

Nomogram for Predicting Survival in Mucinous Adenocarcinoma of Prostate

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Abstract

Background: Few studies on predicting survival in patients with histology of mucinous adenocarcinoma of the prostate have been done.

Objective: Nomogram is a mathematical model in which various important factors are combined to predict a specific end point. The purpose of this study was to evaluate the prognostic value of clinical factors in patients with mucinous adenocarcinoma and to construct nomogram to predict the survival rate.

Design,Setting,and Participants: A nomogram was designed to predict the survival rate of 356 patients with invasive ductal carcinoma selected from the surveillance, epidemiology and final results (SEER) database. Univariate and multivariate models of the cohort were done firstly. And then a model of nomogram that included age, race, grade, stage M and chemotherapy were constructed to predict the 3-year and 5-year survival of prostate cancer patients with histology of mucinous adenocarcinoma. Based on different time, we designed two nomograms.

Results and limitations: After the discrimination and calibration, C-index was 0.8138. The specificity was 86.12%, sensitivity was 55.89% for 3-year nomogram. Its survival was 91.49% and AUC was 0.7467. The specificity was 82.42%, sensitivity was 54.83% for 5-year nomogram. Its Survival was 86.73% and AUC was 0.7555. Respectively, which indicated relative good discrimination of the nomogram.

Conclusions: This clinical model shows a high ability to predict the survival rate of mucinous adenocarcinoma patients with histologically prostate cancer, making this model a novel and attractive model for predicting the survival rate of patients.

Background

Prostate mucinous adenocarcinoma is a rare variant whose prognosis is traditionally been considered to be worse than traditional adenocarcinoma^[1]. The diagnosis of prostate mucinous adenocarcinoma is performed during prostatectomy. A diagnosis can be made when at least 25% of the excised tumors contain extracellular mucin^[2, 3]. The clinical significance of mucosal components of prostate cancer > 25% is unclear. Although some studies^[4, 5] have shown that these tumors show higher invasiveness than typical (non-mucinous) acinar adenocarcinomas, other studies^[6, 7] have shown that these two types of tumors have similar results. The incidence of prostate mucinous adenocarcinoma is approximately 0.2%^[4,8-10]. However, according to the different data of isolated cases or small case series, the prognosis is still controversial compared with typical acinar cancer^[6,11-15]. Therefore, it is necessary to establish a model to accurately assess the prognosis of patients with prostate mucinous adenocarcinoma.

Nomogram is a mathematical model in which various important factors are combined to predict a specific end point^[16]. By integrating these clinical and pathological factors, nomograms can provide individualized estimates of events over time, such as the individual probability of a patient's disease

recurrence and death. Therefore, these algorithms can be used as reliable tools to predict clinical results and guide surgery, monitoring and auxiliary treatment decisions.

The construction of the nomogram is based on independent the relative factors of prognosis through Kaplan-Meier and multivariate Cox proportional hazard models. At present, nomograms have been frequently used to help surgeons formulate treatment schedule and assess the prognosis of cancer, for instance liver cancer^[17], gastric cancer^[18], nasopharyngeal cancer^[19] and breast cancer^[20]. Most important of all, it has been recorded in the NCCN Clinical Guidelines that prostate cancer can be detected early through nomograms^[21]. Therefore, we attempted to evaluate the 3-year and 5-year operating systems based on serer database by establishing two nomograms to provide reference for surgeons.

Methods

Patients' general information

The study enrolled 356 patients with prostate mucinous adenocarcinoma from the SEER database from 2004 to 2015^[22]. Clinical pathological data included age, ethnicity, material status, follow-up time, tumor location, t-stage, n-stage, m-stage, RP, radiotherapy sequence, radiotherapy, chemotherapy, biopsy Gleason score, overall survival, age, and follow-up time. The inclusion of clinicopathological data started on Jan. 1st, 2011. Follow up starts on the date of radical prostatectomy operation, ends on the date of migration, death or December 31, 2015, whichever occurs first. People have missing data were excluded. After modeling, the information of 356 people built in the nomogram.

The mean age was 63.13 year's old. The mean follow-up time was 67.07 months. Ethnic composition includes white, black and other races (Native American / AK, Asian / Pacific Islander). (Table 1)

Survival analysis

Nomogram development

The Nearest Neighbor Estimation(NNE) method was used^[23]. Generalization of the Somers DXY rank correlation of the c-index and the reviewed response variable: $DXY = 2(C-0.5)$. The inverse probability of the censored weight (IPCW) estimates of cumulative / dynamic time-dependent ROC curves.)

Nomogram validation

It is required to verify the accuracy of nomograph through 500 bootstrapping. The fit was evaluated by a consistency index (C-index) and a calibration chart. There are two commands in R software, "rccorrcens" and "calibrate", through which you can obtain C-index and calibration. Statistical package R^[25]and Empower Stats were used for all analyses. We used stratified linear regression model for subgroup analysis. The modification and interaction of subgroups were examined by likelihood ratio test. All

statistical tests were carried out from two aspects, P value less than 0.05 was considered statistically significant.

Results

Patient clinicopathological data

All data are strictly filtered based on SEER database. This study analyzed 356 cases of mucinous adenocarcinoma of prostate. The average age was 63.13 months and the average follow-up time was 67.06 months. There were 238 (66.85%) married patients, 41 (11.52%) single patients, 36 (10.11%) divorced, widowed or separated patients and 41 (11.52%) unknown patients. A total of 283 (79.49%) white patients, 47 (13.20%) black patients, 20 patients of other races (5.62%) and 6 (1.69%) are unknown patients. The details of the validation queue are shown in the table1 Medium.)

Survival analysis and nomogram construction

For overall survival (OS), we conducted univariate and multivariate analysis. The results showed that age, race, material status, follow-up time, tumor area, T stage, N stage, M stage, RP, radiation sequence, radiation, chemotherapy, biopsy Gleason score, total survival time, age, follow-up time. (Table n) Through the univariate and multivariate analysis, the results showed that age, race, grade, stage M and chemotherapy were independent prognostic factors ($P < 0.05$). So, we consider all these factors by set up a nomogram. As shown in table 2.

Nomogram construction and validation

According to the nomograph, sum the total points, and then convert them to OS, because there are parallel lines below the graph, and their scales are linear with each other. We used the guide program to sample and calibrate the internal nomogram 500 times, and drew the graph with the appearance, deviation correction and ideal curve. All of this tells us that the nomogram is very consistent internally. Then, we draw the receiver's operating characteristics (ROC) inside and outside the training and verification set.

After the discrimination and calibration, C-index was 0.8138 (95% CI = 0.7483-0.8793,SD 0.0669). Based on different follow-up time, 3 years and 5 years, we developed two nomograms. (Figure 1, 2). In nomogram for 3 years, the sensitivity was 55.89% and the specificity was 86.12%. The survival was 91.49% and AUC was 0.7467. In nomogram for 5 years, the sensitivity was 54.83% and the specificity was 82.42%. The survival was 86.73% and AUC was 0.7555. (Figure 3, 4). The C-index value is greater than 0.7, and the calibration curve is in good coherence with 45 degree ideal line.

The model from observed data

$0.10409 * \text{age} + 0.23096 * (\text{race} = \text{black}) - 2.07224 * (\text{race} = \text{other}) - 15.04340 * (\text{race} = \text{unknown}) - 0.16936 * (\text{grade} = \text{Poorly differentiated; Grade III}) + 0.53847 * (\text{grade} = \text{Undifferentiated; anaplastic; Grade IV})$

+1.45848*(grade=Unknown)+1.03057*(M stage=M1)-1.05505*(M stage=unknown) +3.27293*(Chemotherapy=yes)

Discussion

We use Kaplan Meier method to calculate the estimated OS rate, which is showing no difference with the study reported by JAMA Oncol^[27]. Through the subsist analysis of the surgical system, we found that the operating system of women was exceed that of men (Fig. 1 and Table 2). In terms of age, we found that the operating system has declined for more than a year. Current results show that most patients are diagnosed after 50 years old^[28]. Our results show that the operating system of patients in black is below that of other races, which is showing no difference with the study ^[29].

The accuracy of the markers in the internal (modeling queue) and external (validation queue) is verified by using the C-index and calibration curve. 3-year and 5-year of operating systems internal validation of C-indexes was 0.8138. C-index value are greater than 0.7. There is excellent commonality between them.

The 3-year OS and 5-year OS for the prediction of prostate mucinous adenocarcinoma by the establishment of pictograms have many obvious advantages. In a word, it is simple and feasible to create an image-free graph to predict the process of 3-year and 5-year operating systems. Secondly, our patient base is large enough and selected from surveillance, epidemiology and end result (SEER) databases to make it more reliable. Secondly, our model has high precision and specificity for predicting 3-year and 5-year operating systems. This may be related to our large number of queues, which makes the relationship between variables and results quite flexible.

Our research has advantages and some limitations. We based SEER database to finished a large sample retrospective research, and a more accurate marking model has been successfully established. A large number of studies have stated clearly that other correlative clinicopathological elements have an impact on the survival of oral cancer patients, for instance HPV^[30], lymph node involvement^[31], tumor thickness^[32], P53 ^[33], EGFR^[34], cigarette and alcohol consumption^[35], and chemotherapy^[36]. However, the SEER database does not contain the above elements. Similarly speaking, we cannot assess disease-free survival and regional control. Therefore, our scale cannot assess aforementioned factors. In order to test these indicators, we will conduct some prospective studies to make up for these limitations.

Finally, we carefully analyzed the survival and successfully established two accurate pictograms, which provided customized clinical treatment plan and personalized prognosis reference for surgeons.

Conclusion

We propose a nomogram which can predict the 3-year and 5-year survival rates. This clinical model shows a high ability to predict the survival rate of mucinous adenocarcinoma patients with histologically prostate cancer, making this model a novel and attractive model for predicting the survival rate of

patients. In the subsequent validation, these promising results strengthen the potential of this prediction tool to predict 3-and 5-year survival rates.

Abbreviations

SEER: surveillance, epidemiology and final results; NNE = Nearest Neighbor Estimation; IPCW = inverse probability of the censored weight; OS = overall survival; ROC = receiver's operating characteristics; C-index = consistency index

Declarations

Ethics approval and consent to participate

All the information was downloaded from the SEER database via SEERStat software. The study was approved by the Ethics Committee of West China Hospital.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during the current study are available in the SEER database, [Http://seer.cancer.gov](http://seer.cancer.gov).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiakun Li and Xi-nan Cui wrote the main manuscript text. Shi Qiu, Lu Yang and Qiang Wei modified the manuscript text. Kun Jin and Xiaonan Zheng analyzed the data. Jiakun Li, Xiang Tu and Liming Ge prepared figures and tables. All authors have read and approved the manuscript.

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Tables

Table 1: Baseline characteristics of participants

	Mean±SD
Follow-up time (month)	67.06 ± 40.70
Age (year)	63.13 ± 9.99
	N (%)
Material status	
Married	238 (66.85%)
Single	41 (11.52%)
Divorced/widowed/Separated	36 (10.11%)
Unknown	41 (11.52%)
Race	
White	283 (79.49%)
Black	47 (13.20%)
Other	20 (5.62%)
Unknown	6 (1.69%)
Grade	
Moderately differentiated; Grade II	70 (19.66%)
Poorly differentiated; Grade III	262 (73.60%)
Undifferentiated; anaplastic; Grade IV	4 (1.12%)
Unknown	20 (5.62%)
Region	
Pacific	182 (51.12%)
East	110 (30.90%)
North	43 (12.08%)
Southwest	21 (5.90%)
T stage	
<=T1C	65 (18.26%)
T2	212 (59.55%)
T3	61 (17.13%)
T4	14 (3.93%)

Unknown	4 (1.12%)
N stage	
N0	313 (87.92%)
N1	17 (4.78%)
Unknown	26 (7.30%)
M stage	
M0	327 (91.85%)
M1	15 (4.21%)
Unknown	14 (3.93%)
RP	
0	114 (32.02%)
1	242 (67.98%)
radiation sequence	
No radiation and/or cancer-directed surgery	331 (92.98%)
Radiation after surgery	25 (7.02%)
Radiation	
Beam radiation	63 (17.70%)
Combination of beam with implants or isotopes	7 (1.97%)
Radioactive implants	9 (2.53%)
None/Unknown	270 (75.84%)
Recommended, unknown if administered	7 (1.97%)
Chemotherapy	
No/Unknown	354 (99.44%)
Yes	2 (0.56%)
Biopsy GS	
<=6	34 (9.55%)
3+4	65 (18.26%)
4+3	44 (12.36%)
3+5	2 (0.56%)

5+3	2 (0.56%)
4+4	32 (8.99%)
4+5	13 (3.65%)
5+4	3 (0.84%)
Unknown	161 (45.22%)
OS	
Alive	301 (84.55%)
Dead	55 (15.45%)

The clinical features were listed above.

SD=Standard Deviation

RP=Radical Prostatectomy

OS=Overall Survival

GS=Gleason Score

Table 2: The results of Univariate and multivariate analyses

Exposure	Univariate	Multivariate
Material status		
Married	1	1
Single	1.10 (0.46, 2.63) 0.8232	0.71 (0.23, 2.24) 0.5639
Divorced/widowed/Separated	0.91 (0.35, 2.31) 0.8358	0.66 (0.22, 2.00) 0.4653
Unknown	1.41 (0.68, 2.94) 0.3555	2.52 (1.00, 6.35) 0.0503
Age	1.10 (1.07, 1.13) <0.0001	1.11 (1.06, 1.17) <0.0001
Race		
White	1	1
Black	0.97 (0.44, 2.14) 0.9335	1.31 (0.45, 3.83) 0.6225
Other	0.29 (0.04, 2.08) 0.2160	0.15 (0.02, 1.33) 0.0882
Unknown	0.00 (0.00, Inf) 0.9959	0.00 (0.00, Inf) 0.9978
Grade		
Moderately differentiated; Grade II	1	1
Poorly differentiated; Grade III	1.17 (0.49, 2.78) 0.7284	0.44 (0.11, 1.79) 0.2496
Undifferentiated; anaplastic; Grade IV	1.90 (0.23, 15.81) 0.5516	1.27 (0.09, 18.35) 0.8596
Unknown	10.09 (3.87, 26.30) <0.0001	7.67 (1.93, 30.45) 0.0038
Region		
Pacific	1	1
East	1.27 (0.71, 2.29) 0.4251	1.03 (0.46, 2.29) 0.9400
North	0.73 (0.28, 1.90) 0.5129	0.79 (0.27, 2.36) 0.6784
Southwest	1.52 (0.58, 3.96) 0.3966	2.49 (0.81, 7.64) 0.1108
T stage		
<=T1C	1	1
T2	0.54 (0.28, 1.01) 0.0523	1.04 (0.42, 2.54) 0.9371
T3	0.35 (0.13, 0.97) 0.0445	0.66 (0.16, 2.72) 0.5681
T4	3.47 (1.24, 9.69) 0.0177	3.22 (0.68, 15.20) 0.1403
Unknown	5.21 (1.49, 18.23) 0.0097	0.25 (0.02, 2.61) 0.2457

N stage		
N0	1	1
N1	1.97 (0.61, 6.37) 0.2576	0.29 (0.04, 2.02) 0.2113
Unknown	4.69 (2.44, 9.00) <0.0001	2.27 (0.48, 10.65) 0.3002
M stage		
M0	1	1
M1	7.13 (3.45, 14.72) <0.0001	3.96 (0.73, 21.53) 0.1111
Unknown	2.27 (0.81, 6.34) 0.1172	0.09 (0.01, 0.77) 0.0282
RP		
0	1	1
1	0.36 (0.21, 0.61) 0.0001	1.42 (0.52, 3.90) 0.4947
radiation sequence		
No radiation and/or cancer-directed surgery	1	1
Radiation after surgery	1.32 (0.53, 3.31) 0.5548	2.36 (0.49, 11.45) 0.2854
radiation		
Beam radiation	1	1
Combination of beam with implants or isotopes	2.31 (0.64, 8.28) 0.1986	3.44 (0.71, 16.66) 0.1243
Radioactive implants	1.51 (0.42, 5.43) 0.5251	3.97 (0.85, 18.52) 0.0794
None/Unknown	0.88 (0.45, 1.72) 0.7070	1.25 (0.43, 3.61) 0.6775
Recommended, unknown if administered	1.66 (0.21, 12.88) 0.6280	4.44 (0.44, 45.08) 0.2077
Chemotherapy		
No/Unknown	1	1
Yes	20.10 (2.60, 155.61) 0.0041	9.59 (0.64, 143.38) 0.1014
Biopsy GS		
<=6	1	1
3+4	0.67 (0.25, 1.79) 0.4189	2.85 (0.49, 16.47) 0.2432
4+3	0.43 (0.12, 1.45) 0.1723	2.15 (0.30, 15.23) 0.4445

3+5	2.59 (0.32, 21.08) 0.3737	10.62 (0.58, 193.05) 0.1103
5+3	0.00 (0.00, Inf) 0.9958	0.00 (0.00, Inf) 0.9981
4+4	1.69 (0.64, 4.45) 0.2859	5.67 (0.87, 37.04) 0.0700
4+5	1.93 (0.56, 6.58) 0.2961	4.10 (0.65, 25.73) 0.1323
5+4	4.10 (0.85, 19.77) 0.0784	13.25 (1.09, 160.82) 0.0425
Unknown	1.45 (0.59, 3.58) 0.4235	2.14 (0.52, 8.87) 0.2928

Data in the table was showed as “HR (95% CI) Pvalue”. Exposure variable was showed as the first column and the result variable was the status of overall survival. In this Cox model, time variable was follow-up time (months).

SD=Standard Deviation

RP=Radical Prostatectomy

OS=Overall Survival

GS=Gleason Score

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