

A novel nomogram to predict the overall survival of patients with colloid adenocarcinoma of the lung

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Background: Colloid adenocarcinoma of the lung is one of rare subtypes of pulmonary adenocarcinoma. The purpose of our study is to establish a predictive model for the overall survival of colloid adenocarcinoma. **Methods:** A total of 749 patients were separated from the Surveillance, Epidemiology, and End Results database between 2011 and 2015. Cox regression was performed to select the predictors of overall survival. The calibration curves, concordance index, the receiver operating characteristic curve, and the area under the curve were used to verify the nomogram. Kaplan-Meier curves were used to illustrate and compare the overall survival of patients in different surgical groups.

Results: Multivariate analyses demonstrated clinical characteristics such as age, sex, race, site, tumor stage, stage T, metastatic sites at diagnosis, surgical treatment were associated with prognosis. In the nomogram, we could predict the probability of overall survival for patients. The concordance index of the novel nomogram was 0.849, which meant that the model had a good discriminated ability. A good consistency was indicated by the calibration curves in the probability of 1-, 3-, and 5-year overall survival between the actual observation and the nomogram prediction. We plotted the receiver operating characteristic curve and the area under the curve was 0.905, 0.923, 0.885, respectively. The Kaplan-Meier curves indicated that overall survival was precisely distinguished by the different surgical status. The survival rate of patients in the surgery group was significantly higher than that of patients without surgery (P<0.0001). Segmentectomy had the highest survival rate than the lobectomy and wedge resection (P=0.0122).

Conclusions: We constructed and validated a nomogram to help predict overall survival for colloid adenocarcinoma. Clinicians could predict individualized survival and give treatment recommendations.

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Introduction

Colloid adenocarcinoma is one of uncommon variants of lung adenocarcinoma that accounts for about 0.24% of all primary lung cancers (1). Colloid adenocarcinoma shows extracellular mucin in abundant pools, which distend alveolar spaces with the destruction of their walls (2). Cystic mucinous adenocarcinoma, mucinous cystadenoma, mucinous cystic tumor, cystic mucinous adenocarcinoma and so on were what it used to be called in the old days (3-9). In 2011, colloid adenocarcinoma was described as

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a variant of adenocarcinoma (2). Because this tumor is rare, only some case reports are reported. The therapeutic recommendations and the risk factors of survival are difficult to understand. This study aims to establish a prognosis prediction model to predict the overall survival of colloid adenocarcinoma by using the Surveillance, Epidemiology, and End Results database.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi. org/10.21037/tcr-20-2795).

Methods

Study population

SEER 18 population-based cancer Registries (1975 to 2017 dataset) were chosen to select patients, which is maintained by the National Cancer Institute and covers nearly 28% of the population in the United States. We strictly grasp the inclusion and exclusion criteria of research objects to ensure good representativeness a collect as much data as possible on objective indicators. The inclusion criteria in our study were (I) patients with lung cancer was colloid adenocarcinoma diagnosed between 2011 and 2015; (II) patients aged 18 years or older who were diagnosed; (III) the information of patient consisted of the age of diagnosis, race, sex, primary site, TNM stage, tumor staging, the pattern of distant metastasis, surgical method, survival status and time. Individuals who had unclear information were subsequently excluded. The demographic data of all eligible cases were collected and retrospectively analyzed.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This article does not contain any studies with human participants or animals performed by any of the authors. All procedures performed in study involving human data were extracted freely from the SEER Research Data available to the public online (https://seer.cancer.gov/data/access.html).

Statistical analysis

An analysis on Cox regression was implemented in order to assess the risk factors of overall survival. It was set up in that P<0.05 was considered statistically significant. R software was used to set up a nomogram based on the numerous possible prognostic factors which could be associated with the overall survival. The validation of the nomogram was executed, and the results were evaluated based on the concordance index, the receiver operating characteristic curve, the area under the curve and calibration curves. The concordance index, receiver operating characteristic curve and the area under the curve were used to denote the predictive accuracy and differentiation ability of each factor of the nomogram. Calibration curves (1,000 bootstrap resamples) were performed to check the calibration of the nomogram. Kaplan-Meier curves were used to illustrate and compare the overall survival of patients in the different surgical groups. Data extraction was collected using the version 8.3.6.1 of SEER*Stat software and data analyses were all performed using R software (version 4.0.0).

Results

Demographics

Overall, 749 patients with colloid adenocarcinoma of the Lung were included among which 373 (49.80%) patients were diagnosed at the age of \geq 70 years. Females accounted for 54.34% and the majority of patients were White (81.98%) which is related to the fact that the United States is a white-dominated country. In terms of the primary site, the percentages of the upper lobe and lower lobe were 39.92% and 49.67% respectively. For the stage, the stage IA and IV had a higher proportion (31.64%, 28.57%, respectively). According to the AJCC guidelines for the staging of tumor nodule metastasis (TNM), T1a, T2a, and T3 had a higher proportion than others. For lymph nodes, N0 (73.97%) is the most common. For the pattern of the distant metastasis, bone metastasis is more common than the brain and liver. More than half of the patients underwent surgery (Table 1).

Cox regression analysis for estimating the risk factors of overall survival

Cox proportional hazards model was used to evaluate the role of each variable in predicting overall survival. Multivariate analyses demonstrated that the clinical characteristics such as such as age, sex, race, primary site, tumor staging, stage T, metastatic sites, surgical treatment were connected with the prognosis of patients (*Table 2*).

Building and validating the novel nomogram

We established a prognosis prediction model which

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 Table 1 Clinicopathologic characteristics of the entire cohort of patients (n=749)

Characteristics	Number (%)
Age (years)	
<70	376 (50.20)
≥70	373 (49.80)
Race	
White	614 (81.98)
Black	75 (10.01)
Other	60 (8.01)
Sex	
Female	407 (54.34)
Male	342 (45.66)
Site	
Upper lobe	299 (39.92)
Middle lobe	43 (5.74)
Lower lobe	372 (49.67)
Other lobes	35 (4.67)
Stage	
IA	237 (31.64)
IB	111 (14.82)
IIA	44 (5.87)
IIB	82 (10.95)
IIIA	53 (7.08)
IIIB	8 (1.07)
IV	214 (28.57)
Т	
T1a	179 (23.90)
T1b	100 (13.35)
T2a	172 (22.96)
T2b	50 (6.68)
Т3	157 (20.96)
Τ4	91 (12.15)
Ν	
NO	554 (73.97)
N1	43 (5.74)
N2	109 (14.55)
N3	43 (5.74)

Table 1 (continued)

Table I (continuea)					
Characteristics	Number (%)				
Bone metastasis					
Yes	101 (13.48)				
No	648 (86.52)				
Brain metastasis					
Yes	43 (5.74)				
No	706 (94.26)				
Liver metastasis					
Yes	17 (2.27)				
No	732 (97.73)				
Surgery					
Wedge resection	124 (16.56)				
Segmentectomy	13 (1.74)				
Lobectomy	291 (38.85)				
No	321 (42.86)				

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including above factors (*Figure 1*). In the nomogram, each predictor was granted a score on a points scale. By adding the total predicted scores on the bottom scale, we could predict the overall survival in patients with colloid adenocarcinoma of the Lung. The concordance index of the novel nomogram was 0.849, which meant that the model had a good discriminated ability. A good consistency was indicated by the calibration curves in the probability of 1-, 3-, and 5-year overall survival between the actual observation and the nomogram prediction (*Figure 2*). We also drew the receiver operating characteristic curve of the 1-, 3-, and 5-year overall survival, and the area under the curve were 0.905, 0.923, 0.885 respectively, which also demonstrated good discrimination (*Figure 3*).

Kaplan-Meier curves of overall survival for patients in the different surgical status

The Kaplan-Meier curves indicated that overall survival in the different surgical status was precisely distinguished. The survival rate of patients in the surgery group was significantly higher than that of patients without surgery (P<0.0001). Among surgical procedures, segmentectomy has the highest survival rate than the lobectomy and wedge resection (P=0.0122) (*Figure 4*).

Zhang and Liu. A nomogram for the survival of lung colloid adenocarcinoma

TADIC 2 COX regression analysis for estimating the risk factors of overall surv.	Table 2	Cox regression	analysis for	estimating the	risk factors	of overall surviva
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Variable	Hazard ratio	95% Cl	P value
Age (years)			
<70	Reference		
≥70	1.333	1.0514-1.6907	0.018
Race			
White	Reference		
Black	0.913	0.6009-1.3885	0.672
Other	0.566	0.3422-0.9364	0.027
Sex			
Female	Reference		
Male	1.270	1.008–1.5988	0.043
Site			
Upper lobe	Reference		
Middle lobe	1.845	1.0927-3.1158	0.022
Lower lobe	1.231	0.9617-1.5749	0.099
Other lobe	1.821	1.1562-2.8694	0.010
Stage			
IA	Reference		
IB	1.054	0.4753-2.3351	0.898
IIA	2.126	0.9664-4.6771	0.061
IIB	4.545	2.3041-8.9648	<0.001
IIIA	4.791	2.4311-9.4395	<0.001
IIIB	4.194	1.4172-12.4108	0.010
IV	7.035	3.8668-12.7994	<0.001
Т			
T1a	Reference		
T1b	1.132	0.6612-1.9374	0.652
T2a	1.219	0.6874-2.1628	0.498
T2b	2.109	1.0739-4.1401	0.030
Т3	1.215	0.6964-2.1186	0.493
T4	1.337	0.7775–2.2987	0.294
Ν			
NO	Reference		
N1	1.420	0.8874-2.2730	0.144
N2	1.222	0.8883-1.6796	0.218
N3	0.956	0.6080-1.5019	0.218

Table 2 (continued)

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Table 2 (continued)

Variable	Haz	ard ratio		95	5% CI		P value	
Bone metastasis								
Yes	Re	ference						
No		0.576		0.421	8–0.7871		<0.001	
Brain metastasis								
Yes	Re	ference						
No		0.607		0.416	4–0.8836		0.009	
Liver metastasis								
Yes	Re	ference						
No		0.728		0.421	4–1.2580		0.255	
Surgery								
Yes	Re	ference						
No		2.892		2.112	3–3.9588		<0.001	
Points Age Race	010 <70 OtherM	20 ≥70 BI	30 ack White	40	50 60 .	. 70 . 80) <u>90</u>	100
Sex	Female Low	er	Middle					
Stage	Upper IB		Other	IIA		IIIB III/	4	
Т	IA T1bT2a			T2b		IIB		IV
Ν	T1bN0 T3	T4 N1	Voc					
Bone	N3 N	2						
Brain	NO		res					
Liver	NO	res						
Surgery	NO Yéo				NO			
Total points								
1-year survival probability	U	50	100	150	200	250	300	350
3-year survival probability			0	.9 0.8	0.7 0.6 0.5	0.4 0.3 0.2 0.1 L		
5-year survival probability	~	0.9	0.8	0.7 0.6 0.5	$0.4 \ 0.3 \ 0.2 \ 0.3$	1		
	0.	.00	0.7 0.	0 0.0 0.4 0.	5 0.2 0.1			

Figure 1 Nomogram to predict the overall survival of patients with colloid adenocarcinoma of lung.

Discussion

Colloid adenocarcinoma of the lung is one of extremely rare subtypes of pulmonary adenocarcinoma (10). Cough, hemoptysis, and thoracalgia are the most common clinical manifestations. But some are asymptomatic which is often detected on a routine health examination (11). In reported series, colloid adenocarcinoma was observed more frequently in females, the finding was like ours. Tateishi *et al.* showed that there was a higher rate of metastasis in the colloid adenocarcinoma than other types of lung cancer, including the pulmonary, lymph node, and hematogenous metastasis (12). But in our study, compared with other lung cancers, colloid adenocarcinoma had a similar metastatic frequency. Some reports have described the discoveries of low attenuation and poor enhancement on contrast CT, low intensity on T1WI, and high intensity on T2WI on



Figure 2 Calibration curve showing nomogram-predicted overall survival compared with the actual overall survival.

MRI. The PET/CT of colloid adenocarcinomas showed a relatively low SUVmax, which might cause higher rates of false-negative results (59–82%) for malignant tumors (13). The possible reasons were as follows: (I) the tumors contained abundant mucus; (II) the metabolism of the tumors was relatively slow (14). We should combine other methods of examination and the history of present illness to make a preliminary clinical diagnosis to reduce the false negative rate of PET/CT. Because of the abundant amount of mucus and few malignant cells in the tumor, it was difficult to diagnose colloid adenocarcinoma by biopsy and most patients required surgical resection for the diagnosis. Histologically, it was difficult somewhile to separate colloid adenocarcinoma of lung from invasive mucinous adenocarcinoma of the lung. In colloid adenocarcinoma, the majority of tumors were made up of mucin pools which could cause an expansive alveolar cavity with the destruction of their walls and tumor cells were partly arranged in the alveolar wall. Some scattered tumor cells were in the mucous cell pool. Compared with



Figure 3 Discrimination plot. The AUC for the ROC were 0.905, 0.923, 0.885 respectively. AUC, area under the curve; ROC, receiver operating characteristic.



Figure 4 Kaplan-Meier curves of overall survival for patients in the different surgical status.

colloid adenocarcinoma, the most common patterns of growth in invasive mucinous adenocarcinoma were acinar, lepidic, micropapillary, papillary, and solid. By using clustering analysis, a genetic trait of mucin-producing lung adenocarcinoma demonstrated that the intermediate and distal respiratory bronchioles might be the origin of colloid adenocarcinoma of lung cancer (15). The reported studies showed the HNF4-A activated the CDX2 (16). The study of Maeda Y indicated that the result of the HNF4-A activated the CDX2 might make progenitor cells differentiate into mucous cells (17). Microscopically, colloid adenocarcinoma consists of two types of tumor cells are found floating in mucin pools: tall columnar goblet cells or signet ring cells. Goblet cell-type mucinous adenocarcinoma is generally stained positive with intestinal-type markers, such as CK20, CDX2 and MUC2, while also positive for CK7 and TTF-1. Signet ring cell-type mucinous adenocarcinoma is immunoreactive for markers of pulmonary origin, such as TTF-1, CK7, and negative for CK20, CDX2 and MUC2.

In our study, the results of the Cox regression analysis showed that male patients over the age of 70 had relatively poor survival. The reasons are that men are more likely to smoke than women, and smoking can have an adverse effect on the prognosis of patients. The function of various organs of the body will be significantly reduced when patients are over 70 years old. The increase of complications and treatment-related complications in elderly patients often makes the elderly unable to successfully complete treatment or abandon treatment, thus affecting the survival time of the elderly. Compare with the upper lobe, middle lobe and

other lobe had relatively poor survival. The perhaps reason was that lymph node metastasis which could cause poor survival was more common in the middle lobe and other lobe than in the upper lobe. Kalhor reported that the stage of colloid adenocarcinoma might influence the prognosis of the patients and there was only some KRAS without EGFR and ALK mutation (18). Targeted therapy is currently not available for KRAS mutation patients, MEK inhibitors (trametinib) and KRAS G12C inhibitors (AMG510, MRTX849) are used in clinical trials. Our study also generally showed that the higher the stage, the worse the prognosis. In a follow-up study of Oka et al., which included 13 patients of colloid adenocarcinoma, the results showed that there was a better prognosis in the primary tumors with diameters ≤ 3 cm. The larger the tumor, the greater the risk of recurrence and intrapulmonary metastasis (19). Our study showed that only the T2b had a poor prognosis than T1 with statistically significant. This suggests that the size of the tumor may not be strongly related to the prognosis. Compared to other adenocarcinomas of the lung, the reason might be that colloid adenocarcinoma exhibited an indolent clinical behavior (20). In terms of treatment, surgery was still the main treatment for colloid adenocarcinoma, which could improve survival in our study. Russell et al. estimated the 5-year survival to be 51% in 9 patients with pulmonary colloid adenocarcinoma who underwent surgical resection (21). Takao et al. also showed that if colloid adenocarcinoma was localized, complete surgical resection could improve the prognosis compared with other adenocarcinomas of the lung (22). Among surgical procedures, segmentectomy offered the best prognosis followed by lobectomy coupled with systematic lymph node dissection. The number of patients with segmentectomy was small, which might lead to certain statistical differences. Rossi et al. also showed that patients with CDX2-/MUC2positive expression than in those with CDX2-/MUC2negative expression tended to have a better prognosis (1).

There still were some several limitations that deserve attention in our study. First of all, it was a retrospective study that had an inescapable confounding bias. Second, the details of chemotherapy and radiotherapy were not obtained in the SEER database, which hindered further prognostic analyses. Third, the population of our study was patients in America, which cannot represent the global population. Finally, because the external validation was not accomplished, the proposed nomogram needed to be replicated and validated before it can be widely applied in clinical practice.

Conclusions

In conclusion, age, sex, race, primary site, tumor staging, stage T, metastatic sites, surgical treatment were associated with patients' survival. We constructed and validated a novel nomogram with relatively good accuracy to help predict 1-, 2- and 5-year overall survival for colloid adenocarcinoma. Clinicians could predict individualized survival and given treatment recommendations by using the prognostic model.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr-20-2795). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This article does not contain any studies with human participants or animals performed by any of the authors. All procedures performed in study involving human data were extracted freely from the SEER Research Data available to the public online (https://seer.cancer.gov/data/access.html).

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