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Development and Validation of Models to Predict Pathologic Outcomes of Radical Prostatectomy in Regional and National Cohorts

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Abstract

Purpose: Prediction models are recommended by national guidelines to support clinical decision-making in prostate cancer. Existing models to predict pathologic outcomes of radical prostatectomy (RP)—the Memorial Sloan Kettering (MSK) models, Partin tables, and the Briganti nomogram—have been developed using data from tertiary care centers and may not generalize well to other settings.

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Materials and Methods: Data from a regional cohort (Michigan Urological Surgery Improvement Collaborative [MUSIC]) were used to develop models to predict extraprostatic extension (EPE), seminal vesicle invasion (SVI), lymph node involvement (LNI), and non-organ-confined disease (NOCD) in patients undergoing RP. The MUSIC models were compared against the MSK models, Partin tables, and Briganti nomogram (for LNI) using data from a national cohort (Surveillance, Epidemiology, and End Results [SEER] registry).

Results: We identified 7,491 eligible patients in the SEER registry. The MUSIC model had good discrimination (SEER AUC EPE: 0.77; SVI: 0.80; LNI: 0.83; NOCD: 0.77) and was well-calibrated. While the MSK models had similar discrimination to the MUSIC models (SEER AUC EPE 0.76; SVI: 0.80; LNI: 0.84; NOCD: 0.76), they overestimated the risk of EPE, LNI, and NOCD. The Partin tables had inferior discrimination (SEER AUC EPE: 0.67; SVI: 0.76; LNI: 0.69; NOCD: 0.72) as compared to other models. The Briganti LNI nomogram had an AUC of 0.81 in SEER but overestimated the risk.

Conclusions: New models developed using the MUSIC registry outperformed existing models and should be considered as potential replacements for the prediction of pathologic outcomes in prostate cancer.

Keywords

Prostate Cancer; Prostatectomy; Prediction Models

INTRODUCTION

Prediction of pathologic outcomes plays an important role in preoperative counseling for men with prostate cancer (PCa) considering radical prostatectomy (RP). In patients with a very low risk of lymph node invasion (LNI), active surveillance may be preferred over RP, and even if RP is determined to be necessary, pelvic lymph node dissection may not be needed, thereby avoiding potential morbidity. On the other hand, patients at high risk of extraprostatic extension (EPE) or seminal vesicle invasion (SVI) may be advised that nerve-sparing RP may not be possible or advisable. Nerve-sparing surgery is associated with better postoperative sexual function,[1] and inability to nerve-spare may have implications on patients' quality of life that will need to be addressed through preoperative counseling and shared decision-making.

The use of prediction models to support clinical decision-making is ubiquitous in prostate cancer due to national guidelines recommending their use[2,3] and the availability of well-validated models. Three sets of models that are widely adopted to predict pathologic outcomes are the Memorial Sloan Kettering (MSK)[4] models, the Johns Hopkins University Partin tables[5], and the Briganti nomogram[6] (for LNI). While the Briganti nomogram is limited to LNI, the others consist of four separate models to predict EPE, SVI, LNI, and the presence of any of the above, which indicates that the PCa has extended beyond the prostate and constitutes non-organ-confined disease (NOCD). All three sets of models were developed using data from tertiary care centers whose populations may not be representative of other prostatectomy populations. Although Memorial Sloan Kettering, Johns Hopkins, and Università Vita-Salute San Raffaele (for the Briganti nomogram) serve demographically

diverse communities, these hospitals also care for some of the most complex cases. As a result, the average risk profile of patients at these institutions is likely much higher than the average patient evaluated for RP in the US. Models developed from patient cohorts with higher case complexity or acuity are known to overestimate the risk of adverse outcomes in settings with lower complexity, a phenomenon known as model miscalibration.[7] Thus, broad adoption of existing models may lead to patients undergoing unnecessary pelvic lymph node dissection due to potential miscalibration in non-tertiary-care settings.

Although miscalibration of these models in a national cohort is a concern, prior external validation efforts using these models have largely ignored calibration[8] or focused on miscalibration at only a single center.[9] However, because urologists rely on the absolute risk estimates to make clinical decisions (e.g., whether to perform a pelvic lymph node dissection), the need for a well-calibrated model is critical. Concerned that existing models may be miscalibration in national cohorts, we developed new models in our regional cohort of 50 urology practices participating in the Michigan Urological Surgery Improvement Collaborative (MUSIC) and compared these against existing models in the national Surveillance, Epidemiology, and End Results (SEER) registry.

MATERIALS AND METHODS

Data sources

Two data sources were used for this study: the regional MUSIC registry and the national SEER registry. Additional details are provided in the Supplemental Methods.

Study cohorts

From the MUSIC and SEER registries, we established 3 study cohorts: the MUSIC derivation cohort, the MUSIC validation cohort, and the SEER validation cohort (Figure 1). The two MUSIC cohorts were established using 2:1 random sampling stratified by practice, with two-thirds of patients assigned to the derivation cohort and one-thirds to the validation cohort. After internally validating the MUSIC models on this validation cohort, we evaluated the MUSIC models on the SEER registry data. As a comparator, we also evaluated the performance of the MSK models, Partin tables, and the Briganti nomogram (for LNI) in both validation cohorts.

In both registries, we included patients in whom the prostate-specific antigen (PSA), clinical T-stage, and biopsy information was available, including Gleason score and number of positive and negative biopsy cores. Patients without pathologic outcomes data available were excluded. A small subset of MUSIC patients in whom the date of surgery was missing were also excluded.

Outcomes

We evaluated the models' ability to predict each of the 3 pathologic outcomes both individually (EPE, SVI, and LNI) and as a group (NOCD). The MSK models and Partin tables have separate models for all four outcomes, and the Briganti nomogram is limited to

LNI. For the newly developed MUSIC models, separate models were fit to each of these outcomes in a comparable fashion.

MUSIC model development

We hypothesized that new models fit using our regional cohort, which includes a diverse set of urology practices, would be better calibrated on a national sample (SEER) than existing models. Logistic regression models for each of the pathologic outcomes (EPE, SVI, LNI, NOCD) were fit using the MUSIC derivation cohort with the following predictors: age, PSA, clinical T-stage, grade group, and the number of positive and negative cores.

MSK models, Partin tables, and the Briganti nomogram

The MSK models were originally developed and validated using data from Memorial Sloan Kettering Cancer Center.[10] Because the models have previously been shown to become miscalibrated over time,[9] they are dynamically updated.[11] The MSK models predict pathologic outcomes using PSA, clinical T-stage, biopsy Gleason score (primary and secondary), and number of positive and negative cores. Although separate MSK models are available for patients who lack data about biopsy cores, we focused our evaluation on the models that included cores data. The last published evaluation of the MSK models (specifically, one focused on LNI) was in 2011.[9] We used the coefficients from the 2018 version of the model.[4]

The Partin tables were originally developed and validated using data from Johns Hopkins University. Although the 2007 version of the Partin tables have been evaluated in SEER data,[8] this evaluation did not consider calibration and does not reflect contemporary practice. The Partin tables were most recently updated using patient data from 2010 to 2015 and predict pathologic outcomes using PSA, clinical T-stage, and Gleason grade group, and this latest version was used in our evaluation.[5] The Partin tables do not include the number of positive or negative cores as predictors.

The Briganti nomogram refers to a set of several models developed by a research group at the Università Vita-Salute San Raffaele between 2006 and 2019.[6,12–14] For this evaluation, we selected the primary model (i.e., “Model 1”) from the Briganti 2017 nomogram[6] because this was the latest version of the model that did not require magnetic resonance imaging data, which was not available in our cohorts.

Model validation

We evaluated all models in the MUSIC validation cohort (for internal validation) and in the SEER validation cohort (for external validation). Performance of these models was characterized in terms of both discrimination and calibration. Discriminative performance was measured using the area under the receiver operating characteristic curve (AUC), and calibration was assessed visually by comparing deciles of predicted risk with observed risk. Bootstrapped 95% confidence intervals were created for the AUC by resampling (unstratified with replacement) the cohort populations 1,000 times. Patients with clinical T3 disease were excluded from evaluations of the Partin tables due to the absence of T3 disease in the Partin tables.[5] The Briganti nomogram requires percentage of positive cores

with highest-grade and lower-grade disease as predictors. Because these were not available in either cohort, we imputed the median values of 29.4 and 27.7, respectively, from the original publication describing the Briganti nomogram's development.[6]

Missing data

After excluding patients with missing PSA, clinical T-stage, and biopsy information (Figure 1), the remaining variables were non-parametrically imputed with bagged trees for the MUSIC models only. Imputation was not required for the MSK models or Partin tables due to complete availability of predictors.

Net benefit

Decision curves were used to calculate the net benefit of all models in the SEER validation cohort. The analysis was focused only on LNI because of previously published threshold ranges of 0-20% risk.[6] The potential clinical impact of the models was examined by comparing the number of patients who would be recommended to undergo lymph node dissection (in the threshold range of 0-20%) against those who actually had LNI.

Software

We used R 3.6.0 for all analyses. The model code is available on GitHub,[15] and the MUSIC model is available as an interactive web calculator[16]. The model coefficients are available in Supplemental Tables 1–4.

RESULTS

We identified 8,736 eligible patients in the MUSIC registry and 7,491 eligible patients in the SEER registry for our study cohorts. In the MUSIC registry, 5,825 (67%) were randomly assigned to a derivation cohort and 2,911 (33%) were randomly assigned to a validation cohort (Figure 1). The SEER validation cohort had higher proportion of grade group 1 PCa (24% versus 18%), a lower number of positive cores (median 5 positive cores in SEER versus 7 and 8 in the MUSIC derivation and validation cohorts, respectively), and a higher proportion of patients with a cT1 disease (77% in SEER versus 71% and 72% in the MUSIC derivation and validation cohorts, respectively) (Table 1). While proportions of EPE, SVI, and LNI were fairly similar between the cohorts, fewer patents in SEER had non-organ-confined disease (37% in SEER versus 45% and 43% in the MUSIC derivation and validation cohorts, respectively) due to more overlap among the individual outcomes (Table 2).

Internal validation (MUSIC registry)

In the MUSIC validation cohort, the MUSIC models had better discrimination than the other models for EPE and NOCD and similar performance to other models for SVI and LNI (Table 3). The MSK models overestimated risk of EPE, LNI, and NOCD, and the Briganti nomogram overestimated the risk of LNI, while both the MUSIC models and Partin tables were generally well-calibrated (Supplemental Figure 1).

External validation (SEER registry)

In the SEER validation cohort, the MUSIC models had similar discriminative performance as compared to the MSK models and the Briganti LNI nomogram, and all outperformed the Partin tables (Table 3). However, the MSK models again overestimated the risk of EPE, LNI, and NOCD and the Briganti nomogram overestimated the risk of LNI, whereas the MUSIC models and Partin tables remained well-calibrated (Figure 2).

Net benefit

In the threshold range of 0-20% risk (to perform a lymph node dissection), the MUSIC model achieved the highest net benefit across this range in the SEER validation cohort (Figure 3), although the difference was modest as compared to the MSK model. The Partin table for LNI is not directly comparable to the others because exclusion of T3 disease (as described in the Methods) leads to a lower prevalence of LNI. A comparison of the potential clinical impact of using the MUSIC and MSK models is provided in Supplemental Figures 2 and 3.

DISCUSSION

In this study, we found that newly developed MUSIC models outperformed existing models in the prediction of pathologic outcomes following radical prostatectomy. While the MUSIC models had relatively similar AUCs to the MSK models and the Briganti nomogram (for LNI), the MSK models overestimated the risk of EPE, LNI, and NOCD, and the Briganti nomogram overestimated the risk of LNI in both our internal validation and external validation cohorts. In contrast, the Partin tables were generally well-calibrated but had inferior discrimination in both cohorts. The MUSIC models had the highest net benefit among all LNI models, though the difference between the MUSIC and MSK model was quite small.

Our findings for model discrimination are consistent with prior evaluations of the MSK models and Partin tables but not consistent with a prior published evaluation of the 2017 Briganti nomogram. An evaluation of the 2007 Partin tables (a prior version) on the 2005 SEER registry found AUCs of 0.62, 0.74, 0.77, and 0.68 for EPE, SVI, LNI, and NOCD, respectively.[8] Our evaluation of the updated Partin tables on 2015 SEER registry data found slight improvements in AUC for EPE (0.67) and NOCD (0.72), a similar AUC for SVI (0.76), and lower AUC for LNI (0.69). A prior meta-analysis evaluating LNI models based on 10,028 patients for MSK models and 69,681 patients for the Partin tables found pooled AUCs of 0.78 for both models.[17] Our evaluation of the MSK models and Partin tables found similar AUCs in the MUSIC validation cohort (0.81 and 0.78, respectively), although the Partin tables performed worse in the SEER cohort (AUC 0.69).

The original paper describing the Briganti paper found an AUC of 0.91, whereas our evaluation found an AUC of 0.81 in both validation cohorts. This difference could be due to both overestimation of model performance in the original publication (due to a small development cohort [681 patients] and reuse of the same population for model validation), and underestimation in our evaluation (due to median imputation of percent highest-grade

and lower-grade cores). However, the overestimation of risk from the Briganti nomogram was *not* caused by imputation because the overall percentage of positive cores in the original publication (which we used for imputation) is actually *lower* than the overall percentage of positive cores in the SEER registry (33.3%[6] vs. 41.2%). Model miscalibration is a known problem in the setting of PCa more broadly.[18] Our finding that several models were miscalibrated on national registry data is important because national guidelines need to consider models on their impact broadly, and not only at the academic medical centers where the models were developed.

Our study has several limitations. Neither the SEER registry nor the MUSIC registry have centralized pathology, so there may be variations in the quality of pathologic reporting. While the SEER registry contains a national sample of patients with PCa, this population may not necessarily be nationally representative. One known limitation of the SEER registry is that it oversamples western states as compared to the rest of the US. However, the fact that our results in the SEER registry were largely concordant with the MUSIC validation cohort —which includes 90% of urology practices in Michigan—supports the notion that patient sampling did not play a large role in the findings. On the other hand, our stringent inclusion criteria based on missingness of crucial information (such as PSA or biopsy Gleason grade) could have impacted our results if this missingness was informative because of significant reductions in cohort sizes. Particularly within MUSIC, where data are collected by trained abstractors with direct access to the urologists, we expect the missingness would have been noninformative.

Our study has national implications because the MSK models, Partin tables, and Briganti nomogram are widely adopted, and because several national guidelines recommend the use of risk stratification as part of preoperative counseling.[2,3] More broadly, our findings also have implications for other models developed using data from tertiary care referral centers. Even if the data are of high quality, selection bias may lead to non-representative estimates of disease risk.

CONCLUSIONS

Our study provides the first external validation of recent MSK models, Partin tables, and the Briganti nomogram in national registry data. Finding the MSK models and Briganti nomogram to be miscalibrated, and the Partin tables to have lower discrimination than other models, our study offers an alternative in the form of newly developed MUSIC models. These models should be considered as potential replacements for the prediction of pathologic outcomes in prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

PCa	Prostate Cancer
AUC	Area Under the Receiver Operating Characteristic Curve
SEER	Surveillance, Epidemiology, and End Results Program
MUSIC	Michigan Urological Surgery Improvement Collaborative
EPE	Extraprostatic Extension
SVI	Seminal Vesicle Invasion
LNI	Lymph Node Invasion
NOCD	Non-organ-confined Disease
MSK	Memorial Sloan Kettering

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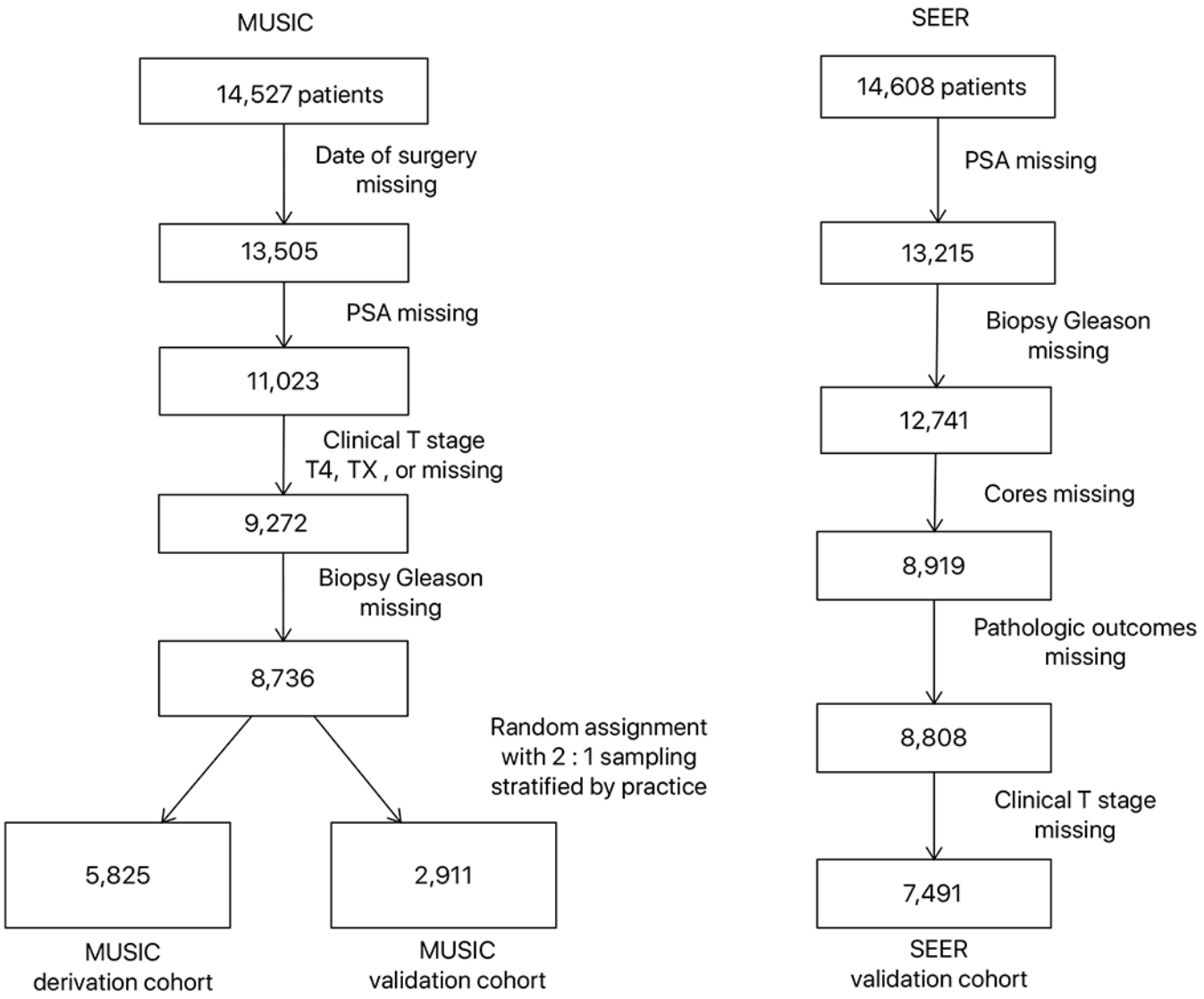

Figure 1.
Flow chart of patient inclusion/exclusion criteria

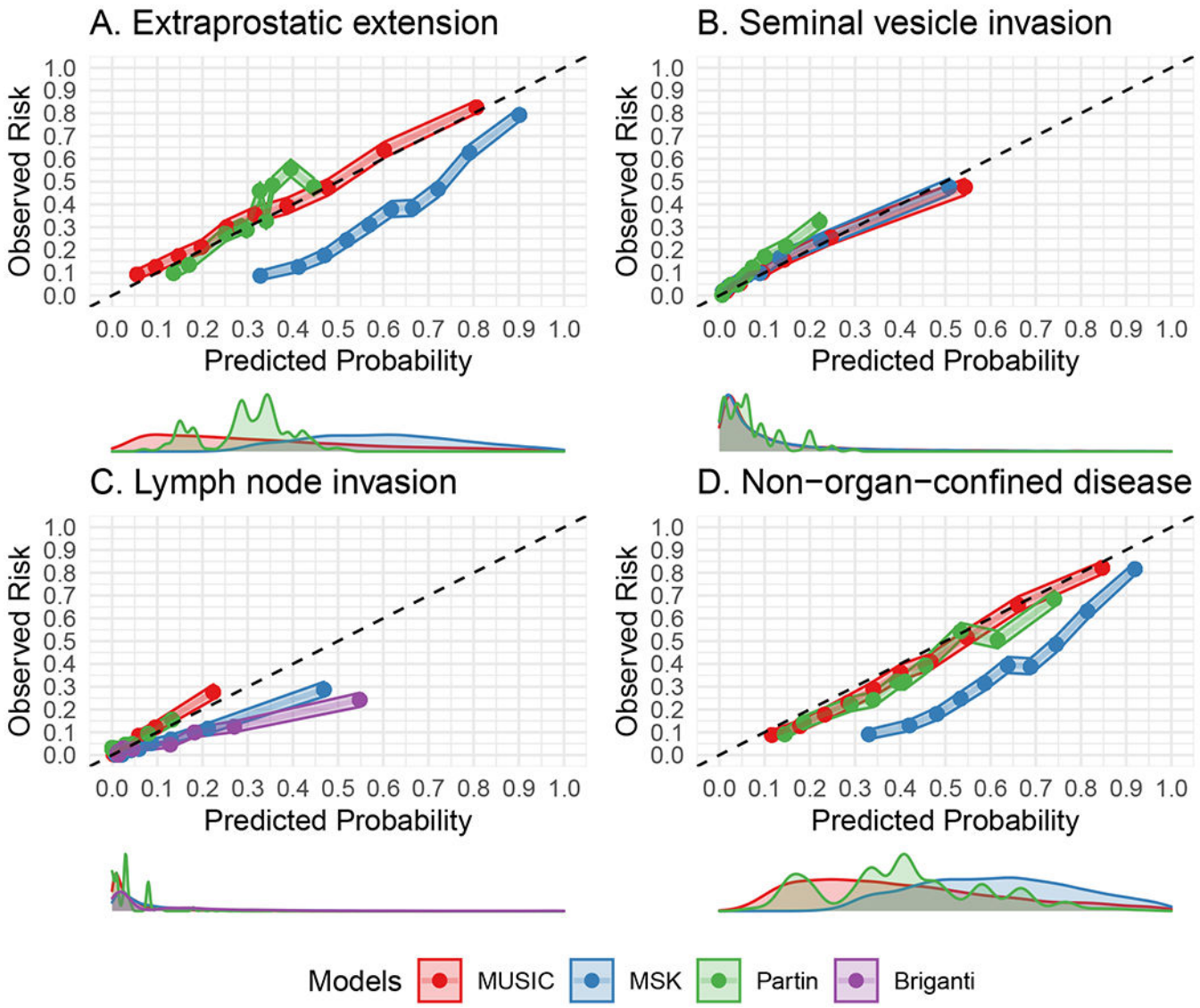

Figure 2.

SEER validation cohort: calibration plot and distributions of the MUSIC, MSK, Partin, and Briganti models, with shaded 95% confidence intervals. Abbreviations: MUSIC: Michigan Urological Surgery Improvement Collaborative; MSK: Memorial Sloan Kettering.

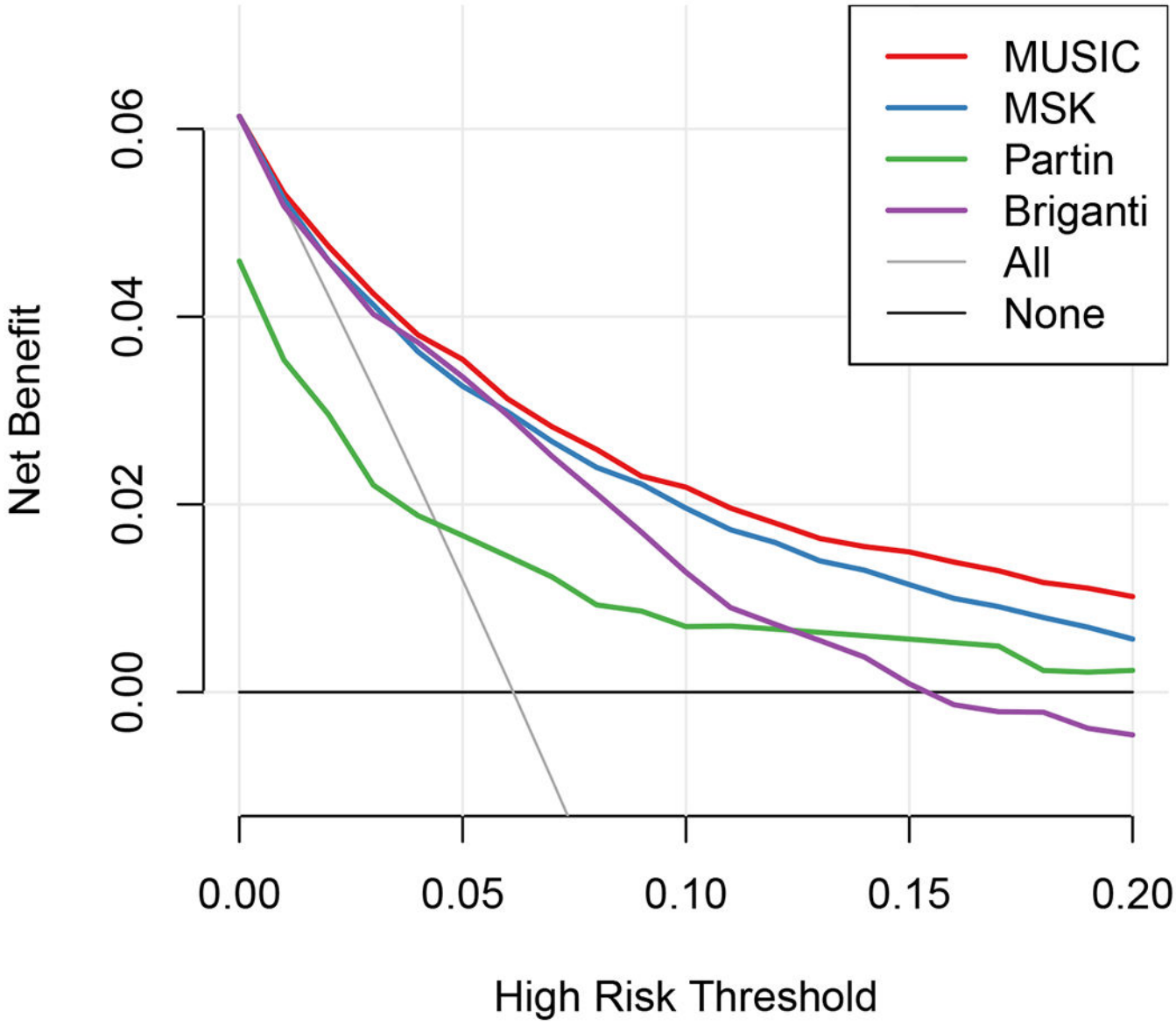

Figure 3.

SEER validation cohort: decision curve analysis for the outcome of lymph node invasion comparing the MUSIC, MSK, Partin, and Briganti models. Abbreviations: MUSIC: Michigan Urological Surgery Improvement Collaborative; MSK: Memorial Sloan Kettering

Table 1.

Patient characteristics by cohort.

Characteristic	MUSIC derivation N = 5825	MUSIC validation N = 2911	SEER validation N = 7491
Age, median (IQR)	63 (58, 68)	64 (58, 68)	62 (57, 67)
Prostate-specific antigen in ng/mL, median (IQR)	6.0 (4.5, 8.7)	6.0 (4.6, 8.9)	6.5 (4.9, 9.6)
Primary Gleason, n (%)			
2	1 (<0.1%)	0 (0%)	1 (<0.1%)
3	3518 (60%)	1785 (61%)	4658 (62%)
4	2207 (38%)	1081 (37%)	2695 (36%)
5	99 (1.7%)	45 (1.5%)	137 (1.8%)
Secondary Gleason, n (%)			
2	1 (<0.1%)	0 (0%)	0 (0%)
3	2265 (39%)	1098 (38%)	3203 (43%)
4	3136 (54%)	1613 (55%)	3672 (49%)
5	423 (7.3%)	200 (6.9%)	616 (8.2%)
ISUP Grade Group (Gleason Score), n (%)			
1 (GS ≤6)	1047 (18%)	515 (18%)	1814 (24%)
2 (GS 3+4)	2434 (42%)	1253 (43%)	2750 (37%)
3 (GS 4+3)	1211 (21%)	577 (20%)	1370 (18%)
4 (GS 8)	683 (12%)	354 (12%)	953 (13%)
5 (GS 9-10)	450 (7.7%)	212 (7.3%)	604 (8.1%)
# of Positive Cores, median (IQR)	7 (5, 10)	8 (5, 10)	5.0 (3, 7)
Missing, n	13	6	0
# of Negative Cores, median (IQR)	7 (5, 10)	8.0 (5, 10)	8.0 (5, 10)
Missing, n	13	7	0
Clinical T stage			
1	4154 (71%)	2087 (72%)	5771 (77%)
2a	847 (15%)	449 (15%)	673 (9.0%)
2b	455 (7.8%)	190 (6.5%)	286 (3.8%)
2c	304 (5.2%)	157 (5.4%)	449 (6.0%)
3	65 (1.1%)	28 (1.0%)	312 (4.2%)

Table 2.

Prevalence of patient outcomes by cohort.

Outcome	MUSIC derivation N = 5825	MUSIC validation N = 2911	SEER validation N = 7491
Extraprostatic extension, n (%)	2028 (35%)	978 (34%)	2697 (36%)
Seminal vesicle invasion, n (%)	674 (12%)	316 (11%)	949 (13%)
Missing, n	57	33	5
Lymph node invasion, n (%)	268 (5.9%)	102 (4.4%)	458 (6.1%)
Missing, n	1245	590	25
Non-organ-confined disease, n (%)	2142 (45%)	1026 (43%)	2757 (37%)
Missing, n	1027	503	19

Note: Percentages represent the proportion of the population with the outcome out of patients with available findings for specified outcome. Also these percentages are not mutually exclusive.

Table 3.

Model performance with bootstrapped 95% confidence intervals.

MUSIC validation cohort (internal validation)				
Models / **Outcomes**	**MUSIC AUC (95% CI)**	**MSK AUC (95% CI)**	**Partin AUC (95% CI)**	**Briganti AUC (95% CI)**
Extraprostatic extension	0.77 (0.75-0.79)	0.70 (0.68-0.72)	0.66 (0.64-0.68)	--
Seminal vesicle invasion	0.82 (0.79-0.84)	0.81 (0.78-0.83)	0.77 (0.75-0.80)	--
Lymph node invasion	0.82 (0.78-0.87)	0.81 (0.78-0.86)	0.78 (0.73-0.83)	0.81 (0.77-0.85)
Non-organ-confined disease	0.74 (0.72-0.76)	0.68 (0.65-0.70)	0.69 (0.67-0.71)	--
SEER validation cohort (external validation)				
Models / **Outcomes**	**MUSIC AUC (95% CI)**	**MSK AUC (95% CI)**	**Partin AUC (95% CI)**	**Briganti AUC (95% CI)**
Extraprostatic extension	0.77 (0.76-0.78)	0.76 (0.75-0.77)	0.67 (0.66-0.69)	--
Seminal vesicle invasion	0.80 (0.79-0.82)	0.80 (0.78-0.81)	0.76 (0.74-0.78)	--
Lymph node invasion	0.83 (0.81-0.85)	0.84 (0.82-0.85)	0.69 (0.66-0.72)	0.81 (0.79-0.83)
Non-organ-confined disease	0.77 (0.76-0.79)	0.76 (0.75-0.77)	0.72 (0.71-0.73)	--

Note: AUC: Area under the receiver-operator-characteristic curve