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Prognostic significance of advanced age in patients with intrahepatic cholangiocarcinoma: A retrospective study of the SEER database.

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Abstract

This study analyzed the prognostic significance of age in patients with intrahepatic cholangiocarcinoma (ICC). Cases diagnosed with ICC between 1988 and 2009 were extracted from the Surveillance, Epidemiology and End Results (SEER) database as the primary cohort. The enrolled patients were divided into 2 groups: the elderly group (≥ 65 y of age) and young group (<65 y of age). The 1, 3 and 5-y cancer-specific survival (CSS) rates were obtained. Kaplan-Meier curves were applied and multivariable Cox regression models were built to analyze the risk factors for prognosis. A multifactorial, integrative nomogram for prognostic prediction was formulated by software R. Cases diagnosed in 2010 from the SEER database were enrolled as the validation cohort. In total, 2161 patients were ultimately included in the primary cohort. The 1, 3 and 5-y CSS rates were 34.3%, 12.5% and 6.5% in the elderly group and 49.8%, 21.3% and 11.5% in the young group, respectively. Univariate (P=0.001) and multivariate (P<0.001) analysis revealed a significant difference in CSS between the two groups. Clinical variables including age, pathological grade, primary tumor stage, lymph node invasion and metastasis were integrated to formulate the nomogram for prognostic prediction, and its predictive power was higher than that of conventional TNM staging. The results were confirmed in the validation cohort. In conclusion, aging could provide important prognostic information for ICC patients and further serve as a critical stratification parameter for the choice of treatment.

Keywords: Intrahepatic cholangiocarcinoma, Elderly, Prognosis, Nomogram, SEER.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC) [1,2]. During the past three decades, its incidence and mortality have increased rapidly worldwide [3]. Clinically, hepatectomy remains the cornerstone of the curative treatment for this fatal malignancy [4].

However, only a few patients can survive long-term after diagnosis because of a high probability of loco-regional recurrence and distant metastasis [5]. Based on critical clinical parameters such as tumor number, vascular invasion and lymph node status, the 7th American Joint Committee on Cancer (AJCC) staging system is currently used for ICC clinical staging and prognostic evaluation.

Circulating biomarkers such as carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen levels should also be considered for predicting ICC outcome [6]. However, due to their relative rarity, other parameters clinically applicable for ICC prognostic prediction are still lacking and require further exploration.

Compared to HCC, ICC shows distinct etiological features; one of which is that it occurs more commonly in elderly patients and age>65 y is considered a general risk factor for cholangiocarcinoma [7,8]. Aging plays a vital role in the initiation and progression of cancer development [9].

In recent years, several large cohort investigations have reported the potential link between aging and ICC [10-12]. However, an explicit correlation between aging and prognosis remains to be clarified. On this point, most of the previous studies were limited by small sample sizes or they did not adjust for potential confounding factors [13-18].

Additionally, those studies merely focused on patients receiving hepatic surgery, but they did not consider the non-operative group when analyzing the prognostic significance of age. In consideration of the low resectability of ICC, especially in elderly patients, the impact of aging on clinical outcome merits further investigation in large cohorts.

In this study, we used data from the Surveillance, Epidemiology and End Results (SEER) database to analyze the prognostic value of age in ICC patients while controlling for background diseases and other confounding factors.

Materials and Methods

Patients

This was a retrospective observational study using the SEER cancer database. The current SEER database represents 18 population-based cancer registries in the USA. This database contains no personal identifiers and produces public-use data for cancer studies. The National Cancer Institute SEER*Stat software (version 8.3.2, http://seer.cancer.gov/seerstat) was used to access the SEER database.

The primary cohort was limited to cases diagnosed with ICC between 1988 and 2009 because data for the AJCC staging system were not provided before 1988. Patients diagnosed in 2010 were enrolled as the validation cohort. To ensure an adequate follow-up time, we excluded cases diagnosed after 2010. To identify ICC patients, we used the International Classification of Diseases for Oncology (3rd edition, ICD-O-3) site recode for the liver (22.0) with the histology code for cholangiocarcinoma (8160), and the site recode for the intrahepatic bile duct (22.1) with histology codes for malignant neoplasm (8000), malignant tumor cells (8001), carcinoma (8010), undifferentiated carcinoma (8020), adenocarcinoma (8140), and cholangiocarcinoma (8160). Exclusion criteria were as follows: HCC, hilar cholangiocarcinoma, extra-hepatic cholangiocarcinoma, gallbladder carcinoma, metastatic adenocarcinoma, incomplete TNM staging, and age<18 y.

Follow-up and survival

The date of last follow-up was defined as the last date the patient was contacted by the hospital or seen by the doctor, or the date of death. The primary endpoint was cancer-specific survival (CSS), which was calculated from the date of diagnosis to the date of cancer-specific death. Deaths attributed to ICC were defined as events, and deaths attributed to other causes were considered as censored data. To investigate the short-term and long-term survival outcomes, 1, 3 and 5-y CSS was calculated.

Ethics statement

This research was based on the publicly available data from the SEER database and the data-use agreement was assigned the reference number 12945-Nov2016. Patients' informed consent was not required because no direct interaction with patients was performed and there was no personal identification. This research was conducted in compliance with the Declaration of Helsinki and approved by the Institutional Review Board of Huashan Hospital, Fudan University, and Shanghai, China.

Statistical analysis

Variables including age, gender, race, pathological grade, primary tumor stage, lymph node invasion and metastasis were extracted from the SEER database. All patients were restaged according to the AJCC Cancer Staging Manual (7th Edition, 2010). Patients diagnosed with ICC were divided into two subgroups according to age: group A (≥ 65 y of age) and group B (<65 y of age).

We used SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) to conduct the statistical analyses. χ^2 tests were used to analyze the correlation of age (elderly and young) with other clinicopathological features. Kaplan-Meier methods were used to generate survival curves, and univariate analyses were performed by log-rank tests between the two groups. Multivariate Cox regression models were applied to analyze risk factors for survival outcomes. All tests were two-sided and $P<0.05$ indicated statistical significance.

Construction and validation of the nomogram

Based on the results of multivariate Cox regression analysis, a nomogram was generated by statistical computing software R version 3.3.1 (https://www.r-project.org/) with the RMS package. A final model selection was conducted using a backward step-down process in accordance with the Akaike information criterion [19].

One thousand bootstrap resamples were applied to calculate the concordance index (C-index) and formulate the calibration curves, which assessed the performance of the nomogram [20]. Comparison between the established nomogram and conventional tumor staging system (AJCC 7th edition staging) was performed by the C-index [21]. A larger C-index implied a more accurate predictive model for prognosis [6]. Calibration curves were conducted by comparing nomogram-predicted survival with observed survival both in the primary and validation cohorts.

Results

Patient characteristics

In the primary cohort, a total of 2161 eligible patients with ICC in the SEER database were identified during the 21-y period (1988-2009), which included 1202 cases (55.6%) in group A and 959 (44.4%) in group B. No significant difference was shown in main demographic and clinical variables between groups A and B. Additionally, 414 patients were ultimately included in the validation cohort. Patients' characteristics are summarized in Table 1.

Table 1. Characteristics of ICC patients from SEER database.

Characteristics	Primary cohort (n=2161)			Validation cohort (n=414)
	Age ≥ 65 (n=1202)	Age<65 (n=959)	P value	
Gender			0.081	
Male	590	507		202
Female	612	452		212
Race			0.073	

Caucasian	951	732		312
Black	79	88		38
Others*	172	139		64
Pathological grade			0.171	
High	64	63		16
Moderate	261	205		96
Poor	220	205		66
Un-differentiation	9	10		3
Unknown	648	476		233
Primary tumor stage			0.099	
T1	562	457		171
T2	164	101		154
T3	304	241		54
T4	172	160		35
Lymph node invasion			0.575	
Yes	313	260		110
No	889	699		304
Metastasis			0.083	
Yes	372	264		121
No	830	695		293
AJCC stage			0.076	
I	358	242		118
II	287	227		81
III	85	68		25
IV	472	422		190
Surgery			0.739	
Yes	307	251		126
No	895	708		288
Radiation			0.704	
Yes	241	186		59
No	961	773		355

Note: ICC: Intrahepatic Cholangiocarcinoma; AJCC: American Joint Committee on Cancer; *Including American Indian, AK Native, Asian, Pacific Islander and unknowns.

Impact of age on short and long-term survival

The 1 and 3-y CSS rates were 34.3% and 12.5% in group A and 49.8% and 21.3% in group B, respectively, which indicated a significant difference (P<0.001, Table 2). The 5-y CSS rate was 6.5% in group A and 11.5% in group B, which also showed a significant difference (P=0.001 and Figure 1).

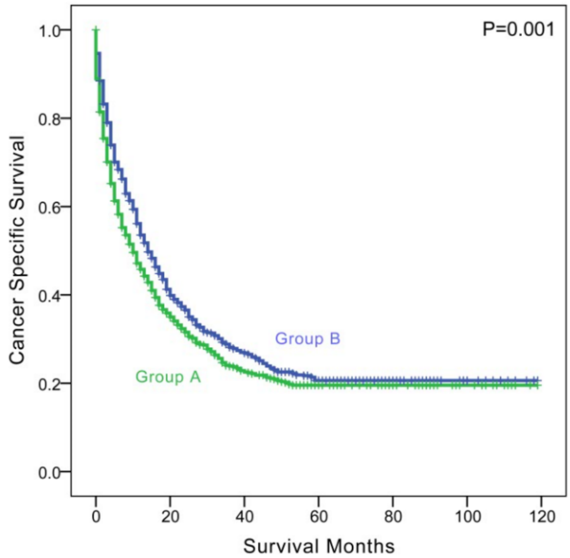

***Figure** 1. Survival curves in the primary cohort according to age status. Group A: age ≥ 65; Group B: age<65. Group A vs. Group B, χ^2=10.422, P=0.001.*

Based on univariate analysis, pathological grade (P<0.001), primary tumor stage (P<0.001), lymph node invasion (P=0.001), metastasis (P<0.001) and AJCC stage (P<0.001) were considered significant risk factors for patient survival in ICC (Table 2). However, prognostic factors did not include surgery (P=0.062) or radiation (P=0.731).

***Table 2.** Univariate survival analysis of various clinical variables for cancer specific survival in the primary cohort.*

Variable	1-y CSS		3-y CSS		5-y CSS	
	Rate (%)	P value	Rate (%)	P value	Rate (%)	P value
Gender		0.039		0.12		0.209
Male	0.386		0.145		0.076	
Female	0.439		0.183		0.099	
Age		<0.001		<0.001		0.001
≥ 65	0.343		0.125		0.065	
<65	0.498		0.213		0.115	

Race		0.142		0.454		0.553
Caucasian	0.417		0.159		0.083	
Black	0.383		0.178		0.102	
Others*	0.399		0.183		0.103	
Pathological grade		<0.001		<0.001		<0.001
High/moderate	0.583		0.291		0.165	
Poor/un-differentiation	0.417		0.137		0.063	
Unknown	0.307		0.099		0.05	
Primary tumor stage		<0.001		<0.001		<0.001
T1-2	0.458		0.218		0.119	
T3-4	0.351		0.092		0.044	
Lymph node invasion		0.292		<0.001		0.001
Yes	0.395		0.08		0.021	
No	0.416		0.187		0.105	
Metastasis		<0.001		<0.001		<0.001
Yes	0.222		0.043		0.015	
No	0.474		0.204		0.111	
AJCC stage		<0.001		<0.001		<0.001
I	0.492		0.271		0.156	
II	0.488		0.198		0.113	
III	0.346		0.124		0.072	
IV	0.313		0.065		0.019	
Surgery		0.095		0.075		0.062
Yes	0.392		0.153		0.073	
No	0.42		0.168		0.093	
Radiation		0.464		0.914		0.731
Yes	0.398		0.174		0.122	
No	0.414		0.162		0.081	

Note: ICC: Intrahepatic Cholangiocarcinoma; AJCC: American Joint Committee on Cancer; *Including American Indian, AK Native, Asian, Pacific Islander and unknowns.

Multivariate Cox regression models were built to evaluate the significant risk factors for survival. Entry variables into the multivariate analysis included age, pathological grade, primary tumor stage, lymph node invasion, and metastasis. Age (old age, hazard ratio (HR) 1.230, 95% confidence interval (CI) 1.107-1.367, using young age as a reference), pathological grade (poor/undifferentiated grade, HR 1.505, 95% CI 1.292-1.753, using high/moderate grade as a reference), primary tumor stage (late primary tumor stage, HR 1.343, 95% CI 1.205-1.498, using early primary tumor stage as a reference), lymph node status (lymph node invasion, HR 1.177, 95% CI 1.039-1.335, using no lymph node invasion as a reference), and metastasis (metastasis, HR 1.909, 95% CI 1.694-2.150, using non-metastatic status as a reference) were independent prognostic factors for ICC (Table 3).

Table 3. *Multivariate Cox regression model analysis of prognostic factors for cancer specific survival in the primary cohort.*

Variable	HR	95% CI	P value
Age			**<0.001**
<65	1	Reference	
≥ 65	1.23	1.107-1.367	
Pathological grade			**<0.001**
High/moderate	1	Reference	

Poor/un-differentiation	1.505	1.292-1.753	**<0.001**
Unknown	1.793	1.580-2.035	**<0.001**
Primary tumor stage			**<0.001**
T1-2	1	Reference	
T3-4	1.343	1.205-1.498	
Lymph node invasion			**0.011**
No	1	Reference	
Yes	1.177	1.039-1.335	
Metastasis			**<0.001**
No	1	Reference	
Yes	1.909	1.694-2.150	

HR: Hazard Ratio; CI: Confidence Interval; ICC: Intrahepatic Cholangiocarcinoma; P values with statistical significance were emphasized in bold.

Stratified analysis of effect of age on CSS

We further analyzed the impact of age on CSS stratified by different races. In Caucasians, elderly patients showed poorer prognosis compared with young patients (P=0.011). In other races, elderly patients were also associated with poorer survival outcome (P=0.036). We also analyzed the correlation between age and CSS stratified by different cancer stages. In both the early stage (AJCC stage I or II) and advanced stage (AJCC stage II or IV), elderly patients showed poorer survival (P<0.001; P=0.005). Additionally, we analyzed the relationship between age and CSS stratified by different therapy methods. In surgical patients, old age were associated with shorter survival time, although not significantly (P=0.125). In non-operative patients, old age was a significant prognostic factor (P=0.005).

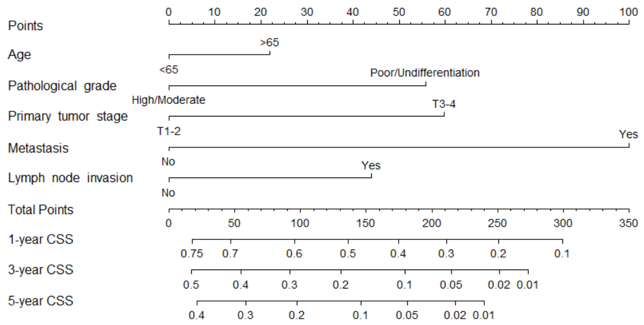

Figure 2. Cancer-specific survival nomogram in ICC patients.

Prognostic nomogram for CSS

A nomogram that integrated all the independent prognostic factors was established (Figure 2). To use the nomogram, an individual patient's clinicopathological parameters were located on each variable axis, and a line was drawn upward to the "points" axis to determine the score for each variable. The sum of these scores was located on the "total points" axis. A line was drawn downward to determine the likelihood of 1, 3 and 5-y CSS.

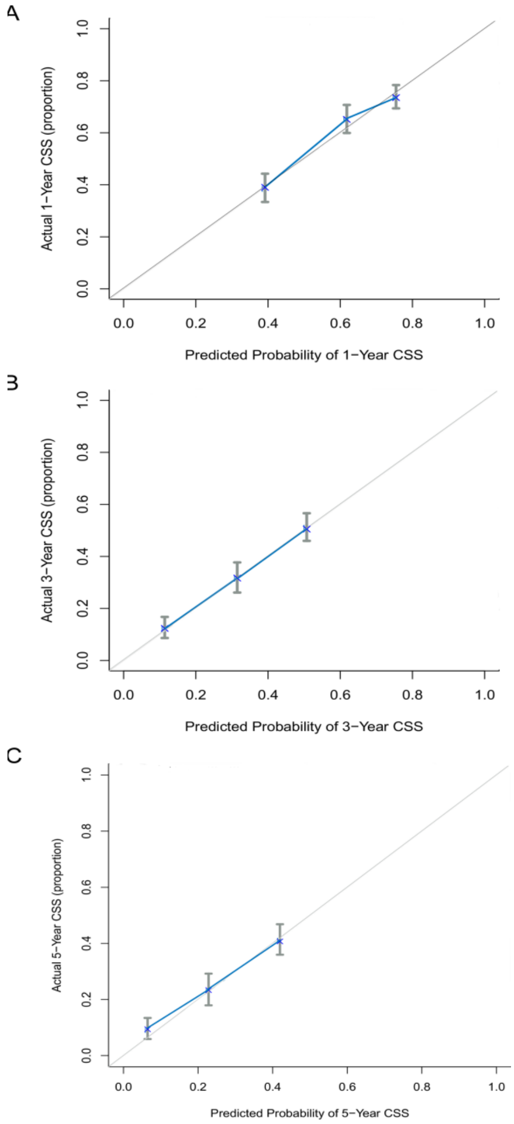

Figure 3. Calibration curves for predicting cancer-specific survival in the primary cohort. A: 1-y CSS; B: 3-y CSS; C: 5-y CSS.

Validation of the predictive accuracy of the nomogram

The predictive power of the established nomogram and AJCC staging system was compared. In the primary cohort, the C-index of our nomogram to predict CSS (0.652, 95% CI 0.630-0.674) was higher than that of the conventional AJCC stage (0.613, 95% CI 0.591-0.635), although this difference was not significant (P=0.187). The C-index was similar in the validation cohort (0.655, 95% CI 0.621-0.689). Additionally, calibration curves were formulated to assess the performance of the nomogram. The calibration curves in the primary cohort showed optimal agreement between prediction and observation in the probability of 1, 3 and 5-y CSS (Figure 3). In the validation cohort, the results also indicated that the nomogram-based prediction was in good agreement with actual observed survival (Figure 4).

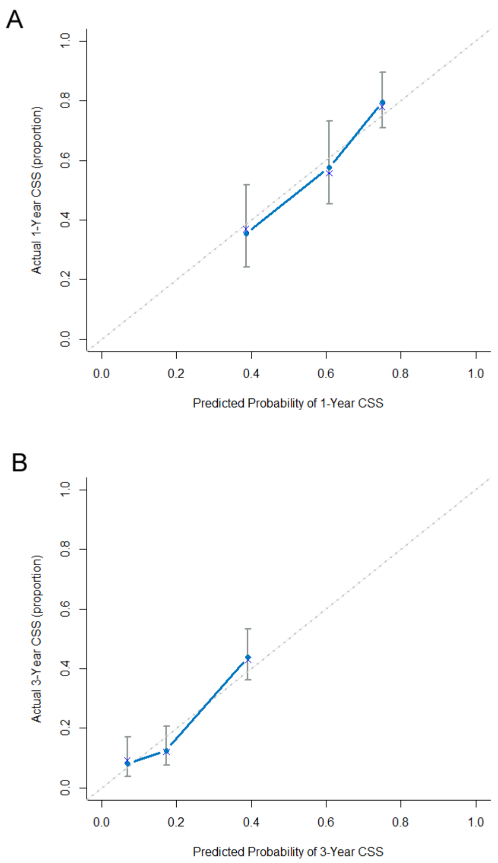

Figure 4. Calibration curves for predicting cancer-specific survival in the validation cohort. A: 1-y CSS; B: 3-y CSS.

Discussion

The concept that advancing age acts as a critical risk factor for cancer has been increasingly highlighted [22,23]. During aging, multiple mechanisms, both intrinsic (accumulation of DNA damage) and extrinsic (decreases in adaptive immunity; age-related pro-tumorigenic inflammatory microenvironment), converge to drive carcinogenesis [9]. Intriguingly, recent studies have also demonstrated that the aged microenvironment can drive cancer metastasis and therapeutic resistance in preclinical models, raising the possibility that aging is involved in cancer metastasis and that aged cancer patients might have poorer prognosis [24,25]. Here, based on the SEER database, we found that aged ICC patients (≥ 65 y) showed poorer short-term and long-term survival than their younger counterparts, especially among patients who did not undergo surgical treatment. Furthermore, by integrating aging and other independent prognostic factors, we established a novel prognostic nomogram for CSS, which demonstrated superior predictive power than the conventional AJCC staging system.

The dismal outcome following surgical resection of ICC is probably multi-factorial, with loco-regional recurrence being the main cause. For this reason, many recent efforts have been devoted to development of clinically relevant prognostic factors for ICC after curative resection. Currently, tumor number, lymph node metastasis, vascular invasion and high preoperative CA19-9 level are all well-established predictive markers for ICC prognosis after curative resection [6,17,26]. However, the prognostic role of aging in ICC after curative resection has remained ambiguous for a long time. Although the prognostic role of aging did not reach statistical significance in several early large cohort studies, it is worth noting that in all of those studies, aging was correlated with better overall survival [6,26-29]. In 2013, results from an international multi-center study and a comprehensive meta-analysis both identified age among the independent clinicopathological parameters predictive of survival after curative resection in ICC [30,31]. Consistently, our study from the SEER database partially supported the prognostic role of old age in ICC patients after curative resection. Considering the small size of the operative group (n=658) compared with the non-operative group (n=1503) in our study, we suggest that other large cohort investigations are still needed to elucidate the prognostic value of aging in ICC patients undergoing curative resection.

Late-stage cases represent a larger percentage of ICC patients who are not amenable to radical resection and have a more dismal outcome, with chemotherapy or radiotherapy being recommended as adjuvant therapy [1]. Intriguingly, in our cohort of non-operative ICC patients, the CSS rates in the elderly group were significantly worse than those in the younger group. Considering the low resectability of ICC, this result is also of clinical relevance, which indicated that the aged non-operative patients were a higher-risk subgroup for cancer progression. All of this evidence points to old age as a bona fide parameter predictive of clinical outcome for ICC after surgical resection and for other therapies.

In light of the emerging role of aging in predicting the CSS of ICC, we support its potential application in optimizing traditional staging models for ICC, such as the AJCC staging system. In recent years, prognostic nomograms were found to be accurate predictive models for cancer patients. Previous prognostic nomograms for ICC were all constructed to predict the OS of ICC after curative resection [6,30,32]. Here, we constructed a novel prognostic nomogram to predict the CSS of all ICC patients irrespective of treatment strategies, which may be helpful for clinical decision-making.

In conclusion, although the prognostic systems for ICC are in a state of evolution with several novel models, our study demonstrated that aging could also provide important prognostic information for ICC patients and further serve as a critical stratification parameter for treatment choice.

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