# Nomograms for predicting survival outcomes in patients with bladder mucinous adenocarcinoma: a large population-based investigation

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# Abstract

**Introduction:** Bladder mucinous adenocarcinoma (BMA) is a very few histological subtypes has an invasive disease progression and poor clinical prognosis. The aim of this study was to investigate prognostic clinicopathological factors in patients with BMA and to develop a nomogram model using a large population-based cancer database.

**Patients and Methods:** A total of 426 patients with BMA with adequate tumor data were determined in the Surveillance, Epidemiology and End Results (SEER) database from 2004 to 2017. Univariate and multivariate Cox regression models were used to identify independent risk factors for constructing the nomograms to forecast the overall survival (OS) and cancer-specific survival (CSS) in BMA patients.

**Results:** Compared with transitional cell carcinoma (TCC), BMA patients are younger and have larger tumors. BMA Patients were also be inclined to experience advanced T stage, lymph node metastasis, and distant metastasis. Older age, poorly differentiated histological grade, extravesical tumor, lymphatic metastasis, distant metastasis, and larger tumor volume were unassociated risk factors, and hence integrated into the models. The C-index values of the nomograms to predict OS and CSS were 0.708 and 0.741, respectively.

**Conclusion:** Two prognostic nomograms were developed that provided an individual prediction of OS and CSS for BMA patients, which may help clinicians make treatment plans.


# 1. Introduction

Currently, bladder cancer is one of the ten most common malignant tumors in the world, with more than 500,000 new cases and nearly 200,000 deaths every year, and it is still growing rapidly (1–3). Bladder cancer origin the urothelial epithelium of the bladder, the predominant histologic subtype is urothelial carcinoma (exceed 90% of all cases) (4). Primary adenocarcinoma in the urinary bladder is an extremely unusual nonurothelial carcinoma with a histologically pure glandular phenotype, occupy only 0.5%-2% of all bladder cancers (5). In the mucinous urinary bladder adenocarcinoma subtype, tumor cells form nests, floating in large amounts of extravasated mucin. In some cases, the mucin contains single tumor cells with a signet-ring morphology (6, 7). Notably, classification according to the World Health Organization (WHO) 2016, signet ring cell carcinoma (SRCC) is does not contain in the primary mucinous adenocarcinoma group (4). Compared with the conventional urothelial carcinoma, bladder mucinous adenocarcinoma (BMA) follows a more tumor-invasive clinical course and worse outcomes (8). However, clinical decisions are mostly according to few clinical case reports and clinical studies due to its rarity and highly malignant condition, and the clinical and diagnostic presentations of BMA are not experienced by many clinicians (9, 10).

This study aimed at investigate prognostic clinicopathological factors and develop nomogram models for patients with BMA using a large population-based cancer database.

# 2. Materials And Methods

## 2.1 Selection of patient cohort

This research adopted the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI). BMA cases were identified according to the International Classification of Diseases-O-3 (ICD-O-3) codes 8480/3 and 8481/3 from 2004 to 2017. Include patients should meet the following 3 criteria: (1) Bladder is the primary location, (2) survival period was ≥ 1 month, and (3) apposite tumor data were available. SEER*Stat software (version 8.3.9) for obtaining medical records from the SEER database.

## 2.2 Data collection and variable definition

Demographic data obtained for each medical record, including age at diagnosis, race and gender. Clinicopathological features including American Joint Committee on Cancer (AJCC) version of cancer stage, histopathological grade, and tumor volume. Treatment and post-condition investigation information included specific type of surgery, vital status, classification of death for specific causes, and survival months. Surgical type codes 50 (Simple/partial surgical resection of primary resection), 60 (Radical cystectomy meanwhile reconstruction), 70 (Pelvic tumor resection, NOS), and 80 (Cystectomy, NOS) for BMA were assembled and integrated as referred to markedas “radical surgery”. Transurethral resection combined with other local tumor-destroying or excisional procedures collectively referred to marketed as "local therapy". The overall survival (OS) period for BMA were marketed as the period from diagnosis to death or last follow-up. The cancer-specific survival (CSS) period for BMA were considered as the time from diagnosis until end of life due to urinary bladder.

## 2.3 Statistical analysis

Clinicopathological variables were exhibited by count and percentage for categorical data. Pearson’s chi-square was conducted to compare the distribution of categorical variables between BMA and transitional cell carcinoma (TCC) patient cohort. The Kaplan-Meier method and log-rank test were utilized to perform survival analysis. Univariate and multivariate Cox regression models were performed to identify independent risk factors to predict OS and CSS of patients with BMA. All analyses were conducted using the R software 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), and a two-sided p value < 0.05 was considered as statistically significant. The “survminer” and “survival” packages were used to perform survival analysis. The “VRPM” and “rms” packages were used to construct the prognostic nomograms.

# 3. Results

## 3.1 Clinicopathological characteristics of patients with BMA and TCC

In total, 426 patients with BMA and 197,753 TCC patients were founded in the SEER database from 2004 to 2017. The clinicopathological features of the two cohorts of patients are shown in **Table 1**. In general, the baseline characteristics of the patient cohorts of the two bladder cancer types differed substantially. For the bladder cancer patient cohort with BMA, the greater part of the patients' type was white (321, 75.4.0%), male (251, 58.9%), with stage III (119, 27.9%) or IV (112, 26.3%) TNM stage, and II (137, 32.2%) or III grade (93, 21.8%). Compared with TCC, patients with BMA tended to be younger (median age: 61.04 years) and had larger tumors (median tumor size: 59.55 mm). Patients with BMA were also more likely to experience advanced T stage (T3/4: 212, 49.8%), node metastasis (50, 11.7%), and distant metastasis (58, 13.6%).

# 3.2 Survival comparison of patients with BMA and TCC

For patients with BMA, the median OS of mucinous adenocarcinoma (MA) and mucin-producing adenocarcinoma (MPA) was 47 and 36 months, respectively **(Supplementary Table 1)**. For both OS and CSS, the survival probabilities were significantly greater for TCC versus BMA (OS, 0.001; CSS, 0.001) **(Figure 1)**. The prognosis was significantly worse for patients with than for those with TCC. Subgroup analysis based on tumor invasion depth (T stage) was performed to further investigate the survival outcome of patients with BMA. However, no survival difference was found between non-muscle-invasive BMA (NMIBMA) patients and those with muscle-invasive BMA (MIBMA) (p = 0.970) **(Figure 2a)**. Notably, patients with extravesical tumor (T4 stage) had a remarkably worse prognosis (p0.001) **(Figure 2b)**. The OS and CSS of patients with non-metastatic MIBMA undergoing different surgical procedures were assessed. However, patients with MIBMA who received radical cystectomy (RC) did not receive a survival advantage, with similar OS probability (p = 0.810) and CSS probability (p = 0.700) compared with patients who underwent local or partial cystectomy **(Figure 3)**.

# 3.3 Univariate and multivariate Cox regression analysis

According to the univariate and multivariate Cox regression models, older age (OS: hazard ratio (HR) = 1.025, p0.001; CSS: HR = 1.017, p = 0.006), poorly differentiated histological grade (grade III /IV) (OS: HR = 1.639, p0.001; CSS: HR = 1.877, p0.001), extravesical tumor (T4 stage) (OS: HR = 1.857, p0.001; CSS: HR = 1.611, p = 0.009), true pelvis single regional lymph node metastasis (N1 stage) (OS: HR = 1.745, p = 0.015; CSS: HR = 1.972, p = 0.007) and multiple regional lymph node metastasis or lymphatic metastasis to common iliac lymph nodes (N2/3 stage) (OS: HR = 2.464, p0.001; CSS: HR = 2.475, p0.001), distant metastasis disease (M1 stage) (OS: HR = 2.460, p0.001; CSS: HR = 2.975, p0.001), and larger tumor volume (≥30 mm) (OS: HR = 1.488, p = 0.018; CSS: HR = 2.025, p0.001) were recognized as no interrelate risk factors for both OS and CSS (**Tables 2** and **3**).

## 3.4 Construction and internal validation of the prognostic nomograms for OS and CSS

Nomograms for predicting 1-, 3- and 5-year OS **(Figure 4)** and CSS **(Figure 5)** were constructed by integrating all the prognostic factors mentioned earlier. By calculating the scores of all the selected covariates, the survival probability of the specific patient could be accurately determined. The C-index values of the nomograms to forecast OS and CSS were 0.708 (0.015) and 0.741 (0.018), respectively, exhibiting satisfactory consistency with actual survival probability. In addition, calibration curves for OS and CSS at 1-, 3-, and 5-years showed that nomogram predictions were in perfect agreement with actual survival outcomes (Figure 6).

# 4. Discussion

Bladder cancer is a pathologically heterogeneous cancer with multiple variant forms. Differing pathology types present diagnostic difficulties and are clinically relevant to inform prognosis and treatment strategies (11). Histological variants of bladder tumors are broadly divided into urothelial and nonurothelial tumors. Nonurothelial tumors include squamous cell neoplasm, glandular neoplasms, Müllerian-type tumors, neuroendocrine tumors, and melanocytic tumors. According to the WHO 2016 classification of urinary bladder cancer, the glandular neoplasms of bladder cancer are subdivided into adenocarcinoma NOS (8140/3), enteric (8144/3), mucinous (8480/3), mixed (8140/3), villous adenoma (8261/0), and urachal carcinoma (8010/3) (4, 6). BMA follows a more invasive clinical course than conventional TCC, with increased frequency of advanced stage and more nodal involvement (12–14). According to EAU-ESMO consensus statements on the treatment of advanced and variant bladder cancer, RC and lymphadenectomy were highly recommended for muscle-invasive pure bladder adenocarcinoma patients (2). BMA Patients currently receive treatment based on the same standard guidelines as for TCC and bladder adenocarcinoma. However, limitations of previous studies were mainly inherent to the small sample volume caused by the rare nature of BMA.

In this SEER-based study, BMA was identified to be more generally connected with advanced TNM stage, larger tumor volume, and younger age compared to TCC. BMA possesses features of biologically aggressive cancers. Our results also show that BMA patients have a significantly worse prognosis compared with TCC patients. In particular, Subgroup analysis accordingto depth of tumor invasion showed no significant difference in survival between NMIBMA and MIBMA patients, implying that the TNM staging system currently in widespread use may not be suitable for BMA. More importantly, MIBMA patients who underwent RC did not experience greater benefit, with similar outcomes compared with patients who underwent local surgery or partial cystectomy. The value of bladder preservation treatment for patients with BMA needs to be further explored to avoid unnecessary radical surgery. These results indicated that BMA was one biologically distinct malignancy, and patients should be individualized with different treatment strategies to obtain the greatest survival benefit. Moreover, the diagnosis of BMA still remains challenging in routine practice due to the diversity of benign and malignant glandular

neoplasms. Pires-Luis et al. performed next-generation sequencing of 36 patients with primary bladder adenocarcinoma, including three BMA patients (15). They found that KRAS, GRIN2A, and AURKB were the most frequent gene mutations in BMA.

This study was a novel, large population study investigating survival of patients with BMA. In the present study, two user-friendly high-precision prognostic nomograms were constructed to predict OS and CSS in BMA patients. Older age, poorly differentiated histology, extravesical tumor, lymph node metastasis, distant metastatic disease, and larger tumor volume were identified as independent risk factors for OS and CSS according to multivariate Cox regression models and were therefore integrated into clinicopathology in the forecasting model.

Interestingly, the classification of the SRCC subtype, which had specific molecular alterations and clinical behavior, changed over time. In 1955, Saphir et al. first described SRCC of the urinary bladder as a mucin-secreting adenocarcinoma (16). In 1991, Grignon et al defined SRCC as a specific histologic subtype consisting of single signet-ring cells diffusely permeating the tissues, with a poorer prognosis compared with the mucinous subtype (14). Notably, signet ring cell variant urothelial carcinoma is now considered as a subset of plasmacytoid urothelial carcinoma according to the WHO 2016 classification of urologic neoplasms (4). Unlike BMA with signet-ring cells, these tumors do not present extracellular mucin production. Considering the specific histological and clinical behavior of SRCC, the present study did not include patients with SRCC for analysis.

Despite some clinically meaningful results, this registration-based research has inevitable limitations. First, the nomograms are constructed according to the retrospective data from the SEER database, and cannot completely avoid selection bias. Second, SEER-based studies lacked detail with regard to relevant information about the decision-making process of the treatment strategy. In addition, the current nomograms were developed and validated only based on the SEER database. Thus, further external validation from multiple centers was expected to generalize the applicability of the nomograms in real-world clinical treatment practice. Despite the limitations of this study, the C-index values and the calibration curves suggested high accuracy of the prediction by nomograms.

# 5. Conclusions

Two prognostic nomograms were developed that provided an individual prediction of OS and CSS for BMA patients. Predicting patient outcomes through using accurate prognostic models can support physicians in patient risk stratification and outcome estimation, and ultimately guides clinical decisions regarding treatment strategies and future research.

# Declarations


### Acknowledgements

Not applicable

### Authors' contributions:

Wu Song, Feng Wang and Qi Fang Lei designed the study. Guan Can Liang and Yu Wang collect the data. Jian Pan, Ying Rui Li and Rui Xiang Dai analyzed the data and presented the results. Jian Pan and Ying Rui Li wrote the manuscript. All of the authors listed have revised, read, and approved the manuscript. Jian Pan and Ying Rui Li contributed equally.

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### Availability of data and materials:

Access to the database may be obtained from the corresponding author on reasonable request. Our data are available and publicly accessible. The original data comes from the Surveillance, Epidemiology, and End Results (SEER) database.

### Declarations

### Ethics approval and consent to participate:

The data that support the findings of this study are openly available in the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute.

### Consent for publication

The requirement for informed consent was waived.

### Conflict of interests:

The authors declare no conflict of interest.

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# Tables

**Table 1**

**Demographic and clinical features comparing patients with bladder mucinous adenocarcinoma to transitional cell carcinoma.**

| | | Mucinous adenocarcinoma (n=426) | | Transitional cell carcinoma (n=197753) | | |
|---|---|---|---|---|---|---|
| | | Count | % | Count | % | *p* value |
| Age at diagnosis | Median (SD) | 61.04 (14.10) | | 71.10 (11.95) | | **0.001** |
| Race | White | 321 | 75.4 | 176291 | 89.1 | **0.001** |
| | Black | 70 | 16.4 | 10793 | 5.5 | |
| | Other | 33 | 7.7 | 8403 | 4.2 | |
| | Unknow | 2 | 0.5 | 2266 | 1.1 | |
| Gender | Male | 251 | 58.9 | 151383 | 76.6 | **0.001** |
| | Female | 175 | 41.1 | 46370 | 23.4 | |
| T stage | T0 | 0 | 0 | 51 | 0.0 | **0.001** |
| | Tis | 2 | 0.5 | 9993 | 5.0 | |
| | Ta | 2 | 0.5 | 100298 | 50.7 | |
| | T1 | 59 | 13.8 | 45327 | 22.9 | |
| | T2 | 118 | 27.7 | 25221 | 12.8 | |
| | T3 | 134 | 31.5 | 6895 | 3.5 | |
| | T4 | 78 | 18.3 | 5985 | 3.0 | |
| | Tx | 33 | 7.7 | 3974 | 2.0 | |
| N stage | N0 | 335 | 78.6 | 185273 | 93.7 | **0.001** |
| | N1 | 24 | 5.6 | 3186 | 1.6 | |
| | N2 | 24 | 5.6 | 2057 | 1.0 | |
| | N3 | 2 | 0.5 | 555 | 0.3 | |
| | Nx | 41 | 9.6 | 6682 | 3.4 | |
| M stage | M0 | 351 | 82.4 | 192355 | 97.3 | **0.001** |
| | M1 | 58 | 13.6 | 4930 | 2.5 | |
| | Mx | 17 | 4.0 | 468 | 0.2 | |
| AJCC $8^{th}$ stage | 0 | 4 | 0.9 | 110099 | 55.7 | **0.001** |
| | I | 51 | 12.0 | 42989 | 21.7 | |
| | II | 96 | 22.5 | 20825 | 10.5 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | III | 119 | 27.9 | 10945 | 5.5 | |
| | IV | 112 | 26.3 | 5730 | 2.9 | |
| | Unknown | 44 | 10.3 | 7165 | 3.6 | |
| Histopathological grade | I | 68 | 16.0 | 23146 | 11.7 | **0.001** |
| | II | 137 | 32.2 | 49601 | 25.1 | |
| | III | 93 | 21.8 | 31529 | 15.9 | |
| | IV | 28 | 6.6 | 59551 | 30.1 | |
| | Unknown | 100 | 23.5 | 33926 | 17.2 | |
| Tumor volume (mm) | Median (SD) | 59.55 (85.59) | | 34.84 (29.43) | | **0.001** |
| Type of surgical procedure | No surgery of primary site | 29 | 6.8 | 12236 | 6.2 | **0.001** |
| | Local tumor treatment or partial cystectomy | 311 | 73.0 | 167934 | 84.9 | |
| | Radical cystectomy | 80 | 18.8 | 16623 | 8.4 | |
| | Unknown | 6 | 1.4 | 960 | 0.5 | |

AJCC: American Joint Committee on Cancer. The bold values indicated that $p < 0.05$.

**Table 2**

**Univariate and multivariate Cox regression analysis for predicting OS of patients with bladder mucinous adenocarcinoma**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *p* value | HR | 95%CI | *p* value |
| **Age** | 1.019 | 1.010-1.029 | **<0.001** | 1.025 | 1.015-1.035 | **<0.001** |
| Gender | | | | | | |
| Male | Ref | | | | | |
| Female | 1.132 | 0.880-1.457 | 0.335 | | | |
| Race | | | | | | |
| White | Ref | | | | | |
| Black | 1.182 | 0.853-1.637 | 0.315 | | | |
| Other | 0.721 | 0.436-1.221 | 0.224 | | | |
| **Grade** | | | | | | |
| I/ II | Ref | | | Ref | | |
| III /IV | 2.218 | 1.655-2.973 | **<0.001** | 1.639 | 1.263-2.129 | **<0.001** |
| Histology | | | | | | |
| MA | Ref | | | | | |
| MPA | 1.259 | 0.914-1.734 | 0.159 | | | |
| **T stage** | | | | | | |
| T0/Ta/Tis/T1/T2/T3 | Ref | | | Ref | | |
| T4 | 2.344 | 1.749-3.140 | **<0.001** | 1.857 | 1.372-2.514 | **<0.001** |
| **N stage** | | | | | | |
| N0 | Ref | | | Ref | | |
| N1 | 3.146 | 1.986-4.985 | **<0.001** | 1.745 | 1.114-2.732 | **0.015** |
| N2/N3 | 3.660 | 2.378-5.631 | **<0.001** | 2.464 | 1.594-3.807 | **<0.001** |
| **M stage of BC** | | | | | | |
| M0 | Ref | | | Ref | | |
| M1 | 2.873 | 2.110-3.912 | **<0.001** | 2.460 | 1.813-3.338 | **<0.001** |
| **Tumor size, mm** | | | | | | |
| <30 | Ref | | | | | |
| ≥30 | 1.798 | 1.213-2.668 | **0.004** | 1.488 | 1.069-2.070 | **0.018** |

OS: overall survival; MA: mucinous adenocarcinoma; MPA: mucin-producing adenocarcinoma; HR: hazard ratio; CI: confidence interval; Ref: reference; AJCC: American Joint Committee on Cancer.

## Table 3

**Univariate and multivariate Cox regression analysis for predicting CSS of patients with bladder mucinous adenocarcinoma**

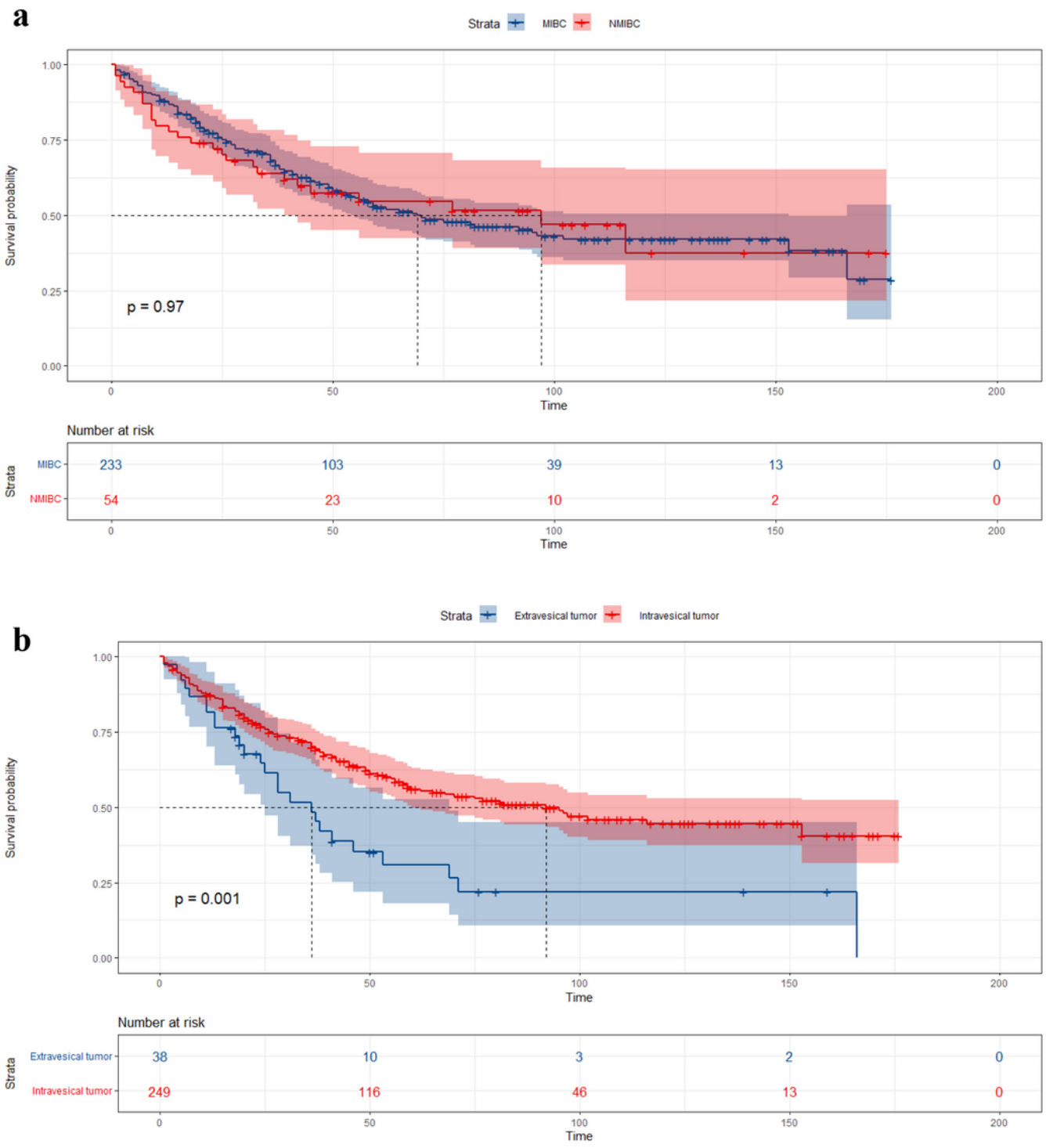
| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *p* value | HR | 95%CI | *p* value |
| **Age** | 1.012 | 1.001-1.024 | **0.031** | 1.017 | 1.005-1.029 | **0.006** |
| Gender | | | | | | |
| Male | Ref | | | | | |
| Female | 1.181 | 0.873-1.599 | 0.281 | | | |
| Race | | | | | | |
| White | Ref | | | | | |
| Black | 1.114 | 0.749-1.658 | 0.594 | | | |
| Other | 0.710 | 0.373-1.351 | 0.297 | | | |
| **Grade** | | | | | | |
| I/ II | Ref | | | Ref | | |
| III /IV | 2.795 | 1.966-3.973 | **0.001** | 1.877 | 1.367-2.579 | **0.001** |
| Histology | | | | | | |
| MA | Ref | | | | | |
| MPA | 1.326 | 0.967-1.938 | 0.146 | | | |
| **T stage** | | | | | | |
| T0/Ta/Tis/T1/T2/T3 | Ref | | | Ref | | |
| T4 | 2.334 | 1.645-3.312 | **0.001** | 1.611 | 1.129-2.298 | **0.009** |
| **N stage** | | | | | | |
| N0 | Ref | | | Ref | | |
| N1 | 4.213 | 2.568-6.912 | **0.001** | 1.972 | 1.202-3.234 | **0.007** |
| N2/N3 | 4.333 | 2.656-7.070 | **0.001** | 2.475 | 1.524-4.020 | **0.001** |
| **M stage of BC** | | | | | | |
| M0 | Ref | | | Ref | | |
| M1 | 3.411 | 2.402-4.845 | **0.001** | 2.975 | 2.079-4.257 | **0.001** |
| **Tumor size, mm** | | | | | | |
| 30 | Ref | | | | | |
| ≥30 | 2.436 | 1.451-4.089 | **0.001** | 2.025 | 1.331-3.081 | **0.001** |

CSS: cancer-specific survival; MA: mucinous adenocarcinoma; MPA: mucin-producing adenocarcinoma; HR: hazard ratio; CI: confidence interval; Ref: reference; AJCC: American Joint Committee on Cancer.

# Figures

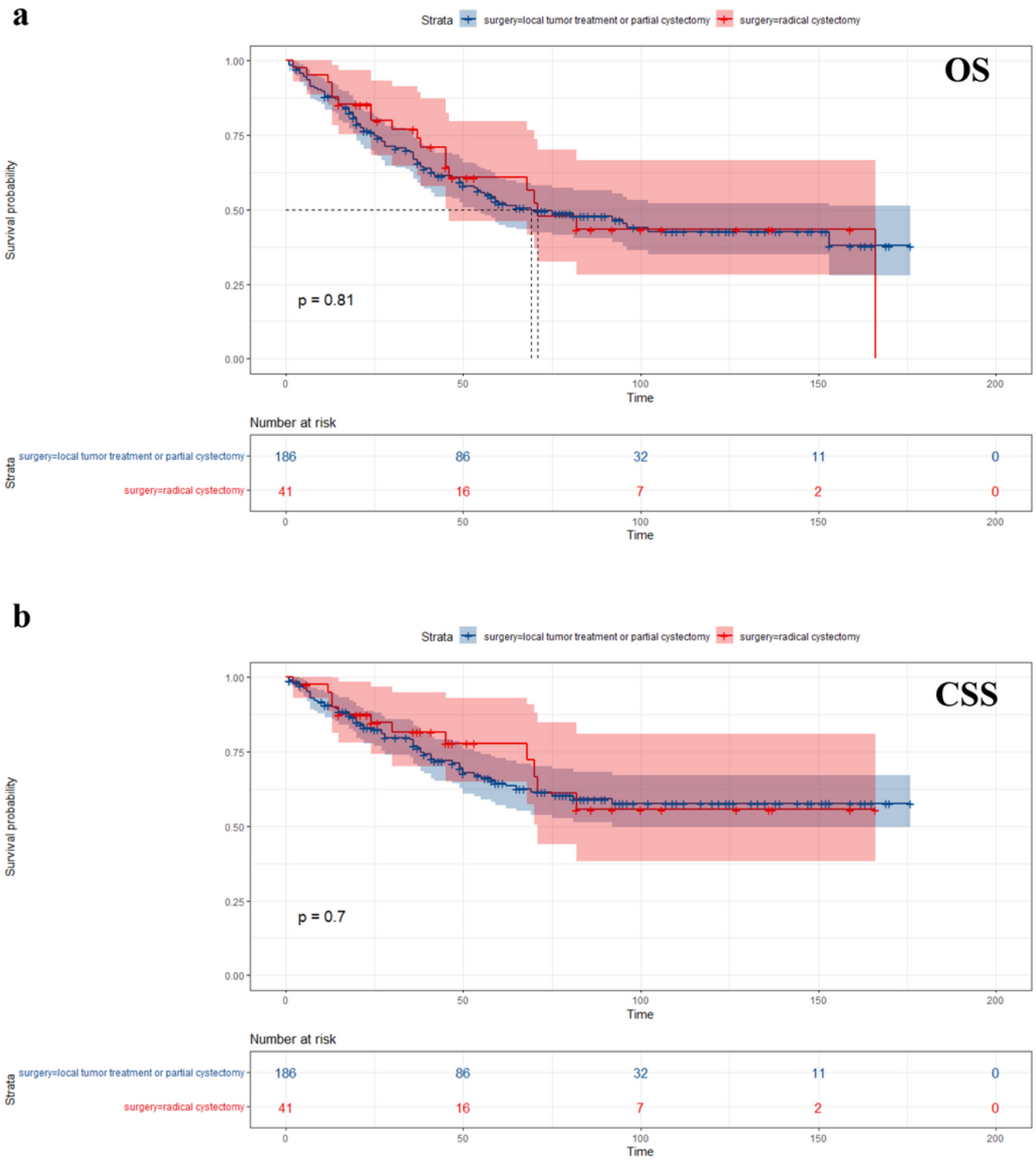
### Figure 1

Kaplan–Meier curves and risk tables for BMA in comparison to primary TCC. **(a)** OS, **(b)** CSS.



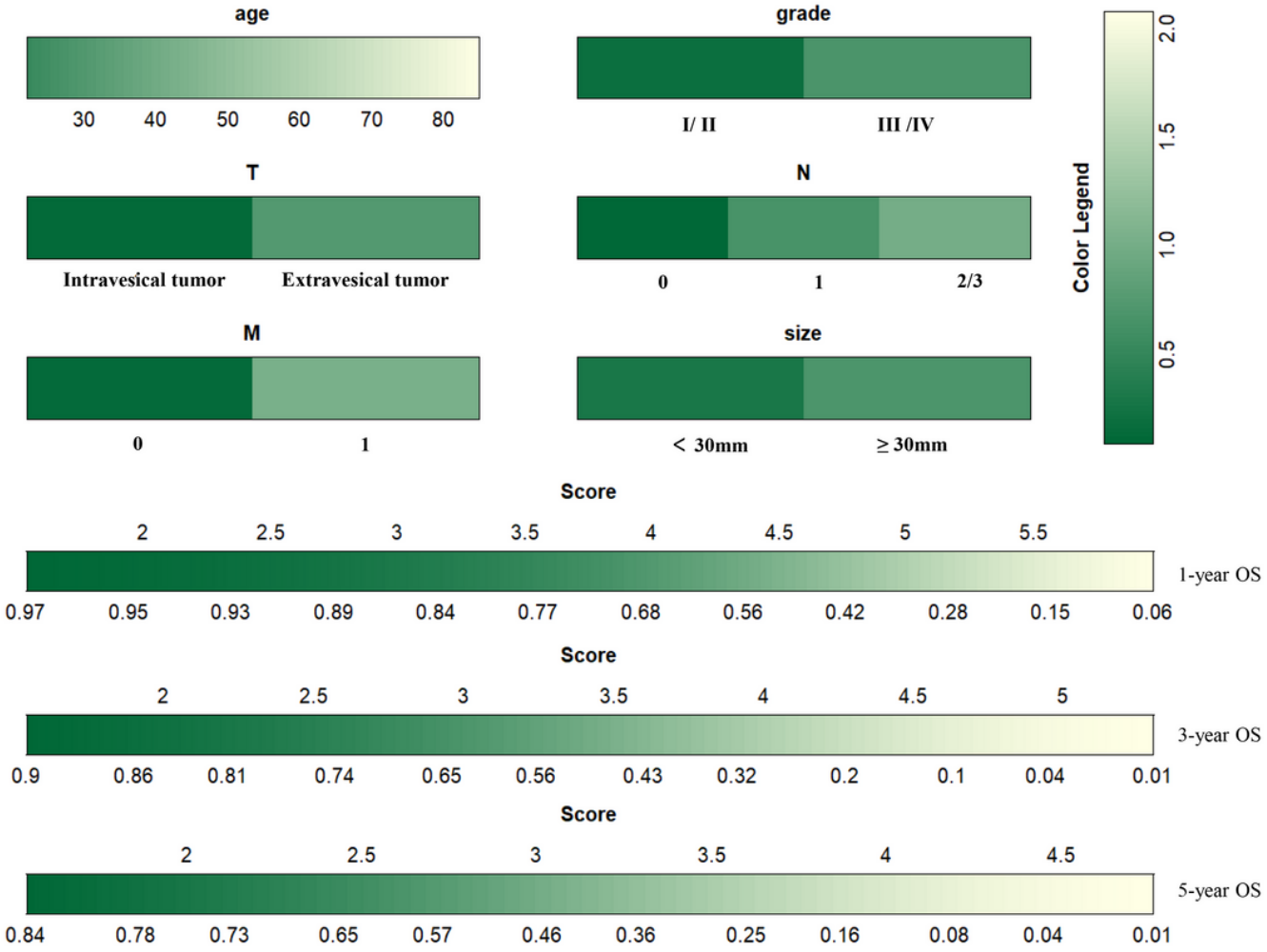

## Figure 2

Kaplan–Meier curves and risk tables for **(a)** NMIBMA in comparison to MIBMA, and **(b)** intravesical BMA in comparison to extravesical BMA.



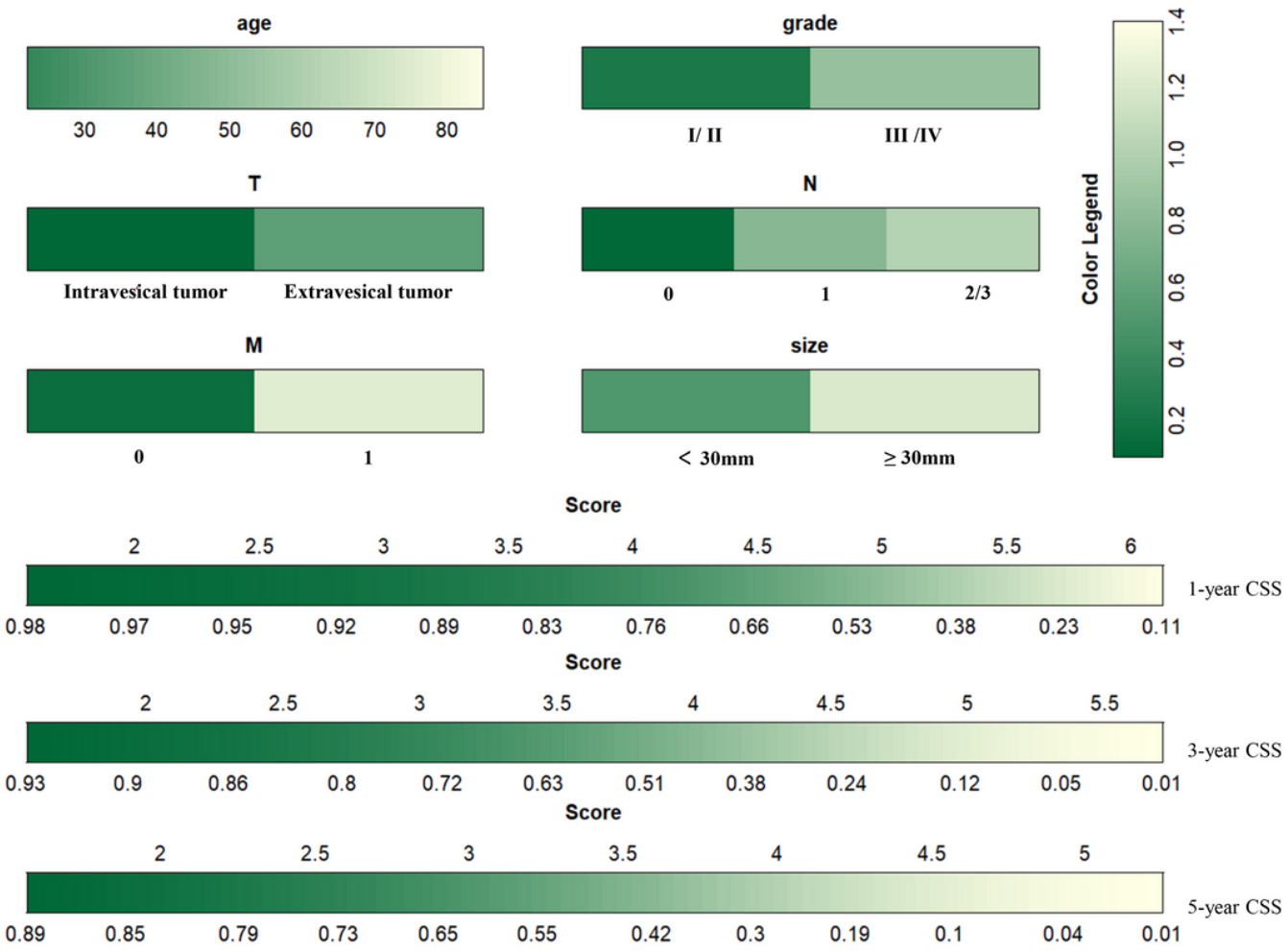

## Figure 3

Kaplan-Meier curves and risk tables comparing surgical benefits for non-metastatic MIBMA patients. **(a)** OS, **(b)** CSS.




## Figure 4

The nomogram for predicting 1-, 3-, and 5-year OS of BMA patients.




## Figure 5

The nomogram for predicting 1-, 3-, and 5-year CSS of BMA patients.

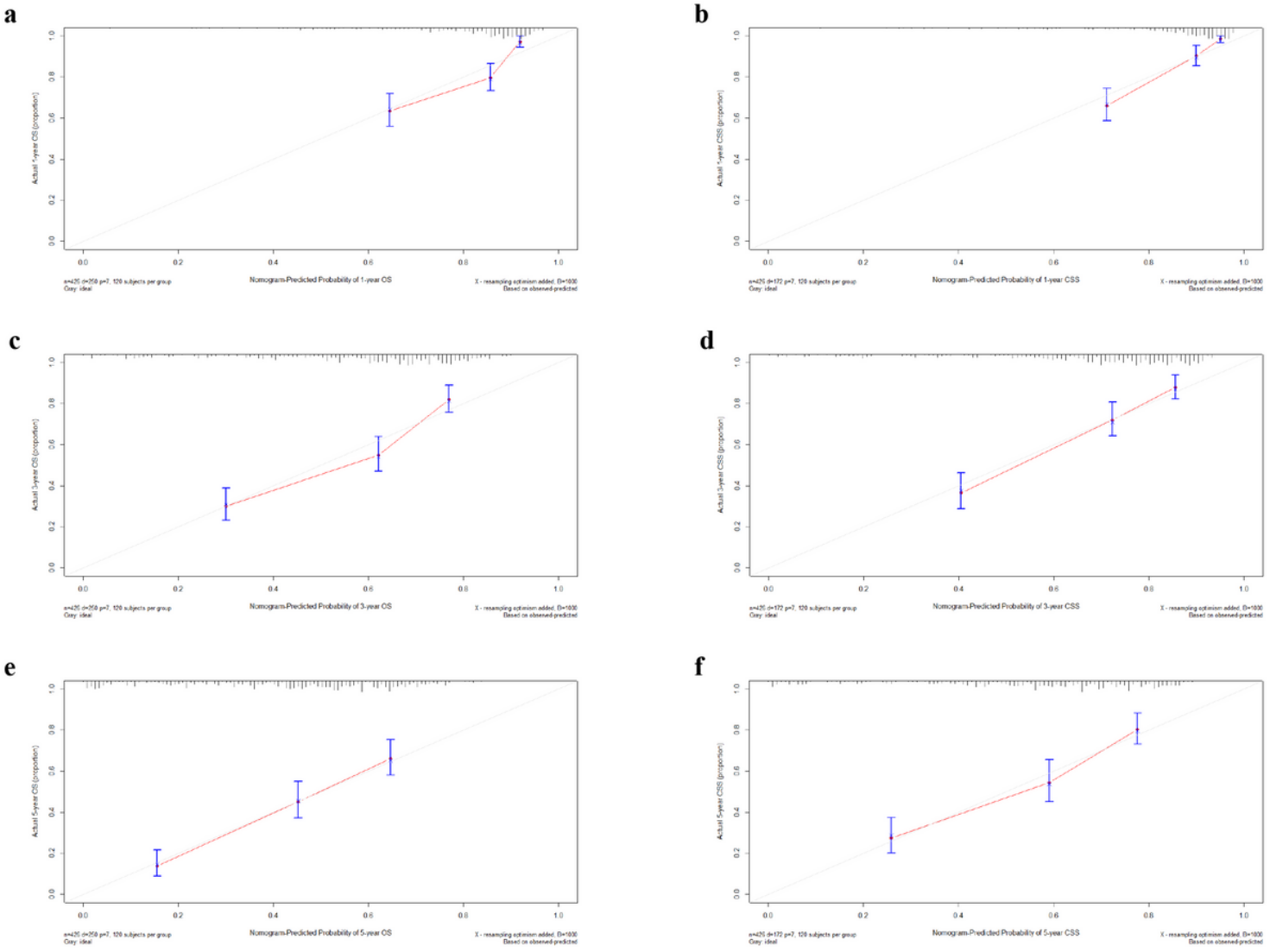



**Figure 6**

Calibration curves of **(a, c, and e)** 1-, 3-, and 5-year OS. Calibration curves of **(b, d, and f)** 1-, 3-, and 5-year CSS.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx