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Development and Identification of a Nomogram Prognostic Model for Patients with Primary Clear Cell Carcinoma of the Liver

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

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Background: Primary clear cell carcinoma of the liver (PCCCL) is an infrequent variant of primary hepatocellular carcinoma (HCC), we retrospectively performed a large population-based cohort study to elucidate the relationships between demographic, carcinoma- and therapy-specific variables and overall survival (OS).

Material/Methods: The Surveillance, Epidemiology and End Results (SEER) database was queried to extract data on 419 patients with pathologically confirmed PCCCL from 1988 to 2015. A nomogram with good accuracy was formulated to predict long-term survival of PCCCL patients.

Results: The OS for PCCCL patients was 25.6 months (95% confidence interval [CI]: 22.2–29 months), the overall 1-year, 3-year, and 5-year survival rates were 59.5%, 39.3%, and 29.9%, respectively. Log-rank analysis revealed that there was no statistically significant discrepancy in clinical outcome between PCCCL and common-type HCC after propensity-matched analysis. Multivariate Cox analysis confirmed that larger lesions (>96 mm), distant metastases and elevated alpha-fetoprotein (AFP) levels were independent prognostic factors for undesirable outcome. Conversely, surgery was an independent protective factor (hazard ratio [HR]=0.23, 95% CI 0.17–0.31), which significantly boosted OS by virtually 35 months (47.3 months versus 12.7 months, $P<0.001$). Radiotherapy or chemotherapy was not associated with OS for PCCCL patients (both $P>0.05$). The nomogram incorporated 4 independent prognostic factors and its concordance index for predicting survival was 0.761.

Conclusions: The prognosis of PCCCL resembled that of common-type HCC. Larger lesions, distant metastases, and enhanced AFP levels were associated with unsatisfactory prognosis. Surgery fulfill favorable prognosis while radiotherapy or chemotherapy exerted no significant effects on survival.

MeSH Keywords: **Adenocarcinoma, Clear Cell • Carcinoma, Hepatocellular • Nomograms • Prognosis • SEER Program**

Abbreviations: **PCCCL** – primary clear cell carcinoma of the liver; **HCC** – hepatocellular carcinoma; **SEER** – Surveillance, Epidemiology and End Results; **OS** – overall survival; **CI** – confidence interval; **AFP** – alpha-fetoprotein; **HR** – hazard ratio; **HCV** – hepatitis C virus; **PSM** – propensity-score matching; **C-index** – concordance index; **EMA** – epithelial membrane antigen; **TACE** – transcatheter arterial chemoembolization

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Background

Clear cell carcinoma prevailingly occurs in the ovary [1] and kidney [2], however, it has been rarely reported in additional locations like the lungs [3], liver [4]. Primary clear cell carcinoma of the liver (PCCCL) is an uncommon pathological subtype of primary hepatocellular carcinoma (HCC), with insufficient comprehension of its clinicopathological characteristics and prognostic factors on account of merely few case reports or clinical cohort studies from small, single institution. PCCCL is commonly endowed with a low-grade malignancy and distinct histopathological profile [5]. It is pathologically characterized by prominent cytoplasmic accumulation of abundant glycogen or/and lipid that are dissolved during hematoxylin and eosin staining, thereby merely showing a clear cytoplasm [6]. PCCCL can develop at any age, with a peak incidence in male patients aging from 50 to 60 years old [4].

The most pressing risk factor for PCCCL is hepatitis C virus (HCV) infection, while PCCCL is not significantly correlative with alcoholism, hepatitis B virus infection, nonalcoholic steatohepatitis, hemochromatosis, and autoimmune liver disease [7]. The onset and clinical manifestations of PCCCL basically resemble those of HCC, characterized by certain unspecific symptoms, such as right upper quadrant pain, fatigue, and anorexia and generally concomitant with medical history of viral hepatitis and cirrhosis as well as elevated alpha-fetoprotein (AFP) levels. Therefore, early detection of PCCCL is difficult. Frequently, representative imaging characteristics of PCCCL are inchoate enhancement and fast washout of contrast medium on dynamic contrast scans, and existence of portal vein thrombus or phyma rupture [8].

Notably, studies have shown that PCCCL cases account for 0.4% to 37% of all HCCs, and these variable reports are primarily attributable to the inconsistency of pathologically diagnostic criteria for such tumor. More precisely, Lai et al. indicated that PCCCL could be diagnosed even though clear cells proportion was less than 30% [9]. In contrast, another study implicated that the definite diagnosis of PCCCL should be made under the condition that clear cells proportion represented over 30% [10]. The majority of physicians support that when clear cells occupy more than 50% through histological examination, it should be diagnosed as PCCCL [11–14]. And PCCCL merely accounts for 2.2–6.7% of all HCC in a large proportion of studies through utilizing this criterion [11,15]. Indeed, Liu et al. reported that PCCCL merely occupied approximately 3.5% of primary HCC in their hospital [15]. Notably, PCCCL is stuck in a diagnostic predicament without the assistance of immunohistochemical staining, as cytokeratin profiling and evidence of immunoreactivity for AFP and epithelial membrane antigen (EMA) are presumably a beneficial criterion to differentiate PCCCL from metastatic clear cell carcinomas originated from adrenals, kidneys, ovaries, and additional tissues [16].

To date, surgical intervention is considered to be the optimal treatment modality for PCCCL. Most patients receiving surgical resection have a desirable curative effect and a promising long-term survival rate.

In accordance with the World Health Organization (WHO) International Classification of Diseases for Oncology, version 3 (ICD-O.3), PCCCL is recognized as one of the subtypes of primary HCC [17]. Because of its rarity, a large number of previous studies are centralized case reports or series or small cohort study from single institutions. Currently, its clinicopathological and prognostic features are not fully elucidated in the literature. Therefore, in our study, we retrospectively analyzed the demographic and clinicopathological information of 419 PCCCL patients registered in the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 2015, which was instrumental in unveiling the prognostic factors influencing its survival.

Material and Methods

Data source

Original information was excavated from the SEER database supported by the National Cancer Institute. The SEER program was comprised of 18 population-based cancer registries, covering ~28% of the US population. The SEER program is publicly accessible, which merely contains anonymized patient information. Thus, our study was exempt from the ethical review or the patient consent.

Patient enrollment

We incorporated all patients with the histologically diagnosed 8174/3 (hepatocellular carcinoma, clear cell type) based on the ICD-O-3/WHO 2008, ranging from 1988 to 2015 registered in the SEER database. Only patients >18 years of age with PCCCL as their "one primary only" tumor were incorporated in the study dataset. Moreover, records with insufficient information concerning survival, histology, or staging data (including tumor size and extension) were eliminated. We stratified total cohort based upon both demographic and clinicopathological characteristics such as age at diagnosis, gender, ethnicity, marital status at diagnosis, pathological differentiation grade, AFP interpretation, fibrosis, tumor size, lymph node invasion, distant metastases, SEER summary stage, TNM stage, and whether surgery, chemotherapy or radiotherapy were received.

Statistical analysis

We downloaded all the data from SEER*Stat Software version 8.3.5 (National Cancer Institute, Bethesda, MD, USA). Statistical

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Table 1. Characteristics of 419 patients with PCCCL.

Characteristics	Number	Percent
Total	419	
Age (years)	64.4±12.3	
≤60	165	31.8%
61–70	117	22.5%
>70	137	26.4%
Gender		
Female	151	36.0%
Male	268	64.0%
Race		
White	275	65.6%
Black	48	11.5%
Unknown	96	22.9%
Marital status		
Married	332	79.2%
Single	73	17.4%
Unknown	14	3.3%
Grade		
Well; I	63	15.0%
Moderately; II	113	27.0%
Poorly; III	38	9.1%
Undifferentiated; IV	6	1.4%
Unknown	199	47.5%
Tumor stage		
T1	168	40.1%
T2	60	14.3%
T3	74	17.7%
T4	94	22.4%
Unknown	23	5.5%
Lymph node metastases		
N0	326	77.8%
N1	19	4.5%
Unknown	74	17.7%
Distant metastases		
M0	325	77.6%
M1	74	17.7%
Unknown	20	4.8%
Summary stage		
Localized	226	53.9%
Regional	99	23.6%
Distance	74	17.7%
Unknown	20	4.8%
TNM stage		
I	136	32.5%
II	51	12.2%
III	91	21.7%
IV	74	17.7%
Unknown	67	16.0%
AFP level		
Elevated	191	45.6%
Normal	62	14.8%
Unknown	166	39.6%
Fibrosis score		
0–4	42	10.0%
5–6	45	10.7%
Unknown	332	79.2%
Surgery type		
Local ablation	28	17.8%
Resection	115	73.2%
Transplant	13	8.3%
Surgery with unknown type	1	0.6%
Surgery		
No	259	61.8%
Yes	157	37.5%
Unknown	3	0.7%
Radiation		
No	393	93.8%
Yes	26	6.2%
Chemotherapy		
No	294	70.2%
Yes	125	29.8%

PCCCL – primary clear cell carcinoma of the liver; AFP – alpha-fetoprotein.

analysis was implemented by the software SPSS 22.0 (IBM Corporation, Armonk, NY, USA). A Student's *t*-test was applied to make a contrast of continuous variables and a chi-squared test was utilized to compare categorical variables. The Kaplan-Meier approach was utilized to estimate survival probabilities and a log-rank test was applied to evaluate significant differences in overall survival (OS) stratified by respective covariate. Cox regression analysis was utilized to analyze the correlations between

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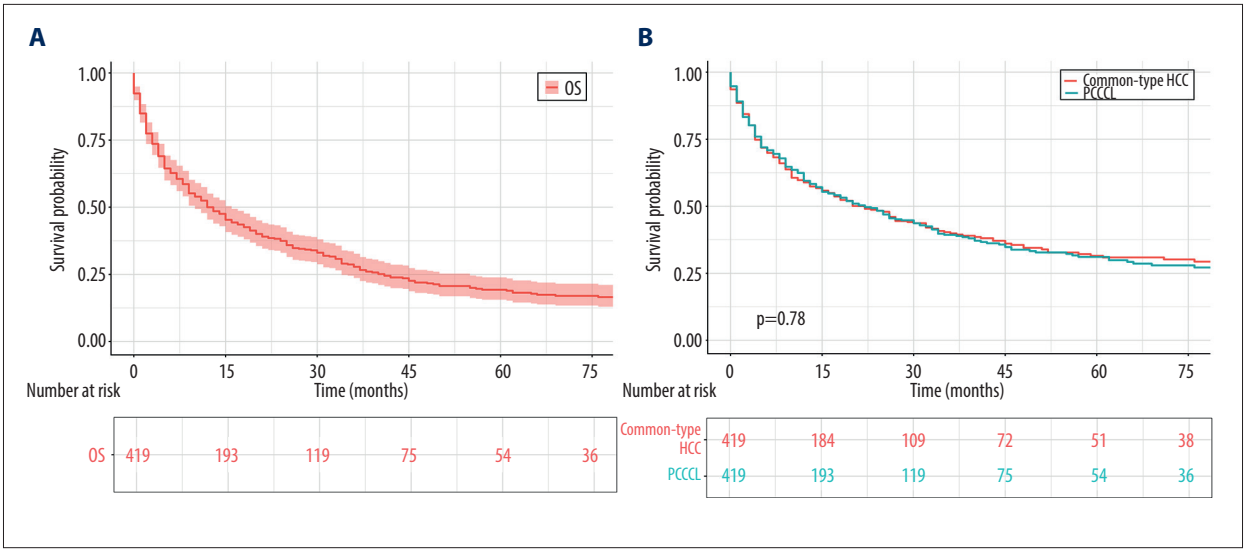

Figure 1. OS for patients with PCCCL. (**A**) OS for 419 patients with PCCCL. (**B**) OS comparison between PCCCL and common type. OS – overall survival; PCCCL – primary clear cell carcinoma of the liver; HCC – hepatocellular carcinoma; PSM – propensity-score matching.

prognostic factors and OS or CSS. We carried out a propensity-score matching (PSM) analysis at a 1: 1 ratio between PCCCL patients and patients pathologically confirmed common-type HCC over the same time period from the SEER database, which modulated the differences between PCCCL and common-type HCC group to compare their prognoses. X-tile software was applied to resolve the optimal cutoff levels of prognostic factors and R language 3.5.3 Software with the rms and survival packages was used to determine the prognostic nomogram, concordance index (C-index), and calibration curve. Two tailed $P<0.05$ was defined to be statistically significant.

Results

Patient characteristics

Our data consisted of a total of 419 qualified patients with PCCCL. Demographic and clinicopathological characteristics of such patients are depicted in Table 1. The number of patients who underwent cancer-oriented surgery was 157 patients (37.5%) in the PCCCL group. Chemotherapy was performed for 29.8% of cases, Supplementary Table 1 shows that younger PCCCL patients with larger or remotely metastatic lesions and elevated AFP levels as well as advanced disease stage were prone to receive chemotherapy. Additionally, patients managed by some form of radiotherapy merely accounted for 6.2% of patients. Analogously, as is shown in Supplementary Table 2, PCCCL patients who were administered with radiotherapy were characterized by larger or metastatic lesions, advanced disease stage and increased AFP levels, compared with those without radiation.

Patient survival

The mean survival time of such PCCCL patients was 25.6 months (95% confidence interval [CI] 22.2–29) (Figure 1A, Table 2). The overall 1-year, 3-year, and 5-year survival probability was 59.5%, 39.3%, and 29.9%, respectively (Table 3). In an attempt to explore the prognostic difference between PCCCL patients and common-type HCC patients, 419 PCCCL patients were matched with 419 patients who were pathologically diagnosed common-type HCC ranging from 1988 to 2015 (1: 1) in the SEER database. As was revealed in Supplementary Table 3, there were no statistically significant discrepancies in clinical characteristics after PSM analysis. Concerning clinically prognostic outcomes at PCCCL patients versus their counterparts with common-type HCC, survival curves and log-rank analysis demonstrated no statistically significant difference (Figure 1B).

OS analysis stratified by clinical features was revealed in Table 2. The OS of patients was not correlated with age (Supplementary Figure 1A). Based on SEER summary stage, patients with more advanced disease stage were endowed with a much more unfavorable prognosis, compared with those with localized or regional disease (Supplementary Figure 1B). Indeed, the 3-year survival rate for patients with localized and regional lesions was 53.3% and 27.3%, respectively, compared with merely 6.1% for patients with distant lesions (Table 3). Analogously, the 1-year and 3-year survival rates for patients with TNM I, II, and III stage were 79.8%, 76.1%, 56.5%, and 64.7%, 54.6%, 19.9%, respectively, compared with merely 22.4% and 9.2% in patients with IV stage disease (Table 3, Figure 2A). Predictably, both lymph node involvement and remotely metastatic lesions in PCCCL patients were intimately associated with

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Table 2. Overall survival stratified by clinical features and univariate Cox proportional hazard analyses for PCCCL patients.

Variables	Mean survival months	95% CI	Univariate analysis	
			HR [95%CI]	P-value
Total	25.6	22.2–29		
Age (years)				
≤60	27.7	21.6–33.8	Ref	
61–70	30.5	23.6–37.5	0.93 (0.68–1.27)	0.665
>70	18.8	14.5–23.2	1.22 (0.9–1.64)	0.200
Gender				
Female	33.1	22.5–33.1	Ref	
Male	36.6	20–28.8	1.04 (0.8–1.34)	0.793
Race				
White	25.6	21.4–29.9	Ref	
Black	21.3	12.1–30.6	1.14 (0.77–1.69)	0.517
Marital status				
Married	27.1	23.1–31.1	Ref	
Single	19.6	13.4–25.8	1.33 (0.97–1.83)	0.079
Grade				
Well	31.6	22.3–40.8	Ref	
Moderately	31.3	24.8–37.8	0.82 (0.55–1.24)	0.358
Poor and undifferentiated	34.5	20.5–48.5	0.96 (0.58–1.59)	0.872
Tumor stage				
T1	36.9	30.5–43.3	Ref	
T2	32.8	22.3–43.3	1.08 (0.7–1.68)	0.723
T3	12.6	8.7–16.5	3.2 (2.25–4.56)	<0.001
T4	14.1	9.4–18.8	3.01 (2.16–4.19)	<0.001
Tumor size				
≤37 mm	49.2	39.7–58.7	Ref	
37–96 mm	28.7	23.1–34.4	2.7 (1.79–4.12)	<0.001
>96 mm	15.1	10.1–20.1	5.28 (3.37–8.28)	<0.001
Lymph node metastases				
N0	28.4	24.4–32.4	Ref	
N1	8.1	3.8–12.3	2.63 (1.51–4.58)	<0.001
Distant metastases				
M0	30.4	26.2–34.6	Ref	
M1	7.7	5.1–10.3	3.25 (2.38–4.45)	<0.001

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Table 2 continued. Overall survival stratified by clinical features and univariate Cox proportional hazard analyses for PCCCL patients.

Variables	Mean survival months	95% CI	Univariate analysis	
			HR [95%CI]	P-value
Summary stage				
Localized	35.7	30.5–41	Ref	
Regional	18.3	12.4–24.2	2.11 (1.55–2.88)	<0.001
Distance	7.7	5.1–10.3	4.17 (2.98–5.84)	<0.001
TNM stage				
I	39.9	32.9–46.9	Ref	
II	35.7	23.7–47.7	1.04 (0.62–1.73)	0.882
III	17.4	12.3–22.5	3.03 (2.11–4.36)	<0.001
IV	7.7	5.1–10.3	5.73 (3.88–8.46)	<0.001
AFP level				
Elevated	22.3	17.8–26.7	Ref	
Normal	31.9	23.9–39.9	0.51 (0.34–0.78)	<0.001
Fibrosis score				
0–4	28.2	20.3–36.2		
5–6	33.6	21.7–45.4	1.09 (0.61–1.95)	0.790
Surgery type				
Local ablation	33	22.8–43.3	Ref	
Resection	45.2	37.4–53.1	0.99 (05–1.97)	0.980
Transplant	100.2	65.0–135.4	0.1 (0.01–0.77)	0.02
Surgery				
No	12.7	10.3–15	Ref	
Yes	47.3	40.3–54.4	0.23 (0.17–0.31)	<0.001
Radiation				
No	26.3	22.7–29.9	Ref	
Yes	15.7	9.2–22.3	1.4 (0.87–2.27)	0.169
Chemotherapy				
No	26.1	21.7–30.4	Ref	
Yes	24.6	19.3–29.8	1.11 (0.85–1.45)	0.441

PCCCL – primary clear cell carcinoma of the liver; AFP – alpha-fetoprotein; CI – confidence interval; HR – hazard ratio.

adverse clinical outcomes (Figure 2B, 2C). Enhanced levels of AFP were correlated with significantly diminished mean survival time (22.3 months versus 31.9 months, $P<0.01$) (Figure 2D). Unexpectedly, the outcome of patients with well or moderately pathologically differentiated tumor was not better than those with poorly differentiated or undifferentiated tumor (Supplementary Figure 1C), which is deserved to be further discussed. Furthermore, liver fibrosis imposed no significant effect on OS (Supplementary Figure 1D).

Additionally, cancer-targeted surgery was capable of significantly prolonging survival time and improving clinical effects

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Table 3. 1-year, 3-year, and 5-year survival rates stratified by clinical features for PCCCL patients.

Characteristics	Cancer specific survival					
	1-years survival	95% CI	3-years survival	95% CI	5-years survival	95% CI
Total	0.595	0.55–0.65	0.393	0.34–0.45	0.299	0.25–0.36
Age (years)						
≤60	0.565	0.49–0.65	0.417	0.34–0.51	0.348	0.27–0.45
61–70	0.656	0.57–0.75	0.434	0.35–0.55	0.327	0.24–0.45
>70	0.574	0.49–0.67	0.312	0.23–0.42	0.219	0.14–0.35
Gender						
Female	0.646	0.57–0.73	0.377	0.3–0.47	0.293	0.22–0.39
Male	0.565	0.51–0.63	0.408	0.35–0.48	0.304	0.24–0.39
Race						
White	0.591	0.53–0.66	0.383	0.32–0.46	0.293	0.23–0.37
Black	0.468	0.34–0.65	0.348	0.23–0.54	\	\
Marital status						
Married	0.659	0.6–0.73	0.460	0.39–0.54	0.395	0.33–0.48
Single	0.499	0.42–0.59	0.279	0.21–0.37	0.161	0.1–0.26
Grade						
Well	0.654	0.55–0.79	0.450	0.33–0.61	0.323	0.21–0.51
Moderately	0.720	0.64–0.81	0.499	0.4–0.62	0.393	0.3–0.52
Poor and undifferentiated	0.725	0.6–0.88	0.356	0.23–0.55	\	\
Tumor stage						
T1	0.746	0.68–0.82	0.588	0.51–0.68	0.47	0.39–0.57
T2	0.706	0.59–0.84	0.470	0.34–0.65	\	\
T3	0.422	0.32–0.57	0.150	0.08–0.29	0.0501	0.01–0.19
T4	0.400	0.31–0.52	0.170	0.1–0.29	0.0969	0.04–0.26
Tumor size						
≤37 mm	0.928	0.87–0.99	0.781	0.69–0.88	0.633	0.52–0.77
37–96 mm	0.646	0.57–0.73	0.402	0.32–0.5	0.281	0.21–0.38
>96 mm	0.397	0.3–0.53	0.147	0.08–0.28	\	\
Lymph node metastases						
N0	0.659	0.61–0.72	0.442	0.39–0.51	0.34	0.28–0.41
N1	0.240	0.1–0.56	\	\	\	\
Distant metastases						
M0	0.672	0.62–0.73	0.460	0.4–0.53	0.354	0.3–0.43
M1	0.242	0.16–0.38	0.061	0.02–0.2	\	\

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Table 3 continued. 1-year, 3-year, and 5-year survival rates stratified by clinical features for PCCCL patients.

Characteristics	Cancer specific survival					
	1-years survival	95% CI	3-years survival	95% CI	5-years survival	95% CI
Summary stage						
Localized	0.741	0.68–0.8	0.533	0.47–0.61	0.425	0.35–0.51
Regional	0.498	0.4–0.62	0.273	0.19–0.4	0.172	0.1–0.31
Distance	0.224	0.14–0.36	0.061	0.02–0.2	\	\
TNM stage						
I	0.798	0.73–0.87	0.647	0.56–0.74	0.516	0.42–0.63
II	0.761	0.65–0.9	0.546	0.4–0.74	\	\
III	0.565	0.47–0.69	0.199	0.12–0.33	0.083	0.03–0.22
IV	0.224	0.14–0.36	0.092	0.04–0.22	\	\
AFP level						
Elevated	0.535	0.47–0.62	0.315	0.25–0.4	0.272	0.21–0.36
Normal	0.803	0.7–0.92	0.612	0.48–0.78	0.386	0.25–0.61
Surgery type						
Local ablation	0.841	0.71–1	0.725	0.55–0.95	\	\
Resection	0.854	0.79–0.93	0.627	0.53–0.74	0.481	0.38–0.61
Transplant	0.873	0.75–1	\	\	\	\
Surgery (Y/N)						
No	0.430	0.37–0.5	0.192	0.14–0.26	0.1176	0.07–0.19
Yes	0.850	0.79–0.91	0.681	0.61–0.77	0.573	0.49–0.67
Radiation						
No	0.600	0.55–0.65	0.403	0.35–0.46	0.316	0.26–0.38
Yes	0.523	0.36–0.76	\	\	\	\
Chemotherapy						
No	0.562	0.51–0.63	0.434	0.38–0.5	0.349	0.29–0.42
Yes	0.667	0.59–0.76	0.310	0.23–0.42	0.234	0.16–0.35

PCCCL – primary clear cell carcinoma of the liver.

(Figure 3A). The OS was 47.3 months for patients administered with surgical procedures, which remarkably exceeded the 12.7 months OS of those who did not receive surgery ($P<0.001$). We also utilized survival curves to compare the efficacy of different surgical categories. As a whole, patients who received a hepatic transplant had a much more satisfactory prognosis than those who underwent local ablation or resection ($P<0.01$ for both) (Table 2, Figure 3D). To eliminate several confounding factors, we performed PSM analysis and thus made two conclusions. That is, patients who received radiotherapy showed no statistically significant differences in OS compared with those without radiotherapy (Figure 3B). Similarly, no significant relationship between chemotherapy and survival benefits was revealed (Figure 3C).

Univariate and multivariate Cox proportional hazard analyses

Prognostic factors for OS of PCCCL are depicted in Tables 2 and 4. For the univariate analysis (Table 2), large lesion size,

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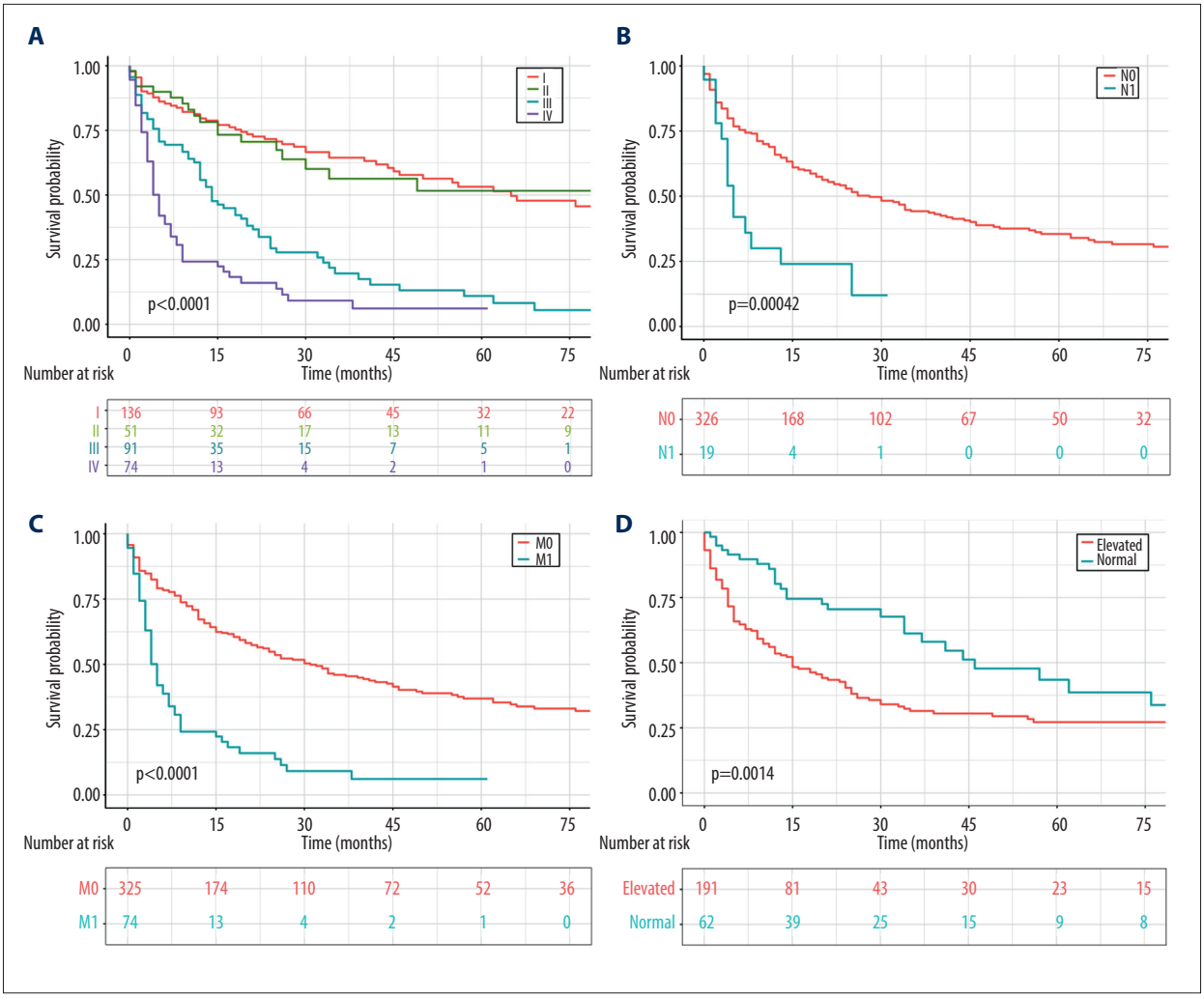

Figure 2. OS for patients with PCCCL stratified by (**A**) different TNM stages. (**B**) Lymph node metastases. (**C**) Distant metastases. (**D**) AFP levels. OS – overall survival; PCCCL – primary clear cell carcinoma of the liver; AFP – alpha-fetoprotein.

lymph node invasion, and remotely metastatic lesions, more advanced TNM stage and SEER stage as well as elevated AFP levels were the risk factors associated with unfavorable prognosis, in contrast, to confer surgical treatment to patients had the capacity to effectively boost OS (P<0.05 for all). In addition to TNM stage and SEER stage, additional aforementioned univariate analysis was included in the multivariate Cox analysis. This is because both stages overlapped with tumor size, lymph node invasion, and distant metastases [18]. As was revealed in multivariate Cox analysis (Table 4), larger or remotely metastatic lesions in conjunction with increased AFP levels were all independent adverse prognostic factors for PCCCL (P<0.05 for all). Conversely, surgical intervention was sufficient to diminish the risk of death in contrast to non-surgical treatment (HR=0.23, 95% CI 0.17–0.31, P<0.001), indicating that surgical treatment was an independent protective factor for enhanced OS.

Specifically, larger lesions (>96 mm) exerted a negative impact on the survival time of PCCCL patients (Figure 4, Table 2). Moreover, X-tile program demonstrated that 37 mm and 96 mm were the optimal cut-points to predict prognosis for tumor size (Supplementary Figure 2). In terms of the optimal cut-points, incorporated PCCCL patients could be classified into 3 groups which displayed statistically significant differences in size-associated OS via the Kaplan-Meier curve analysis.

Prognostic nomogram for PCCCL

In an attempt to predict long-term survival of PCCCL patients, a nomogram was further formulated by incorporating all significant independent indicators for OS identified by the multivariate analyses. As was illustrated in Figure 5, surgery and tumor size made the greatest contributions to clinical prognosis, followed by metastasis category and AFP levels. The C-index for OS prediction was 0.761, and thereby the predictive accuracy

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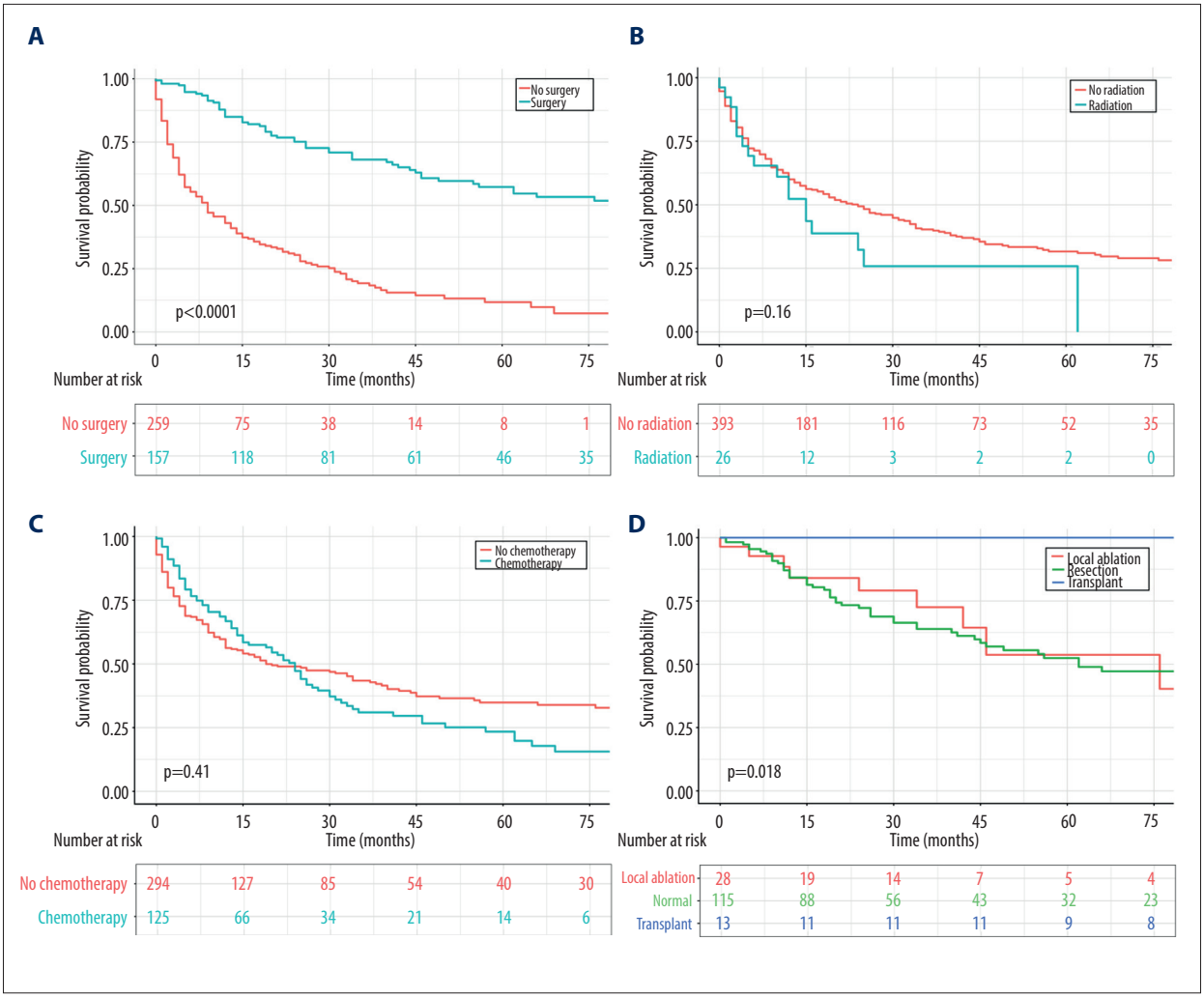

Figure 3. OS for patients with PCCCL stratified by (**A**) surgery. (**B**) Radiation. (**C**) Chemotherapy. (**D**) Different surgical strategies. OS – overall survival; PCCCL – primary clear cell carcinoma of the liver.

of such nomogram was relatively satisfactory. The calibration curves for the OS probability of 1-year, 3-year or 5-year in PCCCL patients cohort displayed an optimal consistency between the prediction via nomogram and practical surveillance (Supplementary Figure 3).

Discussion

PCCCL is a specific and uncommon histological type of HCC, characterized with clear cells embracing glycogen decorated in tubular, papillary, and solid designs [19], whose low incidence in clinical practice has imposed restrictions on our comprehensive understanding of its clinicopathological and prognostic characteristics. In our study, we depicted the clinicopathological features and demonstrated factors influencing OS of 419 PCCCL patients extracted from the SEER database from 1988 to 2015. Additionally, we formulated a prognostic nomogram with satisfactory accuracy for intuitively predicting 1-year, 3-year, and 5-year survival rate of PCCCL patients.

Our study revealed that the age of patients diagnosed with PCCCL ranged from 52 to 76 years old and a large proportion of patients included in the overall cohort were white (65.6%, 275 of 419), which was roughly consistent to the results of the Jernigan et al. study [20]. There was a male preponderance collectively, accounting for 64.0% of total patients, which was a little lower than 69.6% reported in a literature review [21]. Patients had larger tumor size (>96 mm) in the present study in comparison with the previous report representing a tumor diameter of 50 mm, which was correlated with more aggressive PCCCL, respectively [22]. Of patients with PCCCL in the cohort with recorded pathological differentiation grade, tumor with moderate differentiation occupied a maximal proportion (27.0%, 113 of 419), which corresponded to the description in additional studies [4,16,20]. Of those who have

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Table 4. Multivariate Cox proportional hazard analyses of clinical features for overall survival rates in PCCCL patients.

Variables	Multivariate analysis	
	HR [95% CI]	P-value
Tumor size		
≤37 mm	Ref	
37–96 mm	2.54 (1.66–3.89)	<0.001
>96 mm	4.56 (2.86–7.29)	<0.001
Lymph node metastases		
N0	Ref	
N1	1.32 (0.73–2.37)	0.361
Distant metastases		
M0	Ref	
M1	1.45 (1.02–2.06)	0.038
AFP level		
Elevated	Ref	
Normal	0.57 (0.37–0.88)	0.010
Surgery		
No	Ref	
Yes	0.29 (0.21–0.4)	<0.001

PCCCL – primary clear cell carcinoma of the liver; AFP – alpha-fetoprotein; CI – confidence interval; HR – hazard ratio.

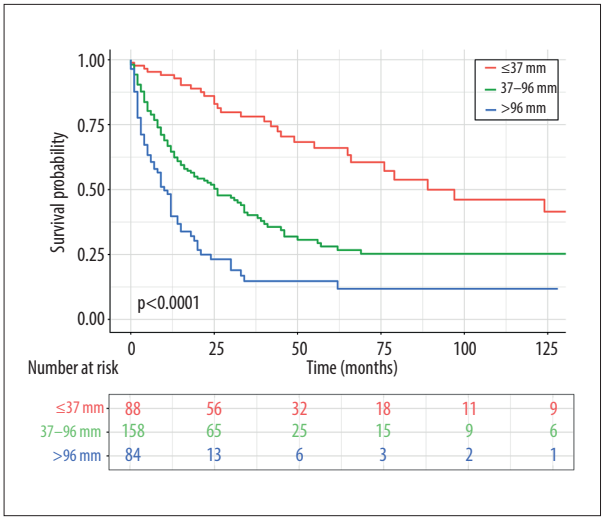

Figure 4. OS for patients with PCCCL stratified by tumor size. OS – overall survival; PCCCL – primary clear cell carcinoma of the liver.

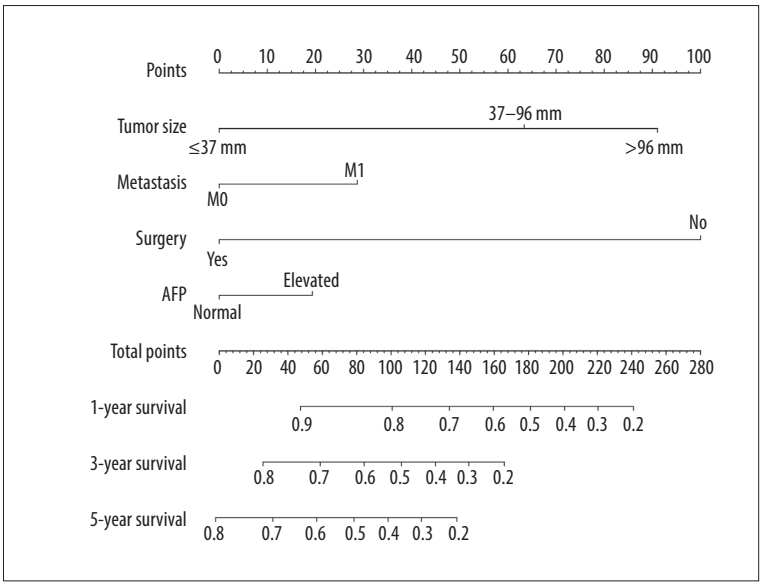

Figure 5. Prognostic nomogram estimated by clinical features for the overall 1-year, 3-year, and 5-year survival rate in PCCCL patients. PCCCL – primary clear cell carcinoma of the liver.

undergone lymph node examinations, lymph node metastases were not usual, representing merely 4.5%, which was also reflected in the TNM pathologic stage, with more likely to be stage I or II, indicating the relatively indolent biology of PCCCL. Accumulating evidence from previous sporadic cases also supported the notion that the majority of PCCCL cases were moderately differentiated, concomitant with comparatively low metastatic potential [4,20,23]. However, a retrospective clinical study showed that up to 18.75% of patients displayed lymph node metastasis and thus 65.6% of them were pathologically diagnosed at TNM stage III or IV through analyzing 64 patients with PCCCL in their hospital [5]. A large

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proportion of patients with PCCCL were accompanied by elevated AFP levels, which were in accordance with additional researches results [4,7,23]. Notably, severe hepatic fibrosis, classically considered as one of indicators of liver inflammation, did not account for a higher proportion in PCCCL patients. Nevertheless, some previous studies revealed that the majority of patients with PCCCL were primarily on the basis of hepatic cirrhosis that was independent risk factors for OS of PCCCL [7,8,23,24].

In the current report, there was no statistically significant discrepancy in prognosis between PCCCL patients and those with common-type HCC. Nevertheless, the prognosis of PCCCL patients is being debated. Multiple studies showed that PCCCL had a more favorable prognosis than additional HCC [5,9,25,26]. A study demonstrated that the clinical outcome seemed to be better in PCCCL patients than their common-type counterparts, and the survival time enhanced with an accumulating apportion of clear cells [9]. Oppositely, some studies revealed that the prognosis of PCCCL patients was analogous to that of those with common-type HCC and potentially even worse [12–14]. Based on our univariate analysis, advanced TNM and SEER summary disease stages were both correlated with adverse prognosis in PCCCL patients. Indeed, OS of PCCCL patients with TNM-I was 36.9 months, compared with merely 14.1 months for patients with TNM-IV. Intriguingly, the present study, unlike the results from additional cohort studies that pathological differentiation degree was one of the valuable prognostic factors in PCCCL, seemed to display no statistically significant dissimilarity in OS in accordance with the pathological differentiation conditions in this tumor. Such inconsistency was supposed to reflect the relatively small sample size and the actuality that cases were primarily composed of tumor with well or moderately pathological differentiation [5,22]. Notably, lymph node metastasis was also a pivotal risk factor in PCCCL in univariate analysis, which would not influence patient OS after modulating for additional variables in multivariate analysis. The reason behind this phenomenon potentially is that our study could acquire very few PCCCL cases with lymph node metastasis from the SEER database. Cox multivariate analysis indicated that patients with larger lesions (> 96 mm) and distant dissemination as well as elevated AFP levels were related to unsatisfactory survival time. Therefore, early detection and surgical treatment may be of great essential to reap optimal outcomes for PCCCL patients.

Cox multivariate analysis indicated that surgical treatment was regarded as the most promising therapeutic intervention to fulfill satisfactory outcomes and reduced the risk of death of PCCCL patients. The 5-year survival rate for patients with PCCCL would reach up to 57.3% if patients undergo surgery timely. Indeed, a prior study also showed that 1-year and 3-year survival rates of all 13 patients managed by surgical resection was 76.5% and 47.1%, respectively, and the longest survival time was up to 97 months [15]. Similarly, a 55-year-old male patient with retroperitoneal and intrahepatic metastasis of PCCCL was performed with surgical resection and transcatheter arterial chemoembolization (TACE), without any recurrence and metastasis during 16 months follow-up [16]. Theoretically, PCCCL is characterized by relatively tardy progress, better tumor differentiation, easier pseudo-capsule formation, lower vascular invasion and lymph node metastasis, which all make great contributions to its high resectability rate [5]. Notably, Liu et al. revealed a much higher formation rate of pseudo-capsule in patients with PCCCL than in non-PCCCL HCC patients (75% versus 49.6%, $P<0.05$) [8]. Such pseudo-capsule is primarily composed of peritumoral hepatic sinusoids with or without fibrosis [7]. With regard to surgical strategies, we found that liver transplantation had the first-rank clinical outcome, followed by surgical resection and local tumor destruction, and surgical resection was still the most momentous and routine tactic to achieve long-term survival for most HCC patients, which was backed up by other studies [20,27]. Currently, literature is confined to researches utilizing surgical resection as the central therapeutic intervention for PCCCL and there are merely several cases of PCCCL that are managed by hepatic transplantation [28]. On account of the rarity of PCCCL cases, confined clinical knowledge is accessible to non-surgical manipulations, including radiofrequency ablation, TACE, percutaneous ethanol injection, or sorafenib as principal intervention measures [7]. For example, in another retrospective study, of those managed by surgical therapy, 81.9% of patients received surgical resection, 16% of them underwent orthotopic liver transplant, and 0.21% of cases were administered with local ablative procedures. And transplantation conferred an obvious and preponderant survival advantage over resection or local ablation [20].

Currently, the efficacy of chemotherapy or radiotherapy as primary intervention or as adjuvant treatment for the prognosis of patient with PCCCL still remains controversial [16]. Our study revealed that both chemotherapy and radiotherapy failed to be considered as prognostic factors and thus were not sufficient to accomplish long-term survival, which potentially was partly attributed to worse physical status of PCCCL patients receiving radiation or chemotherapy. Additionally, a report considered that postoperative adjuvant chemotherapy with calcium folinate and tegafur resulted in no significant improvement in the survival time of PCCCL patients [5]. Similarly, 3 other case reports regarding unresectable PCCCL patients also approved the opinion that PCCCL was not susceptive to chemotherapy and radiotherapy, exhibiting undesirable survival time [12,16,29]. Intriguingly, in 2019, a case report firstly discovered that sunitinib-based systematic therapy clinically cured a male PCCCL patient with multiple metastatic lesions [30]. However, as this is merely a case study, the evidence level of such treatment is

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extremely finite. Whether chemotherapy or radiotherapy exerts conducive effects on the prognosis of PCCCL patients are needed for further investigation.

Notably, in our current study, an exploratory analysis of a rare type of HCC embraced the largest number of PCCCL patients to date, which was accomplished through utilizing large multi-institution databases. PSM analysis further potentiated the credibility of our findings. To our knowledge, we formulated the first nomogram to predict the survival of PCCCL patients, which depended on the SEER database with long-term follow-up. Physicians and patients will have the capacity to produce individualized survival predictions via such an available scoring system. However, it is pivotal to avert overfitting of the model and determined generalizability through validating the nomogram [3].

Nevertheless, it should be mentioned that this study had several limitations which are intrinsic to any retrospective analyses of SEER database. The SEER database failed to confer the comprehensive data concerning the risk factors for tumorigenesis, such as HCV infection, liver cirrhosis [6]. The SEER database also does not provide the momentous additional evaluation indicators to allow for convincing reflection on the severity degree of PCCCL, such as Child-Pugh classification, large vascular invasion or not, and aneuploid deoxyribonucleic acid content [5,15,31]. Both higher proportion of clear cells and capsule formation have been associated with the desirable outcome of the management [4,22], which should be included in this database and thus potentially validate and optimize our nomogram. Indeed, Chen et al. retrospectively analyzed that proportion of clear cells ≥70% indicated better prognosis [22]. Furthermore, specified risk factors regarding PCCCL recurrence are not documented, which limits our capacity to depict therapies patterns administrated after recurrence such as the accurate chemotherapies delivered or radiation schedules. Thirdly, the SEER database merely confers diseases occurring among American population, and additional countries with high incidence of PCCCL fail to be incorporated for integral analysis. Ultimately, the study is retrospective and additional prospective trials are required to investigate to validate a precise conclusion.

Conclusions

Collectively, our study incorporated the comparatively large national sample to reveal certain significant factors influencing PCCCL prognosis. Specifically, larger tumor size, distant metastases, and elevated AFP levels were considered as unfavorably prognostic factors for PCCCL. Oppositely, surgical intervention tended to confer a significant and superior survival advantage to patients, while PCCCL was non-sensitive to chemotherapy and radical therapy. We also formulated an intuitionistic nomogram to readily predict long-term survival, which may be conducive to further facilitating the establishment of clinical management strategies and prospective researches in such patient population.

Conflicts of interest

None.

Supplementary Data

Supplementary Table 1. Patient features by chemotherapy.

Characteristics	No chemotherapy	Chemotherapy	P-value
Total	294	125	
Age (years)	65.7±12.3	61.4±11.8	<0.001
Gender			0.368
Female	110	41	
Male	184	84	
Race			0.852
White	194	81	
Black	32	16	
Unknown	68	28	
Marital status			0.1
Married	228	104	
Single	58	15	
Unknown	8	6	
Grade			0.91
Well; I	43	20	
Moderately; II	79	34	
Poorly; III	25	13	
Undifferentiated; IV	4	2	
Unknown	143	56	

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Characteristics	No chemo-therapy	Chemo-therapy	P-value
Tumor stage			0.03
T1	128	41	
T2	40	20	
T3	43	30	
T4	63	31	
Unknown	20	3	
Lymph node metastases			0.68
N0	226	100	
N1	13	6	
Unknown	55	19	
Distant metastases			0.07
M0	229	96	
M1	47	27	
Unknown	18	2	
Summary stage			<0.01
Localized	169	57	
Regional	60	39	
Distance	47	27	
Unknown	18	2	

Characteristics	No chemo-therapy	Chemo-therapy	P-value
TNM stage			<0.01
I	108	29	
II	34	17	
III	51	39	
IV	47	27	
Unknown	54	13	
AFP level			<0.001
Elevated	165	94	
Normal	126	31	
Unknown	3	0	
Surgery			<0.001
No	165	94	
Yes	126	31	
Unknown	3	0	
Radiation			0.01
No	282	111	
Yes	12	14	

Supplementary Table 2. Patient features by radiation.

Characteristics	No radiation	Radiation	P-value
Total	393	26	
Age (years)	64.6±12.2	60.7±13.7	0.16
Gender			0.56
Female	143	250	
Male	8	18	
Race			0.58
White	255	20	
Black	45	2	
Unknown	92	4	
Marital status			0.23
Married	311	21	
Single	70	3	
Unknown	12	2	

Characteristics	No radiation	Radiation	P-value
Grade			0.29
Well; I	61	2	
Moderately; II	108	5	
Poorly; III	33	5	
Undifferentiated; IV	6	0	
Unknown	185	14	
Tumor stage			0.37
T1	161	8	
T2	56	4	
T3	70	3	
T4	86	8	
Unknown	20	3	

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Characteristics	No radiation	Radiation	P-value
Lymph node metastases			0.43
N0	305	21	
N1	17	2	
Unknown	71	3	
Distant metastases			<0.001
M0	313	12	
M1	62	12	
Unknown	18	2	
Summary stage			<0.001
Localized	222	4	
Regional	91	8	
Distance	62	12	
Unknown	18	2	
TNM stage			<0.001
I	133	4	
II	49	2	
III	85	5	
IV	62	12	
Unknown	64	3	
AFP level			0.01
Elevated	173	18	
Normal	62	0	
Unknown	158	8	
Surgery			0.1
No	241	18	
Yes	150	7	
Unknown	2	1	
Radiation			0.011
No	282	111	
Yes	12	14	

Supplementary Table 3. Patient features for PCCCL and common-type HCC after PSM analysis.

Characteristics	PCCCL	Common-type hepato-cellular	P-value
Total	419	419	
Age (years)	64.4±12.3	64.9±12.0	0.50
Gender			0.38
Female	151	139	
Male	268	280	
Race			0. 81
White	282	282	
Black	48	49	
Unknown	96	88	
Marital status			0.63
Married	332	343	
Single	73	64	
Unknown	14	12	
Grade			0.95
Well; I	63	70	
Moderately; II	113	115	
Poorly; III	38	34	
Undifferentiated; IV	6	6	
Unknown	6	194	
Tumor stage			0.89
T1	168	156	
T2	60	62	
T3	74	78	
T4	94	95	
Unknown	23	28	

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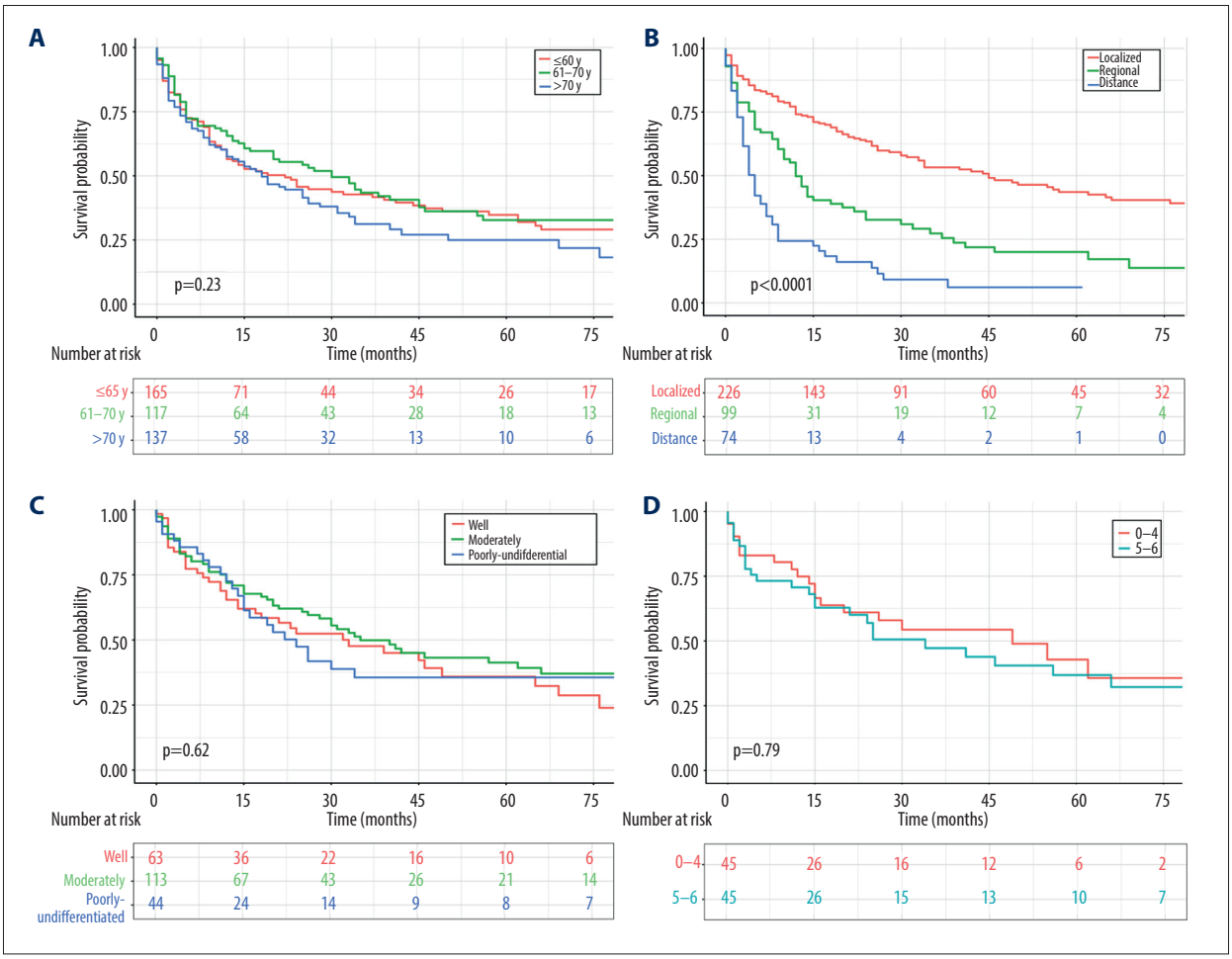
Characteristics	PCCCL	Common-type hepato-cellular	P-value
Lymph node metastases			
N0	326	316	
N1	19	17	
Unknown	74	86	
Distant metastases			0.73
M0	325	316	
M1	74	83	
Unknown	20	20	
AFP level			0.87
Elevated	191	184	
Normal	62	66	
Unknown	166	169	

Characteristics	PCCCL	Common-type hepato-cellular	P-value
Surgery (Y/N)			0.58
No	259	264	
Yes	157	154	
Unknown	3	1	
Radiation			0.36
No	393	395	
Yes	26	24	
Chemotherapy			0.48
No	294	306	
Yes	125	113	



Supplementary Figure 1. OS for patients with PCCCL stratified by (**A**) age. (**B**) different SEER summary stages. (**C**) pathological differentiation grade. (**D**) liver fibrosis score. OS – overall survival; PCCCL – primary clear cell carcinoma of the liver.

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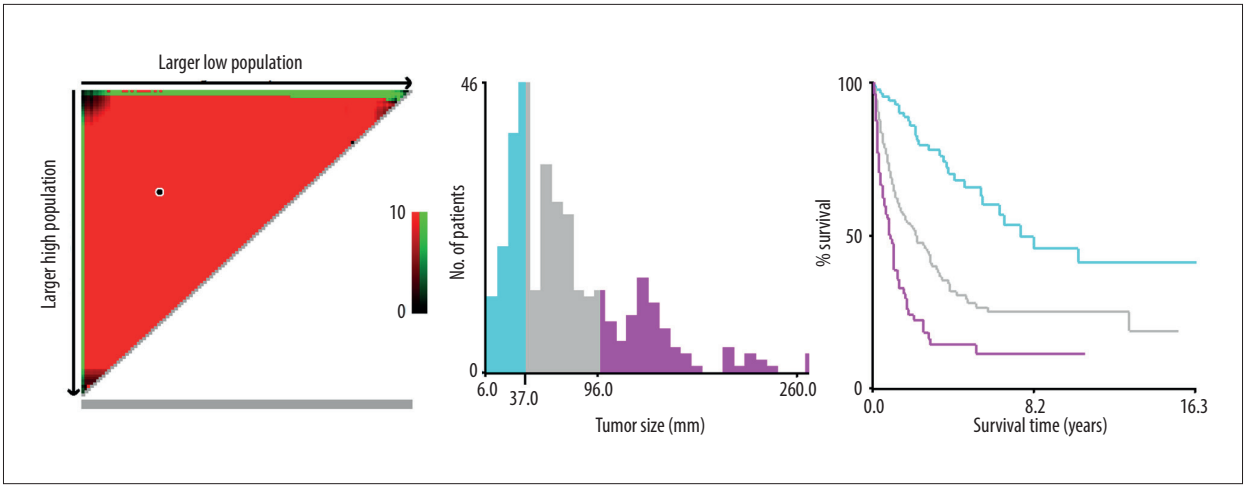
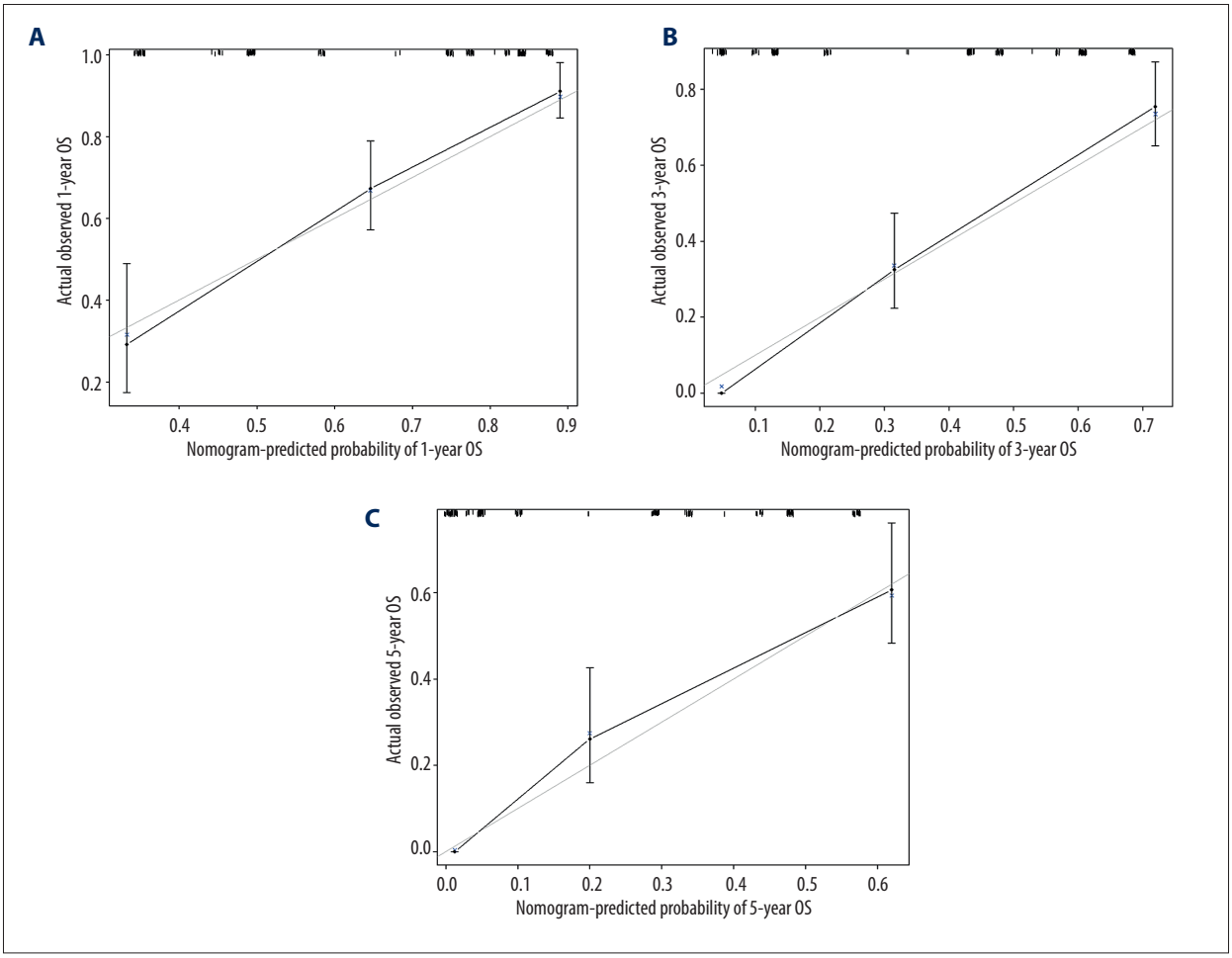


Supplementary Figure 2. The optimal cut-off of tumor size in PCCCL patients. PCCCL – primary clear cell carcinoma of the liver.



Supplementary Figure 3. The calibration plots for predicting PCCCL patient survival at (**A**) 1 years and (**B**) 3 years, and (**C**) 5 years. PCCCL – primary clear cell carcinoma of the liver.

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