60	t=1.804	0.072
ALB (g/L)	39.00 (37.00, 42.00)	39.00 (37.00, 41.00)	39.83±4.20	Z=1.421	0.154
Number of lymph nodes cleared	21.41±5.61	21.64±5.69	21.06±5.49	t=-0.915	0.361

Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; PSM, Propensity Score Matching; Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

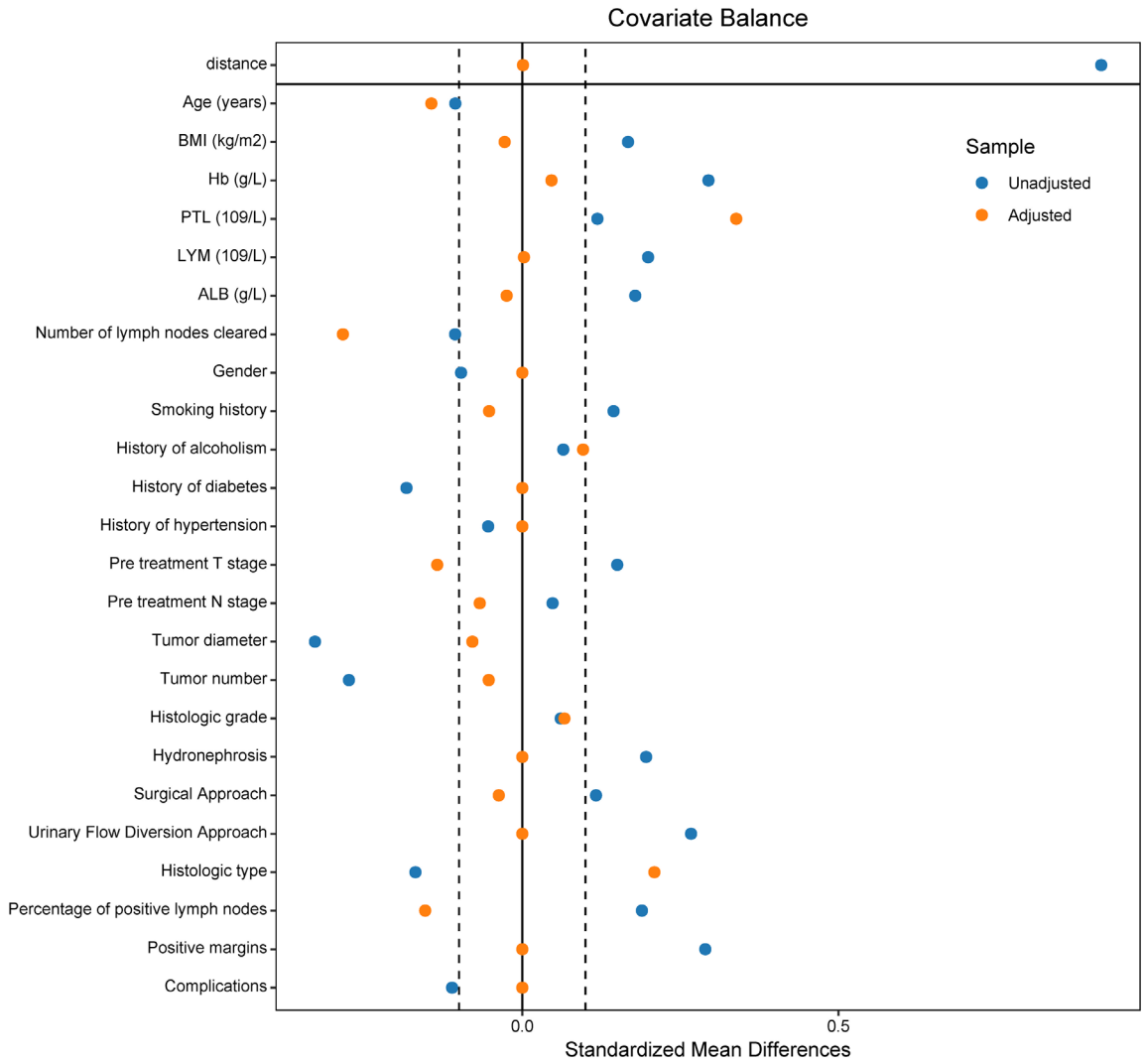

Figure 1. Covariate balance before and after propensity score matching in NAC and NAC+ICI groups. Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

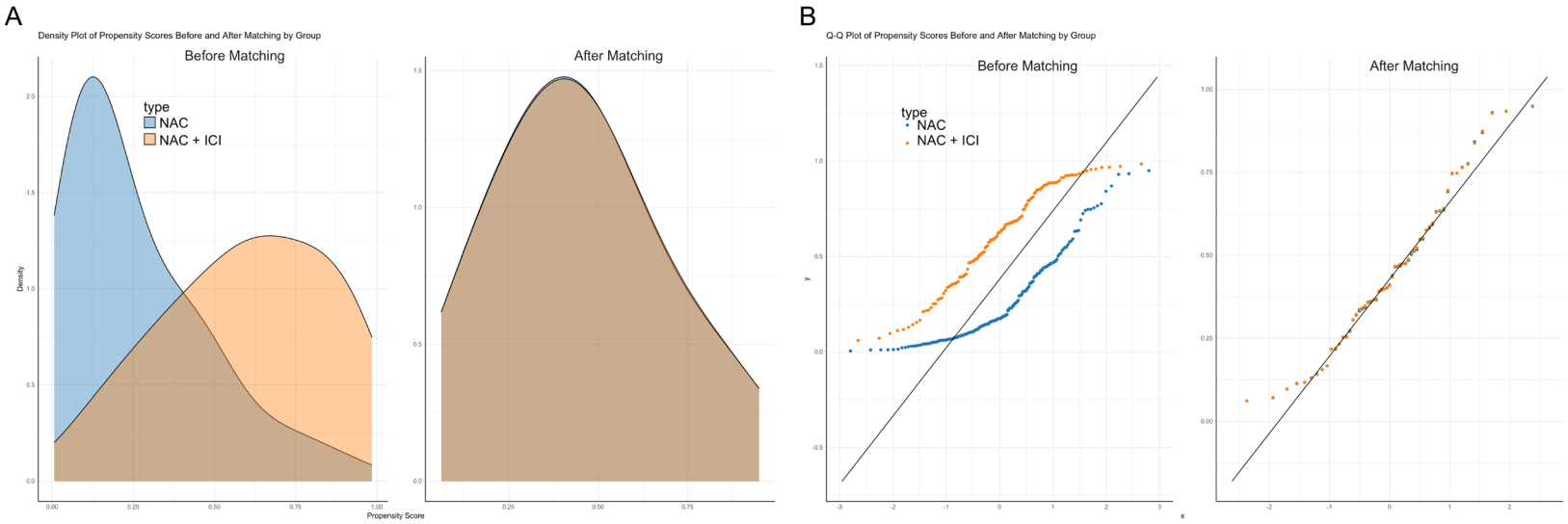

Figure 2. Density plots and Q-Q plots of propensity scores before and after matching in NAC and NAC+ICI groups. A: Density distributions of propensity scores for the NAC and NAC+ICI groups before and after PSM. The left plot illustrates significant differences in score distributions between the two groups prior to matching, whereas the right plot demonstrates that the distributions nearly completely overlap with post-matching. B: Q-Q plots of propensity scores before and after matching. After matching (right plot), the standardized mean differences for all covariates are markedly reduced, with data points aligning more closely to the diagonal line, thereby confirming the effectiveness of the matching process. Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; PSM, Propensity Score Matching.

Table 2. Comparison of baseline characteristics of patients after PSM

Variable	Total	NAC Group (n=77)	NAC+ICI Group (n=77)	Statistic	*P* Value
Gender					
Male	126	63	63	χ^2<0.001	1.000
Female	28	14	14		
Smoking history					
Yes	86	44	42	χ^2=0.105	0.746
No	68	33	35		
History of alcoholism					
Yes	8	3	5	χ^2=0.527	0.468
No	146	74	72		
History of diabetes					
Yes	16	8	8	χ^2<0.001	1.000
No	138	69	69		
History of hypertension					
Yes	28	14	14	χ^2<0.001	1.000
No	126	63	63		
Pre treatment T stage					
T2	78	36	42	χ^2=0.943	0.624
T3	46	25	21		
T4	30	16	14		
Pre treatment N stage					
N0	126	64	62	χ^2=0.175	0.676
N+	28	13	15		
Tumor diameter					
≥3 cm	77	40	37	χ^2=0.234	0.629
<3 cm	77	37	40		
Tumor number					
Single	70	36	34	χ^2=0.105	0.746
Multiple	84	41	43		
Histologic grade					
High-grade	147	73	74	χ^2=0.150	0.699
Low-grade	7	4	3		
Hydronephrosis					
Yes	46	23	23	χ^2<0.001	1.000
No	108	54	54		
Adjuvant Treatment					
Yes	120	60	60	χ^2=0.486	0.784
No	20	9	11		
Surgical Approach					
Robot-assisted surgery	14	8	6	χ^2<0.001	1.000
Laparoscopic surgery	58	29	29		
Open surgery	96	48	48		
Urinary Flow Diversion Approach				χ^2=1.890	0.169
Orthotopic neobladder	121	57	64		
Ileal conduit	33	20	13		
Histologic type					
Urothelial carcinoma	118	56	62	χ^2=1.318	0.517
Other	22	13	9		
Percentage of positive lymph nodes					
0	14	8	6	χ^2=0.000	1.000
45316	146	73	73		
>25	8	4	4		
Positive margins				χ^2<0.001	1.000
Yes	92	46	46		
No	62	31	31		

Complications				χ^2<0.001	1.000
Yes	126	63	63		
No	28	14	14		
Age (years)	55.00 [52.00, 60.00]	55.00 [52.00, 60.00]	55.00 [51.00, 60.00]	Z=-0.697	0.486
BMI (kg/m^2)	23.52±2.76	23.56±2.83	23.48±2.71	t=-0.173	0.863
Hb (g/L)	127.30±21.28	126.82±21.26	127.78±21.43	t=0.279	0.78
PTL (×10^9/L)	272.50 [216.00, 325.00]	259.77±77.41	283.99±65.86	t=2.091	0.038
LYM (×10^9/L)	1.57±0.55	1.57±0.54	1.57±0.55	t=0.018	0.986
ALB (g/L)	39.43±3.70	39.48±3.11	39.38±4.23	t=-0.174	0.862
Number of lymph nodes cleared	20.95±5.31	21.73±5.36	20.17±5.18	t=-1.834	0.069

Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; PSM, Propensity Score Matching; Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

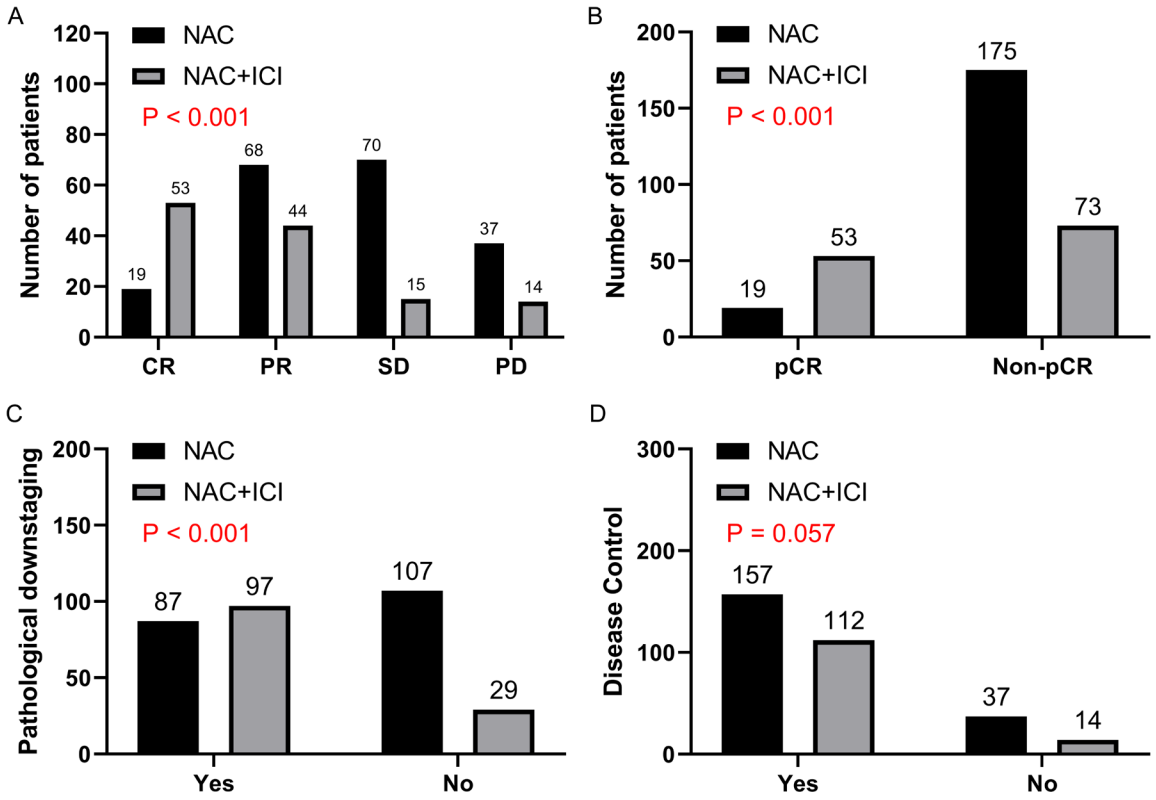

Figure 3. Comparison of clinical outcomes before PSM between NAC and NAC+ICI groups. A: Rates of CR, PR, SD, and PD in the NAC and NAC+ICI groups before PSM. B: Comparison of pCR rates between the NAC and NAC+ICI groups before PSM. C: Assessment of pathological downstaging in the NAC and NAC+ICI groups before PSM. D: Comparison of DC rates between the NAC and NAC+ICI groups before PSM. Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; pCR, Pathological Complete Response; DC, Disease Control; PD, Progressive Disease; PSM, Propensity Score Matching.

test. Receiver Operating Characteristic (ROC) curve analyses assessed the predictive performance of the models. A *p*-value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

Baseline characteristics of the NAC group (n=194) and NAC+ICI group (n=126) are summarized in **Table 1**. No statistically significant differences were observed between the groups in gender, smoking history, history of alcoholism, history of diabetes, history of hypertension, pre-treatment T stage, pre-treatment N stage, histologic grade, hydronephrosis, surgical approach, histologic type, percentage of positive lymph nodes, positive margins, complications, BMI, PLT, ALB, or the number of lymph nodes cleared (all P>0.05). However, significant

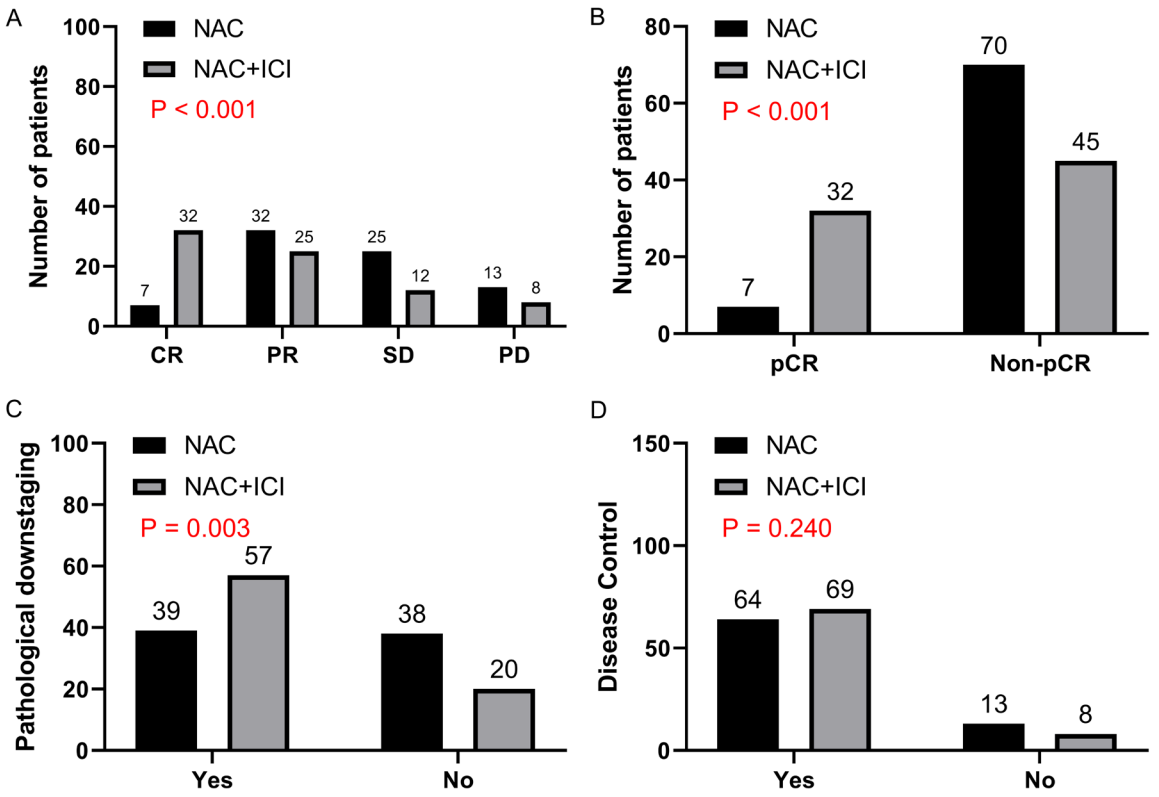

Figure 4. Comparison of clinical outcomes after PSM between NAC and NAC+ICI groups. A: Rates of CR, PR, SD, and PD in the NAC and NAC+ICI groups after PSM. B: Comparison of pCR rates between the NAC and NAC+ICI groups after PSM. C: Assessment of pathological downstaging in the NAC and NAC+ICI groups after PSM. D: Comparison of DC rates between the NAC and NAC+ICI groups after PSM. Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; pCR, Pathological Complete Response; DC, Disease Control; PD, Progressive Disease; PSM, Propensity Score Matching.

differences were found in tumor diameter ≥3 cm (P=0.005), multiple tumors (P=0.019), adjuvant treatment (P<0.001), urinary diversion approach (P=0.016), age (P=0.045), and Hb levels (P=0.012).

Comparison of changes in covariate balance before and after PSM

Before PSM, significant imbalances existed between the NAC and NAC+ICI groups in age, tumor diameter, tumor number, and adjuvant treatment. After PSM, the standardized mean differences for these covariates were substantially reduced, indicating improved balance (**Figure 1**). The propensity score distribution curves for matched samples showed nearly identical densities between the two groups, and Q-Q plots (**Figure 2**) confirmed alignment with the diagonal, demonstrating the effectiveness of the matching process. A total of 154 matched samples were obtained, with 77 patients in each group.

Comparison of baseline characteristics after PSM

Post-PSM, baseline characteristics were well-balanced between the groups, with no statistically significant differences in gender, smoking history, history of alcoholism, history of diabetes, history of hypertension, pre-treatment T stage, pre-treatment N stage, tumor diameter, tumor number, histologic grade, hydronephrosis, adjuvant treatment, surgical approach, urinary diversion approach, histologic type, percentage of positive lymph nodes, positive margins, complications, age, BMI, Hb, LYM, ALB, or the number of lymph nodes cleared (all P>0.05). However, PLT levels remained significantly different (P=0.038, **Table 2**).

Comparison of clinical efficacy before and after PSM

Before PSM, the overall clinical efficacy significantly differed between the groups (P<0.001,

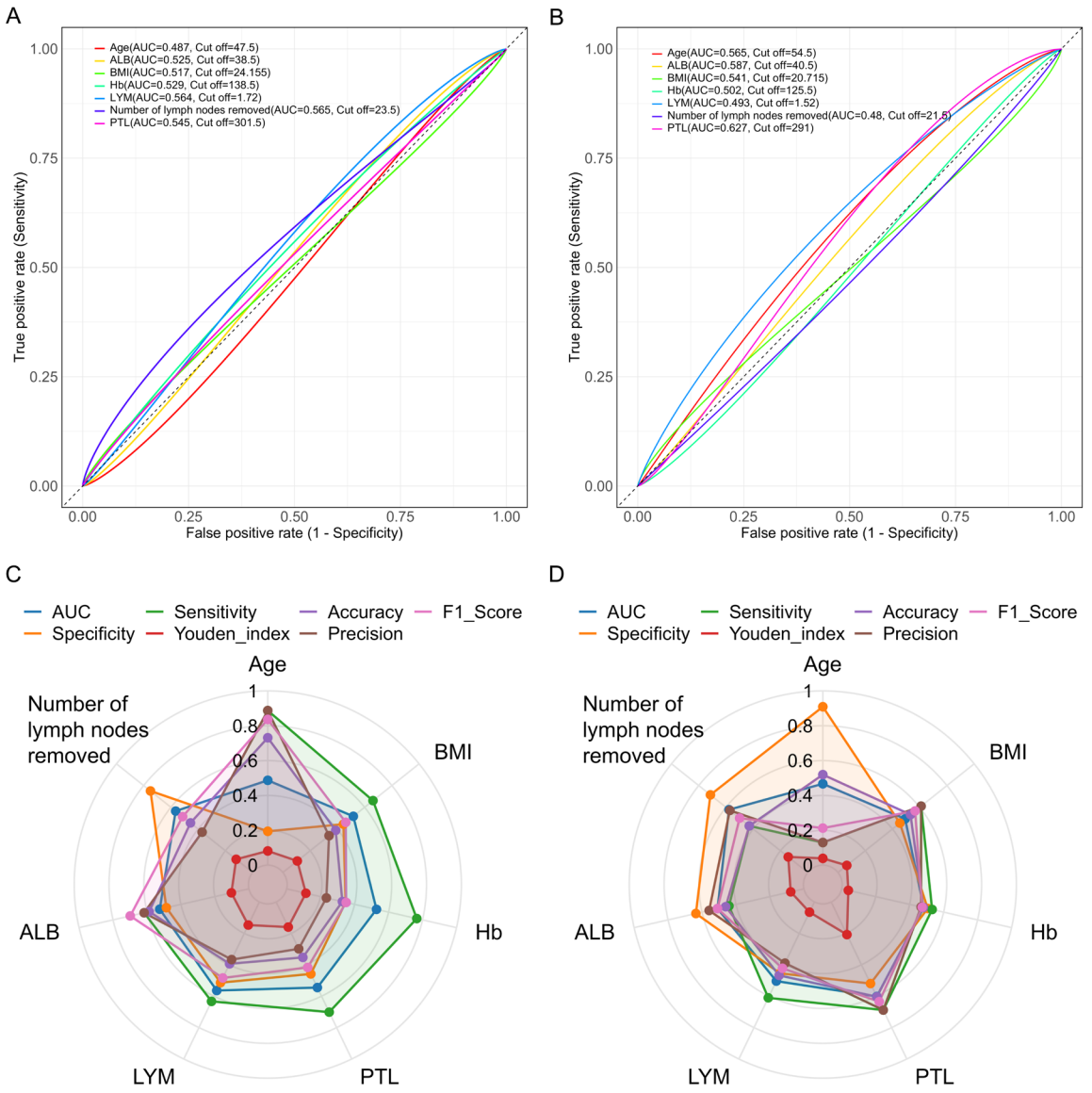

Figure 5. ROC curve analysis and radar plot of quantitative data before and after PSM. A: ROC curve of quantitative data before PSM. B: ROC curve of quantitative data after PSM. C: Radar plot of ROC curve parameters before PSM. D: Radar plot of ROC curve parameters after PSM. Note: NAC, Neoadjuvant Chemotherapy; ICI, Immune Checkpoint Inhibitor; PSM, Propensity Score Matching; ROC, Receiver Operating Characteristic.

Figure 3A). The NAC+ICI group demonstrated higher pCR rates and pathological downstaging rates compared to the NAC group (both P<0.001, **Figure 3B** and **3C**), while disease control rates were comparable (P=0.057, **Figure 3D**). After PSM, the NAC+ICI group continued to show superior clinical efficacy (P<0.001, **Figure 4A**), pCR rates (P<0.001, **Figure 4B**), and pathological downstaging rates (P<0.001, **Figure 4C**), with disease control rates remaining non-significant (P=0.240, **Figure 4D**).

Logistic regression analysis of independent risk factors affecting pCR

Logistic regression was performed to identify independent risk factors influencing pCR. ROC curve analyses were used to determine optimal cut-off values for quantitative variables (**Figure 5**). Before PSM, univariate and multivariate analyses identified treatment regimen (P<0.001, OR=0.161), tumor diameter (P=0.013, OR=2.145), and complications (P=

Table 3. Logistic regression analysis of independent risk factors for pCR in patients before PSM

Variable	Univariate Analysis				Multivariate Analysis			
	P Value	OR	Lower	Upper	*P* Value	OR	Lower	Upper
Treatment Regimen	<0.001	0.150	0.081	0.266	<0.001	0.161	0.086	0.290
Age (years)	0.657	0.870	0.461	1.581				
BMI (kg/m^2)	0.174	1.450	0.845	2.472				
Hb (g/L)	0.921	1.031	0.558	1.847				
PTL (×10^9/L)	0.051	1.711	0.994	2.930				
LYM (×10^9/L)	0.252	1.363	0.800	2.314				
ALB (g/L)	0.067	0.610	0.359	1.036				
Number of lymph nodes cleared	0.833	0.942	0.534	1.629				
Gender	0.208	0.611	0.268	1.263				
Smoking history	0.783	1.076	0.635	1.821				
History of alcoholism	0.283	0.598	0.241	1.622				
History of diabetes	0.957	0.977	0.441	2.398				
History of hypertension	0.800	1.098	0.548	2.362				
Pre treatment T stage	0.829	1.039	0.738	1.483				
Pre treatment N stage	0.510	0.792	0.381	1.541				
Tumor diameter	0.003	2.293	1.343	3.987	0.013	2.145	1.185	3.953
Tumor number	0.086	1.597	0.940	2.750				
Histologic grade	0.309	1.776	0.538	5.181				
Hydronephrosis	0.346	0.767	0.444	1.344				
Surgical Approach	0.376	0.840	0.576	1.255				
Urinary Flow Diversion Approach	0.734	0.911	0.533	1.574				
Histologic type	0.761	1.104	0.571	2.049				
Percentage of positive lymph nodes	0.260	0.798	0.544	1.199				
Positive margins	0.782	0.853	0.238	2.417				
Complications	0.007	2.075	1.222	3.544	0.005	2.339	1.300	4.266

Note: Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

0.005, OR=2.339) as independent predictors of pCR (**Table 3**). Post-PSM multivariate analysis confirmed treatment regimen (P<0.001, OR=0.141) and complications (P=0.019, OR=2.753) as independent risk factors for pCR (**Table 4**).

Cox regression analysis of independent prognostic factors affecting OS

Cox regression analysis identified key prognostic factors for OS before and after PSM. Before PSM, univariate analysis showed significant associations of age (P<0.001, HR=1.059), pre-treatment T stage (P<0.001, HR=2.342), tumor diameter (P=0.005, HR=1.810), histologic type (P=0.043, HR=1.827), and treatment outcome (P<0.001, HR=1.722) with OS (**Table 5**). Multivariate analysis confirmed age (P=0.001, HR=1.062), pre-treatment T stage (P<0.001, HR=2.363), tumor diameter (P=0.018, HR=1.683), and treatment outcome (P<0.001, HR=1.461) as independent prognostic factors (**Table 5**). After PSM, univariate analysis revealed significant associations of age (P=0.004, HR=1.066), pre-treatment T stage (P<0.001, HR=3.152), tumor diameter (P=0.045, HR=1.860), and treatment outcome (P<0.001, HR=1.894) with OS (**Table 6**). Multivariate analysis further confirmed age (P=0.011, HR=1.066), pre-treatment T stage (P<0.001, HR=3.244), tumor diameter (P=0.025, HR=2.077), and treatment outcome (P=0.020, HR=1.444) as independent prognostic factors (**Table 6**). Kaplan-Meier survival curves were generated for single-factor indicators affecting OS before and after PSM, showing significant differences in survival outcomes (**Figures 6** and **7**).

Discussion

MIBC remains the most aggressive and lethal form of bladder cancer, characterized by high

Table 4. Logistic regression analysis of independent risk factors for the pCR in patients after PSM

Variable	Univariate Analysis				Multivariate Analysis			
	P Value	OR	Lower	Upper	*P* Value	OR	Lower	Upper
Treatment Regimen	<0.001	0.141	0.053	0.329	<0.001	0.141	0.051	0.344
Age (years)	0.321	1.719	0.556	4.890				
BMI (kg/m^2)	0.863	1.067	0.513	2.259				
Hb (g/L)	0.460	0.759	0.362	1.573				
PTL (×10^9/L)	0.022	2.567	1.177	5.989	0.130	1.988	0.832	5.009
LYM (×10^9/L)	0.863	0.937	0.443	1.950				
ALB (g/L)	0.047	0.475	0.225	0.989	0.052	0.438	0.187	0.998
Number of lymph nodes cleared	0.679	0.853	0.405	1.834				
Gender	0.146	0.433	0.121	1.221				
Smoking history	0.771	1.114	0.534	2.312				
History of alcoholism	0.983	1.018	0.223	7.156				
History of diabetes	0.566	0.719	0.243	2.415				
History of hypertension	0.361	0.660	0.275	1.670				
Pre treatment T stage	0.166	1.419	0.877	2.383				
Pre treatment N stage	0.319	0.588	0.186	1.563				
Tumor diameter	0.098	1.872	0.899	3.997				
Tumor number	0.521	1.273	0.613	2.690				
Histologic grade	0.287	2.312	0.439	10.968				
Hydronephrosis	0.585	0.805	0.373	1.789				
Surgical Approach	0.963	1.014	0.582	1.886				
Urinary Flow Diversion Approach	0.792	1.107	0.525	2.397				
Histologic type	0.541	0.749	0.278	1.817				
Percentage of positive lymph nodes	0.332	0.765	0.449	1.343				
Positive margins	0.115	3.171	0.717	14.053				
Complications	0.047	2.106	1.011	4.437	0.019	2.753	1.201	6.552

Note: Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

recurrence and mortality rates [19]. Although advancements in immunotherapy and targeted therapies have improved outcomes for some patients, the prognosis for MIBC remains poor due to frequent diagnoses at advanced stages, treatment resistance, and the complexity of managing these patients [20]. Despite the availability of multiple treatment options, many patients experience disease progression or metastasis, resulting in suboptimal survival outcomes.

This study systematically evaluated the efficacy and safety of NAC alone versus NAC combined with ICI in MIBC patients, employing PSM to ensure balanced baseline characteristics. The results demonstrated that the combination of NAC and ICI significantly improved pCR and pathological downstaging rates compared to NAC alone. The NAC+ICI group exhibited significantly higher pCR and pathological downstaging rates than the NAC group, both before and after PSM. These findings highlight the potential of combining NAC with ICI to enhance the effectiveness of neoadjuvant treatment in MIBC patients.

The superior outcomes in the NAC+ICI group can be attributed to the synergistic mechanisms of these therapies. ICIs restore T-cell activity by alleviating immune suppression mediated by tumor cells, thereby enhancing the immune system's ability to target and destroy tumors. When used in conjunction with NAC, this dual approach can further improve pCR and pathological downstaging rates [21]. Additionally, the combination therapy appears particularly beneficial for patients who respond poorly to NAC alone. ICIs may help overcome chemotherapy resistance, reduce tumor bur-

Table 5. Cox regression analysis of the independent prognostic factors in the OS of patients before PSM

Variable	Univariate Analysis				Multivariate Analysis			
	P Value	HR	Lower	Upper	*P* Value	HR	Lower	Upper
Treatment Regimen	0.154	0.711	0.444	1.136				
Age (years)	<0.001	1.059	1.028	1.092	0.001	1.062	1.026	1.100
BMI (kg/m^2)	0.772	0.990	0.922	1.062				
Hb (g/L)	0.687	0.998	0.989	1.008				
PTL (×10^9/L)	0.174	1.002	0.999	1.005				
LYM (×10^9/L)	0.176	0.784	0.550	1.115				
ALB (g/L)	0.749	1.009	0.955	1.066				
Number of lymph nodes cleared	0.313	1.018	0.983	1.054				
Gender	0.146	1.566	0.855	2.865				
Smoking history	0.798	1.054	0.707	1.570				
History of alcoholism	0.135	0.416	0.132	1.314				
History of diabetes	0.322	0.694	0.336	1.431				
History of hypertension	0.824	1.063	0.622	1.817				
Pre treatment T stage	<0.001	2.342	1.826	3.004	<0.001	2.363	1.814	3.078
Pre treatment N stage	0.565	0.868	0.535	1.407				
Tumor diameter	0.005	1.810	1.195	2.741	0.018	1.683	1.095	2.587
Tumor number	0.793	1.055	0.708	1.571				
Histologic grade	0.971	0.983	0.400	2.419				
Hydronephrosis	0.562	1.133	0.742	1.732				
Surgical Approach	0.342	1.157	0.857	1.563				
Urinary Flow Diversion Approach	0.484	0.860	0.565	1.310				
Histologic type	0.043	1.827	1.018	3.276	0.110	1.628	0.896	2.959
Percentage of positive lymph nodes	0.703	0.937	0.670	1.310				
Positive margins	0.530	0.793	0.385	1.636				
Complications	0.780	1.060	0.704	1.597				
Variable	<0.001	1.722	1.394	2.127	<0.001	1.461	1.184	1.802

Note: PSM, Propensity Score Matching; Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

den, and control micrometastasis, leading to more complete surgical resections and lower postoperative recurrence rates [22].

Previous studies have reported similar findings. Hu et al. [23], in a multicenter retrospective study, compared the efficacy of NAC, ICI alone, and NAC combined with ICI in MIBC patients. Their results demonstrated that the NAC+ICI group achieved the highest pCR and pathological downstaging rates, consistent with our findings. They also developed a predictive model to identify patients most likely to benefit from combination therapy. Studies of Peyrottes et al. [24] supported the early use of ICIs in MIBC treatment, noting that single-arm clinical trials showed high pCR rates with ICIs, further validating their potential in combination regimens. Grassauer et al. [25] compared neoadjuvant immunotherapy (NAI), NAC, and no neoadjuvant treatment, finding that NAI achieved similar pCR and OS rates to NAC and was superior to no neoadjuvant therapy. This highlights the potential of ICIs as either an alternative or adjunct to NAC. Kim et al. [26] examined nivolumab combined with GC in MIBC, reporting slightly lower pCR rates than that observed in our NAC+ICI group. Nevertheless, their study confirmed the feasibility and effectiveness of combination therapy.

In this study, PSM effectively minimized baseline differences between the NAC and NAC+ICI groups, enhancing the reliability of our findings. Before PSM, significant differences were observed in baseline characteristics, including tumor diameter, tumor number, and adjuvant treatment. These differences were significantly

Table 6. Cox regression analysis of the independent prognostic factors for OS in patients after PSM

Variable	Univariate Analysis				Multivariate Analysis			
	P Value	HR	Lower	Upper	*P* Value	HR	Lower	Upper
Treatment Regimen	0.673	0.872	0.461	1.648				
Age (years)	0.004	1.066	1.021	1.113	0.011	1.066	1.015	1.119
BMI (kg/m^2)	0.520	1.034	0.933	1.147				
Hb (g/L)	0.790	1.002	0.988	1.016				
PTL (×10^9/L)	0.413	1.002	0.998	1.006				
LYM (×10^9/L)	0.933	0.977	0.567	1.682				
ALB (g/L)	0.903	1.005	0.925	1.092				
Number of lymph nodes cleared	0.277	1.031	0.975	1.091				
Gender	0.203	1.830	0.721	4.643				
Smoking history	0.285	0.724	0.401	1.308				
History of alcoholism	0.379	0.411	0.057	2.982				
History of diabetes	0.802	0.877	0.314	2.451				
History of hypertension	0.933	1.033	0.480	2.223				
Pre treatment T stage	<0.001	3.152	2.147	4.628	<0.001	3.244	2.149	4.898
Pre treatment N stage	0.609	0.826	0.397	1.719				
Tumor diameter	0.045	1.860	1.014	3.414	0.025	2.077	1.097	3.932
Tumor number	0.517	1.216	0.673	2.195				
Histologic grade	0.831	1.167	0.282	4.824				
Hydronephrosis	0.431	1.285	0.689	2.397				
Surgical Approach	0.106	1.413	0.930	2.148				
Urinary Flow Diversion Approach	0.247	1.420	0.784	2.572				
Histologic type	0.111	2.016	0.851	4.774				
Percentage of positive lymph nodes	0.530	1.151	0.743	1.782				
Positive margins	0.809	1.191	0.288	4.921				
Complications	0.630	1.163	0.629	2.150				
Variable	<0.001	1.894	1.397	2.569	0.020	1.444	1.058	1.971

Note: PSM, Propensity Score Matching; Hb, Hemoglobin; PLT, Platelet; LYM, Lymphocyte; ALB, Albumin; BMI, Body Mass Index.

reduced after PSM, greatly improving the comparability of the two groups. This strengthens the conclusion that NAC+ICI therapy offers superior pCR and pathological downstaging rates. Together, these studies underscore the significant clinical advantages of combining NAC with ICIs and the potential of this approach to improve outcomes in MIBC patients.

pCR is a crucial prognostic indicator of treatment efficacy in MIBC and is closely associated with long-term survival. Logistic regression analysis in our study identified the treatment regimen (NAC+ICI) and complications as independent risk factors significantly affecting pCR. NAC+ICI therapy enhances pCR rates through synergistic mechanisms, boosting the antitumor immune response and improving treatment efficacy [27, 28]. Conversely, complications can impair patients' overall health and immune function, reducing treatment tolerance and diminishing the likelihood of achieving pCR. These findings highlight the critical roles of treatment strategy and patient condition in determining pCR outcomes in MIBC treatment.

In Cox regression analysis, independent prognostic factors for OS in MIBC patients included age, pre-treatment T stage, tumor diameter, and treatment outcome. These factors significantly influence survival outcomes by reflecting the patient's overall health, tumor progression, and response to therapy.

Older patients often have more comorbidities and decreased immune function, leading to reduced treatment tolerance and poorer survival outcomes [29]. Higher T stage indicates

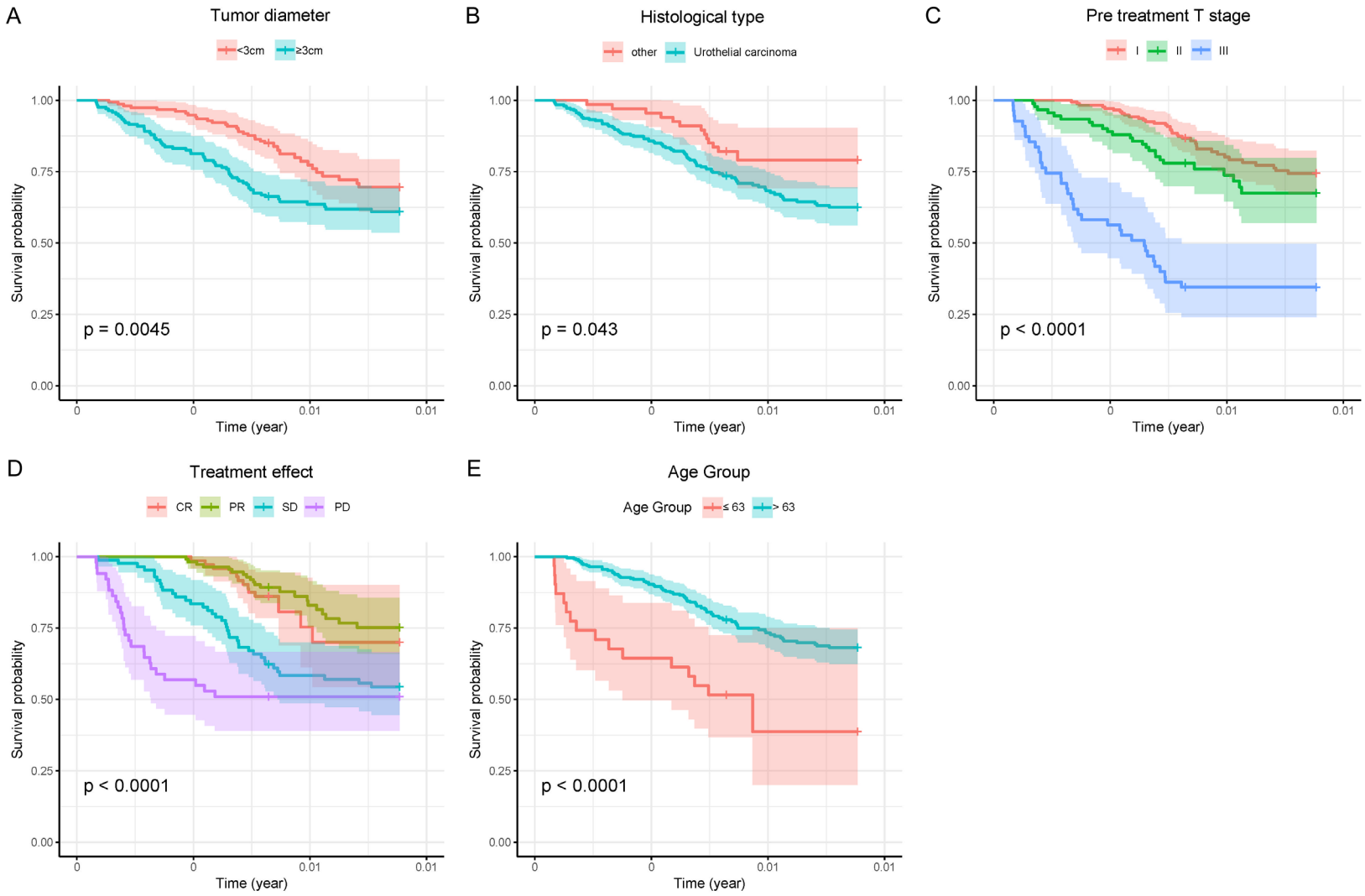

Figure 6. K-M survival curves of univariate factors associated with OS before PSM. A: K-M survival curve based on tumor diameter related to OS. B: K-M survival curve based on histological type related to OS. C: K-M survival curve based on pre-treatment T stage related to OS. D: K-M survival curve based on clinical outcome related to OS. E: K-M survival curve based on age related to OS. Note: OS, Overall Survival; PSM, Propensity Score Matching.

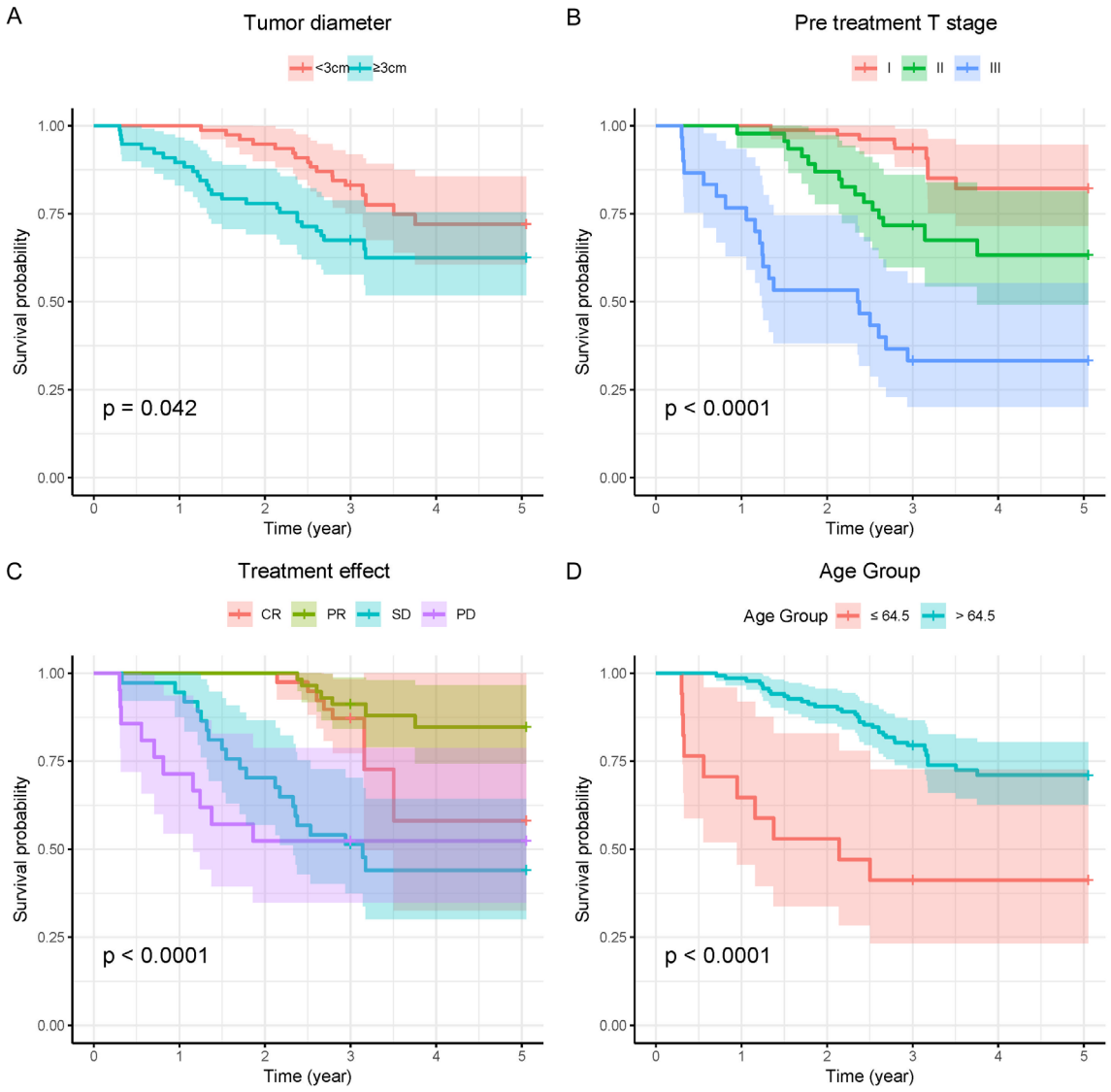

Figure 7. K-M survival curves of univariate factors associated with OS after PSM. A: K-M survival curve based on tumor diameter related to OS. B: K-M survival curve based on pre-treatment T stage related to OS. C: K-M survival curve based on clinical outcome related to OS. D: K-M survival curve based on Age related to OS. Note: OS, Overall Survival; PSM, Propensity Score Matching.

more aggressive and disseminated tumors, increasing treatment complexity and the risk of recurrence, resulting in lower long-term survival rates [30]. Additionally, larger tumors are associated with greater tumor burden, which complicates surgical procedures and increases the risk of local complications, directly impacting prognosis [31]. Finally, treatment outcome, as a direct evaluation indicator, reflects the patient's sensitivity and response to treatment. Favorable outcomes are associated with lower recurrence rates and longer survival, while poor outcomes suggest higher risks of disease progression [32, 33].

The importance of these factors is corroborated by previous studies. Macleod et al. [34] found that MIBC patients who received NAC had significantly better OS compared to those treated with adjuvant chemotherapy, consistent with our findings on the impact of treatment outcome. Zhou et al. [35] reported that patients undergoing NAC combined with radical cystectomy had significantly improved 5-year OS and cancer-specific survival compared to those receiving trimodal therapy, emphasizing the importance of pre-treatment T stage and treatment outcome. Similarly, Tan et al. [36] highlighted that while NAC and adjuvant che-

motherapy yielded comparable outcomes, adjuvant chemotherapy demonstrated better survival benefits in lymph node-positive patients, underscoring the significance of tumor staging and treatment selection. These findings align with our analysis, further validating the roles of age, pre-treatment T stage, tumor diameter, and treatment outcome as critical prognostic factors for OS in MIBC patients.

This study has several limitations. The limited sample size and retrospective nature of the study reduce the generalizability and statistical power of the findings. Although PSM was applied to mitigate confounding factors, inherent biases (e.g., information and selection biases) may still affect the reliability. The absence of long-term data restricts comprehensive evaluation of survival and recurrence risks associated with NAC+ICI treatment. Large-scale prospective studies with complete long-term follow-up data are necessary to validate these findings and improve the generalizability and credibility of the conclusions.

In conclusion, NAC combined with ICIs significantly improved pCR and pathological downstaging rates in MIBC patients, highlighting the efficacy of this combination therapy in enhancing neoadjuvant treatment outcomes. Age, pre-treatment T stage, tumor diameter, and treatment outcome were identified as independent prognostic factors for OS. Older patients often have more comorbidities, while those with higher T stage and larger tumor diameters face poorer prognoses. Achieving favorable treatment outcomes is closely tied to improved survival, underscoring the importance of individualized treatment strategies tailored to patient characteristics.

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Disclosure of conflict of interest

None.

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