Prognostic value of Ki-67 and prediction in patients with hypertension and prostate cancer: A Real-World Study of Chinese Group for Prostate Cancer Party

Zhijun Cao
The Ninth People's Hospital of Suzhou
Mengqi Xiang
First Affiliated Hospital of Soochow University
Zhiyu Zhang
First Affiliated Hospital of Soochow University
Jianglei Zhang
First Affiliated Hospital of Soochow University
Minjun Jiang
The Ninth People's Hospital of Suzhou
Gang Shen
The Ninth People's Hospital of Suzhou
Yongqiang Zhou
The Ninth People's Hospital of Suzhou
Jun Ouyang
The Ninth People's Hospital of Suzhou
Jianjun Chen (dr_chenjianchun@126.com)
Nineth People's Hospital of Suzhou

Research article

Keywords: Prostate cancer, Ki-67, Prognostic model

Posted Date: November 20th, 2019

DOI: https://doi.org/10.21203/rs.2.17510/v1

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Zhijun Cao[1*], Mengqi Xiang[3*], Zhiyu Zhang[2*], Jianglei Zhang[2], Minjun Jiang[1], Gang Shen[1], Yongqiang Zhou[1], Jun Ouyang[2#], Jianchun Chen[1#]

[1]Department of Urology, The Ninth People's Hospital of Suzhou
[2]Department of Urology, The First Affiliated Hospital of Soochow University
[3]Department of Oncology, The First Affiliated Hospital of Soochow University

*These authors are co-first authors

Corresponding authors:
Jianchun Chen
Address: Department of Urology, The Ninth People's Hospital of Suzhou, No.2666 Ludang Street, 215200, Suzhou, China
Tel: +86-0512-63413501
Fax: +86-0512-63413501
E-mail: dr_chenjianchun@126.com

Ouyang Jun
Address: Department of Urology, The First Affiliated Hospital of Soochow University, No.188 Shizi Street, 215000, Suzhou, China
Tel: +86-0512-67781856
Fax: +86-0512-67781850
E-mail: dr_ouyangjun@126.com

Running title: Ki-67 predicts the prognosis of prostate cancer.

Word counts: 245 (Abstract), 2385(Body)

Keywords: Prostate cancer, Ki-67, Prognostic model

Number of references: 43

Number of tables: 3

Number of figures: 5

Abstract

Background Prostate cancer is the second most common malignancy with high mortality among males around the world, especially combine with hypertension. Ki-67 is one of the most reliable markers for growth fraction of neoplastic human cell populations. However, the prognostic value and prediction of Ki-67 in patients with hypertension and prostate cancer remain unclear.

Methods We launched a retrospective analysis of 296 patients with hypertension and prostate cancer from May 1, 2012, to Oct 1, 2015. The overall survival was evaluated using Cox regression models and Kaplan-Meier analysis. A nomogram was established. The accuracy of the model was assessed by calibration curve.

Results Multivariate analysis showed that the Ki-67 (+) class was associated with an over 5-fold increase in the risk of death (HR 5.83, 95% CI 3.35-10.14, $p<0.001$) and a 2-fold increase in the risk of progression (HR 2.06, 95% CI 1.37-3.10, $p<0.001$). Multivariate Lasso regression showed that smoking, heart failure, ACS, Ki-67 expression, serum albumin, prognostic nutritional index, surgery, Gealson score, and stage were positively associated with prognosis in patients with prostate cancer. To quantify the contribution of each covariate to the prognosis, a nomogram of the Cox model was generated and displayed. The nomogram demonstrated excellent accuracy in estimating the risk of death, with a bootstrap-corrected C index of 0.829. There was also a suitable calibration curve for risk estimation.

Conclusions Ki-67(+) predicts worsened outcomes of OM. A cross-validated multivariate score, including Ki-67(+), showed excellent concordance and efficacy of predicting prostate cancer.

Background

Prostate cancer is the second most common malignancy with high mortality among males around the world.[1] According to the global cancer statistics of 2018, the morbidity and mortality of prostate cancer rank fourth in various forms of cancer. For patients with both hypertension and prostate cancer, the mortality is higher. In 2018, there are approximately 1.3 million newly diagnosed cases of prostate cancer and 360,000 related deaths worldwide.[2] In the United States, it is estimated that 12.9% of men will be diagnosed with prostate cancer during their lifetime, which seriously endangers men's health.[3] In recent years, the mortality of prostate cancer have been declined in many countries because of the earlier diagnosis and improved treatment.[4] Nevertheless, the clinical course of prostate cancer is highly variable, and its prediction of prognosis and recurrence is still a problem worthy of our attention.

With the development of immunohistochemistry and the appearance of various specific antigens, many difficult tumors have been diagnosed definitely, providing a choice of treatment for clinical. It is well known that the development of the malignant tumor is closely related to the state of cell proliferation. The indicators of assessing proliferation statuses, such as proliferation-related nuclear antigens and mitotic index, can provide us with some useful information about tumor biology and may serve as a guidance in postoperative chemotherapy regimens.[5] Ki-67, also known as MKI67, is a nuclear protein involved in the regulation of cell cycle and cell proliferation, which is closely related to mitosis. Immunostaining with monoclonal antibody Ki-67 is one of the most reliable markers for rapidly determining the growth fraction of neoplastic human cell populations.[6, 7] This biomarker reflects the tumor cell proliferation rate. It is widely used in routine clinical pathology because of its simple detection technology and important pathological significance.[8] Many previous researches showed that it is strongly associated with metastasis, aggressiveness, and prognosis of many different malignancies, especially breast cancer.[9-12] However, due to conflicting results and limited sample size, the Ki-67 index with its prognostic value of prostate cancer is still in dispute.

To explore the role of Ki-67 on prognosis in patients with prostate cancer, we launched a real-world study in the Chinese population. The prognostic value of Ki-67 was determined via multivariate-adjusted survival analyses. Subsequently, a multivariate score model, including Ki-67 status, was established to predict prognosis in these patients.

Method

Patients and study design

A total of 296 consecutive patients with prostate cancer hospitalized from May 1, 2012, to Oct 1, 2015, in the First Affiliated Hospital of Soochow University and The Ninth People’s Hospital of Suzhou were enrolled in the retrospective cohort. Those patients were all diagnosed with prostate cancer via histological assessment of ultrasound-guided biopsy. Those with severe renal, hepatic dysfunction, or congenital bleeding disorders, without follow-up information or lacking information on Ki-67, were excluded. Patients' age, body mass index (kg/m^2), serum total prostate-specific antigen (ug/L), serum-free prostate-specific antigen (ug/L), serum albumin, neutrophils and lymphocytes count, neutrophil-lymphocyte ratio, level of hemoglobin, platelet counts, prognostic nutritional index, intraoperative or postoperative bleeding, alcohol use, history of smoking, heart failure, acute coronary syndrome, hypertension, diabetes, hyperlipemia, TNM stage, risk stage, history of surgery, hormone therapy, Karnofsky Performance Status, Zubrod-ECOG-WHO score

and chemoradiotherapy status were recorded. The median follow-up length was 60.0 months. Consent and informed signature were obtained from all patients or their immediate family members. All protocols are conformed to the guidelines with the ethic committee of Soochow University and in accordance with the Declaration of Helsinki.

PSA evaluation and morbidity.

PSA (prostate-specific antigen) was estimated, and urinary morbidity (pollakiuria/ urgency, difficulty in urination, urinary incontinence, and mission pain) was recorded at each visit, according to the National Cancer Institute common terminology criteria for adverse events version 3.0 (NCI-CTCAE v3.0).

Immunohistochemical assessment

Representative tumor paraffin-embedded tissue blocks were cut into five micro slides. Immunohistochemistry analysis was performed on each tumor slide block for Ki-67, with standard streptavidin ABC methodology. Two minutes of pressure cooking at pH 6.0 was used for antigen retrieval (BioGenex Inc., San Ramon, CA, USA). An immunohistochemical essay with the tumor markers was performed using the antibodies and conditions. Sections of 5 μm were cut from formalin or 50% alcohol-fixed paraffin-embedded cell blocks and stained with Ki-67 (clone MIB1, 1:160 dilution; DAKO, Carpinteria, Calif., USA) using tonsillar tissue as the positive control. Negative controls were run simultaneously with the primary antibody replaced with a buffer. Antigen retrieval was conducted in citrate buffer at pH 6 under pressure for 3 min. Envision Dual Link Kit (DAKO) was used for detection, with diaminobenzidine as the chromogen and hematoxylin as the counterstain. Staining was considered positive when nuclear positivity was observed. The eight corresponding resections also had their Ki-67 labeling indices quantitated by image analysis.

Statistical analysis

Continuous variates with normal and skewed distributions were presented as mean ± standard deviation and median with interquartile ranges and compared using the unpaired t-test and the Mann-Whitney U test. Categorical variates were presented as percentages and compared using the κ^2 test. Cumulative incidence was visualized using the Kaplan-Meier curve and compared using the log-rank test. Univariate and multivariate survival analyses for OM was assessed using the Cox proportional hazard model. The importance of covariates to the prognosis was visualized using forest plots. Prognostic power conferred by bleeding class beyond other factors was determined using Harrell's c-Index, calibration assay, and reclassification test. NRI and IDI were calculated.

A nomogram was calculated based on the results of multivariate Logistic regression analysis and by using the 'rms' package of R, version 3.6.0 (http://www.r-project.org/). The nomogram is based on proportionally converting each regression coefficient in multivariate logistic regression to a 0- to a 100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned 100 points. The points are added across independent variables to derive total points, which are converted to predicted probabilities. The predictive performance of the nomogram was measured by the concordance index (C-index) and calibration with 1000 bootstrap samples to decrease the overfit bias[13].

Results

A total of 296 patients with prostate cancer were included: The average age of patients with prostate cancer was 71.42±7.99 years. The median follow-up of all patients was 60.0 months (IQR 50.0-75.3). The median level of serum total prostate-specific antigen was 32.91 (IQR 15.84-101.54). Among all of the patients, 116 (39%) have a history of alcohol use, while 191 (65%) patients smoke. Hypertension was found in approximately 46% of patients, and only 12 (4%) and 16 (5%) patients suffered from heart failure and acute coronary syndrome. 46 (16%) patients were diagnosed with diabetes. For therapies, 164 (55%) patients followed the operation, and 97 (33%) patients received hormone therapy. Chemoradiotherapy was applied for only 40 (14%) patients. According to the immunohistochemical assessment, 153 (52%) patients were found Ki-67 positive. When compared with Ki-67 (-), patients with Ki-67 (+) showed a higher level of age, BMI, and serum-free prostate-specific antigen ($p<0.05$). Meanwhile, Ki-67 (+) patients were more susceptible to hypertension (**Table 1**).

Univariate analysis showed that Ki-67 positive was a strong predictor on both overall mortality (hazard ratio [HR] 5.84, 95% confidence interval [CI] 3.46-9.84, $p<0.001$) (**Table 2**) and progress free survival (hazard ratio [HR] 2.80, 95% confidence interval [CI] 1.82-4.32, $p<0.001$) (**Table 3**). Kaplan-Meier curve displayed that patients with Ki-67 (+) had increased cumulative incidence of death compared to those with the Ki-67(-) class (log-rank $p<0.001$) **(Figure 1A**). Meanwhile, patients with Ki-67 (+) displayed a higher PSF compared with the Ki-67 (-) class. Kaplan-Meier curve of progression-free survival (PFS) was displayed (**Figure 1B**). After multivariate adjustment, the Ki-67 (+) class was associated with an over 5-fold increase in the risk of death (HR 5.83, 95% CI 3.35-10.14, $p<0.001$) (**Figure 2**) and 2-fold increase in the risk of progression (HR 2.06, 95% CI 1.37-3.10, $p<0.001$) (**Figure 3**).

Being an important biomarker of prostate cancer, Ki-67 expression showed a significant prognostic value for multiple outcomes. The successful prediction may promote the prophylaxis of progression and is proposed to improve the prognosis of prostate cancer. In this light, we modeled a multivariate risk score for the association with bleeding. Univariate analyses yielded Age, alcohol use, smoking, heart failure, ACS, hypertension, Ki-67 expression, StPSA, SfPSA, serum albumin, count of lymphocytes, hemoglobin level, prognostic nutritional index, surgery, KPS, Gealson score, ZPS, TNM and risk stage as the risk factor for death (**Table 2**). Putting all the variations above into multivariate cox regression, the result showed that smoking, heart failure, ACS, Ki-67 expression, serum albumin, prognostic nutritional index, surgery, Gealson score, and stage were the independent risk factors for death in patients with prostate cancer (**Figure 3**). Among all the variations above, HR of Ki-67 (+) was highest (HR 5.83, 95% CI 3.35-10.14, $p<0.001$). Next, multivariate Lasso regression showed that smoking, heart failure, ACS, Ki-67 expression, serum albumin, prognostic nutritional index, surgery, Gealson score, and stage were positively associated with prognosis in patients with prostate cancer (**Figure 4A, 4B**). To quantify the contribution of each covariate to the bleeding class, a nomogram of the Cox regression model was generated and displayed in **Figure 5A**. The resulting model was internally validated using the bootstrap validation method. The nomogram demonstrated excellent accuracy in estimating the prognosis of patients with prostate cancer, with an unadjusted C index of 0.829 and a bootstrap-corrected C index of 0.829. There was also a suitable calibration curve for risk estimation (**Figure 5B**).

Discussion

This real-world study demonstrated the prognostic value of Ki-67 in patients with prostate cancer. In our analysis, smoking, heart failure, ACS, Ki-67 expression, serum albumin, prognostic nutritional index, surgery, Gealson score, and stage were associated with a significantly worsened prognosis for overall survival (OS) in prostate cancer patients. In addition, the multivariate analysis also indicated that Ki-67 was independent risk factors for favorable OS.

The occurrence of cancer is regarded as a result of genetic, acquired changes, which regulate signal transduction pathways involved in cell proliferation and cell cycle control, especially from G1 to S phase[14]. The studies of cell proliferation are of great significance for the invasiveness and prognosis of various malignancies[15]. With the accumulation of genetic alterations in dysplastic lesions of carcinogenesis, cellular proliferation is getting out of control[16]. When cells are in the state of uncontrolled proliferation, there will be a series of malignant biological behaviors such as abnormal DNA structure and/or function, accelerated transcription and translation during protein biosynthesis, uncontrolled growth of cancer cells, and so on[17]. A large number of studies have shown evidence that tumor proliferation is a significant poor prognostic factor in prostate cancer with a potential for routine application[18-20]. Ki-67 is one of the markers worthy of study in this matter[21].

Ki-67 is a nuclear protein involved with ribosomal RNA synthesis and is important for cell cycle[22]. Previous research has shown that Ki-67 contains an FHA domain at its amino terminus, which is considered an important role in regulatory pathways involving Ser/Thr phosphorylation. This is similar to the structure of other proteins involved in cell cycle regulation[23]. NIFK, Ki-67's another FHA binding partner, is considered to promote cell proliferation and cancer metastasis[24, 25]. Ki-67 was expressed at all stages of the cell cycle except G0 phase[26]. Consequently, Ki-67 has been widely used in histopathology to detect cycling cells, measuring the growth fraction of the tissue[27]. Many studies indicated that Ki-67 has high prognostic significance for various types of cancer, and was related to tumor aggression, vascular invasion, and tumor metastasis[28, 29].

In breast cancer, Ki-67 has been shown to be useful in assessing the prognosis of patients[30]. Although up-regulated Ki-67 has also been confirmed by many researches is a significant poor prognostic maker in prostate cancer[9, 31, 32]. For example, Berlin et al. found that Ki-67 is associated with prognostic in localized prostate cancer after treatment[33]. Richardsen et al. found that Ki-67 expression in metastatic prostate cancer is higher than that in non-metastatic prostate cancer[34]. Our study also indicated that Ki-67 positive was a strong predictor of both overall mortality and progress free survival. However, other researchers have found that there is no significant correlation between the expression of Ki-67 and prostate cancer[6, 35, 36]. In addition, Ki-67 is controversial as well as the lack of standardization in the immunohistochemical assays, quantification methods, cutoff-points used for risk classification, and the biologic tumor heterogeneity[37]. For these and other reasons, Ki-67 has not yet been implemented to assess the prognosis of prostate cancer. Therefore, the prognostic value of Ki-67 in prostate cancer requires extensive prospective studies.

In addition, our study also observed a correlation between Ki-67 and age, hypertension, and some other factors. Some studies showed that the proliferation activity of prostate cells increases with age in male patients, which indicates the high expression of Ki-67 is a systematic age-related phenomenon[38, 39]. This is in agreement with the results of our study. But some other studies have not found that Ki-67 was significantly linked with age[40]. This may be due to the difference in age distribution and racial differences in the population. About hypertension and ACS, its are

pathological conditions that damage the endothelium, triggering cell proliferation, vascular remodeling, and other malignant biological behavior[41, 42]. The previous study considered that the expression of ki-67 in smokers was lower than that in non-smokers[43]. The mechanisms about this are still unclear. There has a meta-analysis manifested that low ki-67 was associated with a lesser risk of developing diabetes mellitus[33]. But our study did not find the association between Ki-67 and diabetes mellitus.

Conclusions

In conclusion, our investigation showed that Ki-67 positive was a strong predictor of both overall mortality and progress free survival, which means Ki-67 is an independent biological marker for predicting the prognosis of prostate cancer patients with hypertension. But the mechanism of Ki-67 in prostate cancer was still unclear, and further investigation needs to be done in the future.

Abbreviations

HF, heart failure; ACS, acute coronary syndrome; BMI: body mass index; Hb: hemoglobin; PLT: platelet; KPS: Karnofsky Performance Status; ZPS: Zubrod-ECOG-WHO; NLR: neutrophil lymphocyte ratio; HR: hazard risk; OS: overall survival; PFS: progression free survival.

Declarations

Ethics approval and consent to participate

This study was approved by the Committee for the Ethical Review of Research at the First Affiliated Hospital of Soochow University, and was conducted in accordance with institutional guidelines and the Declaration of Helsinki. Informed consent was obtained from all patients prior to data collection.

Consent for publication

We have got the consent from all the authors for publication.

Availability of data and materials

All the data and materials were available if necessary.

Disclosure of Conflicts of Interest

The authors declare no competing financial interests.

Authorship Contributions

Zhijun Cao designed and performed research studies, analyzed the data, and wrote the manuscript. Mengqi Xiang and Zhiyu Zhang performed research studies and analyzed data. Hong Wang contributed to the data analysis and manuscript writing. Minjun Jiang and Jianglei Zhang contribute to the collection and analysis of clinical data. Gang Shen and Yongqiang Zhou contributed to the data analysis. Jianchun Chen and Jun Ouyang contributed to the research design, data analysis, writing the manuscript, and supervision of the study.

Acknowledgments

This work was supported by the Suzhou Science and Technology Project (SLC201906 and

SYS2019053).

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Figures and Legends

Figure 1. Multivariate analysis of survival on patients with prostate cancer. **A.** Kaplan-Meier curve in patients with Ki-67 positive in OS compared to those with Ki-67 negative class. **B.** Kaplan-Meier curve in prostate cancer patients with Ki-67(+) in PFS compared to those Ki-67(-). (***p<0.001)

Figure 2. Forest plot for hazard ratio in different risk factors for OS in patients with prostate cancer. It is established by the Cox regression model. (***p<0.001, **p<0.01, *p<0.05.)

Figure 3. Forest plot for odds ratio in different risk factors for PFS in patients with prostate cancer. It is also established by the Cox regression model. (***p<0.001, **p<0.01, *p<0.05.)

Figure 4. The least absolute shrinkage and selection operator (LASSO) binary logistic regression model was used for texture feature selection. **A.** Tuning parameter (l) selection in the LASSO model used 10-fold cross-validation via minimum criteria. The area under the receiver operating characteristic (AUC) curve was plotted versus log(l). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the one standard error of the minimum criteria (the 1-SE criteria). A lambda value of 2.863 was chosen (1-SE criteria) according to 10-fold cross-validation. **B.** LASSO coefficient profiles of the six texture features. A coefficient profile plot was produced against the log (l) sequence. The vertical line was drawn at the value selected using 10-fold cross-validation, where optimal lambda resulted in 3 nonzero coefficients.

Figure 5. Nomogram estimation of severe bleeding or not in patients with prostate cancer and its predictive performance. **A.** Nomogram to estimate the severe bleeding in different variations. To use the nomogram, find the position of each variable on the corresponding axis, draw a line to the points axis for the number of points, add the points from all of the variables, and draw a line from the total points axis to determine the OS probabilities at the lower line of the nomogram. **B.** The validity of the predictive performance of the nomogram in estimating the prognosis of patients with prostate cancer.

Table 1. Study Participant Characteristics at Enrollment

Variation	Total	Cohort, median (IQR)		p.value
		Ki-67 (-)	Ki-67 (+)	
Age, (year)	71.42±7.99	70.24±8.17	72.53±7.69	0.014*
BMI, (kg/m2)	23.74±2.96	23.18±2.91	24.27±2.92	0.002**
Serum total prostate specific antigen, (ug/L)	32.91(15.84,101.54)	25.13(15.3,89.72)	37.39(16.59,105.55)	0.097
Serum free prostate specific antigen, (ug/L)	4.14(1.45,13.97)	3.52(1.25,10)	5.13(1.58,20.5)	0.042*
Serum albumin, (g/L)	40.6(37.68,43.7)	41.6(38.2,43.65)	40.3(37.1,43.7)	0.227
Neutrophils, (10×9/L)	3.68(2.97,4.74)	3.73(3.08,4.75)	3.62(2.85,4.71)	0.349
Lymphocytes, (10×9/L)	1.42(1.17,1.79)	1.44(1.19,1.83)	1.41(1.16,1.76)	0.476
NLR	2.5(1.9,3.5)	2.7(1.8,3.5)	2.4(1.9,3.3)	0.576
Hb, (g/L)	134(121,144)	135(123.5,143.5)	131(119,144)	0.223
PLT, (10×9/L)	188(150,225.25)	192(155,236)	187(150,212)	0.101
Prognostic nutritional index	48.17(43.9,52.51)	49.15(44.75,52.6)	47.5(43.45,52.25)	0.125
Intraoperative bleeding, (ml)	400(217.5,500)	400(200,420)	400(240,500)	0.103
Postoperative bleeding, (ml)	133.5(101.5,205)	130(101,205)	139(102,205)	0.437
Alcohol use, n(%)				0.913
No	180(61)	86(60)	94(61)	
Yes	116(39)	57(40)	59(39)	
Smoking, n(%)				0.500
No	105(35)	54(38)	51(33)	
Yes	191(65)	89(62)	102(67)	
HF, n(%)				0.444
No	284(96)	139(97)	145(95)	
Yes	12(4)	4(3)	8(5)	
ACS, n(%)				1.000
No	280(95)	135(94)	145(95)	
Yes	16(5)	8(6)	8(5)	
Hypertension, n(%)				0.017*
No	160(54)	88(62)	72(47)	
Yes	136(46)	55(38)	81(53)	
Diabetes, n(%)				0.129
No	250(84)	126(88)	124(81)	
Yes	46(16)	17(12)	29(19)	
Hyperlipemia, n(%)				0.565
No	263(89)	125(87)	138(90)	
Yes	33(11)	18(13)	15(10)	
TNM, n(%)				0.507
T1	23(8)	13(9)	10(7)	
T2	210(71)	104(73)	106(69)	
T3	46(16)	20(14)	26(17)	
T4	17(6)	6(4)	11(7)	
Stage, n(%)				0.072
II	182(61)	95(66)	87(57)	
III	23(8)	13(9)	10(7)	
IV	91(31)	35(24)	56(37)	
Risk stage, n(%)				0.159
1	31(10)	17(12)	14(9)	
2	128(43)	68(48)	60(39)	
3	137(46)	58(41)	79(52)	
Surgery, n(%)				0.264
0	126(43)	55(38)	71(46)	
1	164(55)	86(60)	78(51)	
2	6(2)	2(1)	4(3)	
Hormone therapy, n(%)				0.558
No	199(67)	99(69)	100(65)	
Yes	97(33)	44(31)	53(35)	
KPS, n(%)				0.180
10	1(0)	0(0)	1(1)	
30	3(1)	0(0)	3(2)	
40	2(1)	0(0)	2(1)	
50	11(4)	2(1)	9(6)	
60	30(10)	14(10)	16(10)	
70	30(10)	14(10)	16(10)	
80	137(46)	73(51)	64(42)	
90	66(22)	31(22)	35(23)	
100	16(5)	9(6)	7(5)	
Gleason score, n(%)				0.737
1	25(8)	11(8)	14(9)	
2	38(13)	20(14)	18(12)	
3	79(27)	39(27)	40(26)	
4	64(22)	34(24)	30(20)	
5	90(30)	39(27)	51(33)	
ZPS, n(%)				0.005*
1	206(70)	105(73)	101(66)	
2	62(21)	33(23)	29(19)	
3	24(8)	5(3)	19(12)	
4	4(1)	0(0)	4(3)	
Chemoradiotherapy, n(%)				0.337
No	256(86)	127(89)	129(84)	
Yes	40(14)	16(11)	24(16)	

Abbreviation: HF, heart failure; ACS, acute coronary syndrome; BMI: body mass index; Hb: hemoglobin; PLT: platelet; KPS: Karnofsky Performance Status; ZPS: Zubrod-ECOG-WHO; NLR: neutrophil lymphocyte ratio. **p<0.01, *p<0.05.

Table 2. Univariate Cox Regression Analysis of Overall Survival on patients with prostastic cancer

Variation	Harzad Risk (95% CI)	p.value
Alcohol use, Yes vs. No	1.68 [1.14, 2.49]	0.009**
Smoking, Yes vs. No	2.57 [1.59, 4.16]	<0.001***
HF, Yes vs. No	3.02 [1.51, 6.02]	0.002**
ACS, Yes vs. No	2.57 [1.37, 4.82]	0.003**
ki67, Positive vs.Negtive	5.84 [3.46, 9.84]	<0.001***
Hypertension, Yes vs. No	1.41 [0.95, 2.08]	0.087
Diabetes, Yes vs. No	1.37 [0.85, 2.22]	0.199
Hyperlipemia, Yes vs. No	0.69 [0.33, 1.42]	0.312
Hormone therapy, Yes vs. No	0.90 [0.59, 1.37]	0.617
Chemoradiotherapy, Yes vs. No	0.87 [0.49, 1.54]	0.630
Age, ≥65 vs. <65	1.92 [1.05, 3.51]	0.035*
BMI, ≥24 vs. <24	0.93 [0.63, 1.38]	0.726
Serum total prostate specific antigen, ≥33 vs. <33	1.97 [1.32, 2.96]	0.001**
Serum free prostate specific antigen, ≥4 vs. <4	1.98 [1.32, 2.98]	0.001**
Serum albumin, ≥40 vs. <40	0.58 [0.39, 0.85]	0.006*
Neutrophils, ≥3.68 vs. <3.68	0.88 [0.60, 1.31]	0.534
Lymphocytes, ≥1.42 vs. <1.42	0.59 [0.40, 0.89]	0.011*
NLR, ≥2.5 vs. <2.5	1.13 [0.76, 1.67]	0.551
Hb, ≥134 vs. <134	0.38 [0.25, 0.58]	<0.001***
PLT, ≥188 vs. <188	1.10 [0.74, 1.62]	0.645
Prognostic nutritional index, ≥48.17 vs. <48.17	0.41 [0.27, 0.62]	<0.001***
Intraoperative bleeding, ≥400 vs. <400	1.23 [0.81, 1.84]	0.331
Postoperative bleeding, ≥133.5 vs. <133.5	0.93 [0.63, 1.38]	0.713
TNM, T3,T4 vs. T1,T2	2.21 [1.45, 3.36]	<0.001***
Stage, IV vs. III,II	3.62 [2.43, 5.42]	<0.001***
Risk stage, 3 vs. 2,1	1.95 [1.31, 2.90]	0.001**
Surgery, Yes vs. No	0.37 [0.25, 0.56]	<0.001***
KPS, ≥60 vs. <60	0.30 [0.17, 0.53]	<0.001***
Gleason score, ≥4 vs. <4	1.76 [1.18, 2.63]	0.006**
ZPS, ≥2 vs. <2	1.84 [1.23, 2.74]	0.003**

Abbreviation: HF, heart failure; ACS, acute coronary syndrome; BMI: body mass index; Hb: hemoglobin; PLT: platelet; KPS: Karnofsky Performance Status; ZPS: Zubrod-ECOG-WHO; NLR: neutrophil lymphocyte ratio. ***p<0.001, **p<0.01, *p<0.05.

Table 3. Univariate Cox Regression Analysis of Progression Free Survival on patients with prostastic cancer

Variation	Odds Ratio (95% CI)	p.value
Alcohol use, Yes vs. No	0.93 [0.63, 1.37]	0.727
Smoking, Yes vs. No	0.95 [0.65, 1.38]	0.770
HF, Yes vs. No	0.43 [0.11, 1.75]	0.239
ACS, Yes vs. No	1.09 [0.51, 2.35]	0.818
ki67, Positive vs.Negtive	2.80 [1.82, 4.32]	<0.001***
Hypertension, Yes vs. No	1.71 [1.18, 2.48]	0.005*
Diabetes, Yes vs. No	1.15 [0.70, 1.91]	0.585
Hyperlipemia, Yes vs. No	1.39 [0.81, 2.40]	0.237
Hormone therapy, Yes vs. No	0.75 [0.50, 1.11]	0.148
Chemoradiotherapy, Yes vs. No	1.70 [1.10, 2.63]	0.018*
Age, ≥65 vs. <65	0.78 [0.50, 1.22]	0.280
BMI, ≥24 vs. <24	0.76 [0.52, 1.11]	0.152
Serum total prostate specific antigen, ≥33 vs. <33	0.89 [0.62, 1.29]	0.554
Serum free prostate specific antigen, ≥4 vs. <4	1.15 [0.80, 1.66]	0.457
Serum albumin, ≥40 vs. <40	0.83 [0.58, 1.21]	0.336
Neutrophils, ≥3.68 vs. <3.68	1.01 [0.70, 1.46]	0.955
Lymphocytes, ≥1.42 vs. <1.42	1.08 [0.75, 1.56]	0.687
NLR, ≥2.5 vs. <2.5	0.86 [0.60, 1.25]	0.435
Hb, ≥134 vs. <134	0.91 [0.63, 1.31]	0.609
PLT, ≥188 vs. <188	1.14 [0.79, 1.66]	0.474
Prognostic nutritional index, ≥48.17 vs. <48.17	0.71 [0.49, 1.03]	0.074
Intraoperative bleeding, ≥400 vs. <400	1.28 [0.86, 1.90]	0.217
Postoperative bleeding, ≥133.5 vs. <133.5	1.04 [0.72, 1.51]	0.842
TNM, T3,T4 vs. T1,T2	1.24 [0.80, 1.91]	0.332
Stage, IV vs. III,II	1.47 [1.01, 2.14]	0.043*
Risk stage, 3 vs. 2,1	1.49 [1.03, 2.15]	0.034*
Surgery, Yes vs. No	1.04 [0.72, 1.51]	0.826
KPS, ≥60 vs. <60	0.78 [0.41, 1.50]	0.46
Gleason score, ⩾4 vs. <4	1.56 [1.08, 2.27]	0.019*
ZPS, ≥2 vs. <2	1.61 [1.11, 2.34]	0.012*

Abbreviation: HF, heart failure; ACS, acute coronary syndrome; BMI: body mass index; Hb: hemoglobin; PLT: platelet; KPS: Karnofsky Performance Status; ZPS: Zubrod-ECOG-WHO; NLR: neutrophil lymphocyte ratio. ***p<0.001, *p<0.05.

Figure 1

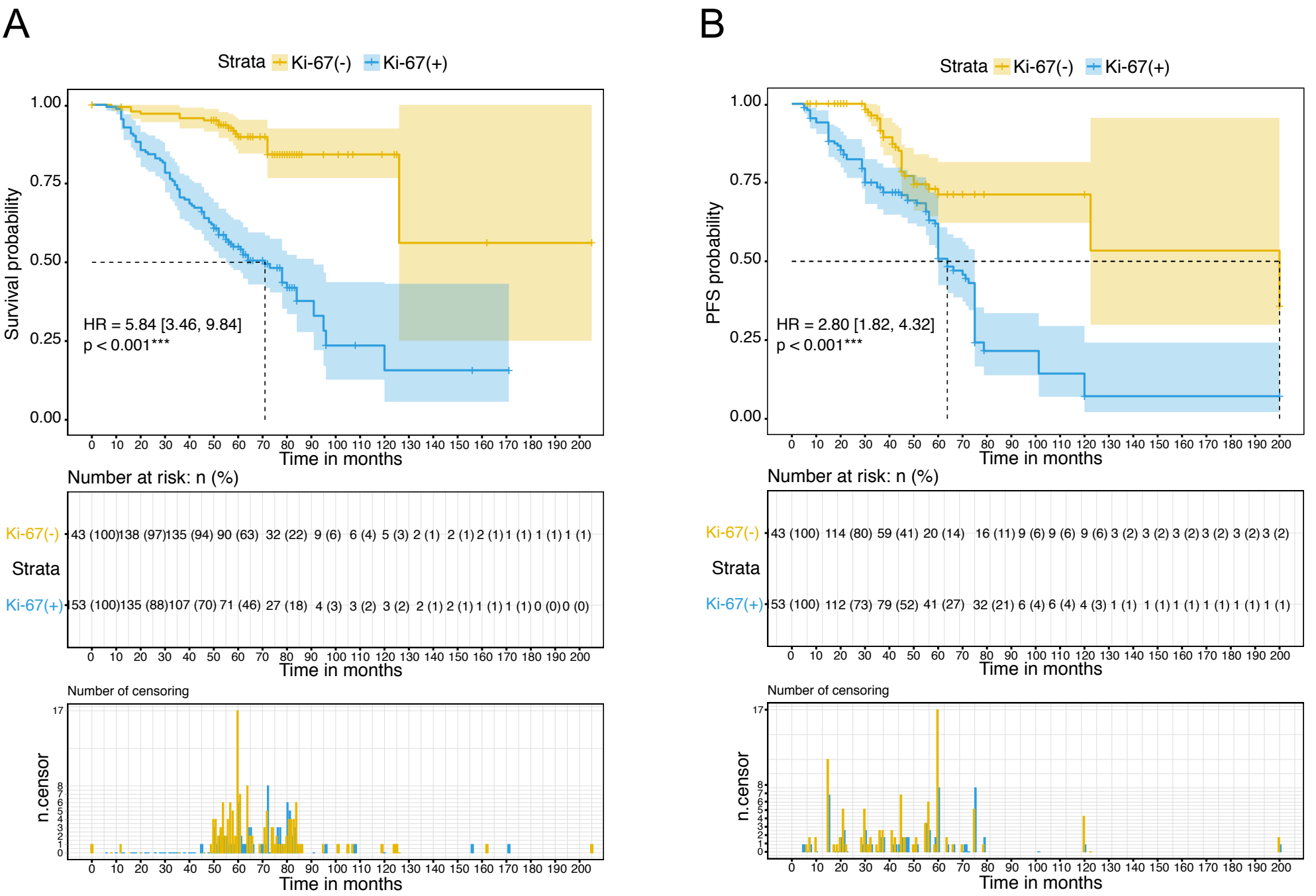

A
Strata Ki-67(-) Ki-67(+)
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 5.84 [3.46, 9.84]
p < 0.001***
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
Time in months
Number at risk: n (%)
Ki-67(-) 43 (100) 138 (97) 135 (94) 90 (63) 32 (22) 9 (6) 6 (4) 5 (3) 2 (1) 2 (1) 2 (1) 1 (1) 1 (1) 1 (1) 1 (1)
Strata
Ki-67(+) 53 (100) 135 (88) 107 (70) 71 (46) 27 (18) 4 (3) 3 (2) 3 (2) 2 (1) 2 (1) 1 (1) 1 (1) 0 (0) 0 (0)
Time in months
Number of censoring
n.censor
0 1 2 3 4 5 6 7 8 17
Time in months
B
Strata Ki-67(-) Ki-67(+)
PFS probability
1.00
0.75
0.50
0.25
0.00
HR = 2.80 [1.82, 4.32]
p < 0.001***
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
Time in months
Number at risk: n (%)
Ki-67(-) 43 (100) 114 (80) 59 (41) 20 (14) 16 (11) 9 (6) 9 (6) 9 (6) 3 (2) 3 (2) 3 (2) 3 (2) 3 (2) 3 (2) 3 (2)
Strata
Ki-67(+) 53 (100) 112 (73) 79 (52) 41 (27) 32 (21) 6 (4) 6 (4) 4 (3) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1) 1 (1)
Time in months
Number of censoring
n.censor
0 1 2 3 4 5 6 7 8 17
Time in months

Figure 2

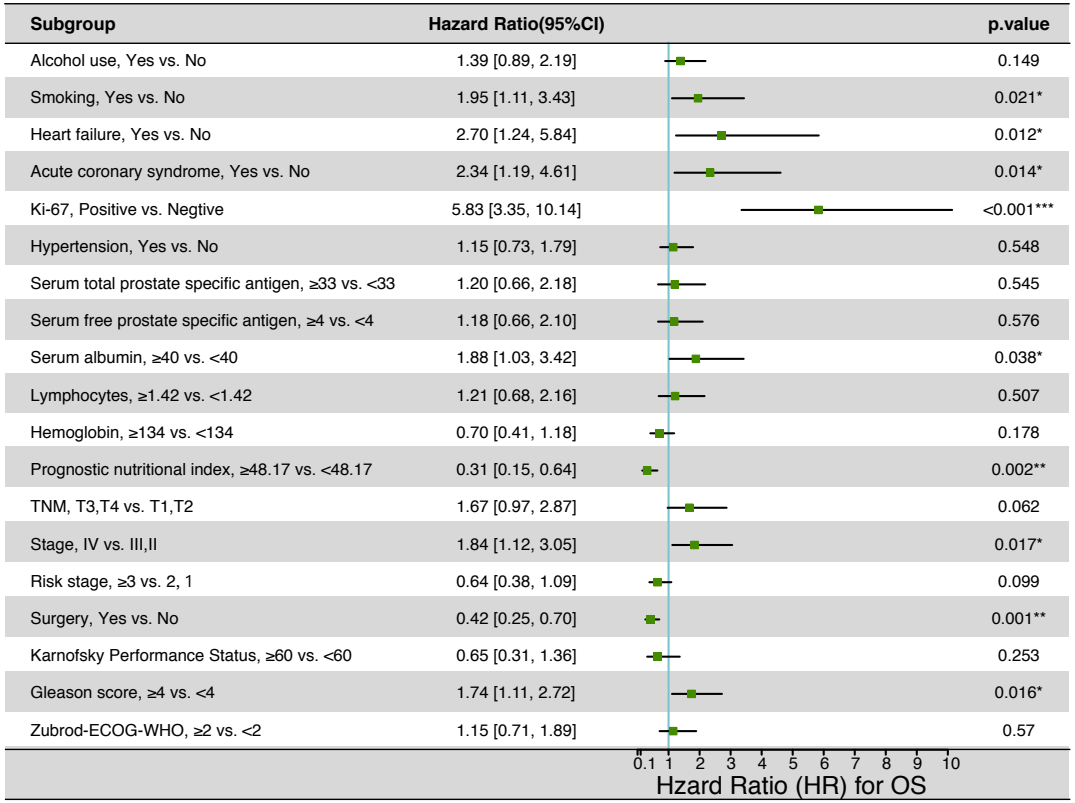


Figure 3

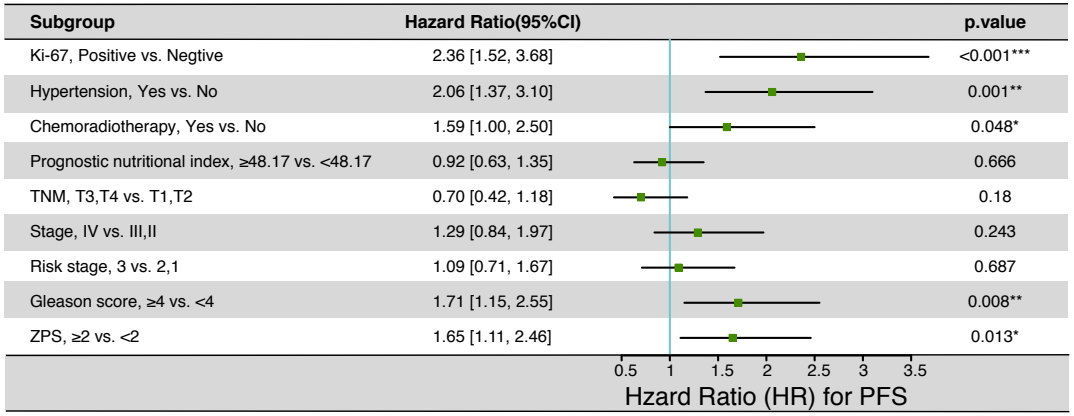


Figure 4

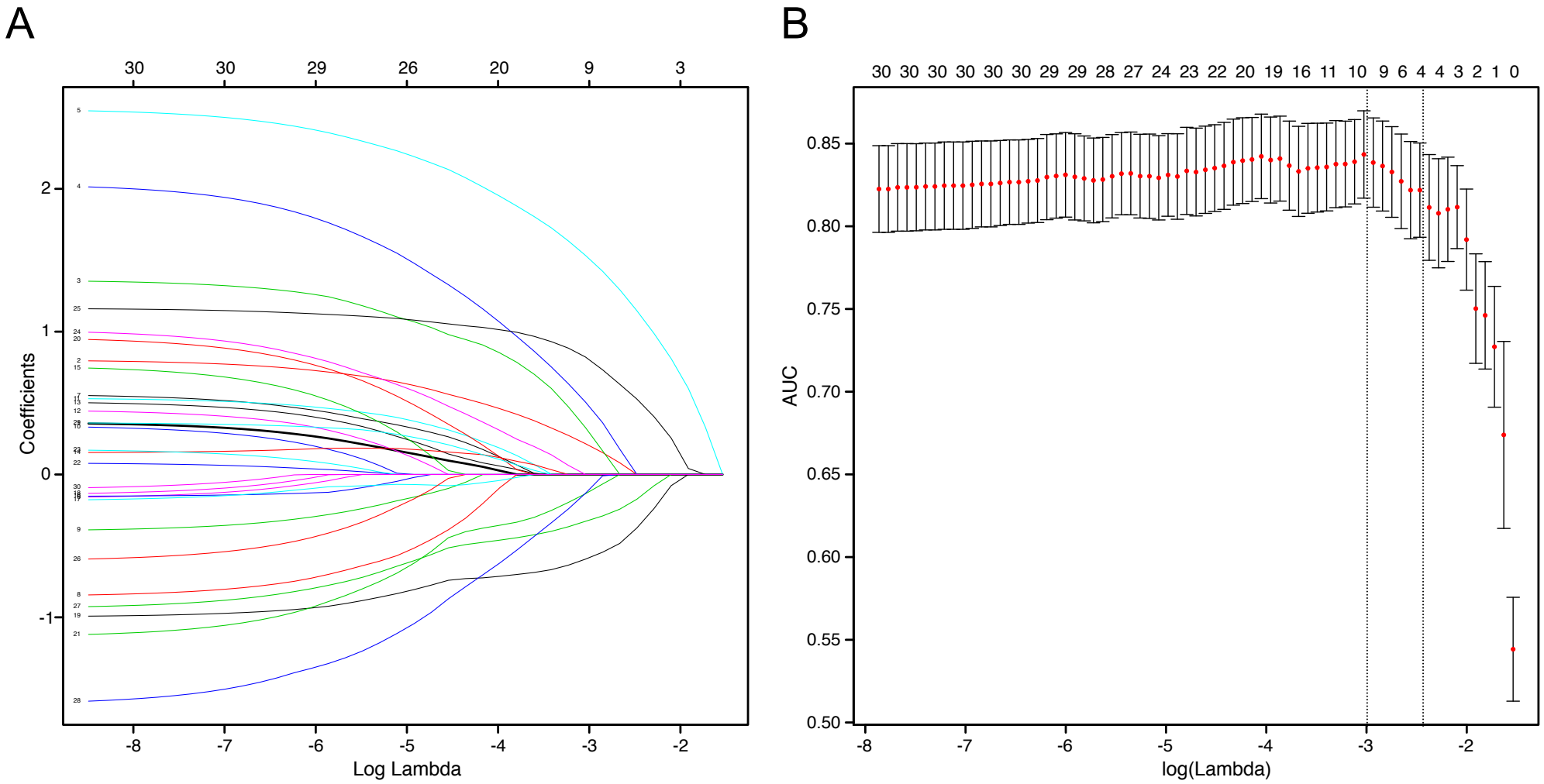
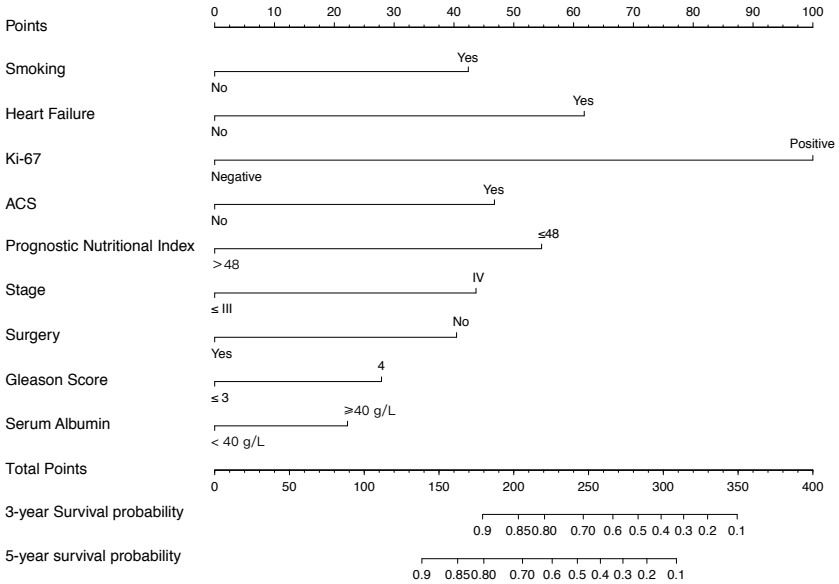
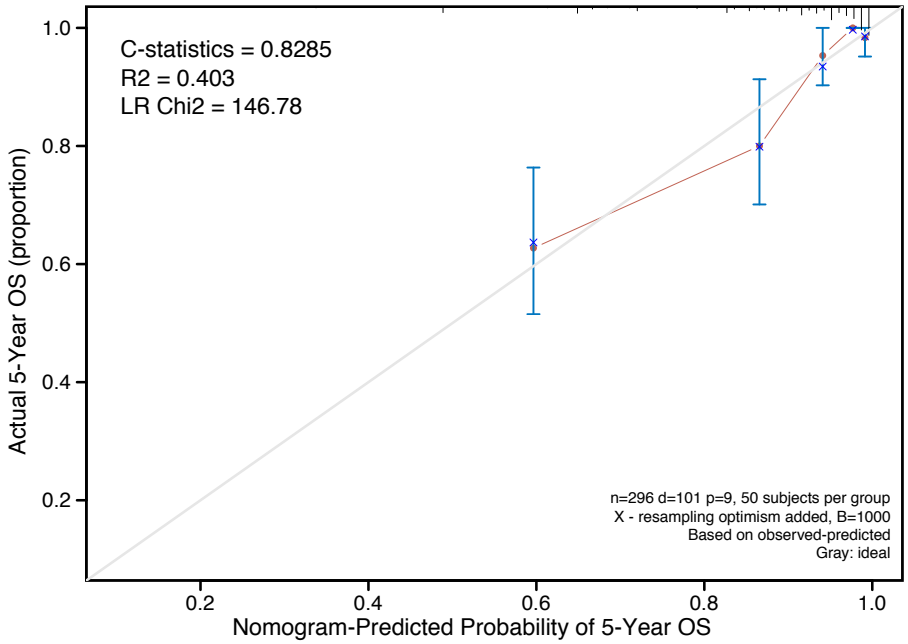


Figure 5

A


Points
0 10 20 30 40 50 60 70 80 90 100
Smoking
Yes
No
Heart Failure
Yes
No
Ki-67
Positive
Negative
ACS
Yes
No
Prognostic Nutritional Index
≤48
>48
Stage
IV
≤III
Surgery
No
Yes
Gleason Score
4
≤3
Serum Albumin
≥40 g/L
< 40 g/L
Total Points
0 50 100 150 200 250 300 350 400
3-year Survival probability
0.9 0.850.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1
5-year survival probability
0.9 0.850.80 0.70 0.6 0.5 0.4 0.3 0.2 0.1

B


C-statistics = 0.8285
R2 = 0.403
LR Chi2 = 146.78
n=296 d=101 p=9, 50 subjects per group
X - resampling optimism added, B=1000
Based on observed-predicted
Gray: ideal
Actual 5-Year OS (proportion)
1.0
0.8
0.6
0.4
0.2
0.2 0.4 0.6 0.8 1.0
Nomogram-Predicted Probability of 5-Year OS