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Original Article

Diagnostic accuracy of cystoscopic biopsy for tumour grade in outpatients with urothelial carcinoma of the bladder and the risk factors of upgrading

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KEYWORDS
Cystoscopic biopsy;
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Diagnostic accuracy;
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Systemic inflammatory markers

Abstract *Objective:* To assess the concordance of tumour grade in specimens obtained from diagnostic cystoscopic biopsy and transurethral resection of bladder tumour (TURBT) and explore the risk factors of upgrading.
Methods: The medical records of 205 outpatients who underwent diagnostic cystoscopic biopsy before initial TURBT were retrospectively reviewed. Comparative analysis of the tumour grade of biopsy and operation specimens was performed. Tumour grade changing from low-grade to high-grade with or without variant histology was defined as upgrading. Logistic regression analyses were performed to identify the risk factors of upgrading.
Results: For the 205 patients, the concordance of tumour grade between specimens obtained from biopsy and operation was 0.639. The concordance for patients who were preoperatively diagnosed with low-grade and high-grade was 0.504 and 0.912, respectively. Univariate and multivariate logistic regression analyses showed that older age, tumour multifocality, high neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and low lymphocyte-to-monocyte ratio (LMR) were significantly associated with upgrading (odds ratio ranging from 0.412 to 4.364). The area under the curve of the different multivariate models was improved from 0.752 to 0.821, and decision curve analysis demonstrated a high net benefit when NLR, LMR, and PLR were added.

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Conclusion: Diagnostic cystoscopic biopsy may not accurately represent the true grade of primary bladder cancer, especially for outpatients with low-grade bladder cancer. Moreover, older age, tumour multifocality, high NLR, PLR, and low LMR are risk factors of upgrading, and systemic inflammatory markers improve the predictive ability.

1. Introduction

Bladder cancer (BCa) is the ninth most common cancer worldwide and ranks 13th in terms of yearly mortality from cancer [1]. More than 90% of BCa cases are urothelial carcinoma, and up to 70% of newly diagnosed cases are non-muscle invasive BCa (NMIBC), which is confined to superficial tumours (stages Ta, T1, carcinoma *in situ*) [2]. Although transurethral resection of bladder tumour (TURBT) is the primary diagnostic and treatment method for NMIBC, tumour recurrence and progression rates remain high [3]. Therefore, the risk stratification of NMIBC is important to aid in individualizing adjuvant treatment strategies and follow-up schedules.

Patients with NMIBC can be stratified into three risk groups according to the number of tumours, tumour size, recurrence rate, tumour stage, and tumour grade [4]. Tumour grade is a reliable determining factor of tumour biology and is classified into low-grade (LG) and high-grade (HG) subtypes according to the 2004 World Health Organization (WHO) grade classification system [5]. In addition, previous studies have revealed that the HG subtype often recurs and progresses to metastasis, even leading to death after local resection compared to the LG subtype [6—8]. Hence, if clinicians can recognize HG BCa early and adjust the grade of patients in advance, it will be of great help in clinical decision making.

Currently, the European Association of Urology strongly recommends performing TURBT as a diagnostic procedure and initial treatment step in patients suspected to have BCa [9]. However, TURBT may be associated with a high residual tumour rate, insufficient pathology staging, and poor prognosis [10]. Therefore, second TURBT, radical cystectomy, and chemotherapy are used for remedial treatment. In China, the majority of outpatients (74.3%) were diagnosed by white-light cystoscopy with biopsy, and TURBT was mostly recommended as part of the therapeutic procedure [11]. However, the reliability of tumour grade through cystoscopic biopsy remains unclear.

Therefore, the present study aimed to validate the diagnostic accuracy of cystoscopic biopsy for tumour grade and to explore the risk factors for upgrading in patients who were initially diagnosed with LG BCa.

2. Patients and methods

2.1. Study population

We retrospectively reviewed the medical records of patients with BCa at our institution between January 2015 and June 2018. The inclusion criteria were: (1) primary diagnosed with BCa by white-light cystoscopic biopsy at our institution; (2) received TURBT as the initial treatment after diagnosed. Patients who were diagnosed with papillary urothelial neoplasm of low malignant potential or active infection (*i.e.*, cold and leukocytosis), or had a history of inflammatory disease (*i.e.*, rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis) or upper urinary tract cancer, as well as patients with incomplete data were exclude from analyses, leaving 205 patients for final analyses. This study was approved by the Committee for Ethics of the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, P.R. China (2014—129).

2.2. Clinicopathological evaluation

Cystoscopic biopsy and TURBT were performed by the same urologist (Fan J or Wu K). The histological subtype of all specimens was diagnosed by two pathologists (Liang H and Zhang G) based on the 2004 WHO classification system. The diagnostic cystoscopic biopsy and preoperative blood cell counts were performed within 3 days prior to TURBT. Patients who were preoperatively diagnosed with LG were categorised as having concordance if the diagnosis was consistent with the tumour grade after TURBT. Moreover, we defined upgrading as tumour histopathology changing from LG to HG with or without variant histology. All cystoscopies were performed using an Olympus 18 Fr rigid digital video cystoscope (Olympus Medical Systems Co., Tokyo, Japan), and all biopsies were taken using a pair of disposable biopsy forceps (1.8 mm, open cup width 4.5 mm, Olympus Medical Systems Co., Tokyo, Japan). Moreover, the most accessible lesion was chosen for biopsy in clinical practice.

Tumour multifocality was defined as the synchronous presence of two or more tumours during cystoscopy examination. Systemic inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and low lymphocyte-to-monocyte ratio (LMR), were assessed as categorical variables according to approximate optimal cut-off points, which were analysed by receiver operating characteristic curves based on the largest Youden index. The area under the curve (AUC) was calculated to assess the improvement in discrimination when adding systemic inflammatory markers to the base model. Decision curve analyses were performed to show the net benefit against the threshold probability of multivariate models that contained preoperative biomarkers.

2.3. Statistical analysis

Data on continuous variables, including age and tumour diameter, are presented as the means or medians with their

respective ranges, and differences between groups were analysed with Student's *t*-test or the Mann-Whitney *U*-test as appropriate. Differences between categorical variables such as sex, smoking status, and systemic inflammatory markers were determined using Pearson's Chi-squared test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression models were used to assess the independent risk factors for upgrading. Statistical analysis was performed using PASW Statistics 18.0 (formerly SPSS, Chicago, IL, USA), and statistical significance was defined as $p<0.05$. Decision curve analysis (DCA), nomogram construction, and calibration curve analysis were performed by R i386 3.5.1 software (R foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Concordance between cystoscopic biopsy and TURBT

Of the 205 patients identified during the study period, 137 (66.8%) were diagnosed with LG BCa, and 68 (33.2%) were diagnosed with HG BCa by preoperative cystoscopic biopsy. Following TURBT, 123 patients were diagnosed with HG BCa without variant histology, while 70 patients were diagnosed with LG BCa. The concordance rate of tumour histopathology between diagnostic cystoscopic biopsy and TURBT is shown in Table 1. There was concordance in 131 (63.9%) patients (69 patients with LG BCa and 62 patients with HG BCa who were diagnosed by cystoscopic biopsy), but 68 (33.2%) patients experienced tumour upgrading, and 6 (2.9%) patients experienced tumour downgrading or had non-urothelial carcinoma based on the final pathological analysis. The concordance rates in patients who were preoperatively diagnosed with LG BCa and HG BCa were 50.4% and 91.2%, respectively. Moreover, for 68 patients who experienced tumour upgrading, 65 (95.6%) patients were preoperatively diagnosed with LG BCa.

In patients diagnosed with LG BCa by cystoscopic biopsy, the tumour grade between biopsy and operation was inconsistent in 68 (49.6%) patients. Among them, there were one patient with non-tumour, papillary urothelial neoplasm of low malignant potential, and sarcoma, respectively. The remaining 65 (47.4%) patients were HG with or without variant histology on pathological analysis.

3.2. Baseline characteristics of the patients diagnosed with LG

The clinical characteristics and tumour appearance of the patients initially diagnosed with LG BCa by cystoscopic biopsy are shown in Table 2. The median patient age was 63 (range: 25–84) years, and 106 (79.1%) patients were male. A total of 47.8% of patients had a history of smoking. Moreover, 73.1% of patients chose bipolar TURBT as the operative method, while 26.9% chose front-firing potassium-titanyl-phosphate green-light laser *en bloc* resection. At the time of cystoscopic examination, the median tumour size was 2.00 (range: 0.50–4.00) cm, and 76 (56.7%) patients had a single tumour. According to receiver operating characteristic curves based on tumour upgrading and concordance, the optimal threshold values of NLR, LMR, and PLR were chosen as 3.73, 123.94, and 4.96, respectively. Thus, 19 (14.2%) patients had NLR $\geq$3.73; 41.0% of patients had PLR $\geq$123.94; and 50 (37.3%) patients had LMR $<$4.96.

Among 137 patients who initially diagnosed with LG BCa, three patients who experienced tumour downgrading or had non-urothelial carcinoma based on the final pathological analysis were exclude from analyses to explore risk factors for upgrading. Thus, the remaining 69 patients were classified as Group A (tumour grade unchanged) and 65 patients were classified as Group B (tumour upgrading) according to the previous definition of upgrading. Most of the clinical characteristics showed no difference between Groups A and B, except for age, tumour number, NLR, PLR, and LMR.

3.3. Risk factors for tumour upgrading

Univariate analysis (Table 3) showed that there were no significant differences between the two groups regarding sex, smoking status, operative methods, or tumour diameter ($p>0.05$). However, differences were observed in terms of age, tumour number, NLR, PLR, and LMR, which were associated with tumour upgrading ($p<0.05$). Multivariate analysis confirmed that older patients might be more prone to upgrading (odds ratio [OR]: 1.049; 95% confidence interval [CI]: 1.005–1.095). In addition, tumour multifocality was an independent predictive factor of upgrading (OR: 3.757; 95% CI: 1.583–8.919). Moreover, patients with higher NLR or PLR values were more likely to experience upgrading (OR: 4.364, 95% CI: 1.068–17.833; OR: 3.578, 95% CI: 1.474–8.685, respectively). However,

Table 1 Concordance of tumour grade between cystoscopic biopsy and TURBT.

Cystoscopic biopsy (tumour grade)	Postoperative tumour grade, *n*									Total, *n*
	Non-tumour	Papillary lesions	PUNLMP	LG	HG	HG with glandular differentiation	HG with squamous differentiation	Sarcoma	Malignant melanoma	
LG	1	0	1	69	61	4	0	1	0	137
HG	0	1	0	1	62	2	1	0	1	68
Total	1	1	1	70	123	6	1	1	1	205

TURBT, transurethral resection of bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; LG, low-grade; HG, high-grade.

Table 2 Characteristics of patients who were preoperatively diagnosed with LG and the comparison between Group A (tumour grade unchanged) and Group B (tumour upgrading).

Characteristic	Cohort ($n=134$[a])	Group A ($n=69$)	Group B ($n=65$)	p-Value
Age, median (range), year	63 (25–84)	59 (25–82)	65 (28–84)	0.001
Sex, *n* (%)				0.547
Female	28 (20.9)	13 (18.8)	15 (23.1)	
Male	106 (79.1)	56 (81.2)	50 (76.9)	
Smoking status, *n* (%)				0.499
Never	70 (52.2)	38 (55.1)	32 (49.2)	
Ever/current	64 (47.8)	31 (44.9)	33 (50.8)	
Operative methods, *n* (%)				0.549
Bipolar TURBT	98 (73.1)	52 (75.4)	46 (70.8)	
KTP laser	36 (26.9)	17 (24.6)	19 (29.2)	
Tumour number, *n* (%)				0.001
Single	76 (56.7)	50 (72.5)	26 (40.0)	
Multiple	58 (43.2)	19 (27.5)	39 (60.0)	
Tumour diameter, median (range), cm	2.00 (0.50–4.00)	1.50 (0.50–3.80)	2.00 (0.50–4.00)	0.286
NLR, *n* (%)				0.004
<3.73	115 (85.8)	65 (94.2)	50 (76.9)	
≥ 3.73	19 (14.2)	4 (5.8)	15 (23.1)	
PLR, *n* (%)				0.001
<123.94	79 (59.0)	50 (72.5)	29 (44.6)	
≥ 123.94	55 (41.0)	19 (27.5)	36 (55.4)	
LMR, *n* (%)				0.001
<4.96	50 (37.3)	16 (23.2)	34 (52.3)	
≥ 4.96	84 (62.7)	53 (76.9)	31 (47.7)	

LG, low-grade; TURBT, transurethral resection of bladder cancer; KTP, front-firing potassium-titanyl-phosphate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

[a] Among 137 patients who initially diagnosed with LG bladder cancer, three patients who experienced tumour downgrading or had non-urothelial carcinoma based on the final pathological analysis were exclude from analyses to explore risk factors for upgrading.

Table 3 Univariable and multivariate analyses for the association between Group A (tumour grade unchanged) and Group B (tumour upgrading).

Characteristic	Univariable			Multivariable		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age (continuous)	1.056	1.020–1.093	0.002	1.049	1.005–1.095	0.027
Sex (female *vs.* male)	0.774	0.336–1.783	0.547	0.967	0.291–3.213	0.957
Smoking status (never *vs.* ever/current)	1.264	0.641–2.493	0.499	1.595	0.640–3.977	0.316
Operative methods (bipolar TURBT *vs.* KTP laser)	1.263	0.588–2.716	0.549	2.385	0.868–6.551	0.092
Tumour number (single *vs.* multiple)	3.947	1.912–8.148	0.001	3.757	1.583–8.919	0.003
Tumour diameter (continuous)	1.290	0.768–2.169	0.336	1.677	0.860–3.271	0.129
NLR (<3.73 *vs.* ≥ 3.73)	4.875	1.524–15.596	0.008	4.364	1.068–17.833	0.040
PLR (<123.94 *vs.* ≥ 123.94)	3.267	1.590–6.710	0.001	3.578	1.474–8.685	0.005
LMR (<4.96 *vs.* ≥ 4.96)	0.275	0.131–0.578	0.001	0.412	0.172–0.990	0.047

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; TURBT, transurethral resection of bladder cancer; KTP, front-firing potassium-titanyl-phosphate; OR, odds ratio; CI, confidence interval.

higher LMR represented a lower risk of upgrading (OR: 0.412; 95% CI: 0.172–0.990).

3.4. Clinical utility of the predictive models

The base model was built based on age, sex, smoking status, operative methods, tumour number, and tumour diameter; the AUC was 0.752. Moreover, the AUC was improved upon adding NLR, PLR, and LMR. Furthermore, when compared to that of the base model, the discrimination of the model that simultaneously contained NLR, PLR, and LMR was significantly improved, and the difference was statistically significant ($p=0.036$) (Table 4). DCA (Fig. 1) showed that the model that simultaneously included NLR, PLR, and LMR could have greater net benefit for predicting upgrading compared to the base model in the range of most threshold probabilities from 0 to 0.8, which meant better clinical utility.

Table 4 Improvement in the predictive accuracy of models when adding systemic inflammatory markers to the base model.

Model	AUC	Improvement	*p*-Value
Base model[a]	0.752		
Base model + NLR	0.777	0.025	0.227
Base model + PLR	0.790	0.038	0.173
Base model + LMR	0.788	0.036	0.122
Base model + NLR + PLR + LMR	0.821	0.069	0.036

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; AUC, area under the curve.

[a] The base model included age, sex, smoking status, operative methods, tumour number, and tumour diameter.

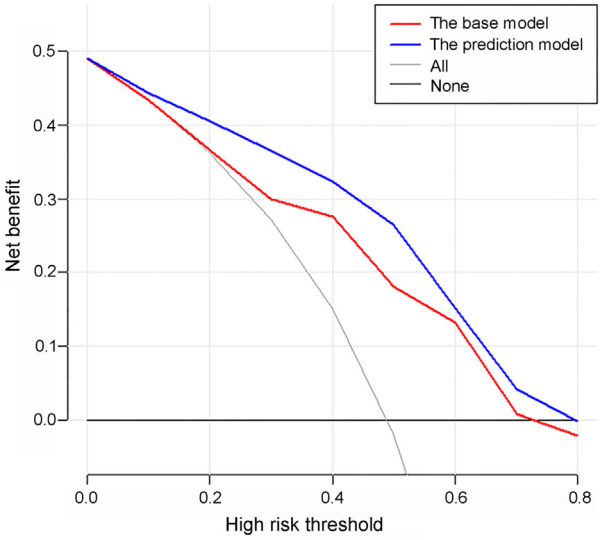

Figure 1 Decision curve analysis of the predictive model. Lateral axis line: assumes no patients have upgrading. Grey line: assumes all patients have upgrading. Red line: the base model with age, sex, smoking status, operative methods, tumour diameter, and tumour number. Blue line: the base model adding NLR, PLR, and LMR. The graph gives the expected net benefit per patient relative to the base model with age, sex, smoking status, operative methods, tumour diameter, and tumour number ("treat none"). The unit is the benefit associated with one upgraded patient evaluated with the base model adding NLR, PLR, and LMR. LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

3.5. Construction and internal validation of the nomogram

Based on our findings, we selected age, tumour number, NLR, PLR, and LMR as variables to develop a nomogram (Fig. 2). Calibration curve analysis (Fig. 3) showed that the mean absolute error of our nomogram was 3%, which meant the correspondence between the predicted and actual risks of upgrading was almost consistent.

4. Discussion

In China, the histological evaluation of sampled tissue during cystoscopy is the most common diagnostic method in an outpatient setting and plays a crucial role in the management of BCa [11]. Urinary cytology is noninvasive and not associated with pain or bleeding compared to preoperative biopsy. However, urinary cytology cannot replace the role of cystoscopic biopsy in the clinical practice. In clinical practice, mostly patients still choose cystoscopic examination and biopsy during follow-up. Thus, the application rate of urinary cytology is still extremely low (11.9%) in China [11]. In 205 patients of our study, only 29 (14.1%) patients underwent urinary cytology. Moreover, in patients with LG tumours by preoperative biopsy, only 15 (10.9%) patients underwent the examination of urinary cytology and the results were mostly negative. Furthermore, we found that the results of urinary cytology were not associated with upgrading (OR: 1.792; 95% CI: 0.563–63.984; $p=0.138$).

Owing to its higher specificity and lower cost, mostly patients with grossly haematuria would like to choose biopsy during cystoscopy examination to clarify the nature and malignancy of the lesion. Therefore, the histopathological examination of the cystoscopic biopsy not only gives the diagnosis, but also provides the additional information to the urologist for further treatment choice. For patients who were diagnosed with HG by cystoscopic biopsy, if they simultaneously had multiple high-risk factors (such as multifocality lesions, >3 cm larger tumours, and hydronephrosis) or multi-parameter magnetic resonance imaging indicated muscle-invasive, radical cystectomy rather than TURBT was then recommended. According to the data from Chinese Bladder Cancer Consortium, which include 14 260 cases from 44 Chinese Bladder Cancer Consortium centres from January 2007 to December 2012, the majority of BCa in outpatients (74.3%) were diagnosed by white-light cystoscopy with biopsy, while only 16.9% outpatients would choose a diagnostic TURBT. Thus, preoperative biopsy still accounts for a large proportion in the management of BCa in China, which may avoid unnecessary procedure, reduce the burden on current hospital resources, and decrease the cost of patients. However, the diagnostic accuracy of tumour grade through cystoscopic biopsy is still unclear. In the present study, we found that cystoscopic biopsy may not be a reliable method to determine the grade of primary diagnosed BCa. Approximately one-third of patients experienced tumour upgrading after TURBT, and most of these patients were initially diagnosed with LG BCa.

The reasons for the failure of cystoscopic biopsy in accurately diagnosing the grade of BCa remain unclear. One possible explanation is the intratumoural heterogeneity. As shown in Supplementary Table 1, for 137 patients who were diagnosed as LG BCa, there were only 12 (8.8%) patients had upgrading in specimens from biopsy by a different pathologist. After reviewing the specimens of TURBT by another pathologist, 7 (10.1%) patients had upgrading from LG to HG with or without variant history (Supplementary Table 2). Thus, intratumoural heterogeneity may be the main cause of this phenomenon since various studies have reported that the heterogeneity in the tumour grade of BCa

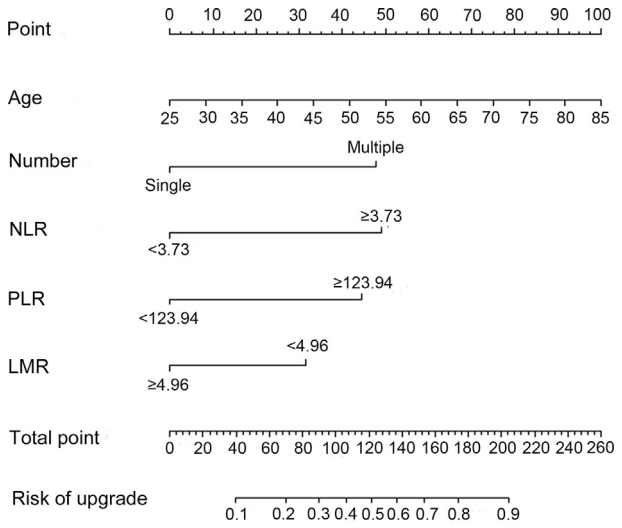

Figure 2 A nomogram to predict the tumour upgrading of LG diagnosed by cystoscopic biopsy before first-time TURBT. Directions: age, tumour number, NLR, PLR, and LMR positive for an individual patient. A line is drawn upwards to the number of points in each category. The points are totalled, and then a line is drawn downwards to find the probability of upgrading before the first TURBT in patients who were diagnosed with LG by preoperative cystoscopic biopsy. When the total points are over 0.9 or below 0.1 of the probability, this indicates extremely high (over 0.9) or low risk (below 0.1), respectively. LG, low-grade; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TURBT, transurethral resection of bladder tumour.

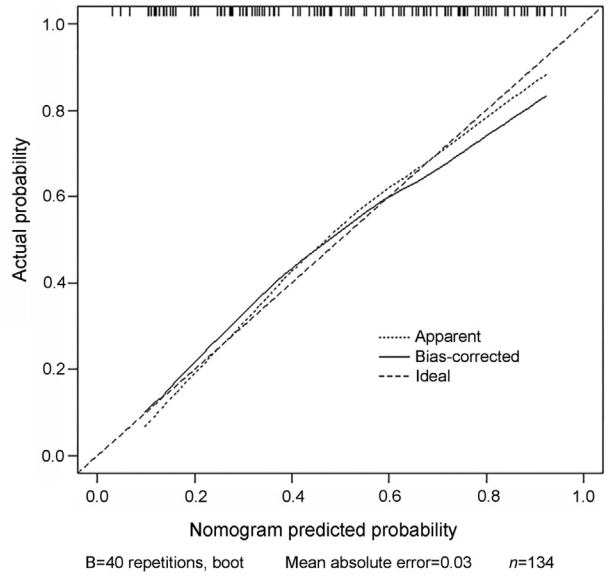

Figure 3 Calibration curves of nomogram performance. The bias-corrected calibration plots showed only a limited departure from the ideal predictions. The mean absolute error was 0.03.

is as much as about 40% [12—14]. Moreover, another retrospective study reported that different areas from the same tumour in patients with BCa are often molecularly different, which might possess a predictive characteristic and have an impact on response to treatment [15]. In our study, we found that 67.2% of patients with multiple tumours experienced upgrading after surgery. This finding validated the conception that different areas of the tumour have different biological behaviour, even for a single tumour. Another reason is that urologists mostly choose superficial lesions that are easily obtained in cystoscopic biopsy. Therefore, the grade of the tumour in a single-point biopsy may not represent the malignancy of the tumour and may lead to improper therapy decisions. Thus, these findings indicate that multiple random biopsies of tumours should be taken during cystoscopic examination, even for a single tumour.

In addition, the difficult reproducibility of tumour grading reports and vague subjective judgement criteria could explain the inconsistency between the biopsy and postoperative tumour grade. How to assign a grade for a borderline lesion (between LG and HG) is a dilemma for pathologists. Therefore, the International Consultation on Urological Diseases recommends the consideration of the presence or absence of tumour number, size, and prior recurrence rate as part of the pathologist's decision on whether to "upgrade" a borderline lesion to a HG lesion [16]. However, we believe that it is not enough to consider only these risk factors to solve this problem, and clear cut-off points and other cost-effective biomarkers need to be explored.

Age is a strong and independent risk factor for the incidence and mortality of BCa [17]. However, there is still no conclusion on the biological and clinical aggressiveness of BCa in young versus old patients. Various studies have documented that older age is associated with poor differentiation and aggressive behaviour in BCa [18—20]. In addition, a recent study conducted by Shapur et al. [21] revealed that advancing age is a significant risk factor for HG BCa ($p<0.0001$, OR: 1.05; 95% CI: 1.03—1.06). Subsequently, we revealed that older patients might be more likely with HG tumour (OR: 1.041; 95% CI: 1.005—1.078; $p=0.025$) (Supplementary Table 3). Furthermore, our study also found that older patients might be prone to upgrading from LG to HG (OR: 1.049; 95% CI: 1.005—1.095). Taken together, these results strongly indicate that older patients are associated with a more aggressive disease pattern.

In the current study, the AUC of the predictive model that only comprised patient and tumour characteristics was 0.752. This result strongly suggests that clinical features alone are insufficient to identify the biology of tumour. Recently, Lotan et al. [22] analysed the data of 206 patients with clinically localized BCa and found that molecular subtyping could help urologists identify patients who were more likely to have aggressive disease. However, molecular subtyping may not be widely used due to its expensive cost. Increasing evidence has shown that immune cells play important roles in tumourigenesis, tumour development, and metastasis [23]. The reduction in lymphocytes results in deficient cytotoxic conditions and impairs anti-tumour activity, while high neutrophil, monocyte, or platelet levels reflect an inflammatory reaction with an increased production of growth factors, cytokines, and chemokines [24—26]. Thus, universally available, easily accessible,

cost-effective, and reproducible biomarkers such as NLR, PLR, and LMR are gradually being used to identify the biology of tumours. The data of 302 patients with BCa were analysed by Tang. et al. [27], and they pointed out that a preoperative high NLR was associated with HG. In addition to NLR, a recent study found that PLR and LMR were also related with HG BCa and the correlations between PLR, NLR, and LMR were strong [28]. The same conclusion was reached by this present study that patients with higher NLR, PLR, or lower LMR might be associated with HG BCa (OR: 2.509, 95% CI: 1.198—5.258, $p=0.015$; OR: 4.321, 95% CI: 2.155—8.665, $p=0.01$; OR: 0.549, 95% CI: 0.305—0.987, $p=0.045$, respectively) (Supplementary Table 3). These results indicated that urologists should pay attention to the possibility of upgrading in patients with abnormal systemic inflammatory markers.

Systemic inflammatory markers, including NLR, PLR, and LMR, are easily measured and cost-effective. Moreover, the predictive accuracy of the model that simultaneously included NLR, LMR, and PLR was significantly improved when compared to the base model (0.821 *vs.* 0.752; $p=0.036$). Additionally, DCA was used to validate the clinical utility of the models and showed that the net benefit of the model that included the systemic inflammatory markers was higher across a wide range of threshold probabilities. Thus, we deemed that the use of systemic inflammatory markers could be helpful in identifying subjects harbouring aggressive tumours in routine clinical practice.

As with all retrospective studies, this study was limited by its study design and limited sample size from a single institution, which might lead to selection bias. Furthermore, leukocyte count can be influenced by geographical and ethnic differences, and the cut-off values of these systemic inflammatory markers are still unclear [29]. Since most of patients will undergo TURBT, it is still necessary to explore the necessity of preoperative cystoscopy biopsy plus serum inflammation markers in predicting the risk of upgrading. Therefore, further prospective multicentre studies are warranted to support our findings.

5. Conclusion

Diagnostic cystoscopic biopsy is a safe and simple way to diagnose BCa, but it may not accurately represent the grade of primary diagnosed BCa, especially for patients who are initially diagnosed with LG BCa. Furthermore, based on the characteristics of the patients and the tumour, systemic inflammatory markers, which are cost-effective and easily measurable, can significantly improve the ability to identify the risk of upgrading in patients who are preoperatively diagnosed with LG. However, TURBT is still recommended for most of patients with primary diagnosed BCa due to its diagnostic and therapeutic benefits, and preoperative biopsy plus serum inflammatory markers could not replace it.

Author contributions

Study concept and design: Dalin He, Kaijie Wu.
Data acquisition: Junjie Fan, Hua Liang, Xinqi Pei, Tao Yang.
Data analysis: Junjie Fan, Xinqi Pei, Tao Yang.
Drafting of manuscript: Junjie Fan, Jinhai Fan, Lei Li.
Critical revision of the manuscript: Dalin He, Kaijie Wu.
Administrative, technical, or material support: Hua Liang, Guanjun Zhang, Jinhai Fan, Lei Li, Kaijie Wu.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2021.09.003.

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