

Preoperative prediction of muscle invasion in bladder cancer: a preliminary development and validation of diffusion-weighted-imaging-based habitat analysis

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Abstract

Objectives

To develop a model that integrated based on diffusion-weighted imaging (DWI) MRI for preoperative assessment of muscle-invasion (MI) in bladder cancer and to evaluate its diagnostic performance and impact on clinical decision-making.

Methods

One hundred and seventy-five patients with pathologically confirmed bladder urothelial carcinoma were prospectively included in this study. Each patient underwent 3.0 T MRI scan with T2WI, multi-b-value DWI, and dynamic contrast-enhanced imaging (DCE). Their clinical and imaging features were analyzed by two radiologists. Unsupervised clustering of DWI parameters resulted in four habitats. Finally, receiver operating characteristic (ROC) analysis, logistic regression, and validation were performed on the CMH model integrating clinical, MRI, and habitat factors.

Results

Habitat analysis showed significant differences between muscle-invasive and non-muscle-invasive bladder cancer groups. The habitat factors indicated a good predictive performance in both nomogram and univariate/multivariate regression analysis. Habitat 1, length, and stalk were the independent risk factors of MI. The CMH model integrating habitat, clinical and MRI factors achieved a better AUC of 0.777 than the CM model integrating clinical and MRI factors (0.740). The CMH model also had the best prediction efficiency in the calibration curve and DCA analysis. Model interpretability was affirmed by SHAP analysis.

Conclusion

Habitat analysis based on functional DWI sequences improves the assessment of bladder cancer muscle invasion and supports clinical decision-making.

1. Introduction

Muscle invasion (MI) is a critical prognostic factor for bladder cancer [1]. Muscle-invasive bladder cancer (MIBC), which accounts for approximately 25% of newly diagnosed bladder cancers, is associated with higher risk of progression and recurrence. Treatment paradigms are vastly different between NMIBC and MIBC [2]. For MIBC, more comprehensive and aggressive treatments are required, usually a multidisciplinary approach including systemic chemotherapy, radical cystectomy (RC), immunotherapy integrated with chemotherapy, and/or radiation [3]. Considering the invasive procedure of diagnosing

bladder cancer before surgery involves time consuming, pain, and higher charges, non-invasive accurate preoperative diagnosis of MIBC is of great significance in clinical practice. Additionally, bladder cancer that presents molecular heterogeneity makes early diagnosis and prognosis more complicated and leads to confounding clinical outcomes [4]. Therefore, more emphasis should be placed on the status of muscle invasion and tumor heterogeneity when considering biomarkers of bladder cancer.

The significance of DWI has been widely acknowledged over the past few decades, with its critical role in the evaluation of bladder cancer being well established [5–8]. A markedly high signal intensity on DWI sequences is of substantial diagnostic value in both the detection and staging of bladder cancer. Intravoxel incoherent motion (IVIM) and diffusion kurtosis imaging (DKI), as advanced DWI techniques, have also been reported to possess remarkable clinical values. IVIM has been developed as a method to simultaneously quantify both diffusion and perfusion information of tumors, while DKI has been proposed to reflect the true diffusion of water molecules and the non-Gaussian behavior of water diffusion in-vivo [9, 10]. Many studies have reported the correlation between advanced DWI techniques and muscle invasive bladder cancer [11–19]. However, there is currently no literature reporting on the utilization of DWI-based habitat analysis for predicting MI in bladder cancer patients.

Radiomics is the transformation of traditional visual medical images into mining high-dimensional data to achieve objective quantitative assessment of biological characteristics and has been shown to be correlated with the status of muscle invasion and chemoradiation responsiveness of bladder cancer [20, 21]. Habitat radiomics analysis, an emerging approach with advanced machine learning specifically aimed at identifying distinct tumor areas or cell subpopulations, represents a promising imaging technique [22, 23]. While traditional radiomics assumes uniform feature distribution within a lesion or its surrounding area, habitat analysis has the potential to non-invasively characterize tumor heterogeneity by accurately segmenting the tumor and its surrounding area into subregions that reflect the diverse characteristics and heterogeneity of the tumor [24].

As a result, our study aimed to prospectively explore the value of habitat analysis in differentiating MIBC from non-muscle-invasive bladder cancer (NMIBC) (Fig. 1). We hope this study will provide insights into habitat imaging and peritumoral radiomics for future investigations.

2. Materials and Methods

2.1 Patients

This prospective study was approved by the Institutional Review Board of our hospital. The written informed consent was obtained from each patient. A total of 365 patients suspected of having bladder tumors underwent pelvic MRI examinations. The inclusion criteria were as follows:

(a) patients who didn't receive preoperative treatment or biopsy before MRI examinations;

(b) transurethral resection of bladder tumor (TURBT) or radical cystoscopy (RC) within 1 months after MRI examinations and confirmed to have bladder urothelial carcinoma by pathology.

The exclusion criteria were as follows:

- (a) patients with contraindications for MRI such as claustrophobia, renal insufficiency or cardiac pacemaker;
- (b) lesions too small (diameter less than 5mm) for placing regions of interest (ROIs) or the existence of severe motion artifacts that could affect the analysis of images;
- (c) pathologically confirmed benign lesions or carcinoma in situ (CIS) which cannot be identified on DWI images; or absence of pathological findings.

The detailed flowchart of the study was shown in Fig. 2. All lesions were divided into MIBC (T stage > 1) and NMIBC (T stage < 2) according to the 8th American Joint Committee on Cancer (AJCC) staging system. The pathological grade of all bladder tumors was classified according to the 2016 WHO classification [20] as low grade (LG) and high grade (HG).

2.2 MRI protocol

All patients underwent MR examinations on 3-T MRI scanners (750, GE Medical Systems; and 770, United Imaging Healthcare) in the supine position. Participants were asked to void and to drink 500 ml of water at least one hour before the MR examination to properly distend the bladder. The MR examination included T2-weighted MRI, T1-weighted MRI, dynamic contrast-enhanced imaging (DCE) and multi-b-value axial DWI. The protocol of MRI scan was shown in the supplementary table S1.

2.3 Clinical and radiological characteristics

A comprehensive analysis was conducted on various clinical and radiological characteristics, including age, sex, the presence of gross hematuria, chronic urinary tract infection, diabetes, schistosomiasis infection, smoking status, tumor location, tumor size, hemorrhage, the presence of tumor stalk, and tumor contact length (TCL). The radiological characteristics were assessed independently by two experienced radiologists who were blinded to pathologic results (A with 8 years of experience and B with 20 years of experience in urinary system imaging diagnosis). In case of discrepancies between two observers, a third more experienced radiologist was consulted (C with over 30 years of experience in radiology).

2.4 Imaging analysis

All MRI images were acquired and evaluated via a picture archiving communication system (PACS) station. The volume of interests (VOIs) on the DWI images ($b = 800 \text{ s/mm}^2$) using 3D Slicer [25] were manually delineated to incorporate the entire bladder lesion.

IVIM and DKI parameters were measured and processed based on VOIs on multiple b values DWI sequence. DWI, IVIM, and DKI parameters were computed using following equations:

$$S(b) = S_0 \cdot \exp \cdot (-b \cdot ADC);$$

$$S(b) = S_0 \cdot \{f \cdot \exp \cdot (-b \cdot D_p) + (1 - f) \cdot \exp \cdot (-b \cdot D_t)\};$$

$$S(b) = S_0 \cdot \exp \cdot (-b \cdot D_{app} + b^2 \cdot D_{app}^2 \cdot K_{app}/6).$$

$S(b)$ is the signal intensity at different diffusion values, S_0 is the signal intensity at $b = 0$ s/mm²; f , D_t , and D_p are the abbreviations of perfusion fraction, true diffusion coefficient, and pseudo diffusion coefficient. f represents the intra-voxel volume fraction of perfusion. D_p and D_t represent perfusion- related diffusion and pure diffusion. D_{app} is the kurtosis corrected diffusion coefficient, and K_{app} is a unitless metric representing the deviation of water motion from Gaussian distribution. ROIs were manually drawn to include every plane of the tumor, avoiding the areas of hemorrhage, inflammation and necrosis. The parametric fitting of IVIM was based on the b values of 0, 10, 25, 50, 80, 100, 150, 200, 500, 800, 1000, and 1500 s/mm², while that of DKI was based on the b values of 200,500,800, 1000, 1500, and 2000 s/mm².

2.5 Habitat mapping and feature extraction

The multi-regional similarity matrix (MSI) features were calculated from habitat images and corresponding ROIs using the Pyradiomics package. Then, the MSI features were reduced via principal component analysis (PCA), retaining components that collectively explained $\geq 95\%$ of the variance. The optimal number (k) of subgroups was determined using the within-groups sum of squares (WSS). Finally, the K-means clustering method was conducted using the optimized k value to identify the patient subgroups. Peri-habitat regions were also included calculating by axially dilating the ROI with 5 voxels. Finally, 39 features were extracted, including first-order features (e.g., mean, variance, skewness) and second-order texture features derived from gray-level co-occurrence matrix (GLCM), gray-level size-zone matrix (GLSZM), and gray-level run-length matrix (GLRLM).

2.6 Statistical analysis

Statistical analyses were performed with SPSS (version 25.0; SPSS Software) and R project v. 4.4.2 (<http://www.r-project.org/>). Continuous variables were presented as mean $\pm$ standard deviation (SD), while categorical variables were presented as numbers. Kolmogorov-Smirnov test was performed to ascertain the distribution of continuous data. Wilcoxon test and Kruskal-Wallis test were used for clinical and habitat variables between MIBC and NMIBC groups. Categorical variables were analyzed using the Pearson's chi-squared test.

ROC curves were generated to compare various models. Statistical significance of AUC differences was evaluated using the DeLong test, with $p < 0.05$ denoting significant performance disparities. The diagnostic performance of the models was evaluated using AUCs and calibration curves. Decision curve analysis was employed to compare the net benefit obtained from models.

3. Results

3.1 Patients' characteristic

A total of one hundred and seventy-five patients (median age, 69 years; range, 40–91 years), concluding one hundred and thirty-two with NMIBC (75.4%; median age, 68 years; range, 26–91 years) and forty-three with MIBC (24.6%; median age, 72 years; range, 40–87 years), were enrolled in this study. Based on the WHO classification, 44 lesions (25.1%) were classified as low grade (LG) and 131 lesions (74.9%) were confirmed high grade (HG). The interval between MRI scan and surgery treatment was 12.4 ± 6.9 days. There were 129 patients (73.7%) received TURBT and 46 patients (26.3%) received RC. Clinical and radiological characteristics were shown in Table 1.

Table 1
Clinical and radiological characteristics

Variables	NMIBC (n = 132)	MIBC (n = 43)
Age*	68	72
Gender		
Male	104 (78.7%)	28 (65.1%)
Female	28 (21.2%)	15 (34.9%)
Gross hematuria		
Absent	49 (37.1%)	16 (37.2%)
Present	83 (62.9%)	27 (62.8%)
Chronic urinary tract infection		
Absent	92 (69.7%)	24 (55.8%)
Present	40 (30.3%)	19 (44.2%)
Diabetes		
Absent	111 (84.1%)	37 (86.0%)
Present	21 (15.9%)	6 (14.0%)
Schistosomiasis infection		
Absent	130 (98.5%)	43 (100.0%)
Present	2 (1.5%)	0 (0%)
Smoking		
Absent	102 (77.3%)	32 (74.4%)
Present	30 (22.7%)	11 (25.6%)
Location		
Other walls	106 (80.3%)	35 (81.4%)
Trigone	26 (19.7%)	8 (18.6%)
Tumor size	2.13 ± 1.32	3.49 ± 1.78
Hemorrhage		
Absent	122 (92.4%)	34 (79.1%)
Present	10 (7.6%)	9 (20.9%)
*data: median (interquartile ranges)		

Variables	NMIBC (n = 132)	MIBC (n = 43)
Stalk		
Absent	72 (54.5%)	32 (74.4%)
Present	60 (45.5%)	11 (25.6%)
TCL		
≤ 3 cm	108 (81.8%)	14 (32.6%)
> 3 cm	24 (18.2%)	29 (67.4%)
*data: median (interquartile ranges)		

3.2 Habitat analysis

Each BC lesion underwent habitat analysis and clustering. According to the Calinski–Harabasz score, the optimal number of clusters were identified as 4, representing their categorization into four distinct subregions/habitats in our cohort. The elbow method of clustering and distribution of four clusters in IVIM, DKI, and ADC values were illustrated in Fig. S1.

For group comparison between MIBC and NMIBC, MIBC has significantly higher fraction than NMIBC in habitat 1 ($p < 0.001$), and there were no significant differences in habitat fraction of habitat 2, habitat 3 and habitat 4 between MIBC and NMIBC, as shown in Fig. 3. Additionally, Fig. 4 presents a representative habitat imaging from a muscle-invasive bladder cancer lesion. The relevant representative regions of the four habitats in the image as well as the pseudo-color maps of each parameter were included.

3.3 Analysis of the predictive factors for MIBC

Univariate and multivariate analyses were performed to investigate the predictive value of radiological features in differentiating MIBC from NMIBC and the results are presented in Table 2 and Table 3. In univariate analysis, habitat 1 ($p < 0.001$), the length of the lesion ($p < 0.001$), the presence of hemorrhage ($p = 0.02$), the presence of stalk ($p = 0.02$), TCL ($p < 0.001$) were significantly different between NMIBC and MIBC. The significant radiological features above were subsequently subjected to multivariate analysis. In multivariate analysis, habitat 1, length and TCL were the independent risk factor of MIBC ($p < 0.05$, $p < 0.001$, and $p = 0.03$, respectively).

Table 2
Explore the MI risk factors with univariate logistic regression analysis

Variable	Odds Ratio	95%CI	p value
Habitat1	1.03	1.01–1.04	< 0.001
Habitat2	1.00	0.98–1.01	0.739
Habitat3	1.00	0.99–1.01	0.865
Habitat4	0.98	0.97–1.00	0.017
Gender	1.99	0.94–4.23	0.073
Age	1.01	0.98–1.05	0.370
Location	0.93	0.39–2.25	0.875
Length	1.72	1.36–2.19	< 0.001
Stalk	0.41	0.19–0.89	0.023
Hemorrhage	3.23	1.22–8.58	0.019
TCL	1.48	1.23–1.76	< 0.001
Smoking	1.17	0.53–2.59	0.701
Hematuria	1.00	0.49–2.03	0.992
Cystitis	1.82	0.90–3.69	0.097
Infections	0.00	0.00–Inf	1.00
Diabetes	0.86	0.32–2.29	0.758

Table 3
Explore the MI risk factors with multivariate logistic regression analysis

Variable	Odds Ratio	95% CI	p value
Habitat1	1.03	(1.01–1.04)	<0.05
Length	1.56	(1.22–1.99)	<0.001
Stalk	0.39	(0.17–0.90)	0.03

3.4 Construction and validation of preliminary nomogram for differentiating MIBC from NMIBC

A preliminary nomogram was developed to differentiate MIBC from NMIBC, concluding various MRI features in multivariate logistic regression analysis (Fig. 5). The C-index was calculated to assess the

formulated nomogram and other indicators. The C-index for combined nomogram was 0.721, which was significantly higher than that of clinical nomogram, which was 0.666. As shown in Fig. 6A, CM model which integrates clinical and MRI features reached an AUC of 0.740 (95%CI: 0.644–0.837). Meanwhile, the CMH model which integrates clinical features, MRI features and habitat analysis achieved a higher AUC value of 0.777 (95%CI: 0.692–0.862).

As shown in Fig. 6B and 6C, the calibration curve indicated superior consistency between estimation and observation for the discrimination performance in distinguishing MI status. Furthermore, the DCA exhibited that the CMH model performed improved discriminative values compared with the CM model, indicating that the CMH model could serve as a more robust method for differentiating MIBC from NMIBC. As shown in Table S2, 5-fold cross validation indicated that the model was notable and steady. The SHapley Additive exPlanations (SHAP) algorithm was employed to generate an importance ranking. By calculating the SHAP values for the three selected characteristics, interpretability was provided for the output of the combination model, as demonstrated in Fig. S2.

4. Discussion

In our study, we investigated the efficacy of DWI-based habitat analysis in predicting muscle invasiveness of bladder cancer and screened independent risk factors for muscle-invasive bladder cancer (MIBC). Specifically, we enrolled a diverse cohort of patients diagnosed with bladder cancer, including individuals with varying stages and grades of the disease, ensuring a wide range of cases for analysis. Subsequently, we employed advanced DWI-based habitat analysis techniques, which involved intricate imaging procedures and data processing methods. Simultaneously, we aimed to screen for independent risk factors for MIBC and proposed a model that could provide substantial support in predicting clinical prognosis and formulating clinical decision-making strategies.

Tumors with higher malignancy tend to present denser cellularity and a more complex micro-environment than benign lesions, inducing more diffusion barriers. Previous studies reported that MIBC was more aggressive compared with NMIBC, comprised of atypical cells, heterogenous cellular components, and compact microstructure[26]. Nonetheless, the accurate reflection of the true diffusion by DWI could be affected by the existence of macromolecules, organelles and cellular membrane in MIBC. Based on the DWI model, IVIM and DKI was proposed to reflect the true diffusion and non-Gaussian distribution of in vivo water molecules. They have already been proved to show reliable efficacy in evaluating muscle-invasive bladder cancer[14, 27].

Several studies have shown the clinical applications of radiomics in bladder cancer[28, 29]. While traditional radiomics focuses on analyzing tumor features such as shape, texture, and intensity, habitat radiomics enables the segmentation of tumors into distinct "habitats," each representing unique biological characteristics—such as necrosis, hypoxia, and high cellular density. Kong et al.[19] developed a VHRiS model that combined conventional radiomics, habitat radiomics, and clinical features to detect bladder cancer with variant histology. In this research, an unsupervised clustering based on all

IVIM and DKI parameters within the VOI calculated from the same MRI sequence with same image resolution were utilized for habitat imaging analysis. Tumor subregions were clustered into four habitats according to the *k*-means analysis in our study. The clustering approach could minimize bias in the obtained data and simultaneously provide information on diffusion, perfusion, and kurtosis.

In the univariate regression analysis, both habitat 1 and habitat 4 demonstrated strong performance, whereas in the multivariate regression analysis, habitat 1 remained statistically significant. These findings suggest that high cell density, true diffusion characteristics, and non-Gaussian distribution are key indicators of bladder cancer invasiveness. The results also reveal that tumors with higher invasiveness were inherently heterogeneous with multiple distinct microenvironments, which have a significant impact on treatment response and clinical outcomes.

Logistic regression model revealed that length and stalk were also independent risk factors for MIBC, which was in keeping with previous research concerning the applications of multi-parameter MRI to bladder cancer [13, 30–32]. Previous studies have also emphasized the importance of these anatomical features in predicting the aggressiveness and progression of MIBC. The length of the tumor may be related to its growth rate and the extent of invasion. Stalk, which was once called by “inchworm sign”, has been demonstrated to be associated with stage T1 of bladder cancer [6, 32, 33].

Furthermore, we developed and validated a preliminary model and constructed a nomogram incorporating multiparametric MRI characteristics and clinical characteristics to streamline the statistical model and optimize the predictive accuracy of MIBC. Calibration curve presented a superior consistency between nomogram predicted probability and actual observed probability. While the DCA revealed better predictive benefits with a broader range of threshold probability, which guaranteed the reliability of the developed nomogram. Habitat fraction serves as a measure that reflects the tumor composition and may be more sensitive in monitoring the progression and proliferation of bladder cancer. A relatively larger area under the decision curve of the CMH model than the CM model suggested the proposed method in this research could offer net benefit during identifying the MI risk.

An unsupervised clustering method based on quantitative data from IVIM and DKI was first employed in determining MI status of bladder cancer. This approach reduces the subjectivity inherent in traditional imaging judgment and enhances objectivity, thereby rendering the assessment of MI status more reliable. The reason we conduct habitat analysis using quantitative data obtained from IVIM and DKI instead of from the traditional DWI sequence is that the parameters of IVIM and DKI are able to capture a more extensive range of information, covering tumor perfusion and the extent of deviation from the Gaussian distribution. Therefore, even without an external validation group, the results of our study provide a new analysis perspective for predicting muscle invasive potential, and the predictive ability is better than clinical factors alone.

Several limitations in this study should be noted. First, the lesions of our study were obtained in a single center, which led to the possibility of model overfitting and a relatively low reproducibility. Second, despite the unsupervised clustering, no external validation was performed using data from cohorts in

other external centers. The lack of external validation could limit the generalizability of the findings and their applicability to broader populations. Third, the corresponding tumor regions of different habitats are not clear due to the technical challenges and ethical considerations. Thus, although it is an accessible and feasible tool for doctors to evaluate the muscle invasion of BC, the model still needs to be further investigated in a larger cohort with external validation. Subsequent studies should involve the matching and sampling of surgical tissue specimens to corresponding MRI habitats for integrated bioinformatic analysis and validation. Besides, more efforts should be made to probe into the grading of BC and therapeutic effect of BC treatment.

5. Conclusion

Habitat analysis based on functional DWI sequences could serve as an effective measurement of the muscle invasion of BC. Combining with clinical and MRI features, the DWI-based habitat model could potentially enhance the accuracy and effectiveness of clinical decision-making processes, thereby contributing to more optimized patient management.

Declarations

Compliance with Ethical Standards

Human Ethics and Consent to Participate declarations: the study was approved by the Institutional Review Board of Zhongshan hospital affiliated to Fudan University. The written informed consent was obtained from each patient.

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Author Contribution

Credit author statement Qing Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - Original DraftYibo Tang: Data Curation, Investigation, Formal analysis, MethodologyBohong Cao: Data Curation, Investigation, Formal analysis, MethodologyHaitao Sun: Methodology, Formal analysis, Writing - Review and EditingPu-Yeh Wu: Software, Visualization, Formal analysisShaofeng Duan: Conceptualization, Software, ResourcesJiaqi Wang: Software, ResourcesShuai Jiang: Conceptualization, Resources, Supervision, Project AdministrationShengxiang Rao: Project Administration, SupervisionJianjun Zhou: Conceptualization, Project Administration, Supervision, Validation, Writing - Review and EditingAll authors reviewed the manuscript.

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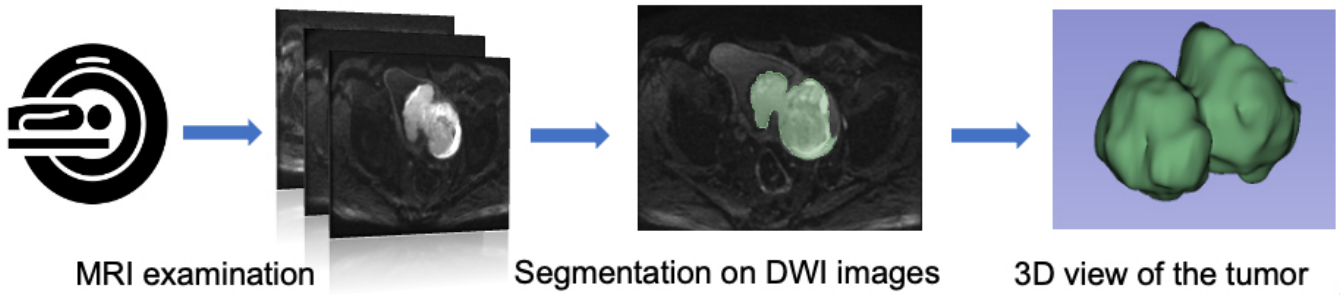
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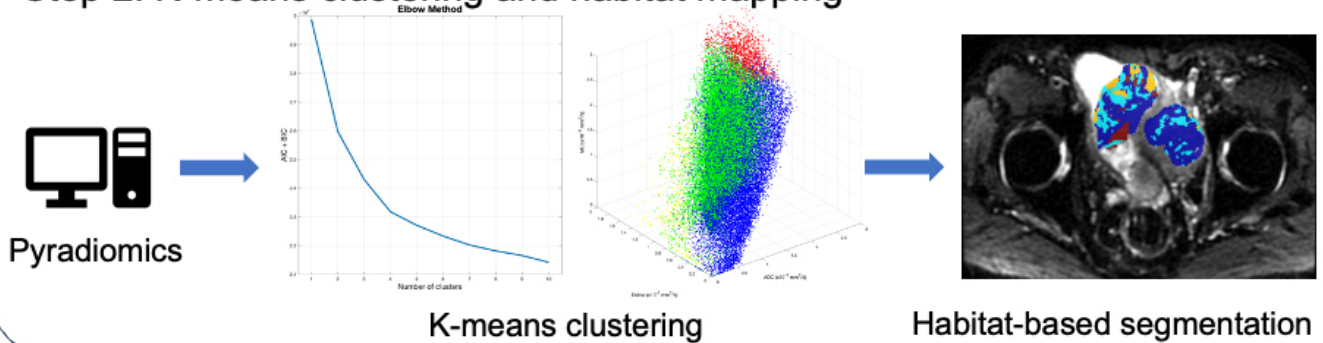
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Figures

Step 1: MRI examination and VOI segmentation



Step 2: K-means clustering and habitat mapping



Step 3: Model construction and validation

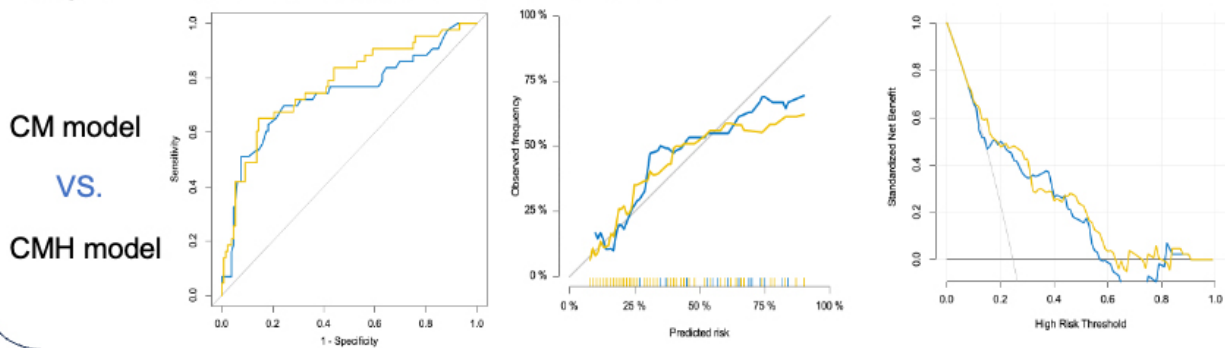


Figure 1

The overall technical roadmap of this study

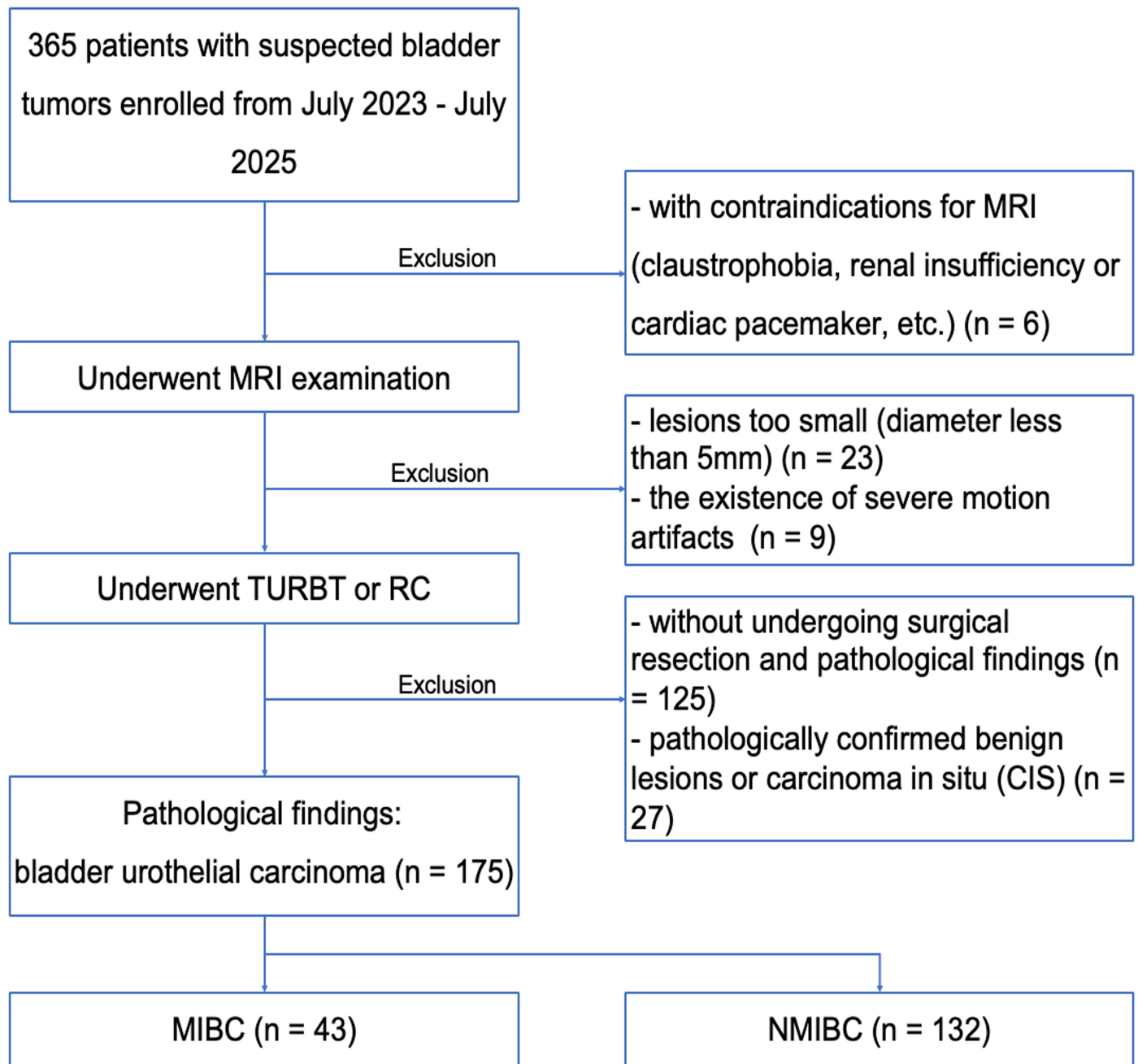


Figure 2

The flowchart of patients' enrollment

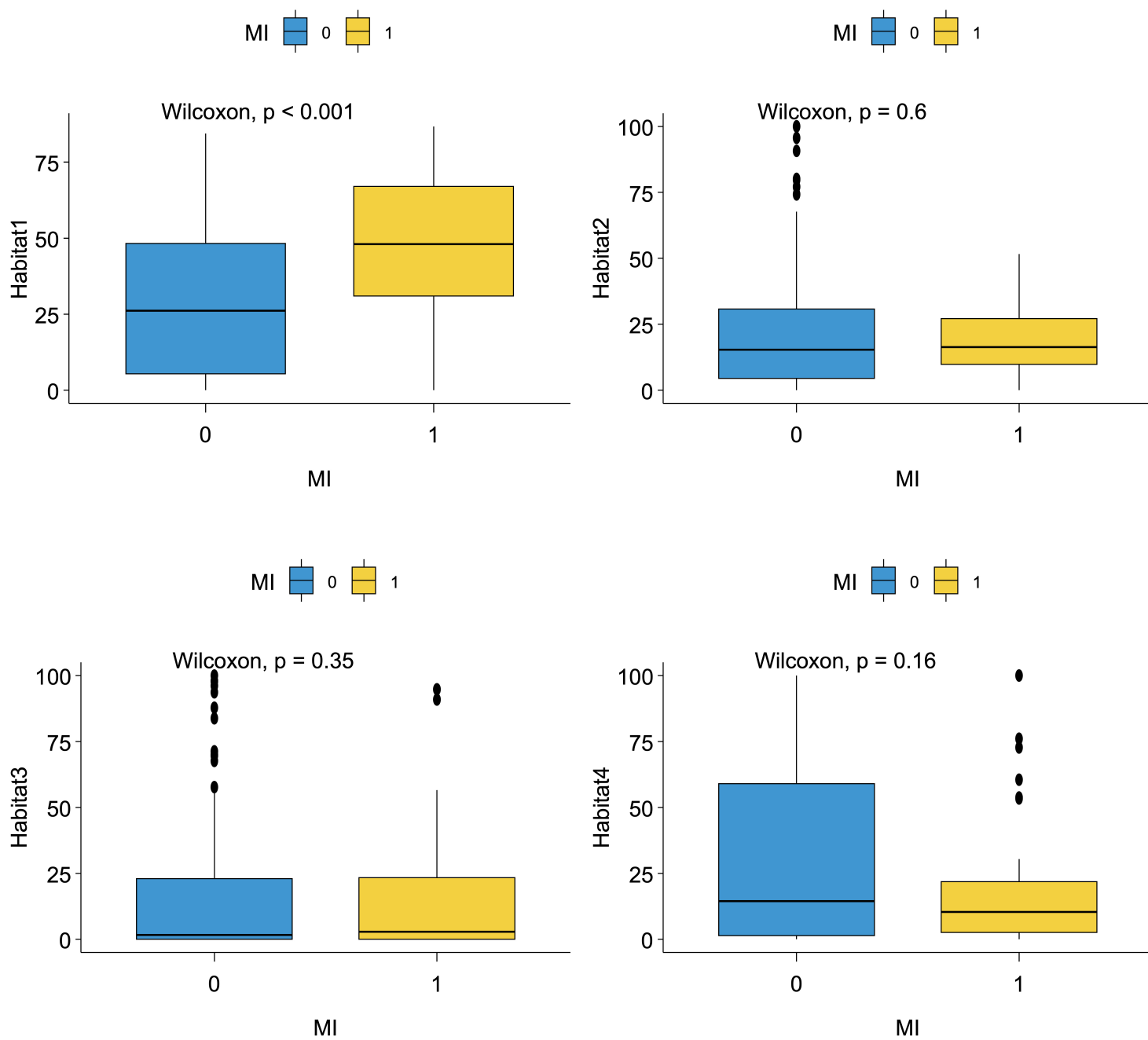


Figure 3

Group comparison of habitats between MIBC and NMIBC

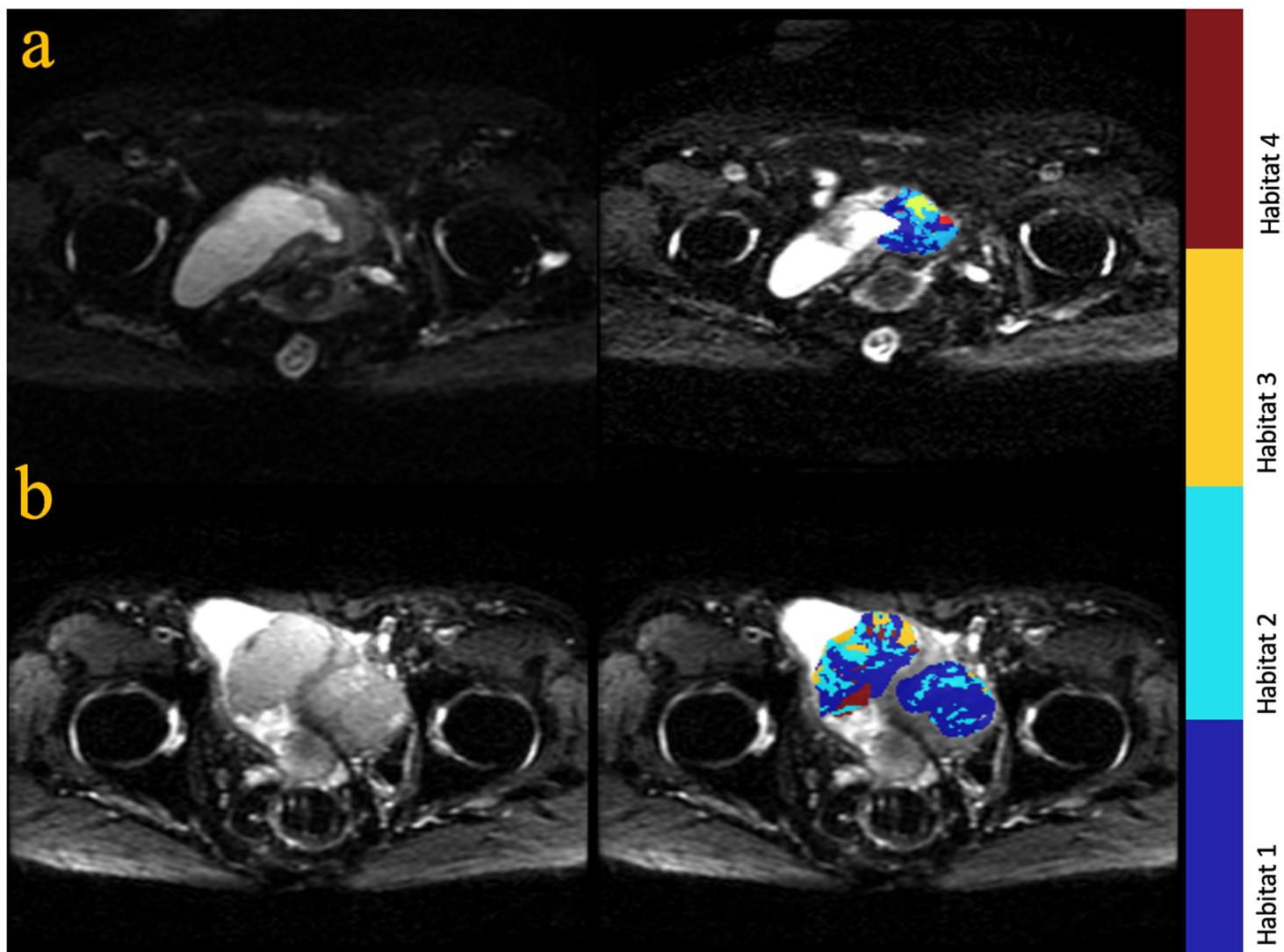


Figure 4

Representative MRI images of a NMIBC lesion (**a**) as well as an MIBC lesion (**b**). Note: Each color represents a tumor habitat

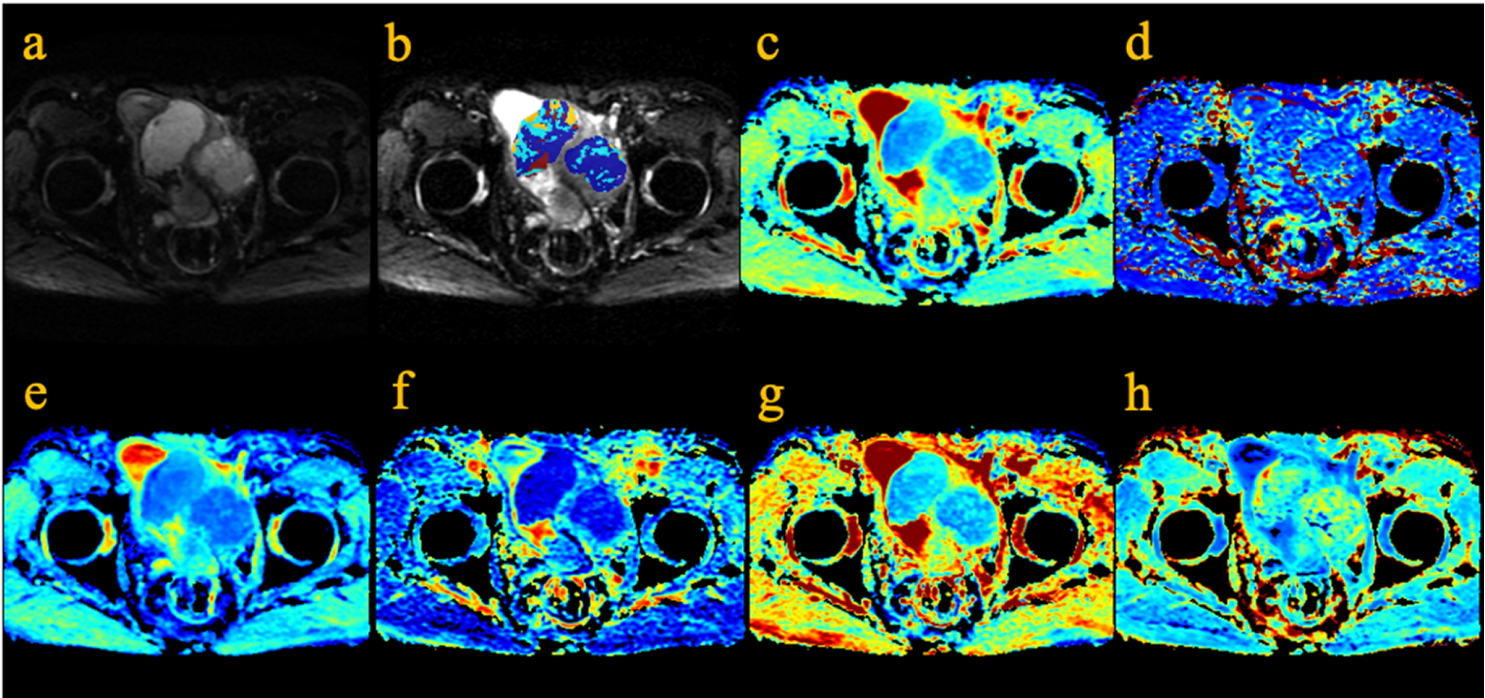


Figure 5

a-h: a. The original DWI image of a 75-year-old patient with MIBC, $b = 800\text{mm/s}^2$; b-h: The pseudo color map of Cluster, ADC, D_{fast} , D_{slow} , D_{app} , and K_{app} , respectively

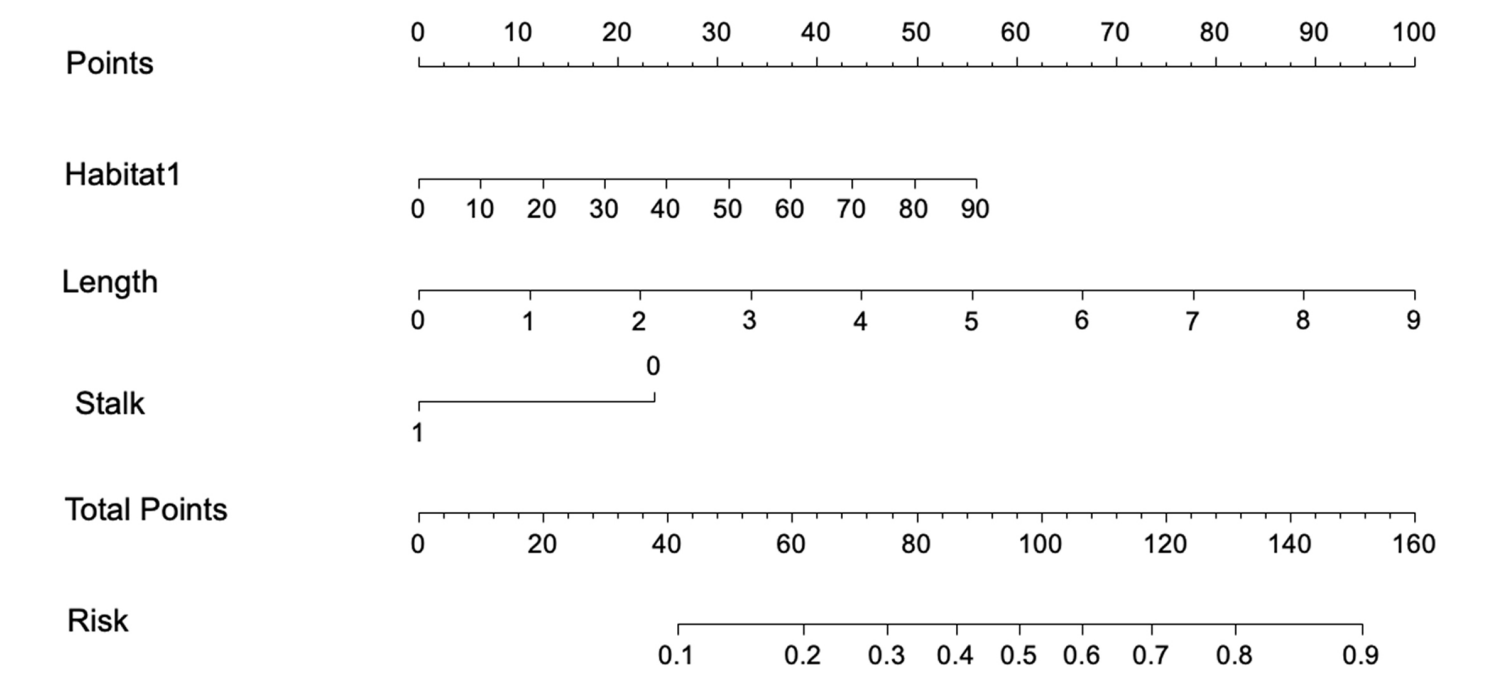


Figure 6

The nomogram for differentiating MIBC from NMIBC

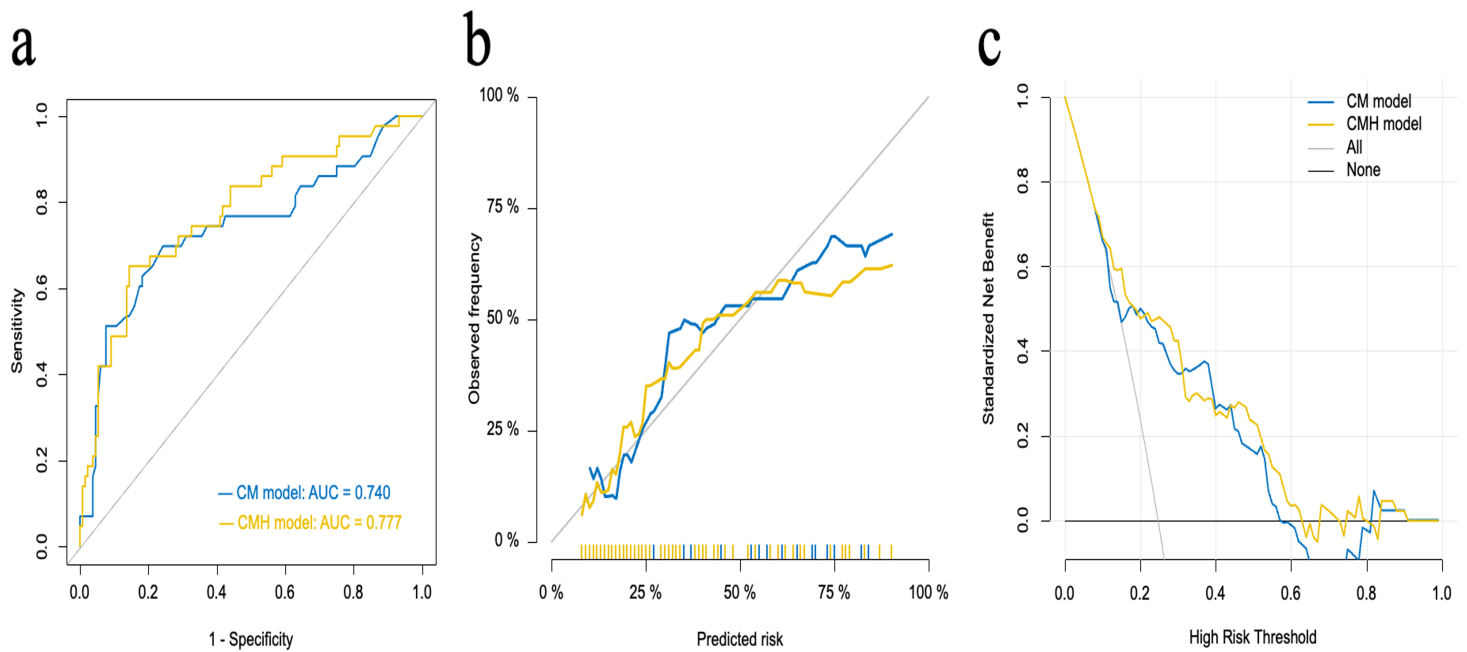


Figure 7

ROC, calibration curve and decision curve analysis of CM model and CMH model

Supplementary Files

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