

Original Article

Association of interleukin-6 serum levels with local tumor stage and lymph node metastasis of urothelial carcinoma

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Abstract

Introduction: Elevated preoperative interleukin-6 (IL-6) blood levels in urothelial carcinoma (UC) patients undergoing radical cystectomy (RC) have been linked to adverse pathological features. The aim of this prospective study of patients undergoing RC was to analyze whether preoperative IL-6 serum levels (i) correlate with local tumor stage, (ii) are associated with lymph node metastasis, and (iii) are elevated in patients with other oncologic or nononcologic indications for RC.

Materials and Methods: Patients undergoing RC for oncologic or nononcologic indications were prospectively included. IL-6 serum levels were measured preoperatively. Statistical analysis included Spearman correlation analysis and Receiver Operating Characteristics (ROC) analysis. ClinicalTrials.gov: NCT05153694.

Results: Between December 2021 and November 2024, 214 patients underwent RC at our department. Preoperative IL-6 serum levels were measured in 169 patients who provided informed consent. In UC patients, IL-6 levels correlated with local tumor stage ($r = 0.30$, $P = 0.001$) and higher levels were associated with lymph node metastasis ($P = 0.001$). The AUC was 0.678 (95% CI 0.58–0.77) and 0.681 (95% CI 0.58–0.79) for non-organ confined tumor growth and lymph node metastasis, respectively. No significant difference in preoperative IL-6 serum levels was observed between UC patients and patients with other oncologic or nononcologic indications for RC.

Conclusion: This prospective study found that elevated preoperative IL-6 serum levels correlated with local tumor stage and were associated with lymph node metastasis in UC patients undergoing RC. However, IL-6 levels were also elevated in patients with other oncologic or nononcologic indications for RC, underscoring the need for careful interpretation of this marker. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords: Radical cystectomy; Interleukin-6 (IL-6); Predictive marker; Urothelial carcinoma; Muscle invasive bladder cancer (MIBC); Staging; Blood-based biomarkers

1. Introduction

The treatment of patients with urothelial carcinoma (UC) of the bladder is heavily dependent on accurate tumor

staging [1,2]. The current guidelines of the European Association of Urology recommend the use of computed tomography (CT) for staging of patients with confirmed muscle-invasive bladder cancer (MIBC) [2,3]. However, nearly 50% of patients undergoing radical cystectomy (RC) are clinically understaged [1]. There are innovative radiological approaches like multiparametric magnetic resonance

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imaging (mpMRI) of the urinary bladder, which use standardized imaging and reporting of bladder cancer with the Vesical Imaging Reporting and Data System (VI-RADS) scoring classification [4]. Although this method shows promising first results for local tumor staging, it can still be severely limited by distortion from prior transurethral resection of the bladder or the tumor's location [5,6]. Besides the assessment of local tumor stage, preoperative lymph node staging is also a challenge in UC patients. A meta-analysis of 20 CT studies staging UC patients prior to RC reported a CT sensitivity of 0.40 (95% CI 0.33–0.49) and a specificity of 0.92 (95% CI 0.86–0.95) [7]. Gresser et al. developed a machine learning model utilizing radiomics features from preoperative CT images to classify lymph node status in patients with UC [8]. Their radiomics model with manual segmentation demonstrated superior lymph node discrimination compared to radiologist assessments, though the difference was not statistically significant [8]. Furthermore, a feasibility study by Unterrainer et al. explored the use of fibroblast activation protein inhibitors (FAPI), a novel positron emission tomography (PET) ligand, and found it to be a promising new biomarker for metastatic UC patients, suggesting that [⁶⁸Ga]Ga-FAPI-46 PET might improve the detection of metastatic sites compared to CT alone [9]. Taken together, both innovative approaches, radiomics and [⁶⁸Ga]Ga-FAPI-46 PET CT, have not yet met the clinical need for detecting occult lymph node metastases.

A different approach for tumor staging is the use of blood-based biomarkers [10]. A promising marker for UC patients undergoing RC is interleukin-6 (IL-6) [11,12]. Malignant cells exhibit high proliferative activity, driven by inflammatory molecules like IL-6, which are continuously secreted by various types of cells within the tumor microenvironment [13]. Dysregulation of IL-6 plays a fundamental role in the development of inflammation, autoimmune diseases, and cancer [14,15], as interleukins can create a supportive environment that promotes and accelerates cancer growth [16]. The first study to analyze preoperative plasma levels of IL-6 as marker in UC patients undergoing RC was conducted by Andrews et al. in 2002 [11]. In their preliminary study including 51 patients, they reported an association of elevated levels of IL-6 with adverse pathological features, including muscle invasion and lymph node metastasis [11]. An external validation study 20 years later by Schuettfort et al., [12] involving 1,036 patients, confirmed an independent association between preoperative plasma levels of IL-6 and an increased risk for \geq pT3 disease and lymph node metastasis. Both studies were significantly limited by the absence of an adequate control group. Andrews et al. used only healthy controls [11], while Schuettfort et al. [12] did not include any control group. Furthermore, neither study addressed common conditions that are known to influence IL-6 levels, like infections [17,18], obesity [19], diabetes [20], or smoking [21]. This could result in

overinterpretation of their results, as IL-6 is not a specific marker for UC [14].

The aim of this prospective study of patients undergoing RC was to analyze whether preoperative IL-6 serum levels (i) correlate with local tumor stage, (ii) are associated with lymph node metastasis, and (iii) are elevated in patients with other oncologic or nononcologic indications for RC.

2. Material and methods

2.1. Study design and patient cohort

We prospectively enrolled patients who underwent RC for either oncologic or nononcologic indications between December 2021 and November 2024 at the Department of Urology, LMU University Hospital Munich, Germany. Written informed consent was obtained from all patients before enrollment. Preoperative serum IL-6 levels were measured 1 to 3 days before cystectomy using a quantitative electrochemiluminescent immunoassay (ECLIA, Roche diagnostics). Clinicopathological characteristics were collected prospectively during the hospital stay. Patients who underwent neoadjuvant chemotherapy before RC were not excluded to reflect a real-world setting. As they represented only a small proportion of patients, they were not separately analyzed as ypT cases; instead, pT staging includes both patients with and without neoadjuvant chemotherapy. At our hospital, all eligible patients receive detailed counseling about neoadjuvant chemotherapy through either our outpatient department or their community urologist. We adhere to EAU guidelines, administering 4 cycles of gemcitabine and cisplatin. The analysis of organ confinement only included patients in whom tumor was found in the RC specimen. These patients were then divided into those with organ-confined and those with nonorgan-confined tumors. Lymph node dissection was performed at the treating surgeon's discretion and omitted in certain cases, such as patients with NMIBC or palliative indications. Lymph node metastasis refers to pathologically confirmed metastases (pN+). For the analysis of lymph nodes, we only assessed those cases where lymph nodes were removed and could be evaluated pathologically. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, approved by the university ethics committee and registered on ClinicalTrials.gov (NCT05153694).

2.2. Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables are presented as proportions. For IL-6 values below the detection limit (<1.5 pg/ml), a value of 0.75 pg/ml was assigned for the correlation analysis. To compare continuous variables, Levene's test was used to assess equality of variances, and the Shapiro-Wilk test was used to test for normal distribution. When normal distribution and equal variances were

found, a 2-tailed independent samples t-test was performed. If either equal variance or normal distribution was not met, a Mann-Whitney U test was performed. The Kruskal-Wallis test was employed to compare the distributions of 3 or more independent groups when the data did not meet the assumptions of normality or homogeneity of variance. Spearman correlation analysis was used to assess the strength and direction of the association between preoperative IL-6 serum levels and pathological tumor stage. For comparison between categorical variables, a Fisher's exact test was used. Significance was set at a 5% level. All statistical analyses were performed using DATAtab Team (DATAtab e.U., Graz, Austria).

3. Results

3.1. Clinicopathological characteristics and preoperative IL-6 serum level

Between December 2021 and November 2024, 214 patients underwent radical cystectomy (RC) at our department. Preoperative IL-6 serum levels were measured in 169 patients who provided written informed consent to participate in the study. Table 1 presents clinicopathological characteristics of all included patients and compares the different indications for radical cystectomy. Specifically, 149 patients (88%) had UC, 5 patients (3%) had other oncologic indications, and 15 patients (9%) had nononcologic indications for RC. Among the other oncologic indications, 3 patients had prostate cancer with bladder infiltration, 1 had a neuroendocrine tumor of the bladder, and 1 had metastasis of a malignant melanoma in the bladder. The nononcologic indications included 4 patients with therapy-

resistant hemorrhagic/radiation cystitis, 4 with (vesico-) urethral strictures, 4 with contracted bladder, and 3 with bladder fistula formation.

The clinicopathological characteristics are presented in Table 1. The median age of the patients was 72.4 years, with 82% of the cohort comprising male subjects. The median body mass index (BMI) was 25.8 kg/m². According to the American Society of Anesthesiologists (ASA) physical status classification, 78% of patients had severe systemic disease (ASA class >2). The median number of pack years was 15. Additionally, 31 patients (18%) had diabetes. Six patients (4%) reported chronic infectious diseases. Of 149 patients with UC, 26 patients (17%) had received neoadjuvant chemotherapy. Nonorgan-confined tumor growth (≥T3a) was observed in 42% of cases. Positive lymph nodes were found in 28 of 127 cases with an oncologic indication for cystectomy (22%). The median preoperative IL-6 serum level was 4.7 pg/ml (IQR 5.7 pg/ml). There was no difference in preoperative IL-6 serum levels between patients who had received neoadjuvant chemotherapy and those who did not (median 3.45 pg/ml vs. 4.7 pg/ml, $P = 0.942$). A comparison of clinicopathological characteristics between UC patients who received neoadjuvant chemotherapy and those who did not is shown in Supplementary Table 1. Patients receiving neoadjuvant chemotherapy were younger, with no other significant differences observed.

3.2. Association of preoperative IL-6 serum levels with local tumor stage and lymph node status of UC patients

The association between preoperative IL-6 serum levels and pathologic characteristics in patients with UC undergoing RC is shown in Table 3 and Fig. 1. We found a significant difference in preoperative IL-6 serum levels across the different local tumor stages ($P = 0.011$). Spearman correlation analysis demonstrated a moderate positive correlation between preoperative IL-6 serum levels and local tumor stage ($r = 0.30$, $P = 0.001$). Significantly higher IL-6 values were observed in patients with nonorgan-confined tumors compared to those with organ-confined tumors (median 4.2 pg/ml for organ-confined vs. 7.5 pg/ml for nonorgan-confined; $P = 0.002$). Similarly, significantly higher IL-6 values were found in patients with lymph node metastasis compared to those without (median 4.0 pg/ml for no lymph node metastasis vs. 7.5 pg/ml for lymph node metastasis; $P = 0.001$). The area under the ROC curve (AUC) for predicting nonorgan confined tumors was 0.678 (95% CI 0.58–0.77), and for predicting lymph node metastasis, the AUC was 0.681 (95% CI 0.58–0.79) (Fig. 2). In 25 of 149 patients (17%), no tumor was found in the RC specimen after RC, despite a definitive UC diagnosis following initial TUR-B (pT0). There was no significant difference in IL-6 levels between patients with NMIBC and those with pT0 (median 4.0 pg/ml for NMIBC vs. 3.9 pg/ml for pT0; $P = 0.60$). Taken together, IL-6 levels positively correlated

Table 1
Clinicopathological characteristics and known influence factors on IL-6 levels of the included 169 patients who underwent radical cystectomy (RC).

Characteristic	All
	$n = 169$ (100%)
Age (years)	72.4 (± 14.3)
Gender	
Male	139 (82%)
Female	30 (18%)
BMI (kg/m ²)	25.8 (± 4.9)
ASA class >2	131 (78%)
Pack years	15 (± 40)
History of smoking	120 (71%)
Diabetes	31 (18%)
Chronic infectious disease	6 (4%)
Neoadjuvant chemotherapy	26/149 (17%)
Non-organ confined tumor	54/129 (42%)
Positive lymph nodes	28/127 (22%)
Preoperative IL-6 (pg/ml)	4.7 (± 5.7)

Continuous variables are presented as median with interquartile range (IQR), categorical variables are presented as proportions. (%).

Abbreviations: ASA = American Society of Anaesthesiologists;

BMI = body mass index; IL-6 = interleukin-6.

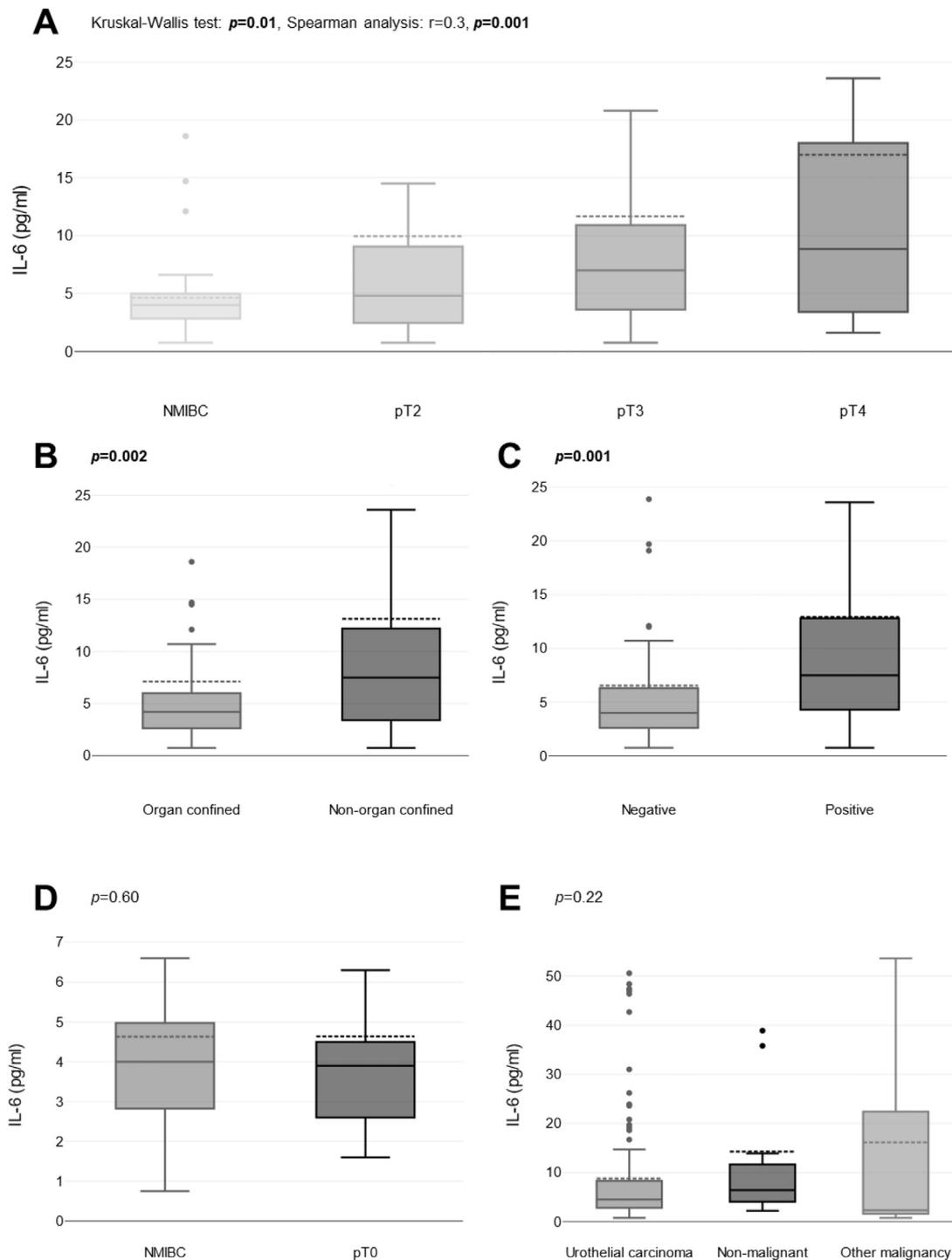


Fig. 1. Boxplot diagrams of preoperative serum levels of interleukin-6 (IL-6) of patients undergoing RC. RC: radical cystectomy. UC: urothelial carcinoma. NMIBC: nonmuscle invasive bladder cancer. Extreme outliers are not shown in the boxplot diagrams for better clarity (A) Different local tumor stages of patients with UC, Kruskal-Wallis test: $P = 0.011$; Spearman correlation analysis: $r = 0.3$, $P = 0.001$ (B) UC patients with organ confined vs. nonorgan confined tumor in UC patients, Mann-Whitney U test: $P = 0.002$ (C) UC patients with negative lymph nodes vs. positive lymph nodes, Mann-Whitney U test: $P = 0.001$ (D) UC patients with pT0 vs. NMIBC in final histopathological report after RC, Mann-Whitney U test: $P = 0.604$ (E) UC vs. other cancers vs. non-malignant indication for RC, Kruskal-Wallis test: $P = 0.222$.

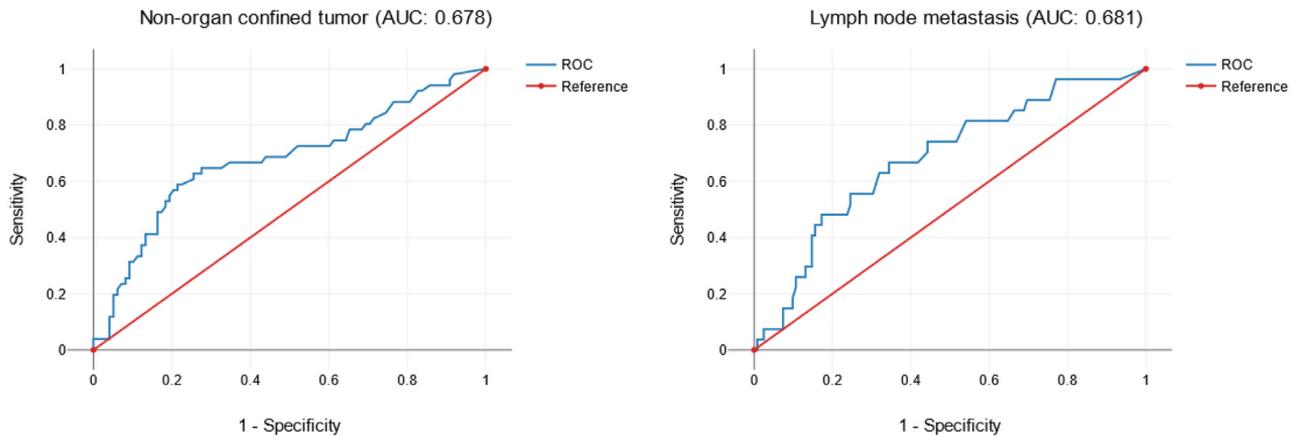


Fig. 2. Receiver operating characteristic (ROC) curves for prediction of (A) nonorgan confined tumor (AUC: 0.678 (95% CI 0.58–0.77)) and (B) lymph node metastasis (AUC: 0.681 (95% CI 0.58–0.79)) based on preoperative IL-6 serum levels for patients with urothelial carcinoma undergoing radical cystectomy. AUC: area under the ROC curve.

with local tumor stage of UC, and higher levels were associated with lymph node metastasis.

3.3. Preoperative IL-6 serum levels in patients with other oncologic or nononcologic indications for RC

There was no significant difference ($P = 0.22$) in preoperative IL-6 serum levels between UC patients (median 4.5 pg/ml, IQR ± 5.5), other oncologic indications (median 2.3 pg/ml, IQR ± 20.8), and nononcologic indications for RC (median 6.4 pg/ml, IQR ± 7.6) (Fig. 1 and Table 2). Furthermore, no significant discrepancies were observed in the clinicopathological characteristics or in known common influencing factors on IL-6 levels (BMI, smoking, diabetes, chronic infectious diseases) across the 3 groups (Table 2). Multiple linear regression analysis was performed to assess potential confounding factors influencing IL-6 levels (Supplementary Table 2). None of the examined variables (age,

BMI, smoking status, or diabetes) showed a statistically significant association with preoperative IL-6 levels.

4. Discussion

This prospective study evaluated the association of preoperative IL-6 serum levels with pathological features in patients undergoing RC for UC. To our knowledge, this is the second largest study available on this topic. Our findings demonstrate a moderate positive correlation between preoperative IL-6 serum levels and local tumor stage in UC patients. Elevated IL-6 levels were significantly associated with nonorgan-confined tumor growth and lymph node metastasis. The ROC analysis indicated that preoperative IL-6 serum levels had moderate predictive accuracy for both nonorgan confined tumor growth and lymph node metastasis.

In Germany, neoadjuvant chemotherapy is administered in 13% of MIBC patients undergoing RC on average [22].

Table 2

Comparison of clinicopathological characteristics and known influence factors on IL-6 levels between patients with urothelial carcinoma, other oncologic indications, and nononcologic indications.

Characteristic	Urothelial carcinoma <i>n</i> = 149 (88%)	Other oncol. indication <i>n</i> = 5 (3%)	Nononcol. indication <i>n</i> = 15 (9%)	<i>P</i> -value
Age (years)	72.3 (± 14.2)	71.5 (± 9.7)	76.0 (± 17)	0.73
Gender				
Male	123 (83%)	3 (60%)	13 (87%)	0.33
Female	26 (17%)	2 (40%)	2 (13%)	
BMI (kg/m ²)	25.8 (± 5.5)	27.2 (± 2.6)	25.9 (± 3.9)	0.70
ASA class >2	115 (78%)	4 (80%)	12 (80%)	1.00
Pack years	15 (± 38.5)	8.5 (± 23)	20 (± 43.5)	0.67
Diabetes	28 (19%)	1 (20%)	2 (13%)	0.99
Chronic infectious disease	4 (2.7%)	1 (20%)	1 (6.7%)	0.08
Nonorgan confined tumor	51/124 (41%)	3/5 (60%)	-	0.70
Positive lymph nodes	27/124 (22%)	1/3 (33%)	-	0.53
Preoperative IL-6 (pg/ml)	4.5 (± 5.5)	2.3 (± 20.8)	6.4 (± 7.6)	0.22

Continuous variables are presented as median with interquartile range (IQR), categorical variables are presented as proportions. (%). Abbreviations: ASA = American Society of Anaesthesiologists; BMI = body mass index; IL-6 = interleukin-6.

Table 3
Association of preoperative IL-6 serum levels and pathological features of patients with urothelial carcinoma undergoing radical cystectomy.

Pathological features	Preoperative IL-6 serum level (pg/ml)	P-value
Local tumor stage		
NMIBC, n = 38 (31%)	4.0 (±2.2)	0.01
pT2, n = 35 (28%)	4.8 (±6.6)	
pT3, n = 37 (30%)	7.0 (±7.3)	
pT4, n = 14 (11%)	8.9 (±14.6)	
Organ vs. nonorgan confined	4.2 (±3.4) vs. 7.5 (±8.8)	0.002
Negative vs. positive lymph nodes	4.0 (±3.7) vs. 7.5 (±8.5)	0.001
NMIBC vs. pT0	4.0 (±2.2) vs. 3.9 (±1.9)	0.60

Abbreviations: NMIBC: nonmuscle invasive bladder cancer; IL-6: interleukin-6.

Although this rate is gradually increasing, it still falls significantly short of the guideline recommendations [2]. In our cohort, 17% of MIBC patients received neoadjuvant chemotherapy prior to RC, which reflects real-world data. The largest study to date investigating IL-6 in cystectomy patients by Schuetfort et al. [12] excluded patients with neoadjuvant chemotherapy. As neoadjuvant chemotherapy represents the guideline-recommended standard of care, we deliberately chose not to exclude these patients in order to reflect a real-world clinical setting [2]. Indeed, neoadjuvant chemotherapy may influence IL-6 levels, for example through tumor downstaging [23]. However, even though neoadjuvant chemotherapy can cause tumor downstaging, the core statement of our study does not change: The IL-6 level at the time of surgery correlates with the tumor stage at the time of surgery.

Our study extends the limited existing research by including an appropriate control group. By comparing UC patients to those with other oncologic or nononcologic indications for radical cystectomy, we can present a more nuanced interpretation of IL-6 levels. We observed that elevated IL-6 levels were also present in patients with other indications for RC, which underscores the necessity for cautious interpretation of this marker. Inflammation is strongly associated with several types of cancer [13]. A meta-analysis of 20 studies including 7,276 patients evaluated CRP as a survival biomarker and reported that elevated CRP levels were significantly associated with poor overall and cancer-specific survival in UC patients [24]. Furthermore, UC is highly immunogenic, which also explains the success of immunotherapy in this entity [25,26]. However, IL-6 levels are elevated not only in UC but also in other urological malignancies, such as prostate cancer [27] and renal cell carcinoma [28]. Also, a multitude of common nonmalignant conditions have been linked to elevated IL-6 levels, including acute infections [17,18], obesity [19], diabetes [20], or lifestyle factors like smoking [21]. Consequently, the measured IL-6 levels in UC patients may not be solely attributed to the tumor burden of UC. However, in our study,

there was no association between obesity, diabetes, smoking, or age and preoperative IL-6 levels.

The results of our study indicate that IL-6 may serve as a valuable biomarker for the preoperative assessment of local tumor stage and lymph node metastasis in UC patients undergoing RC. Future prospective studies should focus on combining IL-6 levels of UC patients with radiomics, to investigate whether it can improve preoperative detection of occult lymph node metastasis.

4.1. Limitations

Despite its prospective design, this study has limitations. Firstly, it was conducted at a single center. Secondly, the relatively small number of patients undergoing cystectomy for indications other than UC reduces the statistical power of group comparisons. Thirdly, comparing IL-6 levels before and after neoadjuvant chemotherapy would be of interest but these data were not available. Fourthly, our sample size was insufficient for stratified analysis comparing tumor stages between patients with and without neoadjuvant chemotherapy, which would be necessary to properly assess the impact of neoadjuvant treatment on IL-6 levels.

5. Conclusion

This prospective study revealed a significant correlation between elevated preoperative IL-6 serum levels and local tumor stage, as well as an association with lymph node metastasis in UC patients undergoing RC. However, it is crucial to note that markedly elevated IL-6 levels were also observed in patients with other oncologic and nononcologic indications for RC. This finding underscores the necessity for cautious interpretation of IL-6 as a biomarker in RC patients. Despite these limitations, IL-6 shows promise as a supportive diagnostic tool for predicting local tumor stage and lymph node metastasis in UC. Future studies should explore the combined use of IL-6 levels with advanced imaging techniques, such as radiomics, to enhance diagnostic accuracy and clinical decision-making.

Ethics statement

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, approved by the university ethics committee (project number: 18-059) and registered on clinicaltrials.gov (NCT05153694).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Microsoft Copilot and DeepL in order to enhance the fluency of the text and to perform grammar checks. After using this tool/service, the authors reviewed and edited the

content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Benedikt Ebner: Writing – original draft, Data curation, Conceptualization. **Judith Hirsch:** Writing – review & editing, Data curation. **Annkathrin Holz:** Writing – review & editing, Data curation. **Yannic Volz:** Writing – review & editing. **Lennert Eismann:** Writing – review & editing. **Julian Hermans:** Writing – review & editing. **Nikolaos Pyrgidis:** Writing – review & editing. **Marc Kiddess:** Writing – review & editing. **Marie Semmler:** Writing – review & editing. **Sarah Takayama Fouladgar:** Writing – review & editing. **Iason Papadopoulos:** Writing – review & editing. **Michael Chaloupka:** Writing – review & editing. **Maria Apfelbeck:** Writing – review & editing. **Julian Marcon:** Writing – review & editing. **Philipp Weinhold:** Writing – review & editing. **Alice Ewert:** Writing – review & editing. **Philipp Kazmierczak:** Writing – review & editing. **Christian G. Stief:** Writing – review & editing, Supervision. **Gerald B. Schulz:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urolonc.2025.08.026>.

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