A Novel Risk Classification Model Predicts Overall Survival and Locoregional Surgery Benefit in Colorectal Patients with Distant Metastasis at the Initial Diagnosis

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Research

Keywords: Colorectal cancer, Metastasis, Nomogram, Prognosis, Surgery

Posted Date: December 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-117490/v1

Abstract

Background and aims: In this research, we aimed to construct a risk classification model to predict overall survival (OS) and locoregional surgery benefit in colorectal cancer (CRC) patients with distant metastasis.

Methods: We selected a cohort consisting of 12741 CRC patients diagnosed with distant metastasis between 2010 and 2014, from the Surveillance, Epidemiology and End Results (SEER) database. Patients were randomly assigned into training group and validation group at the ratio of 2:1. Univariable and multivariable Cox regression models were applied to screen independent prognostic factors. A nomogram was constructed and assessed by the Harrell's concordance index (C-index) and calibration plots. A novel risk classification model was further established based on the nomogram.

Results: Ultimately 12 independent risk factors including race, age, marriage, tumor site, tumor size, grade, T stage, N stage, bone metastasis, brain metastasis, lung metastasis and liver metastasis were identified and adopted in the nomogram. The C-indexes of training and validation groups were 0.77 (95% confidence interval [CI] 0.73-0.81) and 0.75 (95% CI 0.72-0.78), respectively. The risk classification model stratified patients into three risk groups (low-, intermediate- and high-risk) with divergent median OS (low-risk: 36.0 months, 95% CI 34.1-37.9; intermediate-risk: 18.0 months, 95% CI 17.4-18.6; high-risk: 6.0 months, 95% CI 5.3-6.7). Locoregional therapies including surgery and radiotherapy could prognostically benefit patients in the low-risk group (surgery: hazard ratio [HR] 0.59, 95% CI 0.50-0.71; radiotherapy: HR 0.84, 95% CI 0.72-0.98) and intermediate risk group (surgery: HR 0.61, 95% CI 0.54-0.68; radiotherapy: HR 0.86, 95% CI 0.77-0.95), but not in the high-risk group (surgery: HR 1.03, 95% CI 0.82-1.29; radiotherapy: HR 1.03, 95% CI 0.81-1.31). And all risk groups could benefit from systemic therapy (low-risk: HR 0.68, 95% CI 0.58-0.80; intermediate-risk: HR 0.50, 95% CI 0.47-0.54; high-risk: HR 0.46, 95% CI 0.40-0.53).

Conclusion: A novel risk classification model predicting prognosis and locoregional surgery benefit of CRC patients with distant metastasis was established and validated. This predictive model could be further utilized by physicians and be of great significance for medical practice.

Background

Colorectal cancer (CRC) is among the most frequent malignant tumors of both genders (third for men, second for women) globally. Annually, 1.8 million patients were newly diagnosed, leading to nearly 0.86 million deaths per year (1, 2). Though its incidence and mortality rates show an optimal tendency for slow declining thanks to early detections via colonoscope in USA, its worldwide incidence remains high and mortality rate keeps dreadful, mainly attributable to distant metastasis (3, 4).

About one fifth of CRC patients have metastatic lesions at the time of diagnosis, majority of which involving liver or lung. Approximately 50% of CRC patients will ultimately progress into metastasis in their lifetime, indicating the end stage of cancer progression and poor prognosis (5). Yet different metastatic organs result in different survival outcomes. Subset with isolated metastasis to liver and/or lung of CRC has currently been regarded as potentially curable with surgery, while for other specific metastatic CRC,

treatment can be palliative, mainly consisting of systemic chemotherapy (6). The pervasive applications of systemic chemotherapy remain controversial. Piling researches reported chemotherapy paradigms consisting of diverse agents and indications (7–9).

However, because of the tumor heterogeneity as well as various demographic risk factors, standard therapy does not benefit patients of all backgrounds (10, 11). Efficacy of systemic treatments depends on geography, race, age, and other clinicopathological features (12). Personalized regimen would be required for better therapeutic effect on individual, which should be guided by a comprehensive prognostic model to predict possible survival outcomes under given circumstances (13). By far, no such predictive model for CRC patients was constructed. Therefore, we aimed to build a risk classification model, which would be capable of visualizing the quantified risk factors and applying for clinical practice.

Materials And Methods

Study population

Patients included in this research were collected from the SEER database via SEER*Stat. Access authority to the published data pool has been acquired officially from the SEER website (www.seer.cancer.gov). The SEER database has gained the inform consent before publishing the documents.

Among 185498 patients diagnosed with CRC registered in SEER between 2010–2014, we included cases meeting the criteria as follows: 1. CRC was pathologically identified as primary and the only malignancy; 2. patients had unequivocal metastasis with TNM stage rated as “M1”; 3. intact information on clinical and pathological parameters was documented in SEER database. Patients of multiple malignancies, vague diagnostic evidence, none or uncertain metastatic status, as well as incomplete information on clinicopathological data were excluded.

The final cohort consists of 12741 patients, whose documented data on demographic, clinicopathological and treatment parameters including race, age, marital status, tumor site, tumor size, tumor grade, T and N stage, metastatic status on bone, bran, liver and lung, treatment information about radiotherapy, chemotherapy and surgery, vital status and survival months were abstracted from the SEER database. For continuous variables like age and tumor size, we applied the X-tile software to transfer them into categorical variables based on the cut-off values of optimal significance (age is divided into “<55 years”, “55–75 years” and “>75 years”, and tumor size is divided into “<3cm”, “3-5cm” and “>5cm”). For better analysis, marital status and treatment data including radiotherapy, chemotherapy and surgery was simplified as dichotomous variables (“married” or “unmarried”, “yes” or “no”). Vital death was defined as the main outcome event. Overall survival (OS) time was calculated as the timespan between diagnosis and death of all causes.

Statistical analysis

We randomly assigned the included 12741 cases into the training and validation group at the ratio of 2:1. The training group was regarded as the data resource for constructing the prognostic model, while validation group would be the validation for the model. Initially descriptive analysis on demographic and clinicopathological baseline characteristics of the entire cohort was performed via Chi-square analysis. The survival analysis was performed by the Kaplan-Meier method in each subgroup. Median survival time with 95% confidence interval (95% CI) was presented along with the frequency distributions. Univariate and multivariate analyses were performed to identify independent risk factors for overall survival. Factors sustaining statistically significant in multivariate model were eventually accepted for constructing the nomogram via R software (Version 1.1.456). The packages “rms”, “VIM” and “survival” were applied in R software. Two- and three- year overall survival were adopted as endpoints in the nomogram. Harrell’s concordance index (C-index) was used as evaluation indictor for the discriminative capacity of the prognostic model. Calibration curves were plotted to visualize the consistency between the predicted and observed survival time in given timespans, for assessing the predictive veracity of the model. Quantified scores of each risk factor were given by monogram considering weighted risk degrees. Total prognostic scores of patients were calculated by adding points of each risk factor, and patients were classified according to their prognostic scores for risk stratifications. Statistically significant were defined as two-sided *P*-values < 0.05. Statistically analysis involved in this study were accomplished via SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinicopathological characteristics

In total, 12741 patients were selected based on the inclusion and exclusion criteria and their clinical information was abstracted from the SEER database (detailed selection protocol shown in **Fig. 1**). The whole cohort was randomly assigned into the training and validation groups at the ratio of 2:1, 8510 cases in the training set and 4231 cases in the validation set, respectively. Baseline clinicopathological parameters of the two sets are shown in Table 1, along with the OS and 95% CI of each subgroup. For demographic factors such as race, gender, age and marital status, the frequency distributions are relatively homogeneous between the two sets. For clinicopathological factors, about 3.1%, 1.0%, 16.9% and 70.0% patients in the training group presented metastasis to bone, brain, lung and liver, respectively, indicating a tendency to liver metastasis in CRC patients.

Table 1
Baseline clinicopathological characteristic of patients in the training and validation cohort.

Clinicopathological characteristics	Training set			Validation set		
	No. of patients (%)	OS (months)		No. of patients (%)	OS (months)	
		Median	95% CI		Median	95% CI
Gender						
Female	4023 (47.3)	19.0	17.9-20.1	2050 (48.5)	20.0	18.6-21.4
Male	4487 (52.7)	21.0	20.1-21.9	2181 (51.5)	21.0	19.7-22.3
Race						
White	6476 (76.1)	20.0	19.2-20.8	3177 (75.1)	21.0	19.3-22.7
Black	1267 (14.9)	19.0	17.6-20.4	639 (15.1)	20.0	18.1-23.9
OthersΔ	767 (9.0)	24.0	21.3-26.7	415 (9.8)	23.0	20.3-25.7
Age, years						
<55	2441 (28.7)	27.0	25.4-28.6	1240 (29.3)	27.0	23.3-30.7
55-75	4429 (52.0)	21.0	20.1-21.9	2176 (51.4)	22.0	19.9-24.1
>75	1640 (19.3)	8.0	7.2-8.8	815 (19.3)	8.0	7.5-10.5
Marriage						
Married	4495 (52.8)	23.0	22.0-24.0	2185 (51.6)	23.0	20.8-25.2
Unmarried	4015 (47.2)	17.0	16.0-18.0	2046 (48.4)	18.0	16.1-19.9
Site						
Right Colon	4076 (47.9)	15.0	13.8-16.2	2068 (48.9)	16.0	14.8-17.2
Left Colon	2643 (31.1)	24.0	22.8-25.2	1383 (32.7)	25.0	21.1-26.9
Rectus	1791 (21.0)	25.0	23.3-26.7	780 (18.4)	25.0	23.5-28.5

Tumor size, cm						
<3	824 (9.7)	26.0	23.3-28.7	409 (9.6)	28.0	22.8-33.2
3-5	3609 (42.4)	21.0	19.9-22.2	1809 (42.8)	22.0	20.7-23.3
>5	4077(47.9)	18.0	17.0-19.0	2013 (47.6)	19.0	17.7-20.3
Grade						
I	409 (4.8)	33.0	29.3-36.7	222 (5.2)	37.0	25.3-50.7
II	4991 (58.6)	24.0	23.1-24.9	2508 (59.3)	24.0	22.1-25.9
III	2068 (24.3)	13.0	12.2-13.8	947 (22.4)	14.0	12.4-15.6
IV	1042 (12.3)	10.0	8.6-11.4	554 (13.1)	13.0	9.9-18.1
T stage						
T1	475 (5.6)	24.0	17.2-30.8	227 (5.4)	24.0	17.2-30.8
T2	262 (3.1)	24.0	22.9-25.1	130 (3.1)	21.0	20.1-21.9
T3	4204 (49.4)	16.0	14.8-17.2	2102 (49.7)	16.0	14.8-17.2
T4	3569 (41.9)	13.0	10.4-15.6	1772 (41.8)	15.0	12.0-20.0
N stage						
N0	2124 (25.0)	23.0	21.5-24.5	1111 (26.3)	24.0	22.2-25.8
N1	2761 (32.4)	21.0	19.3-22.8	1371 (32.4)	23.0	20.6-25.4
N2	3625 (42.6)	17.0	16.1-17.9	1749 (41.3)	17.0	15.8-18.2
Bone metastasis						
No	8244 (96.9)	21.0	20.3-21.7	4103 (97.0)	21.0	19.5-22.5
Yes	266 (3.1)	8.0	5.9-10.11	128 (3.0)	7.0	4.1-9.9

Brain metastasis						
No	8425 (99.0)	20.0	19.3-20.7	4191 (99.1)	21.000	19.6-22.4
Yes	85 (1.0)	5.0	2.7-7.3	40 (0.9)	4.000	1.9-6.1
Lung metastasis						
No	7076 (83.1)	20.0	19.2-20.8	3503 (82.8)	21.0	19.3-22.7
Yes	1434 (16.9)	18.0	16.4-19.6	728 (17.2)	19.0	16.6-21.4
Liver metastasis						
No	2556 (30.0)	22.0	20.5-23.5	1272 (30.1)	24.0	20.7-27.3
Yes	5954 (70.0)	19.0	18.2-19.8	2959 (69.9)	19.0	17.4-20.6
ΔOthers include American Indian, AK Native, Asian, and Pacific Islander. OS: overall survival; CI: confidence interval.						

Univariate and multivariate analyses for overall survival

We applied univariate analysis of all the clinical parameters for screening out potential prognostic indicators. As revealed in Table 2, 12 parameters were included for further multivariate analysis. Multivariate Cox regression analysis identified race (black: HR 1.12, 95% CI 1.04–1.21; others: HR 0.84, 95% CI 0.76–0.93; white as reference), age (> 75 years: HR 1.95, 95% CI 1.80–2.12; 55–75 years: HR 1.23, 95% CI 1.14–1.31; <50 years as reference), marriage (unmarried: HR 1.11, 95% CI 1.05–1.18; married as reference), tumor site (rectus: HR 0.74, 95% CI 0.76–0.91; left colon: HR 0.84, 95% CI 0.78–0.90; right colon as reference), tumor size (> 5cm: HR 1.23, 95% CI 1.14–1.34; 3-5cm: HR 1.11, 95% CI 1.03–1.19; <3 cm as reference), grade (grade IV: HR 2.10, 95% CI 1.77–2.43; grade III: HR 1.79, 95% CI 1.54–2.04; grade II: HR 1.17, 95% CI 1.01–1.34), T stage (T4: HR 1.45, 95% CI 1.39–1.51; T3: HR 1.14, 95% CI 1.09–1.19; T2: HR 1.09, 95% CI 1.02–1.16; T1 as reference), N stage (N2: HR 1.27, 95% CI 1.15–1.39; N1: HR 1.07, 95% CI 1.04–1.10; N0 as reference), bone metastasis (bone metastasis: HR 1.66, 95% CI 1.44–1.88; no metastasis as reference), brain metastasis (brain metastasis: HR 1.75, 95% CI 1.37–2.13; no metastasis as reference), lung metastasis (lung metastasis: HR 1.33, 95% CI 1.23–1.43; no metastasis as reference) and liver metastasis (liver metastasis: HR 1.54, 95% CI 1.44–1.64; no metastasis as reference) as independent risk factors for OS (Table 2). The HR with 95% CI of each subgroup was also presented in a Forest plot (Fig. 2). Thus, these independent risk factors were all adopted for constructing the nomogram.

Table 2
Univariate and multivariate analyses for overall survival.

Variable	Univariable analysis *P*	Multivariable analysis	
		HR (95% CI)	*P*
Gender	0.680		
Male			
Female			
Race	< 0.001		< 0.001
White		Reference	
Black		1.12 (1.04–1.21)	0.005
OthersΔ		0.84 (0.76–0.93)	0.001
Age, years	< 0.001		< 0.001
< 55		Reference	
55–75		1.23 (1.14–1.31)	< 0.001
> 75		1.95 (1.80–2.12)	< 0.001
Marriage	< 0.001		< 0.001
Married		Reference	
Unmarried		1.11 (1.05–1.18)	< 0.001
Site	< 0.001		< 0.001
Right colon		Reference	
Left colon		0.84 (0.78–0.90)	0.012
Rectus		0.74 (0.76–0.91)	< 0.001
Tumor size, cm	< 0.001		< 0.001
< 3		Reference	
3–5		1.11 (1.03–1.19)	0.006
> 5		1.23 (1.14–1.34)	< 0.001
Grade	< 0.001		< 0.001
I		Reference	
II		1.17 (1.01–1.34)	0.042
III		1.79 (1.54–2.04)	< 0.001

Variable	Univariable analysis *P*	Multivariable analysis	
		HR (95% CI)	*P*
IV		2.10 (1.77–2.43)	< 0.001
T stage	< 0.001		< 0.001
T1		Reference	
T2		1.09 (1.02–1.16)	0.038
T3		1.14 (1.09–1.19)	0.021
T4		1.45 (1.39–1.51)	< 0.001
N stage	< 0.001		< 0.001
N0		Reference	
N1		1.07 (1.04–1.10)	0.021
N2		1.27 (1.15–1.39)	< 0.001
Bone metastasis	< 0.001		< 0.001
No		Reference	
Yes		1.66 (1.44–1.88)	< 0.001
Brain metastasis	< 0.001		< 0.001
No		Reference	
Yes		1.75 (1.37–2.13)	< 0.001
Lung metastasis	< 0.001		< 0.001
No		Reference	
Yes		1.33 (1.23–1.43)	< 0.001
Liver metastasis	< 0.001		< 0.001
No		Reference	
Yes		1.54 (1.44–1.64)	< 0.001

ΔOthers include American Indian, AK Native, Asian, and Pacific Islander. HR: hazard ratio; CI: confidence interval.

Nomogram construction and validation

All the verified independent risk factors in Table 2 were incorporated to construct the prognostic model. The Plot function in R language visualized the digital model as the nomogram (Fig. 3). Explicitly, age (> 75 years: score 95; 55–75 years: score 29), brain metastasis (score 89) and bone metastasis (score 69),

as well as tumor grade (grade IV: score 69; grade III: score 57; grade II: score 16) are factors contributing most to the prognosis, followed by T stage (T4: score 52; T3: score 29; T2: score 4) and liver metastasis (score 35) that make moderate contribution. Factors including N stage (N2: score 27; N1: score 5), tumor size (> 5cm: score 26; 3-5cm: score 16), tumor site (right colon: score 26; left colon: score 7), marital status (unmarried: score 25), lung metastasis (score 22) and race (black: score 22; white: score 10) make relatively less contribution to OS. All involved factors in nomogram were assigned with quantified scores (Table 3).

Table 3
Scores of clinical variables in each subgroup.

Variable	Points	Variable	Points
Race		T stage	
White	10	T1	0
Black	22	T2	4
Others	0	T3	29
Age, years		T4	52
< 55	0	N stage	
55–75	29	N0	0
> 75	95	N1	5
Grade		N2	27
I	0	Bone metastasis	
II	16	No	0
III	57	Yes	69
IV	69	Brain metastasis	
Marriage		No	0
Married	0	Yes	89
Unmarried	25	Lung metastasis	
Site		No	0
Left colon	7	Yes	22
Right colon	26	Liver metastasis	
Rectus	0	No	0
Tumor size, cm		Yes	35
< 3	0		
3–5	16		
> 5	26		

Based on individual condition, scores of each parameter were calculated and added up to total points. The total score was matched to an estimated 2- and 3-year overall survival rate according to the bottom two lines in the nomogram (Fig. 3). As the indicator to evaluate the coherence degree of the prognostic model, C-indexes of both the training and validation groups were 0.77 (95% CI 0.73–0.81) and 0.75 (95%

CI 0.72–0.78), respectively. Moreover, calibration curves for 2- and 3-year OS were created, showing satisfying consistency between the predicted and virtual survival rates in both internal and external validation cohort (Fig. 4).

A novel risk classification system for prognosis

According to the quantified scores assigned to each risk factor, we calculate all included patients' prognostic scores by adding points of every risk factor. Based on the final scores, patients were divided into three different risk groups: low-risk group (3078/12741, score < 150), intermediate-risk group (8443/12742, score 151–275) and high-risk group (1220/12741, score > 275). The median OS in the low-, intermediate- and high groups were 36.0 months (95% CI 34.1–37.9), 18.0 months (95% CI 17.4–18.6) and 6.0 months (95% CI 5.3–6.7), respectively. The risk stratification of three groups can be clearly seen by Kaplan-Meier analysis (Fig. 5). The established risk stratification system was proven to be accurate in predicting survival outcomes of CRC patients with distant metastasis.

Prognostic benefit of locoregional and systemic therapies in classified risk groups

For further investigation on clinical significance of risk stratification, we then compared therapeutic benefit that each group could gain from locoregional surgery, as well as that from systematic chemotherapy. Notably, surgical resection of the primary tumors showed survival benefit in the low-risk group (HR 0.59, 95% CI 0.50–0.71, $P < 0.0001$) and intermediate risk group (HR 0.61, 95% CI 0.54–0.68, $P < 0.0001$), but not in the high-risk group (HR 1.03, 95% CI 0.82–1.29, $P = 0.823$) (Fig. 6). Moreover, locoregional radiotherapy showed prognostic benefit in the low-risk group (HR 0.84, 95% CI 0.72–0.98, $P = 0.028$) and intermediate risk group (HR 0.86, 95% CI 0.77–0.95, $P = 0.005$), but not in the high-risk group (HR 1.03, 95% CI 0.81–1.31, $P = 0.787$) (Fig. 7). Additionally, all the risk groups could benefit from the systemic therapy (low-risk group: HR 0.68, 95% CI 0.58–0.80, $P < 0.0001$; intermediate-risk group: HR 0.50, 95% CI 0.47–0.54, $P < 0.0001$; high risk group: HR 0.46, 95% CI 0.40–0.53, $P < 0.0001$) (Fig. 8).

Discussion

In the current research, we constructed a prognostic nomogram for predicting the overall survival of CRC patients with distant metastasis, and validated the model in both training and validation cohorts. In all, 12 demographic and clinicopathological parameters were identified as independent risk factors to OS. Further C-index calculation in both training and validation groups indicated accepted coherence degree of the nomogram. Calibration curves in both groups confirmed the model's predicting capacity on 2- and 3-year OS in CRC patients with distant metastasis. Risk stratification on patients according to weighted risk scores given by the nomogram can effectively distinguish differed OS outcomes of patients, suggesting potential application for clinical practice.

In views of epidemiology, age has been widely accepted as a major risk factor for sporadic CRC (14). This is consistent with our findings in the study. Previous epidemic researches suggested that CRC incidence,

especially large bowel caner, begins to increase in the ages of 40, and age-specific incidence rates keep increasing in the succeeding decades (15, 16). In this research, we further elaborated that not only incidence but also survival outcomes would be independently influenced by age. CRC patients older than 55 years ended with less life expectancy, and those older than 75 years may be even worse. Different outcomes according to race appear to be attributable to different life behaviors and genetic backgrounds. We were surprised to notice that marital status also contributed to patients' survival outcomes. There have been studies indicating the correlation between marital status and survival outcomes of cancer patients (17, 18). Some of them owed this connection to socioeconomic status and family care and support. We believe more investigations should be required for providing more guidance for social support.

Though liver is the dominant metastatic site for patients with CRC, brain metastasis turned out to be related to the worst prognosis, followed by bone, liver and lung metastasis. The AJCC guidelines for CRC management have pointed out that regional treatment like surgery for CRC with isolated liver metastasis may be recommended to be combined with systemic chemotherapy (19). Our findings supported the propose that for CRC with isolated metastasis in liver and lung, relatively aggressive treatment for optimal survival may be considered. The idea that malignancies from solid organs may manifest organ-specific metastasis tendency influencing survival outcomes differently has long been raised. We previously reported the metastatic preference of extrahepatic cholangiocarcinoma ultimately determined variant prognosis (20). Depicting characteristic metastasis patterns of malignancies can be of vital significance guiding treatment and prognosis prediction.

We also found that differed primary sites resulted in differed survival outcomes, with rectus the best, right colon the worst. Classification of CRC based on primary site has been long been a hot-discussed issue (21, 22). In this research, we defined the site classification as the canonical pattern put, that right colon includes colon starting from cecum to proximal splenic flexure, while left colon refers to segments from distal splenic flexure to sigmoid colons. In the view of embryology, right colon mainly originates from midgut and left colon formation initiates from hindgut. Differed histological derivation determines different malignant degrees for carcinogenesis. Owing to the characters of thin walls and mucus secretion, malignancy originating from right colon can be symptom-latent at the early phase (23, 24). Delayed onset of symptoms leads to ignorant detection during the early phase of the cancer.

Both adjuvant and neoadjuvant chemotherapy as an essential part of systemic treatment for metastatic CRC patients have been explored in last decades. Profound promotion in patients' long-term survival has been achieved by newly emerged chemo-regimens like FOLFOX and FOLFIRI (25). With the assistance of systematic chemotherapy, indications for surgery on CRC with distant metastatic sites have also been widen. Previously distant metastasis used to be absolute contradictions to surgical resections. Now surgical options on CRC with distant metastasis have been more radical than ever (26). Yet, not all evidence supports that surgical treatment promotes prognosis of advanced CRC patients in all. In this research, we found that for CRC patients of high risk could not benefit from surgeries, suggesting that accurate screening on risk factors be necessary for CRC patients with distant metastasis to consider

surgical interventions. Moreover, roles of locoregional radiotherapy in treatment for metastatic CRC patients have been controversial (27). Several RCT and meta-analysis have been debating on the question that whether and to what fraction should radiotherapy be added to treatments of advanced CRC (28, 29). We once reported that for advanced HCC patients, internal radiation therapy may achieve better therapeutic effect than external ways (30). However, in this retrospective research we identified radiotherapy as a non-beneficial treatment to CRC patients of high-risk, even though it can moderately promote prognosis for patients of low and intermediate risk. Conclusively, for CRC patients of high-risk, locoregional treatment options including surgery and radiation therapy may not achieve survival benefit as systematic chemotherapy does. Caution should be put on evaluating CRC patients' risk stratification before making medical decisions.

As far as we are concerned, this study is among the pioneering work to construct a visualized prognostic model in metastatic CRC patients. Still, as a retrospective study, there exist several limitations. Also, information on treatment provided by SEER database is general and relatively superficial. Detailed information on doses and regimens of chemotherapy and radiation remains unknown. Moreover, external validation in the nomogram was still performed based on cases from the SEER database, requiring independent external cohorts investigating its performance.

To conclude, in this study, an innovative prognostic nomogram was built based on data abstracted from the SEER database, to predict survival outcomes of patients with metastatic CRC. We anticipate this prognostic model can be further confirmed by well-designed clinical trials and be of great significance for guiding medical practice and decision making.

Conclusion

We established and validated a novel risk classification model predicting prognosis and locoregional surgery benefit of CRC patients with distant metastasis. This predictive model could be further utilized by physicians and be of great significance for medical practice.

Abbreviations

CRC, Colorectal Cancer; OS, Overall Survival; HR: Hazard Ratio; CI: Confidence Interval; SEER: Surveillance, Epidemiology, and End Results.

Declarations

AVAILABILITY OF DATA AND MATERIALS

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

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Contributions

ZW, DYH and XW contributed to conception and design. MC and TEL analyzed the data. PZD drafted the manuscript. MC, TEL, PZD, and JJP contributed critical revision of the manuscript. All authors read and approved the final manuscript.

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ETHICS DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

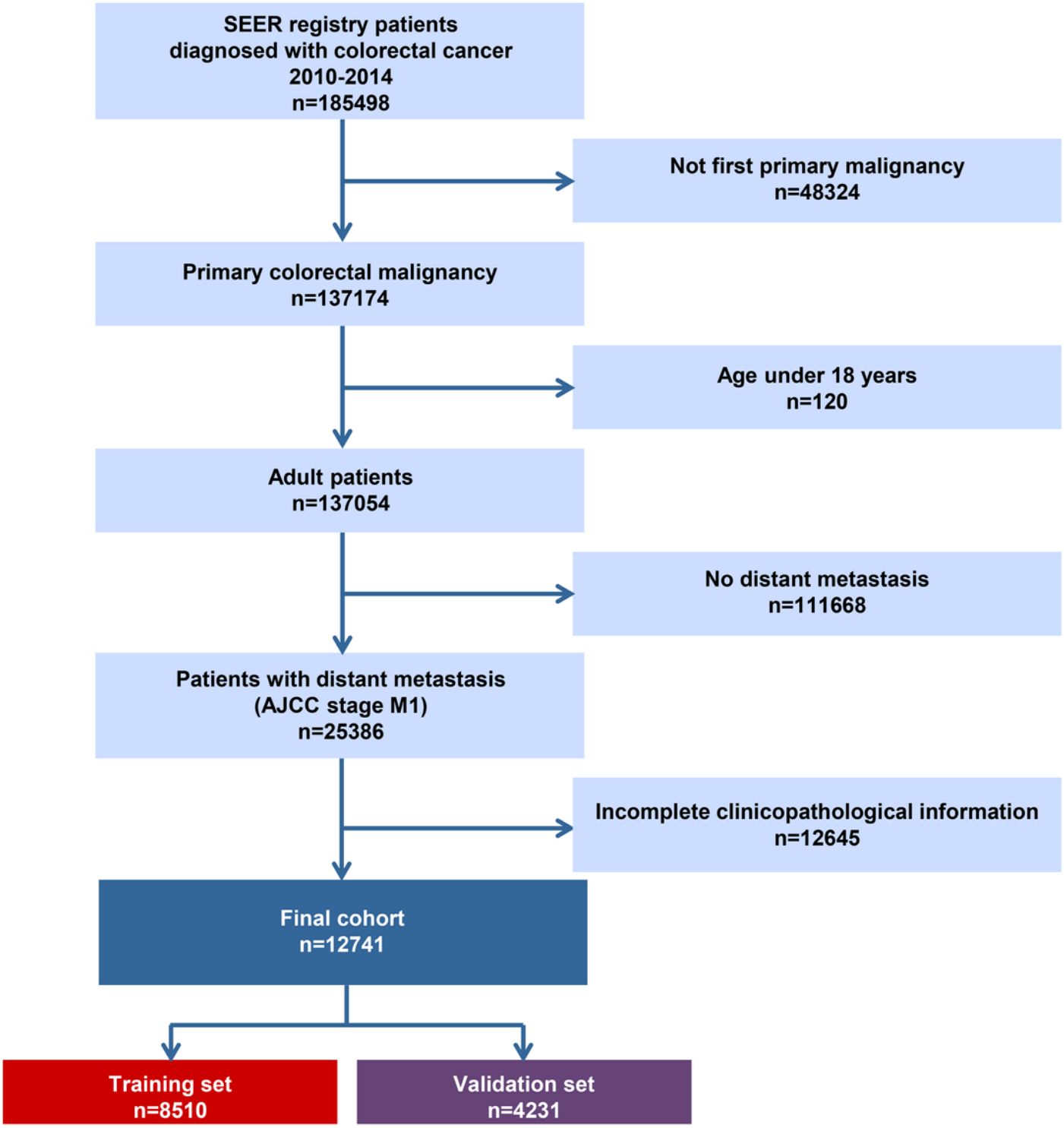
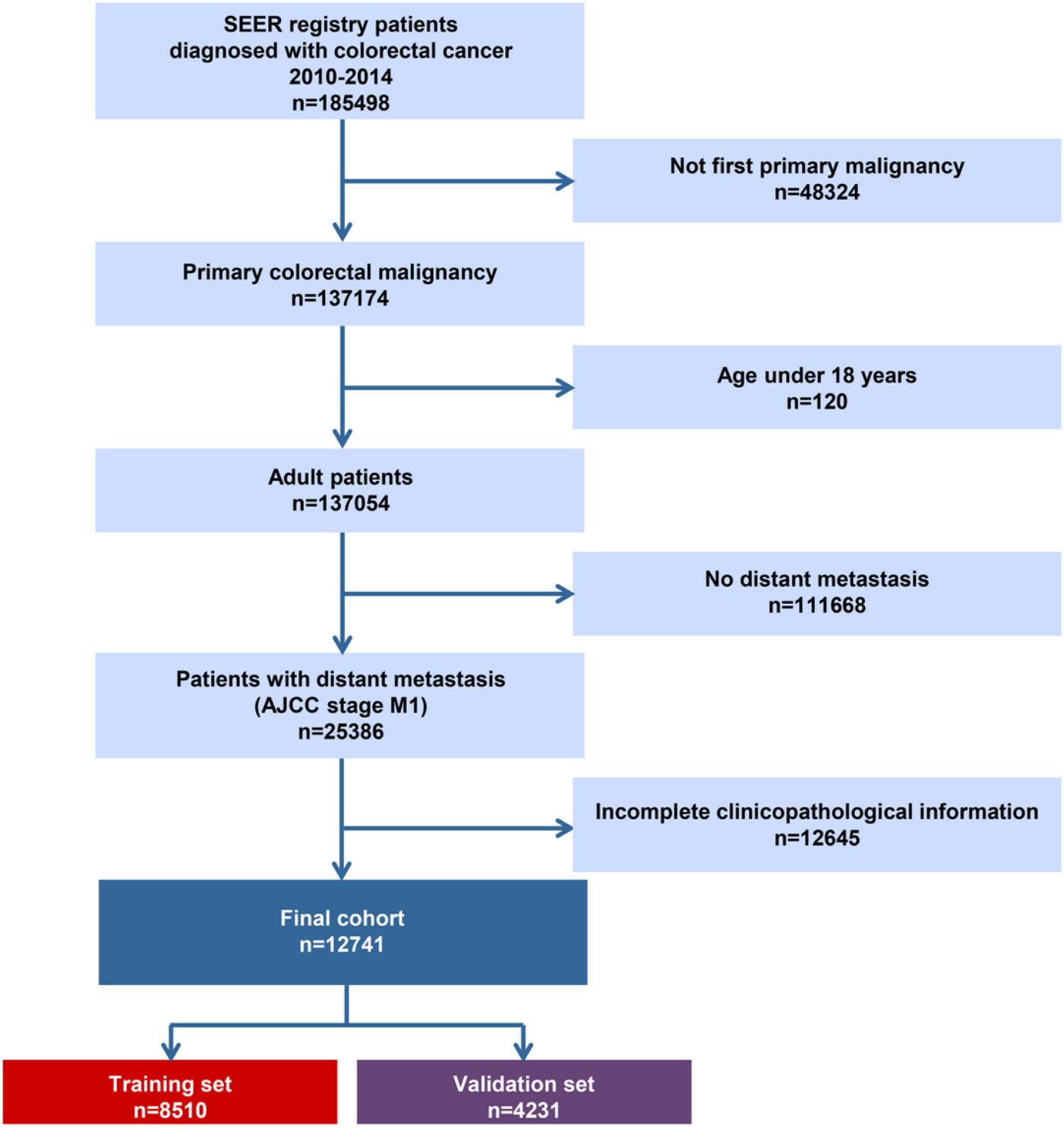


Figure 1

Patient selection flowchart.



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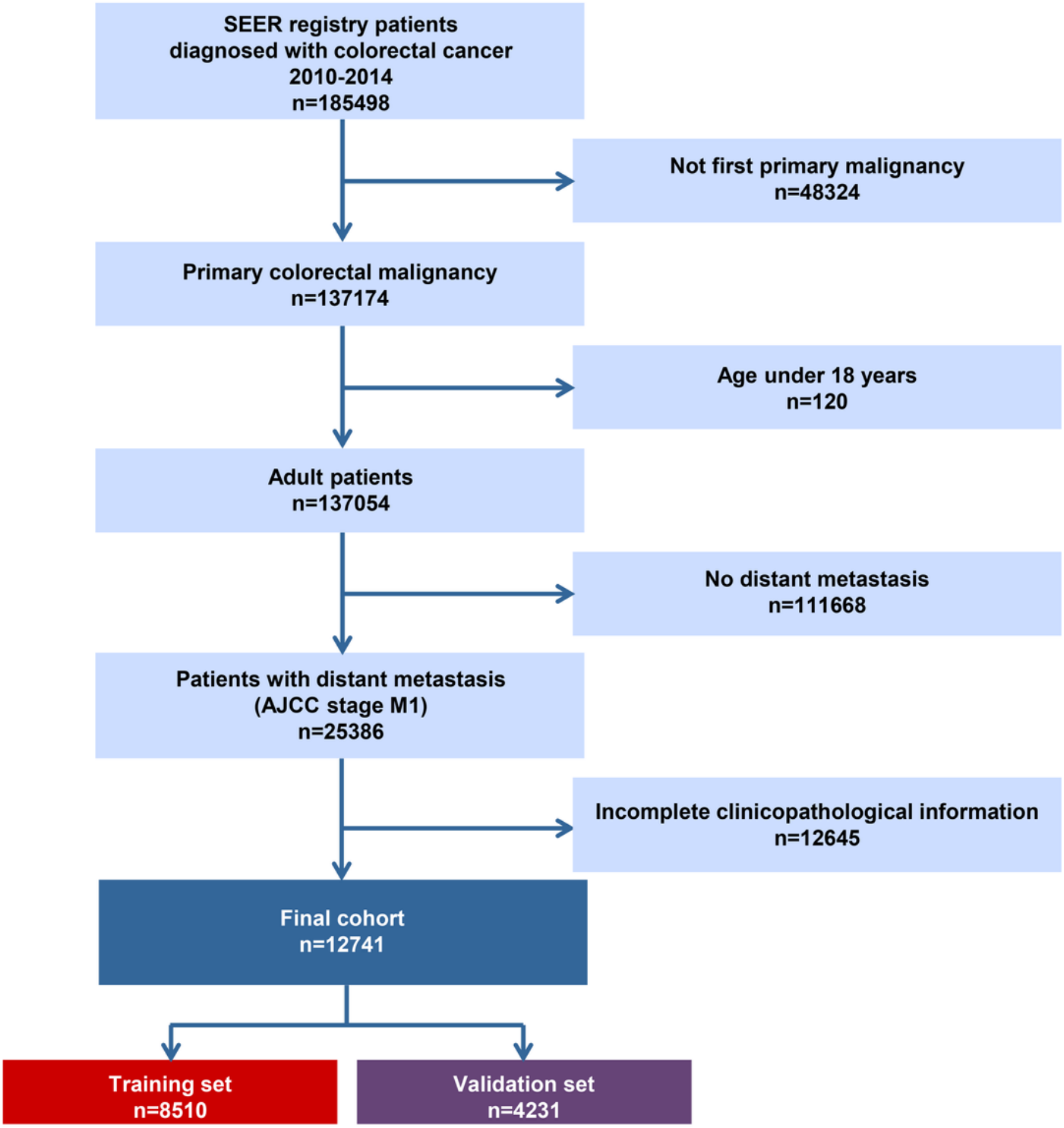

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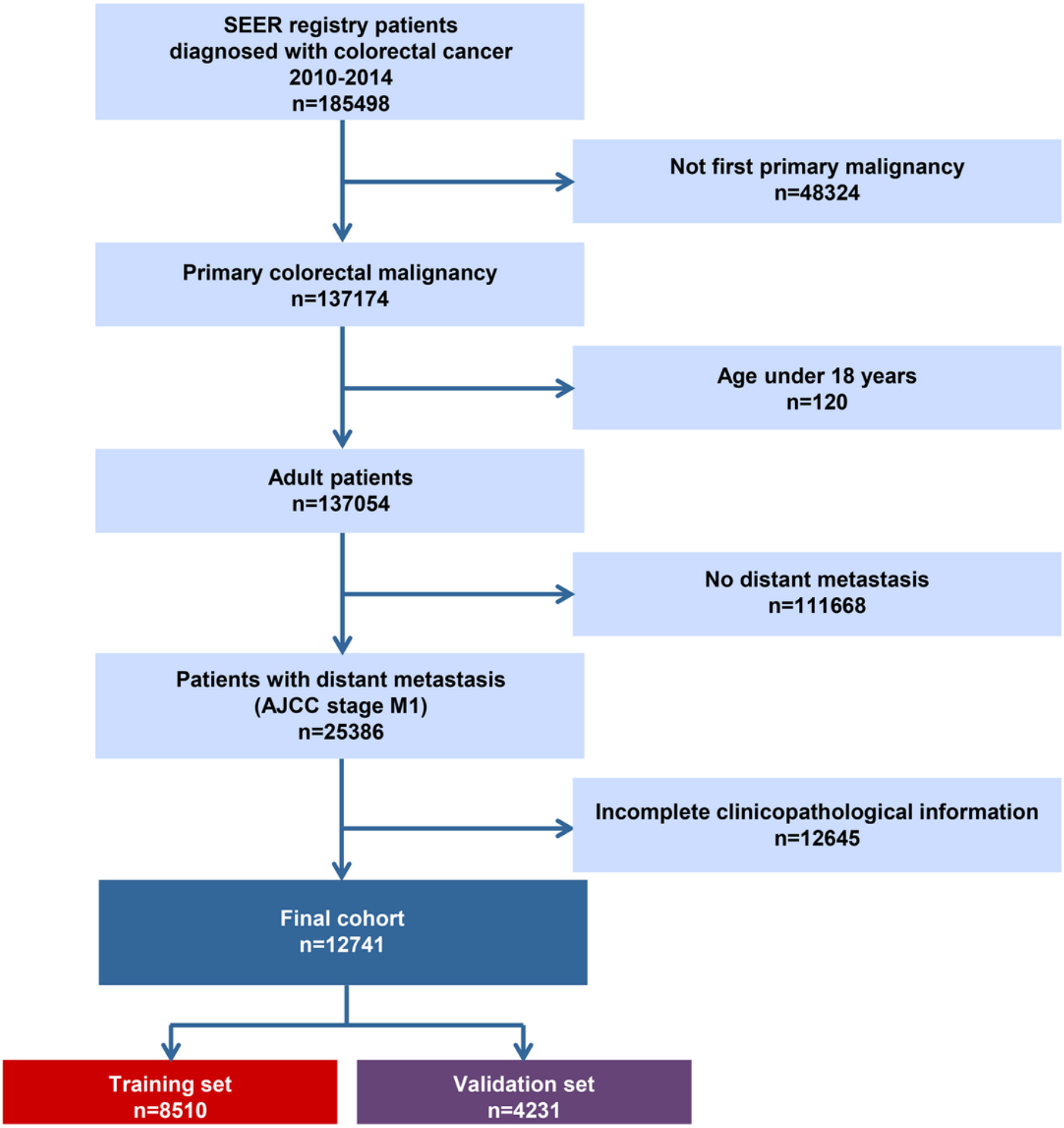

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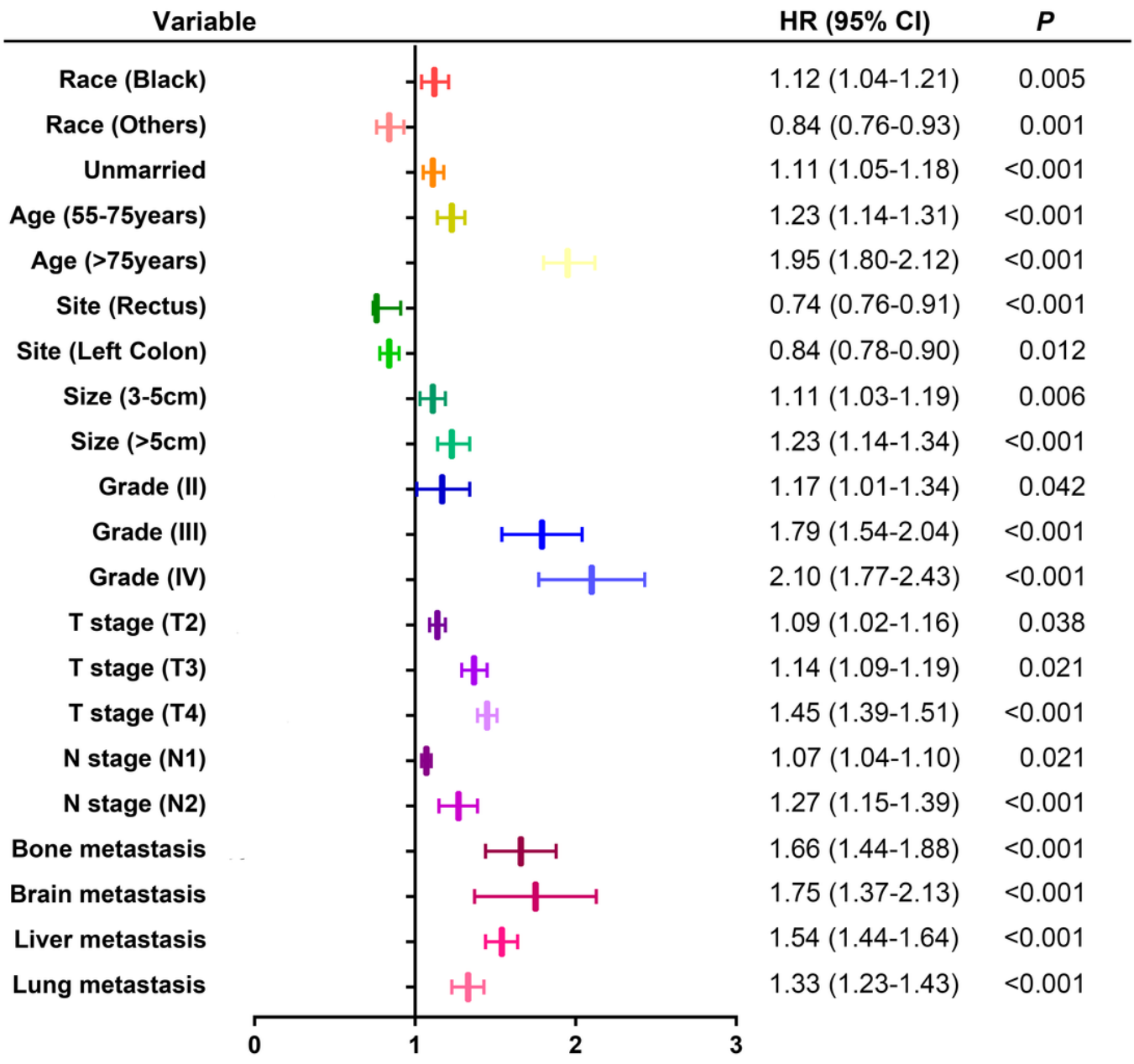
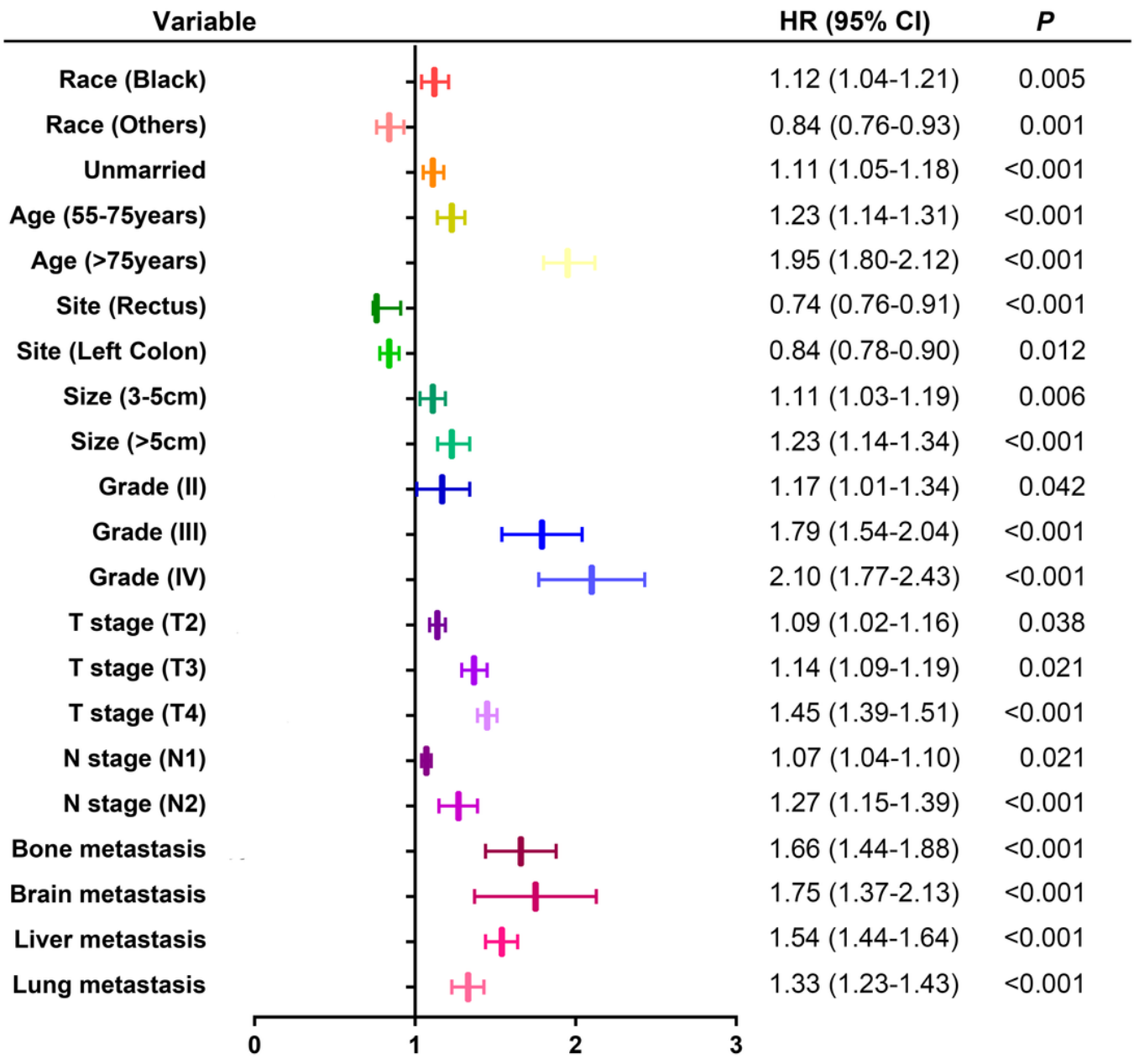


Figure 2

Forest plot showing multivariate analysis to identify independent risk factors for overall survival.



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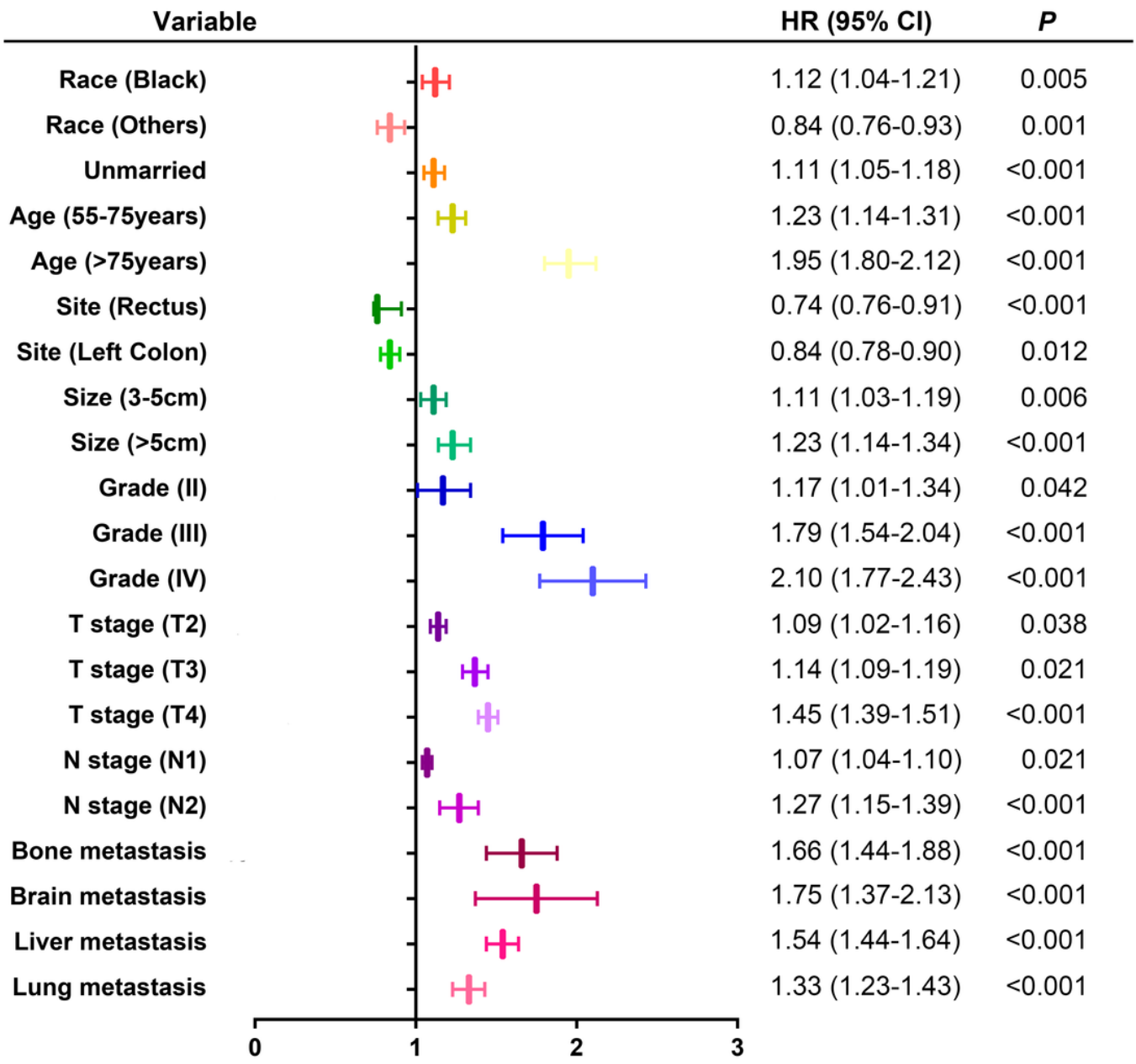

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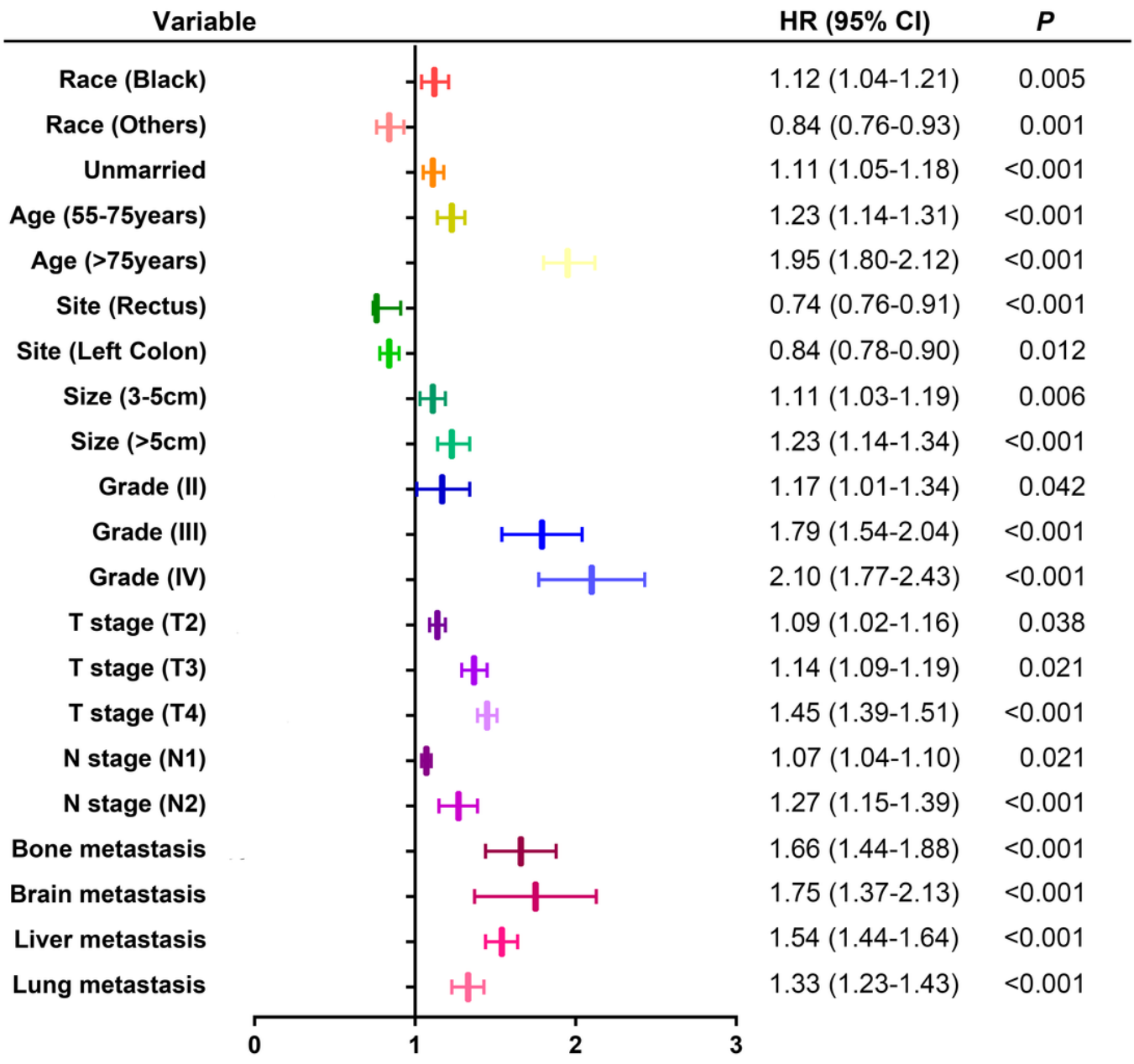

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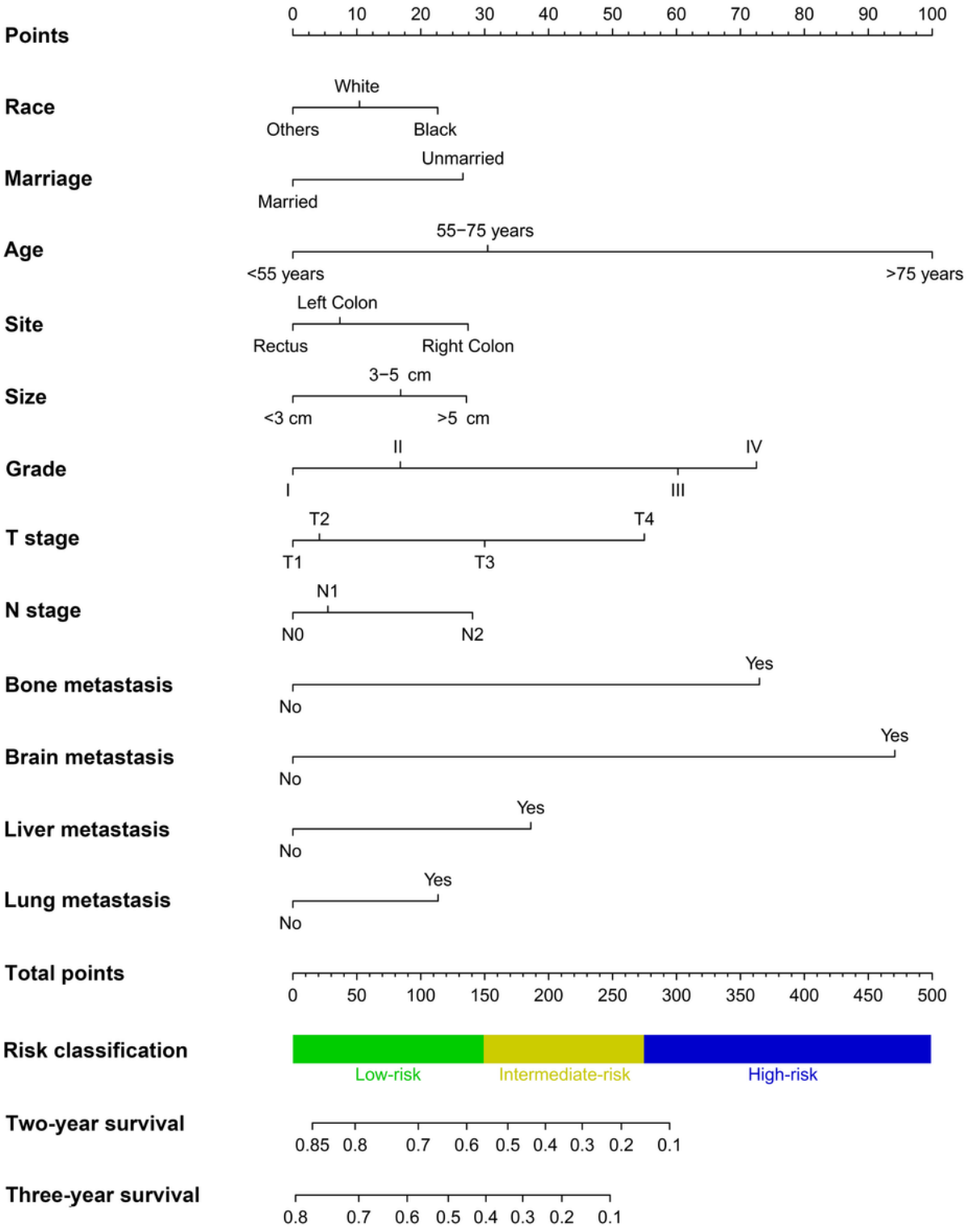
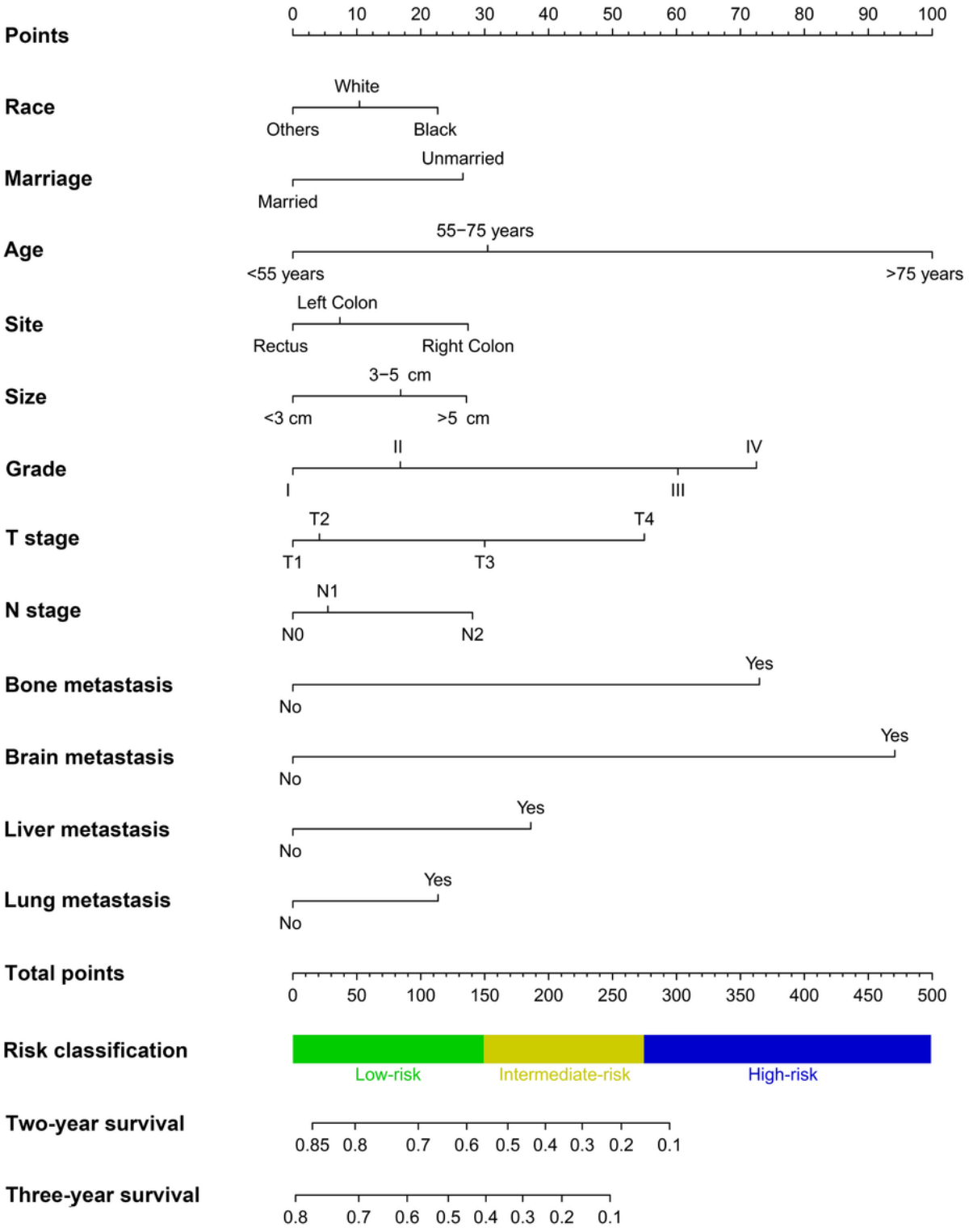


Figure 3

Nomogram for predicting 2- and 3-year overall survival in CRC patients with distal metastasis.



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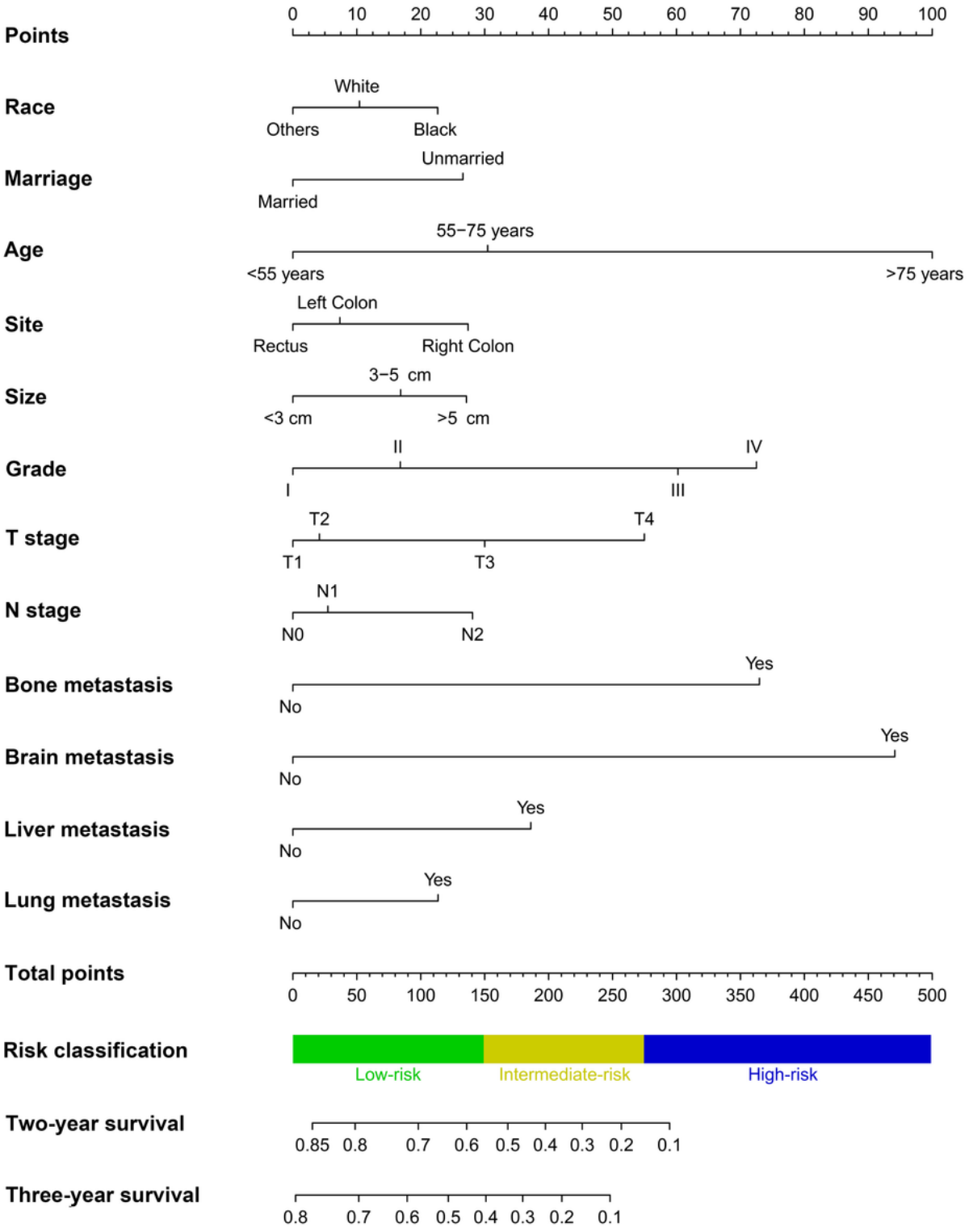

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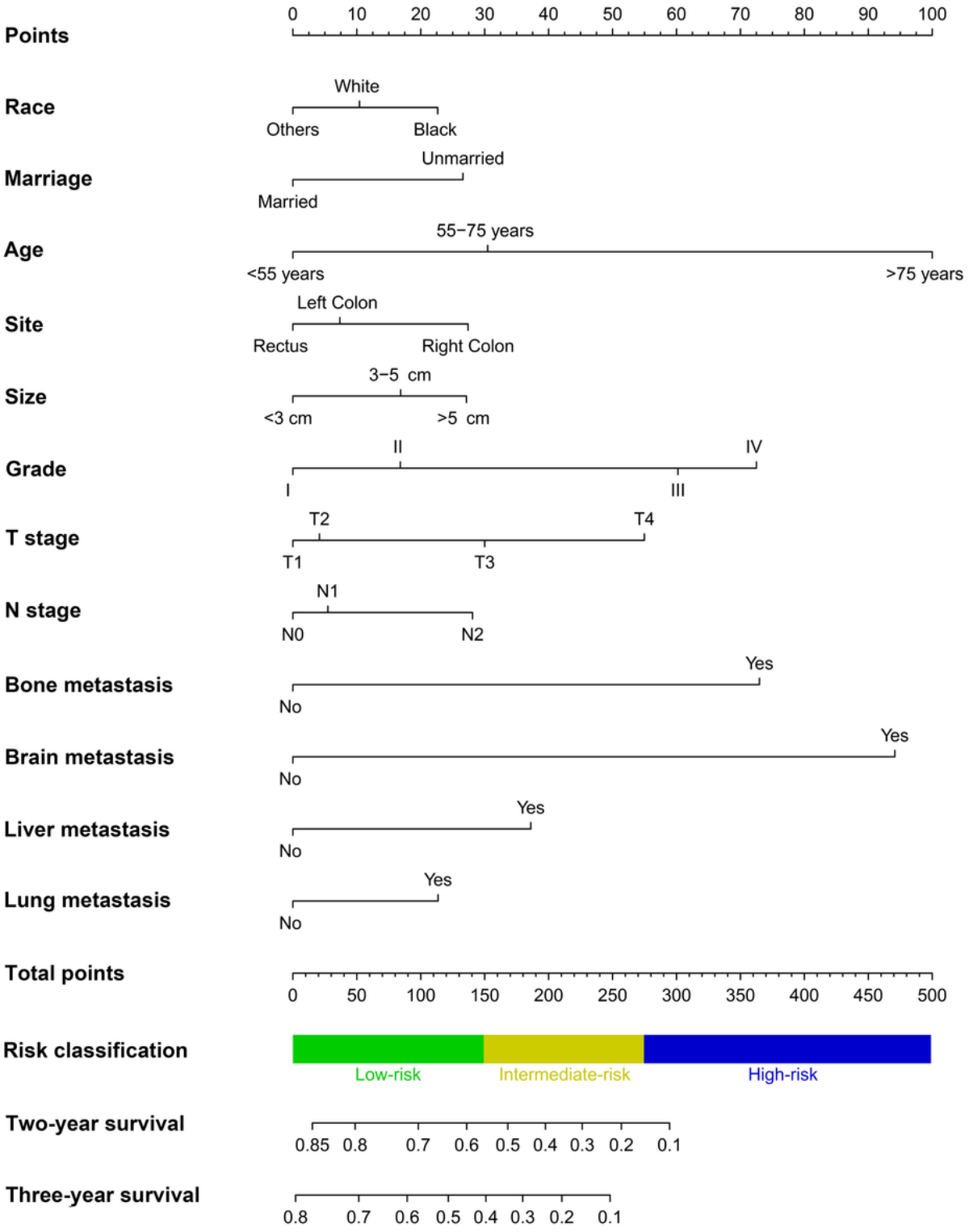

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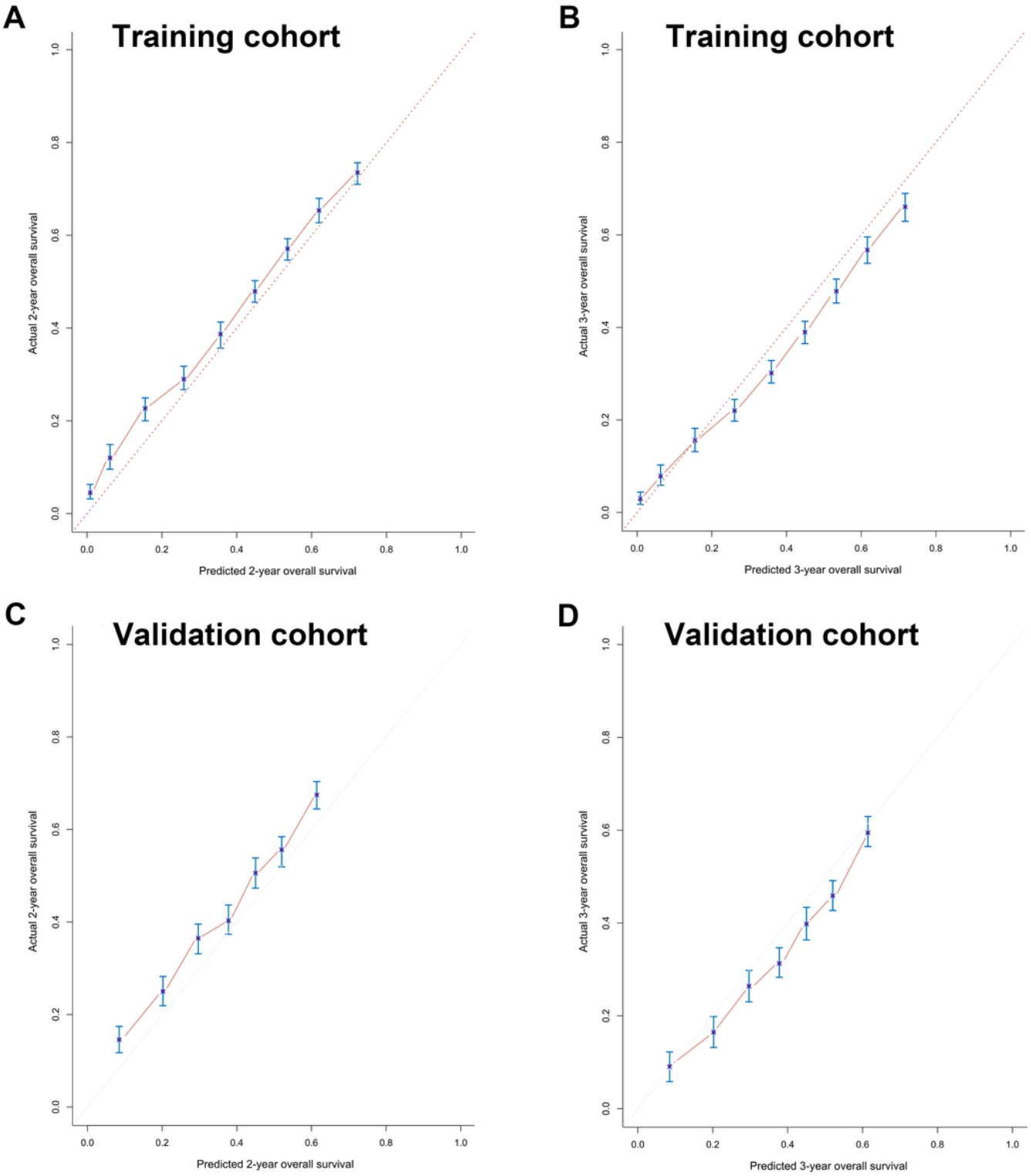
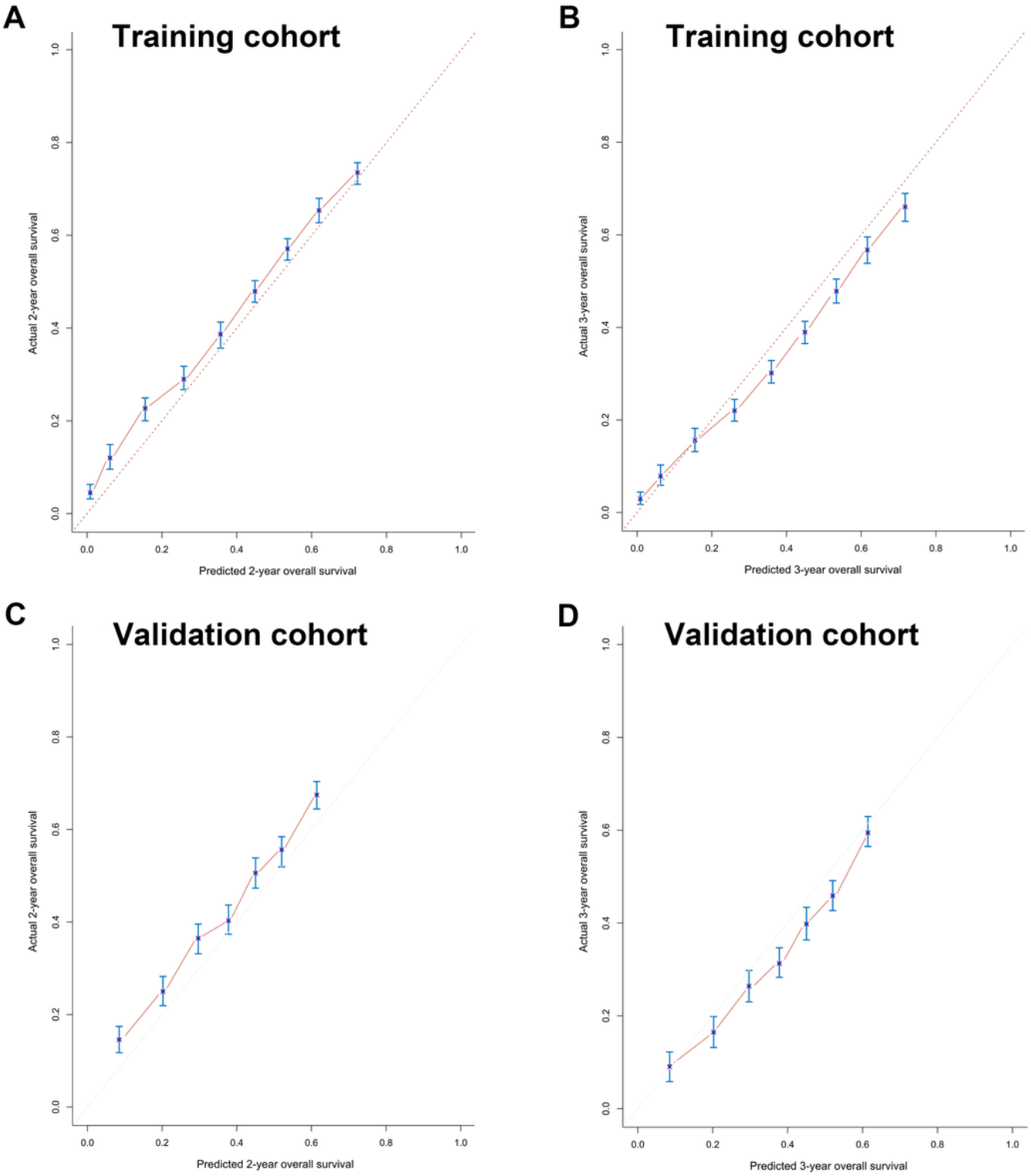


Figure 4

Calibration curves for predicting 2-year (A) and 3-year (B) overall survival in the training cohort and 2-year (C) and 3-year (D) overall survival in the validation cohort.



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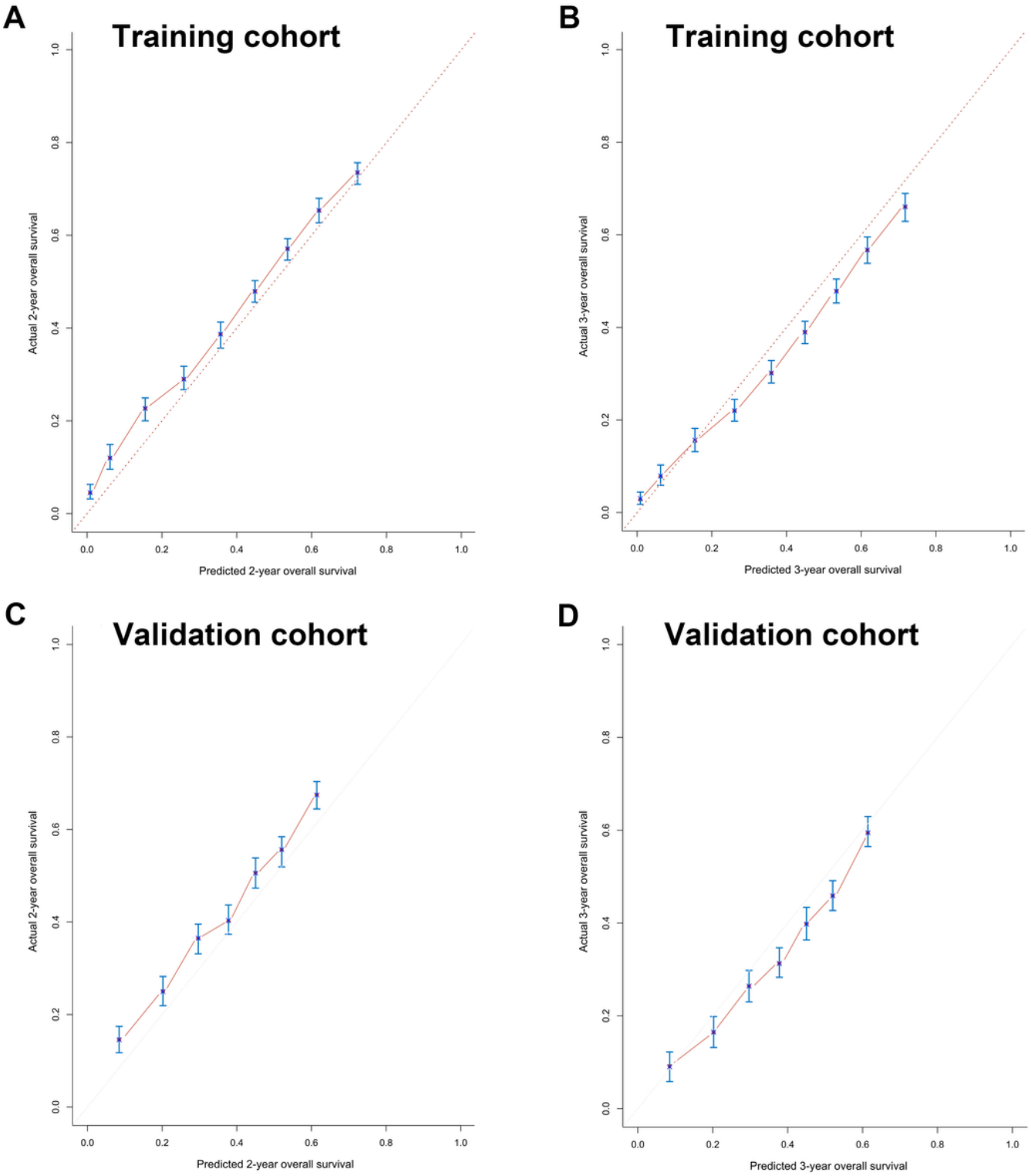

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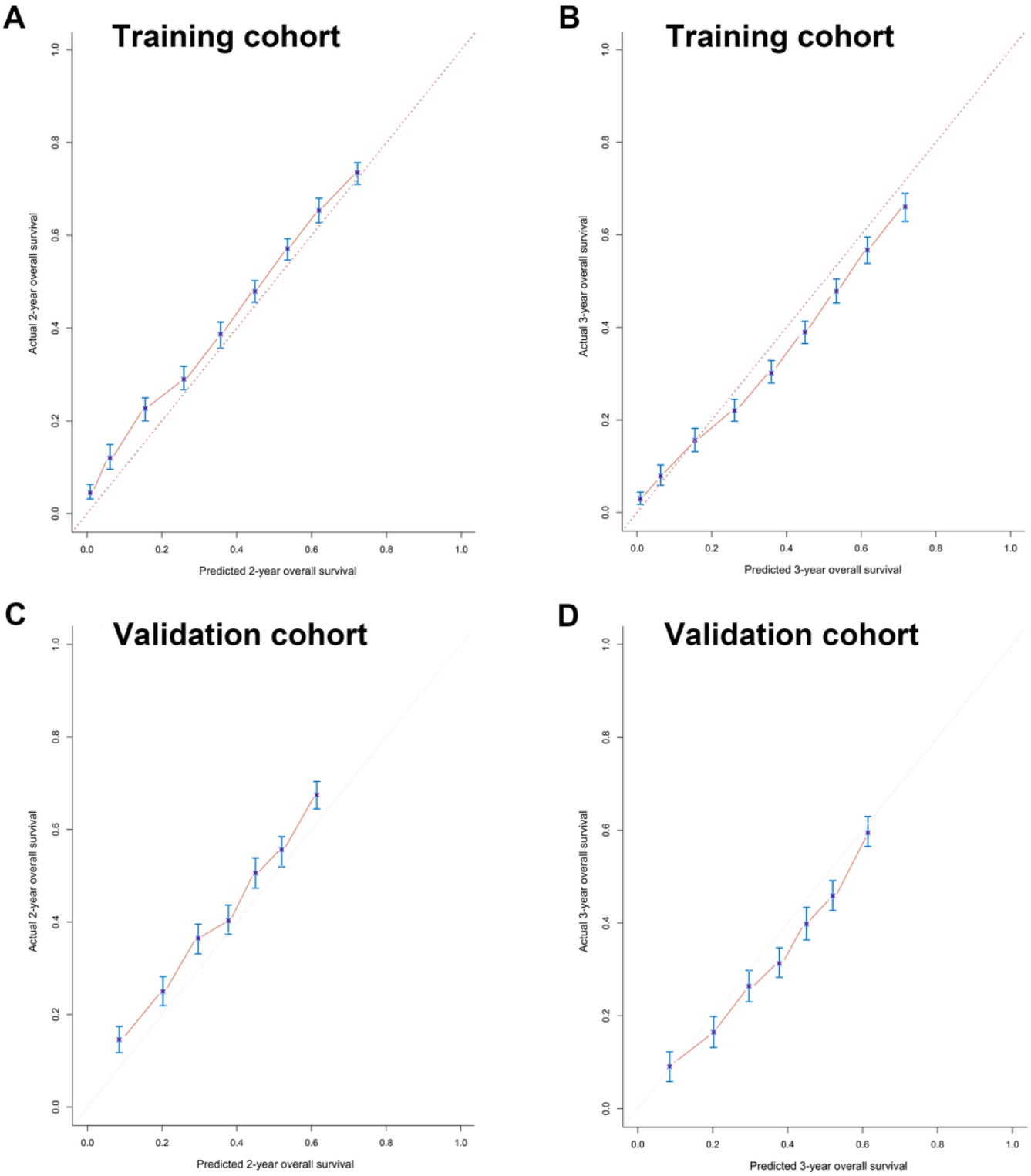

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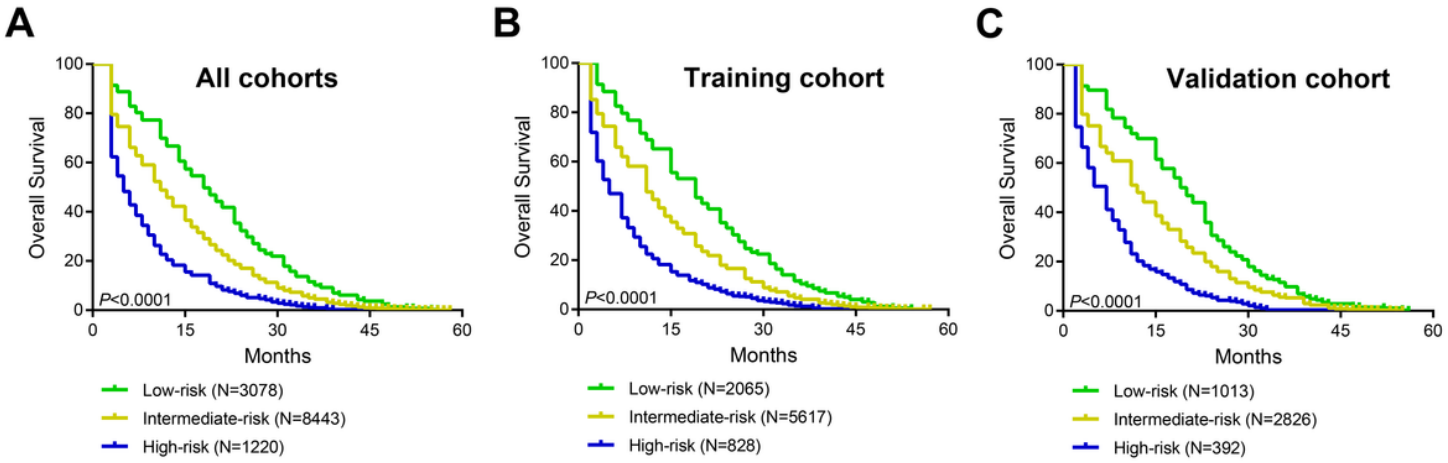
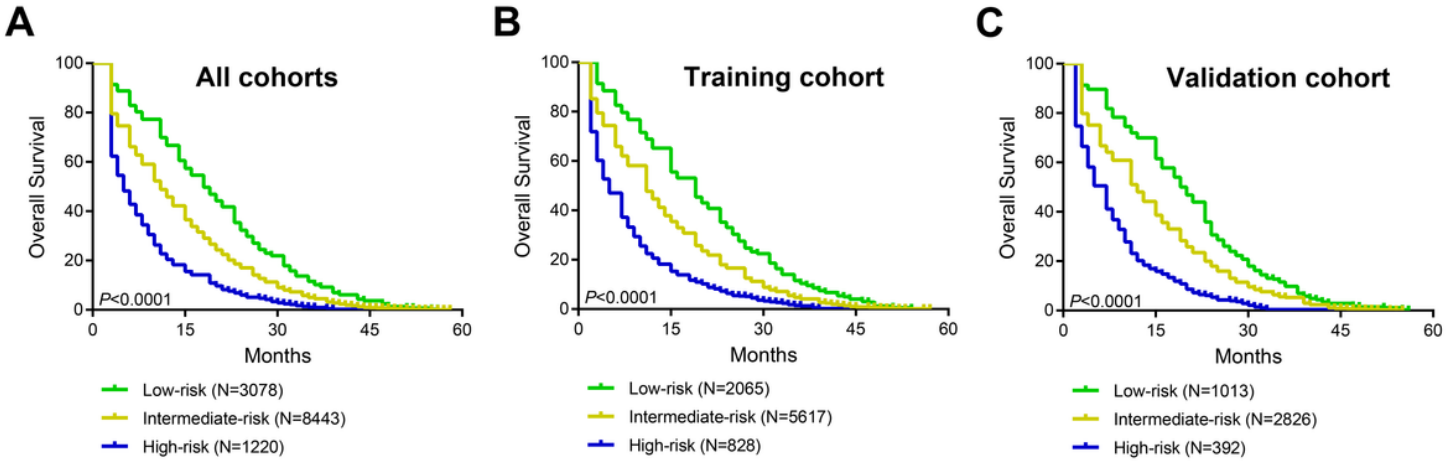


Figure 5

Prognostic classification of low-, intermediate- and high-risk groups in all cohorts (A), training cohort (B) and validation cohort (C).



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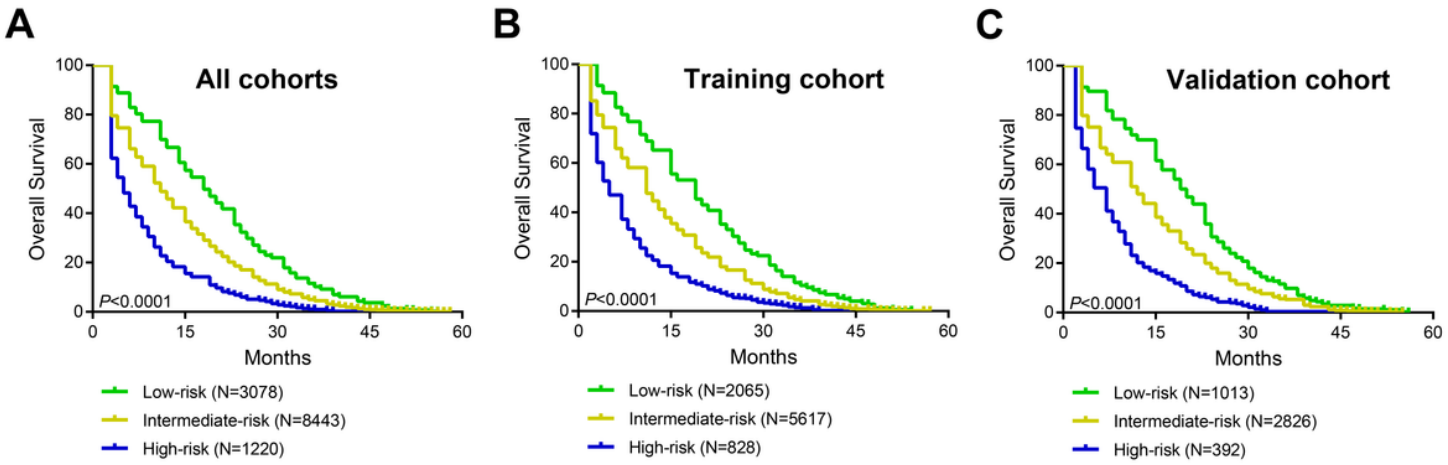

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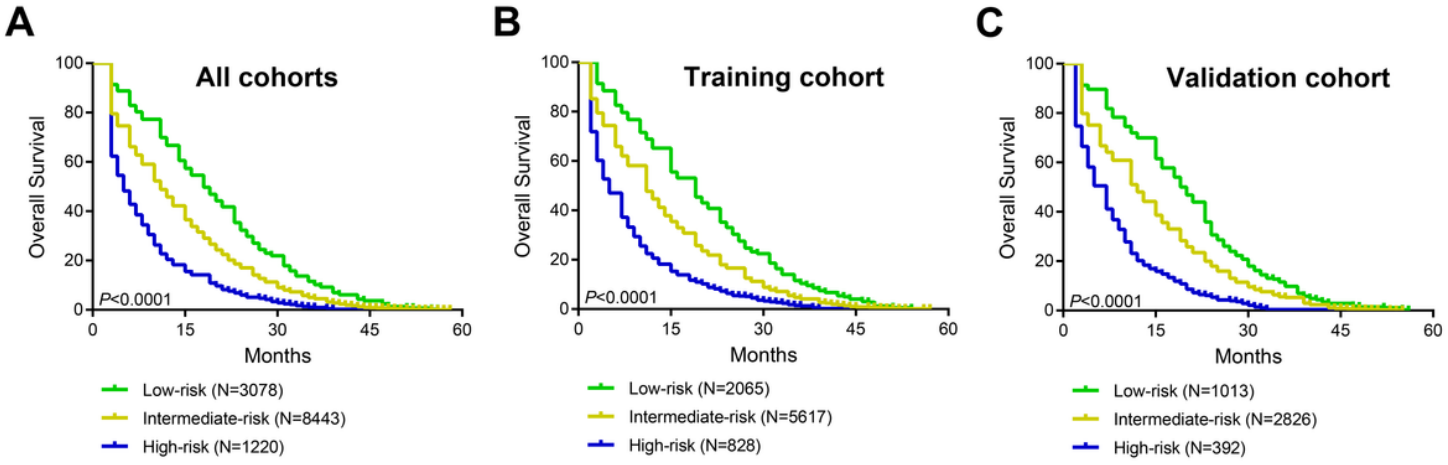

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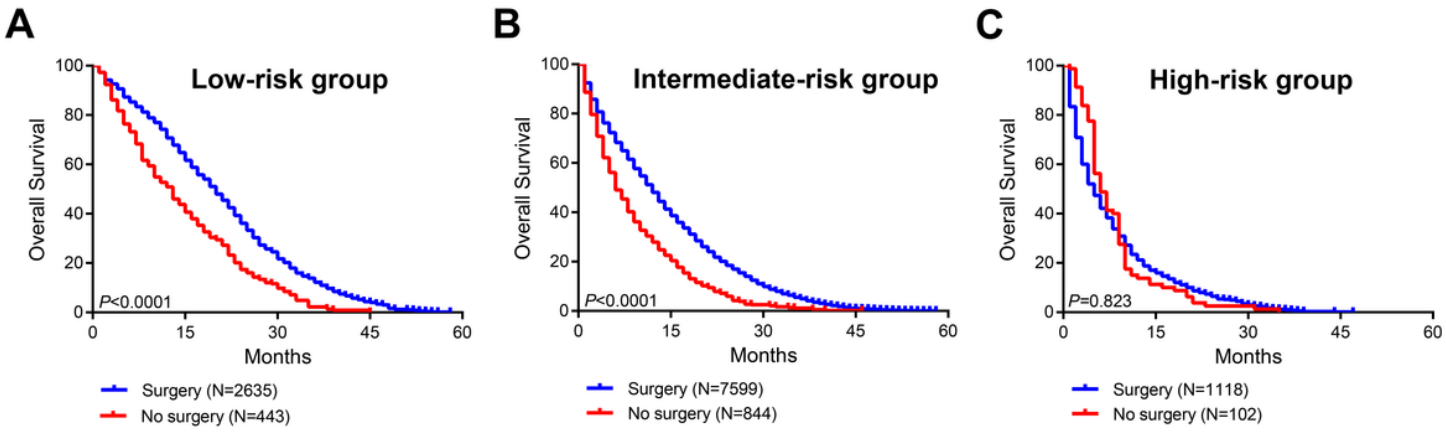
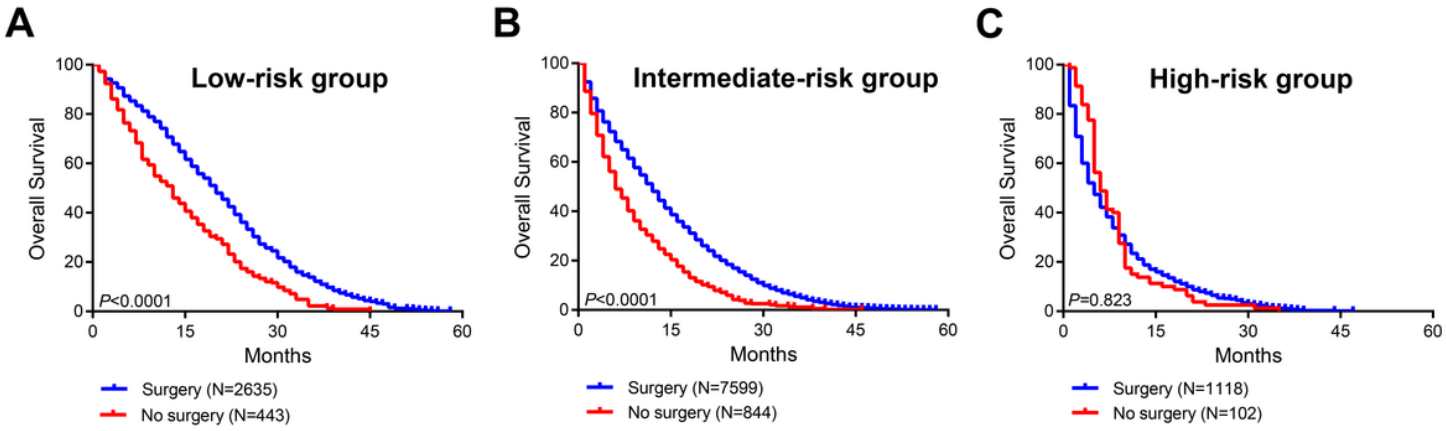


Figure 6

Prognostic benefit of locoregional surgery in low-risk (A), intermediate-risk (B) and high-risk (C) groups.



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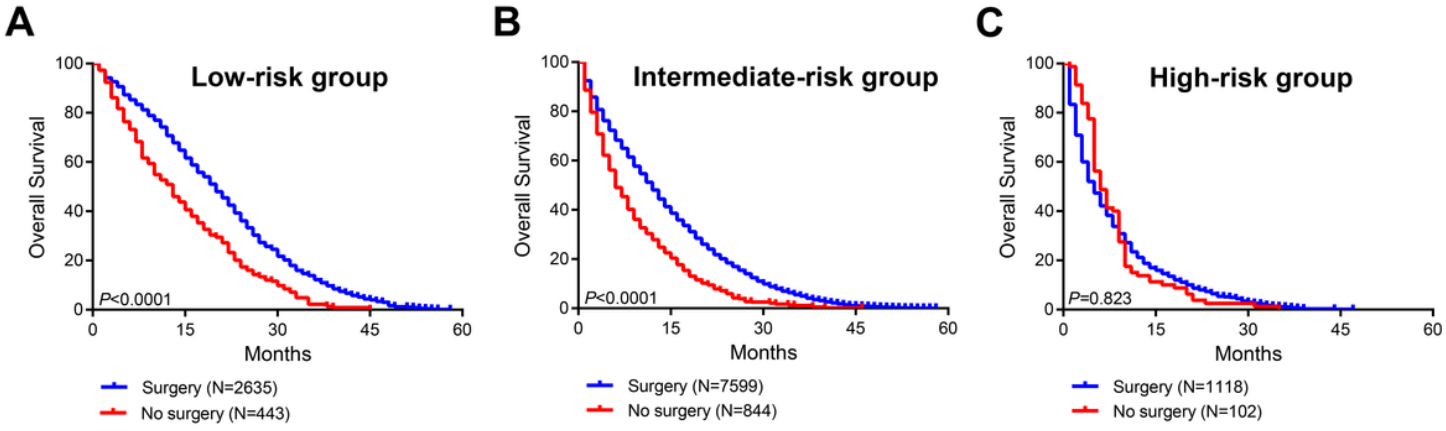

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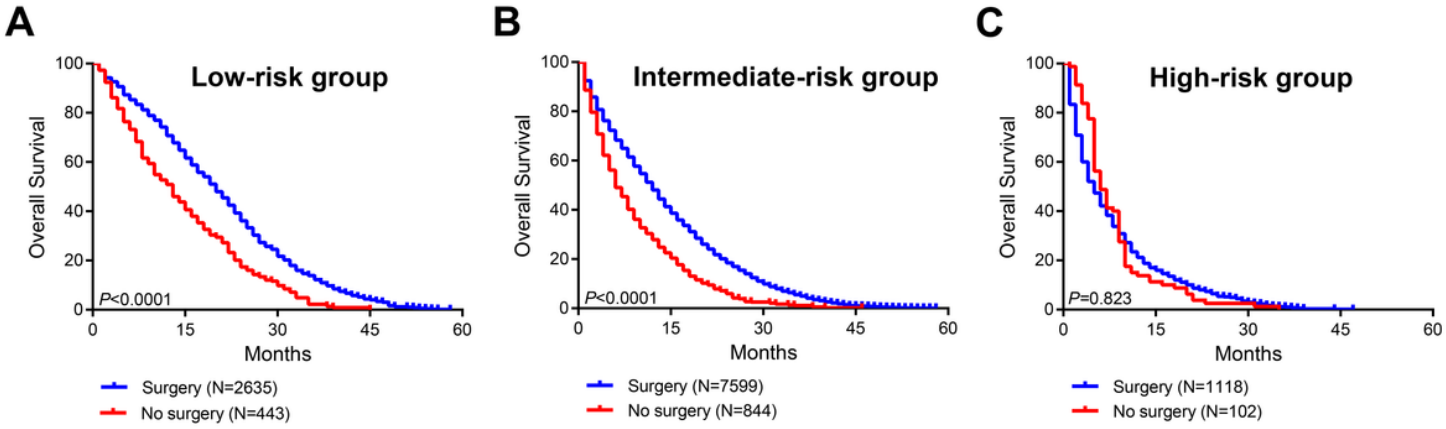

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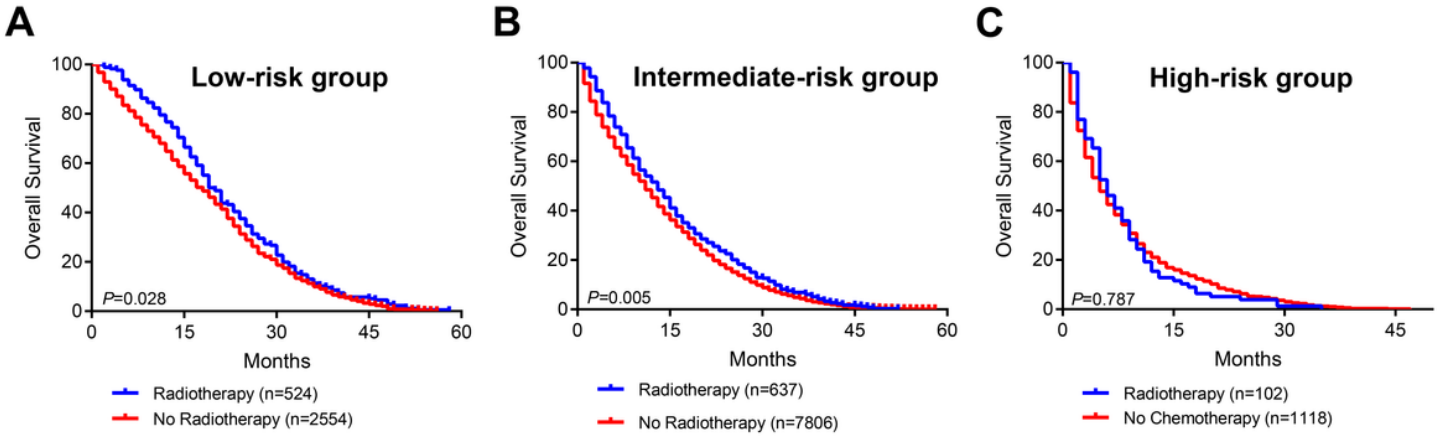
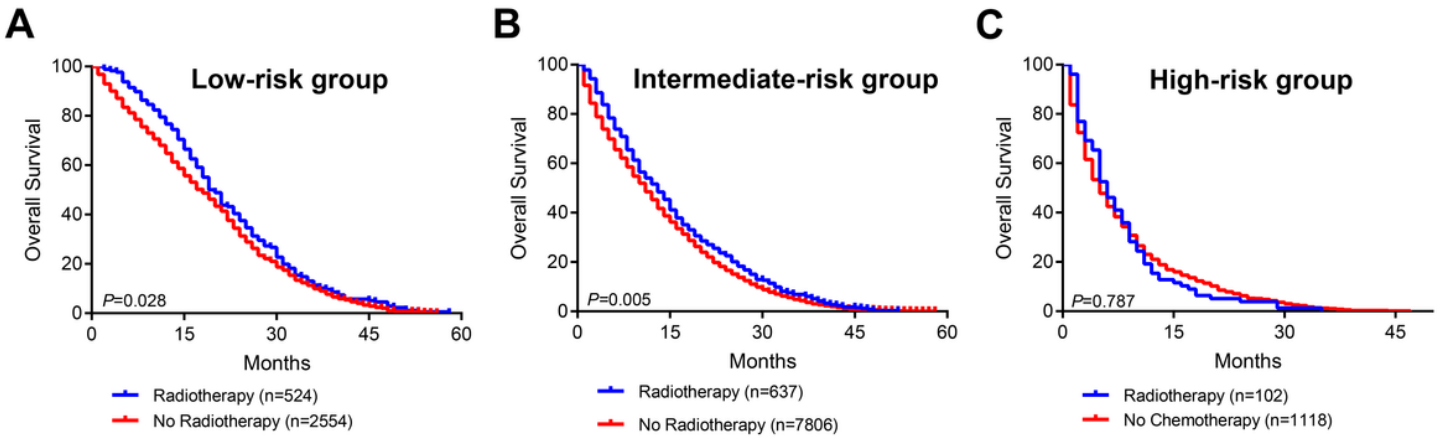


Figure 7

Prognostic benefit of locoregional radiotherapy in low-risk (A), intermediate-risk (B) and high-risk (C) groups.



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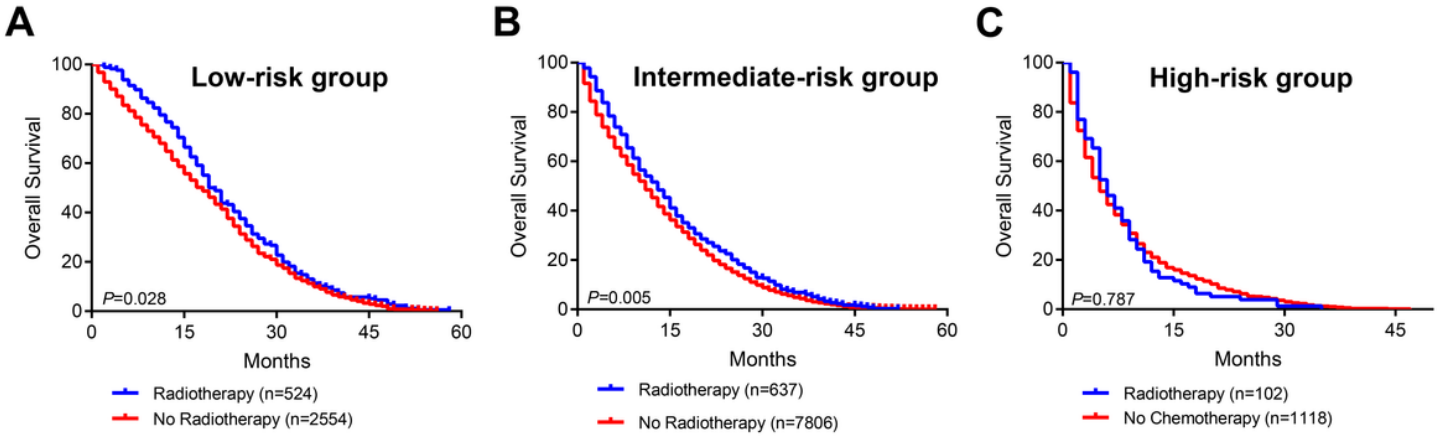

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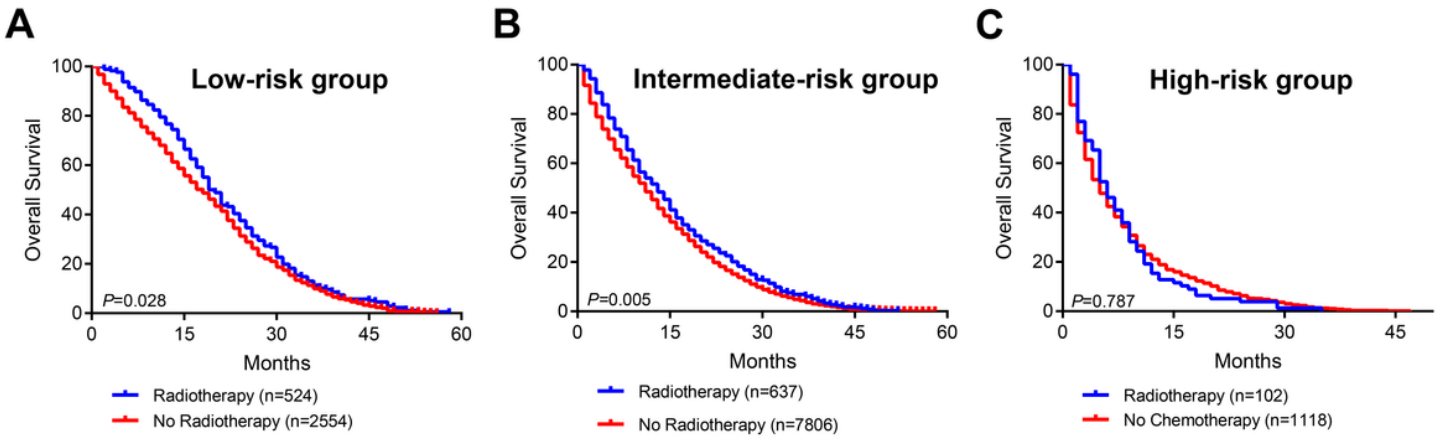
Prognostic benefit of locoregional radiotherapy in low-risk (A), intermediate-risk (B) and high-risk (C) groups.



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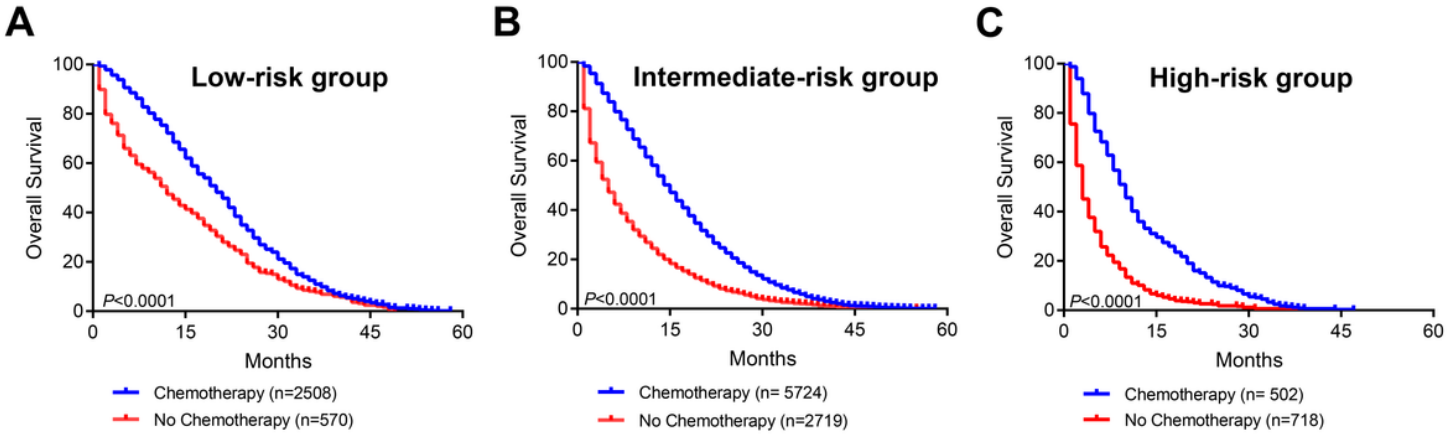
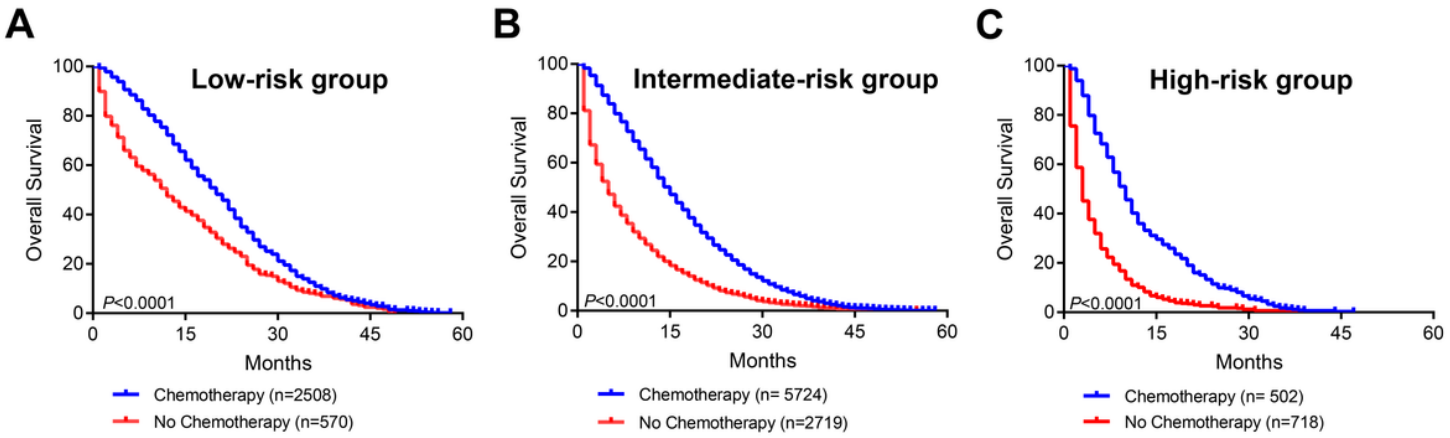


Figure 8

Prognostic benefit of systemic chemotherapy in low-risk (A), intermediate-risk (B) and high-risk (C) groups.



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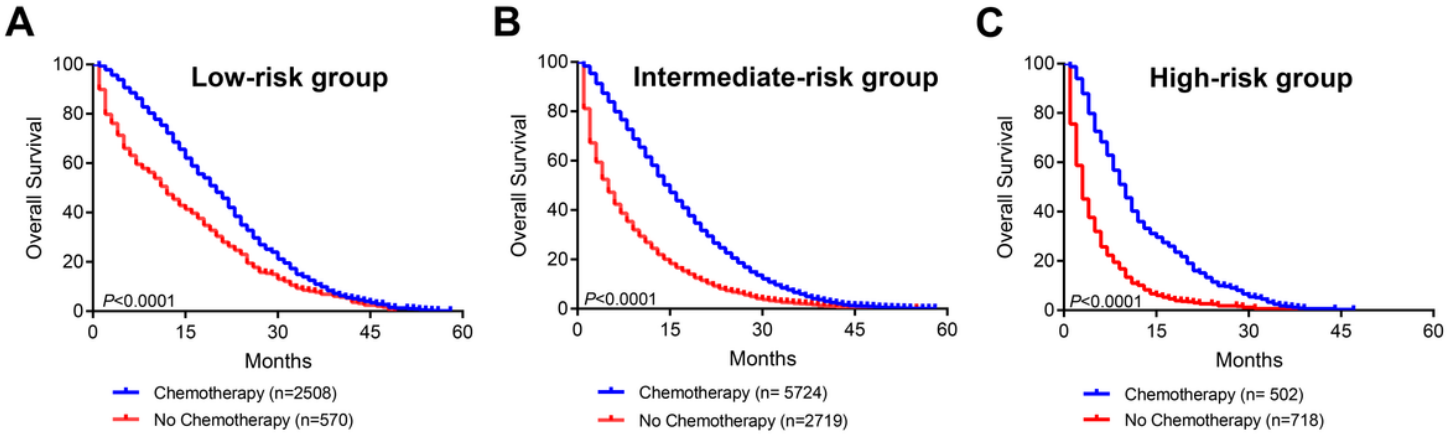

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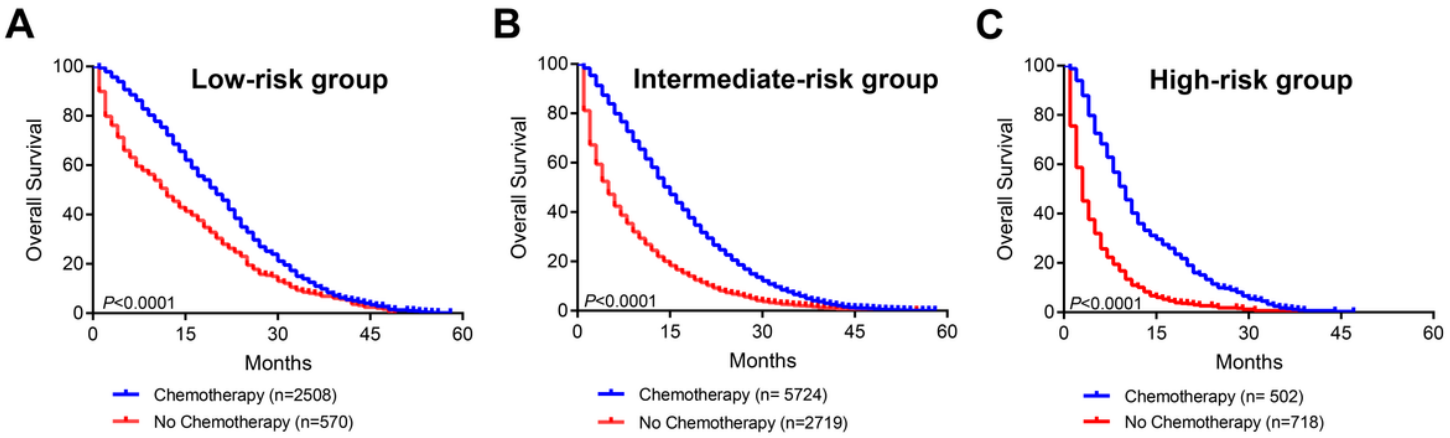

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