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Klatskin Tumor: A Population-Based Study of Incidence and Survival

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: Klatskin tumor (KCC) is a rare type of tumor, with an annual incidence rate of no more than 1: 100 000. Because of its rarity, KCC is difficult to investigate. The present study provides new insights into KCC by a using public database.

Material/Methods: We used the Surveillance, Epidemiology, and End Results (SEER) database to conduct the analysis. Klatskin tumor patients were identified and compared with patients that had other kinds of cholangiocarcinomas (OCC). We identified differences between the 2 groups of patients and assessed tumor characteristics. We used Cox regression analysis to identify the prognostic indicators for KCC. The propensity score 1-to-1 matching method was used to compare the survival difference between KCC and OCC.

Result: We extracted data on 26 137 patients diagnosed with cholangiocarcinomas between 1973 and 2014 from the SEER database: 1341 cases were diagnosed with KCC and 24 796 cases were diagnosed with OCC. The number of diagnoses has gradually increased in both groups. There were significant differences in pathology grades, T stage, N stage, M stage, and SEER historic stage between the KCC and OCC groups. Survival analysis showed that the OCC group had better survival compared to the KCC group, both in matched and unmatched cohorts. The Cox regression results showed that older age, higher M stages, and higher pathology grades were associated with worse prognosis for KCC patients.

Conclusions: KCC patients have worse survival compared to OCC patients. Older age, higher M stages, and higher pathology grades were associated with worse survival in KCC patients.

MeSH Keywords: Cholangiocarcinoma • Klatskin's Tumor • SEER Program

Abbreviations: **KCC** – Klatskin tumor; **OCC** – other kinds of cholangiocarcinomas; **SEER** – Surveillance, Epidemiology, and End Results database; **CSS** – cancer-specific survival; **OS** – overall survival; **AJCC** – American Joint Committee on Cancer

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Background

Klatskin tumor (hilar cholangiocarcinoma or central bile duct carcinoma, KCC) is a rare type of tumor, with an annual incidence of no more than 1: 100 000 [1]. It originates from the bifurcation of the extrahepatic bile duct and was first described in 1965 by Gerald Klatskin who reported 15 cases and defined some features in these cholangiocarcinomas [2–4]. Most KCCs are adenocarcinomas with poor differentiation degree, spreading along the duct and nerve sheath [5]. There are some risk factors, including primary sclerosing cholangitis (PSC), liver fluke infection (C. sinensis and Opisthorchis viverrini), and intrahepatic bile duct stones, but most KCCs are sporadic with no obvious predisposing factors [6]. The symptoms are usually fatigue, jaundice, and cachexia, indicating metastatic or advanced tumors. Most patients have biliary symptoms, including painless jaundice. About 10% of patients also simultaneously present with cholangitis [7].

The only curative treatment is a complete surgical resection with histologically negative margins. Current surgical strategies usually include choledochectomy, extended hepatectomy, and portal resection. Due to the local anatomy, the proximal and lateral safety margin R0 resection is a surgery that demands excellent technique [5]. Molina et al. reported that lymph node involvement and metastasis were important prognostic factors. The median survival of inoperable patients is 6 to 12 months, and the most common causes of death are liver failure and septic complications [8].

To investigate KCC was quite difficult in the past because of its rarity in the general population. The present study gives new insights into KCC by using population data in the Surveillance, Epidemiology, and End Results (SEER) database. The aim of our study was to analyze a large sample and to compare the data between patients with KCC and those with other kinds of cholangiocarcinomas (OCC) to clarify the epidemiologic characteristics, frequency, and survival rates patients with this rare malignant tumor.

Material and Methods

We used SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (1973–2014 varying) to conduct the analysis, which contained patient information from 18 cancer registries. Institutional review board (IRB) approval was not needed because no patient identifiers were used. To obtain the necessary data, International Classification of Diseases and Oncology, third edition (ICD-O-3), codes was used. We used histology codes (8162/3) to obtain the KCC data. We also used topography codes corresponding to the bile biliary tract (22.1, 24.0, 24.1, 24.8, and 24.9) to obtain OCC except for KCC and made a comparison. We excluded patients whose first tumor was not biliary duct-derived, and patients for whom the tumor was not histologically confirmed. We report 2000–2014 incidence data (per 100 000 people) adjusted to the standard 2000 population US Census. Cancer-specific survival (CSS) and overall survival (OS) were selected as the endpoints.

Statistical analysis

We used Surveillance Research Program, National Cancer Institute SEER*Stat software (*www.seer.cancer.gov/seerstat*) version 8.3.4 to conduct frequency analysis and extract data, as well as to determine the incidence annual percentage change based on 1-year end-points. Continuous data are shown as means and standard deviations and were compared using the *t* test. We used frequencies and percentages to display the categorical variables and compared them using the chi-square test or Fisher's exact test. Kaplan-Meier method with log-rank test was used to conduct survival analysis. Univariate and multivariate Cox regression were conducted to identify the prognostic indicators for KCC. We conducted propensity score 1-to-1 matching to decrease the selection bias and mimic the randomized controlled trials. We divided patients into a KCC group and an OCC group, and baseline characteristics were entered into the logistic model using nearest-neighbor matching with a stringent caliper of 0.05 [9]. After we generated the matched datasets, we used them to compare the survival difference between KCC and OCC patients. We used SPSS, version 24.0 (SPSS Inc., Chicago, IL) to conduct the analysis, and 2-sided $P<0.05$ was considered statistically significant.

Results

Demographics

In total, 26 137 patients diagnosed with cholangiocarcinomas between 1973 and 2014 were extracted from the SEER database. Among them, 1341 cases were diagnosed with KCC and 24 796 cases were diagnosed with OCC (Table 1). The number of diagnoses has gradually increased in recent years for both Klatskin tumor and other cholangiocarcinomas ($P<0.001$). Males constituted 51.2% of KCC cases and 51.5% of OCC cases, and most patients in both groups were white. Most of the patients in both groups had undergone surgeries (73.4% for KCC and 67.3% for OCC). There was no significant difference in age distribution between the 2 groups of patients ($P=0.095$), but the difference in survival time was obvious ($P<0.001$).

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Table 1. Baseline characteristics of KCC and OCC patients.

Patient characteristics	Klatskin tumor (n=1341)	Other biliary tract malignancies (n=24796)	P value
	No. (%)	No. (%)	
Year of diagnosis			<0.001
2000–2004	278 (20.7)	6992 (28.2)	
2005–2009	424 (31.6)	7869 (31.7)	
2010–2014	639 (47.7)	9935 (40.1)	
Gender			0.866
Male	687 (51.2)	12769 (51.5)	
Female	654 (48.8)	12027 (48.5)	
Race			<0.001
White	1101 (82.1)	19285 (77.8)	
Black	217 (16.2)	1845 (7.4)	
Other	21 (1.6)	3502 (14.1)	
Unknown	2 (0.2)	64 (0.3)	
Treatment			<0.001
No surgery	984 (73.4)	16682 (67.3)	
Surgical treatment	297 (22.1)	7512 (30.3)	
Unknown	60 (4.5)	602 (2.4)	
Age			0.095
Range	19–01	1–117	
Median	71.0	70.0	
Mean	69.7	69.1	
Survival			<0.001
Range	0–119	0–179	
Median	4	6	
Mean	8.4	16.8	

Tumor characteristics and incidence trends

As shown in Table 2, there were significant differences between KCC and OCC groups in pathology grades (P<0.001), T stage (P=0.040), N stage (P<0.001), M stage (P<0.001), and SEER historic stage (P<0.001). There was no obvious difference in tumor size. Between 2000 and 2014, the overall incidence rate trend of KCC was decreasing and the trend for OCC was increasing (Figure 1). The annual percent change (APC) for KCC was –2.962 (P=0.001) and 3.688 for OCC (P<0.001).

Survival analysis

In the original groups, as shown in Figure 2A, 2B, the CSS and OS for the OCC group were significantly better than for the KCC group (P<0.001) and the 1-, 3-, and 5-year CSS rates were higher in OCC patients (Table 3). Then, we stratified patient survival using the 6th AJCC staging system. Figure 3 and Table 3 show that the 6th AJCC staging system performs well in classifying OCC patient survival, but did not perform well in KCC patients. Considering the significant differences of baseline characteristics between the KCC and OCC groups, we conducted 1-to-1 propensity score matching; 1046 patients were selected into a matched group and all baseline characteristics were well matched for further analysis (Table 4). We used the matched group to compare survival between the KCC and OCC groups. As shown in Figure 2C, 2D, the OCC group had better survival than the KCC group (P<0.001).

Finally, we used the original cohort to conduct univariate and multivariate Cox analysis. Gender, year of diagnosis, age, race, pathology grades, and T, N, and M stage were entered into analysis. As shown in Table 5, age, M stage, and pathology grades were brought into the final model. Older age, higher M stages, and higher pathology grades were associated with worse prognosis for KCC patients.

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Table 2. Baseline tumor characteristics of the KCC and OCC patients.

Tumor characteristics	Klatskin tumor (n=1341)	Other biliary tract malignancies (n=24796)	P value
	No. (%)	No. (%)	
Pathological grade			<0.001
G1	53 (4.0)	1538 (6.2)	
G2	227 (16.9)	5111 (20.6)	
G3	223 (16.6)	4006 (16.2)	
G4	14 (1.0)	195 (0.8)	
Gx	824 (61.4)	13946 (56.2)	
T stage			0.040
T0	11 (0.8)	165 (0.7)	
T1	223 (16.6)	4230 (17.1)	
T2	104 (7.8)	2100 (8.5)	
T3	241 (18.0)	4149 (16.7)	
T4	177 (13.2)	2663 (10.7)	
Tx	585 (43.6)	11489 (46.3)	
N stage			<0.001
N0	607 (45.3)	9921 (40.0)	
N1	277 (20.7)	4660 (18.8)	
Nx	457 (34.1)	10215 (41.2)	
M stage			<0.001
M0	582 (43.4)	10810 (43.6)	
M1	368 (27.4)	5525 (22.3)	
Mx	391 (29.2)	8461 (34.1)	
SEER historic stage			<0.001
Localized	277 (20.7)	4440 (17.9)	
Regional	401 (29.9)	8827 (35.6)	
Distant	447 (33.3)	7129 (28.8)	
Unstaged	216 (16.1)	4400 (17.7)	
Size			0.225
Median	3.0	3.0	
Mean	4.29	4.05	
Incidence	0.097	2.526	
APC	–2.962 (P=0.001)	3.688 (P<0.001)	

Discussion

Cholangiocarcinoma is a malignant tumor of epithelial cells, originating from different locations in the biliary tree, and shows markers of biliary cell differentiation. Cholangiocarcinoma is classified according to anatomical location, including intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, and distal cholangiocarcinoma. About 50% of cholangiocarcinomas are perihilar cholangiocarcinoma, 40% of cholangiocarcinomas are distal cholangiocarcinoma, and less than 10% of cholangiocarcinomas are intrahepatic cholangiocarcinoma [10]. The perihilar cholangiocarcinoma is also called Klatskin tumor. Due to its rarity, there has been little progress in many research aspects of Klatskin tumor. Therefore, we conducted the present study using the SEER database to resolve this problem.

Klatskin tumor is an advanced disease that usually occurs in patients over age 60 years, which is similar to our results

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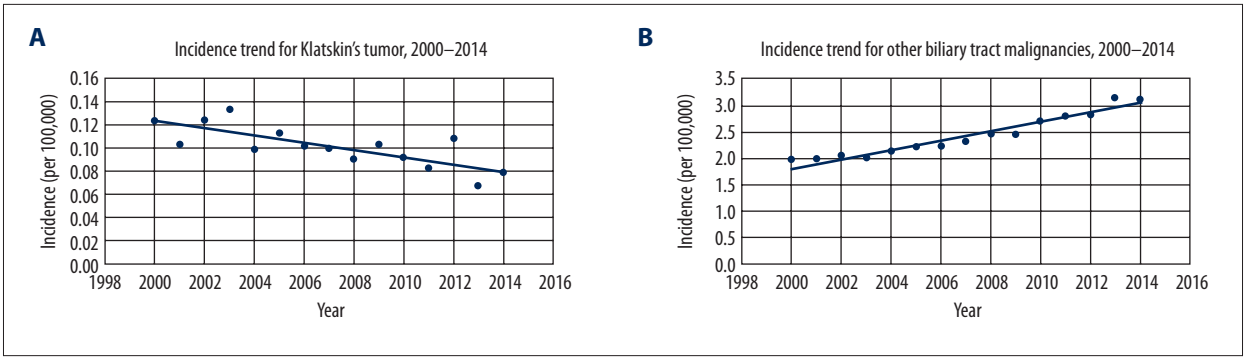

Figure 1. The incidence trend for KCC (**A**) and OCC (**B**).

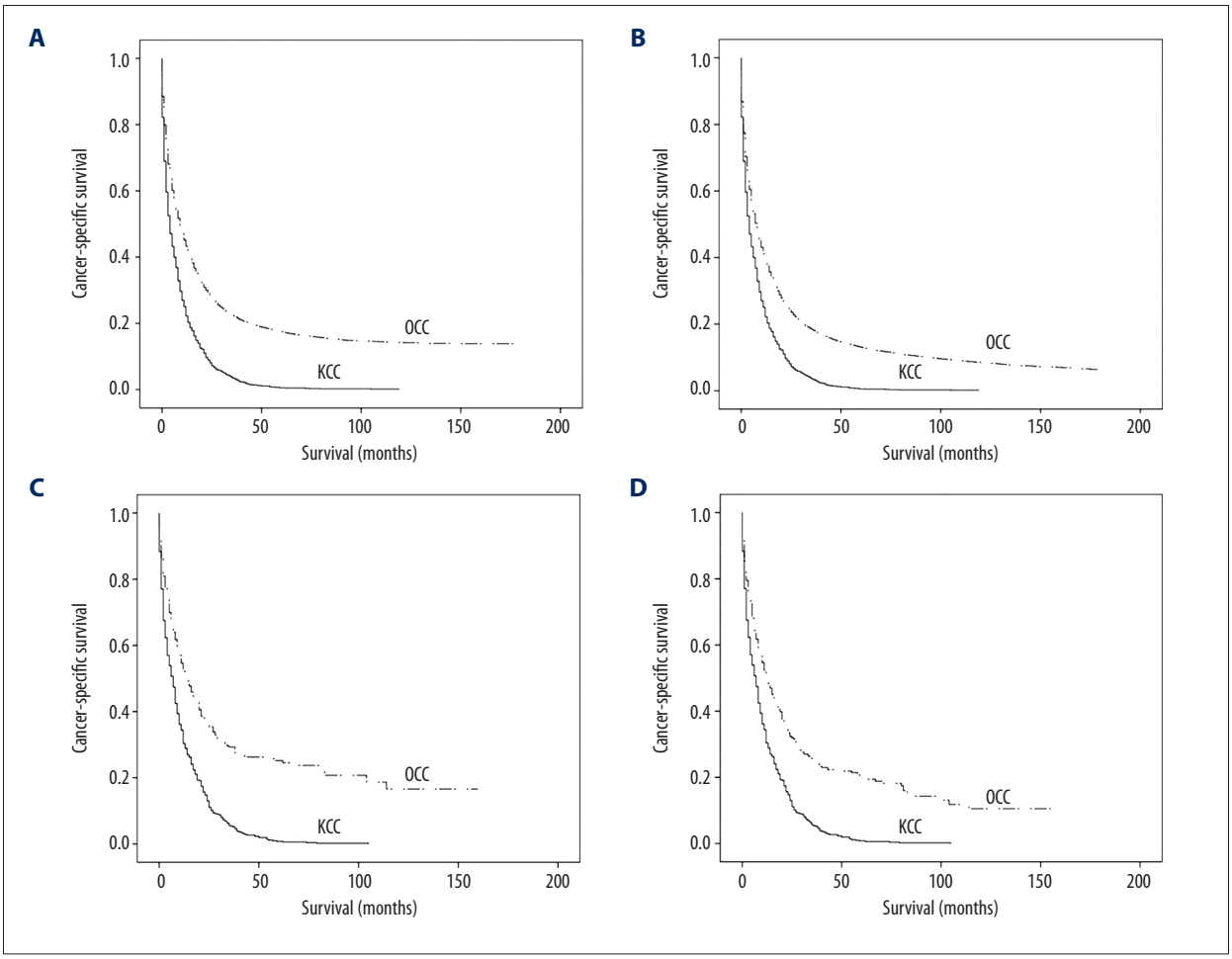

Figure 2. Kaplan-Meier curves for KCC and OCC patients in original and matched cohorts. (**A**) CSS of patients in original group; (**B**) OS of patients in original group; (**C**) CSS of patients in original group; (**D**) OS of patients in matched group.

(median age: 71 years) [11]. Males and females were affected roughly equally in our study, but some studies have shown that males have a slightly higher incidence. Globally, the highest incidence of Klatskin tumor is in Southeast Asia, and the disease is rare in the United States [12].

The cause of Klatskin tumor is still unclear, but many risk factors have been identified. Infection seems to be closely related to the development of cholangiocarcinoma in Asian countries. Liver flukes, including *Clonorchis* trematode and Thai liver fluke, can chronically infect the bile duct and cause the development of cholangiocarcinoma [13]. Other risk factors related to Klatskin tumor include alcoholism, hepatitis B and hepatitis

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Table 3. Survival status stratified by AJCC 6th stage.

	Klatskin tumor				Other biliary tract malignancies			
	n	Survival rates, %			n	Survival rates, %		
		1 year	3 years	5 years		1 year	3 years	5 years
All	1311	22.2	3.4	0.5	24366	43.2	22.2	17.5
6th AJCC stage								
I	207	26.1	3.4	1	3636	64.0	44.8	38.7
II	143	40.6	9.1	0.7	3295	65.3	35.5	27.8
III	163	31.3	3.1	–	2622	54.4	23.0	16.7
IV	367	11.7	0.8	0.3	5514	21.7	4.8	2.3

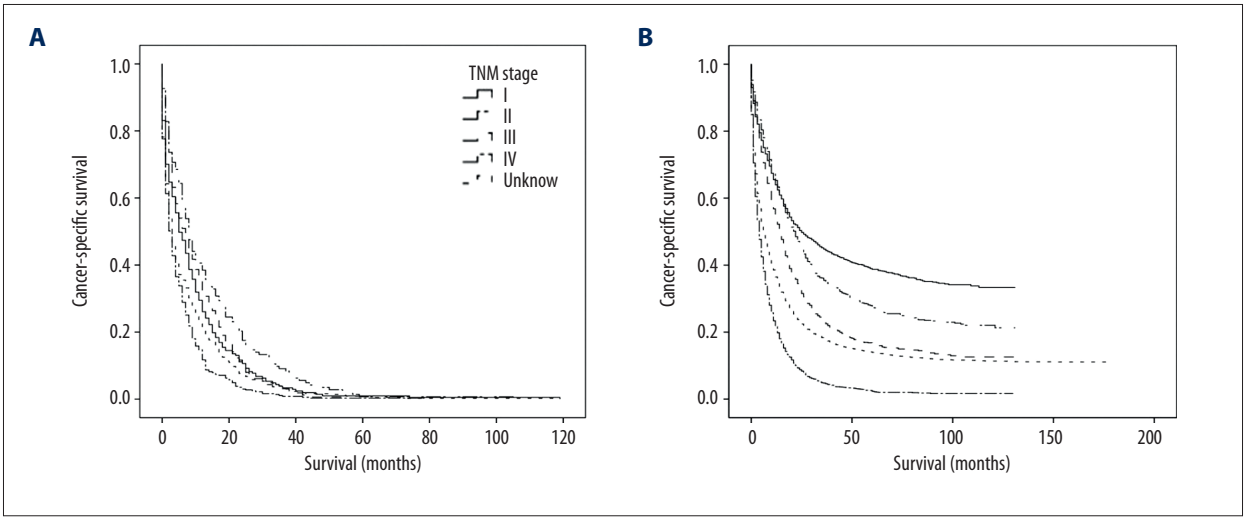

Figure 3. The Kaplan-Meier curves for LSCC patients in different AJCC 6th stages. CSS curves for (**A**) patients in KCC group; (**B**) patients in OCC group.

C viruses, chronic pancreatitis, primary sclerosing cholangitis, choledochal cysts, and cholelithiasis [14].

Current unresectable disease criteria include major portal vein involvement or encapsulation, bilateral spread, bilateral hepatic artery involvement, unilateral liver arterial involvement, and the presence of distant lymph nodes or organ metastases [15]. For patients whose tumors are operable, the current primary treatment is surgery. Several studies have shown that patients undergoing resection have significantly longer survival than in non-surgical patients, and the overall 5-year survival rate for highly selected patients is close to 53%.

The resection for Klatskin tumor involves achieving an R0 surgical margin and then trying to improve the survival time. A number of studies have shown that, compared with R1 resection, the overall survival rate of the R0 surgical margin increased significantly [16].

There are also some other surgical factors and tumor features related to longer survival time after surgery. Studies showed that the presence of lymph node metastasis was associated with poor survival [17,18]. Some case analyses showed that elevated preoperative serum bilirubin, histological tumor type, and tumor differentiation in patients are associated with lower survival rates, although these findings vary from study to study [19–21]. In our analysis, older age, higher M stages, and higher pathology grades were related to the worse prognosis.

To the best of our knowledge, this is the first study to investigate the clinical characteristics of KCC and identify the difference between KCC and OCC. Although we used the SEER database, which contains massive patient data, there are still several deficiencies. It cannot provide the risk factors related to the KCC, and the surgical margin status is not available. Also, the recurrence data and detailed therapeutic methods are not provided. Even with these limitations, our study is the first to use a large public database cohort of KCC to investigate the characteristics of patients and tumors.

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Table 4. Baseline characteristics of the patients in the matched cohort.

	Klatskin tumor	Other biliary tract Malignancies	P value
Year of diagnosis			0.990
2000–2004	77	77	
2005–2009	164	162	
2010–2014	282	284	
Gender			0.620
Male	253	245	
Female	270	278	
Race			0.875
White	441	450	
Black	72	63	
Other	9	9	
Unknown	1	1	
Treatment			0.194
No surgery	302	285	
Surgical treatment	219	238	
Unknown	2	0	
Pathological grade			0.653
G1	18	13	
G2	132	141	
G3	134	146	
G4	6	4	
Gx	233	219	
TNM stage			0.981
I	78	76	
II	110	106	
III	117	121	
IV	124	120	
Unknown	94	100	
T stage			0.995
T0	8	8	
T1	98	94	
T2	76	74	
T3	149	153	
T4	86	82	
Tx	106	112	

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Table 4 continued. Baseline characteristics of the patients in the matched cohort.

	Klatskin tumor	Other biliary tract Malignancies	P value
N stage			0.788
N0	254	243	
N1	177	183	
Nx	92	97	
M stage			833
M0	317	314	
M1	124	120	
Mx	82	89	
SEER historic stage			0.996
Localized	98	96	
Regional	264	268	
Distant	142	140	
Unstaged	19	19	

Table 5. Univariate and multivariate analysis of the effect of different factors on survival outcomes in KCC patients.

	CSS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender				
Female	Reference			
Male	1.01 (0.90–1.12)	0.900		
Year of diagnosis				
2000–2004	Reference			
2005–2009	1.00 (0.85–1.16)	0.947		
2010–2014				
Age at diagnosis				
≤70 years	Reference		Reference	
>70 years	1.33 (1.19–1.48)	<0.001	1.33 (1.19–1.49)	<0.001
Race				
White	Reference			
Black	1.09 (0.94–1.27)	0.233		
Others	1.11 (0.71–1.73)	0.650		
Unknown	0.54 (0.13–2.14)	0.377		
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.03 (0.77–1.40)	0.834	1.07 (0.79–1.45)	0.664

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Table 5 continued. Univariate and multivariate analysis of the effect of different factors on survival outcomes in KCC patients.

	CSS			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Poorly differentiated	1.47 (1.09–1.99)	0.012	1.55 (1.14–2.10)	0.005
Undifferentiated	1.39 (0.77–2.51)	0.277	1.40 (0.78–2.54)	0.259
Unknown	2.01 (1.51–2.66)	<0.001	1.90 (1.43–2.52)	<0.001
T stage				
T0	Reference			
T1	0.94 (0.51–1.72)	0.835		
T2	0.72 (0.39–1.35)	0.306		
T3	1.02 (0.56–1.86)	0.956		
T4	1.43 (0.78–2.62)	0.253		
Unknown	1.19 (0.66–2.17)	0.566		
N stage				
N0	Reference		Reference	
N1	0.80 (0.70–0.93)	0.002	0.88 (0.76–1.02)	0.090
Unknown	1.03 (0.91–1.17)	0.598	1.01 (0.80–1.28)	0.949
M stage				
M0	Reference		Reference	
M1	1.12 (1.05–1.19)	<0.001	1.43 (1.24–1.64)	<0.001
Unknown			1.07 (0.93–1.22)	0.332

Conclusions

KCC patients have worse survival compared to OCC patients. Older age, higher M stages, and higher pathology grades were associated with worse KCC patient survival.

Conflict of interests

None.

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