Predictors and survival of Primary clear cell carcinoma of liver: a population-based study of an uncommon primary liver tumor

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Abstract

Background: The clinicopathological features and prognostic factors of primary clear cell carcinoma of the liver (PCCCL) remain unknown.

Aims: We aimed to determine the clinical, pathological, demographic, and therapeutic characteristics of PCCCL and the effects of these factors on the prognosis.

Methods: Patients were selected from the "Surveillance, Epidemiology and End Results" (SEER) database. Data were analyzed with the Kaplan-Meier, Cox proportional hazards regression, and multivariate ordinal regression analyses.

Results: We included 248 PCCCL patients with an average age of 64.1 years. The majority (50.4%) had low pathological grade (grade I/II). The 3-, 5-, and 10-year overall survival (OS) probabilities and disease-specific survival (DSS) rates were 33.8%, 23.2%, 12.2%, and 39.8%, 28.3%, 19.1%, respectively. The widowed patients (OS, P=0.271; DSS, P=0.022) with tumor ≥ 1 cm (OS, P=0.001; DSS, P=0.002) had a higher risk of death. Uninsurance and medicaid were independently associated with a shorter survival (OS, P=0.029; DSS, P=0.017). Among surgical means, total proctectomy along with total colectomy, and wedge or segmental resection/partial proctosigmoidectomy were more beneficial to PCCCL. The black PCCCL patients had a poorer survival than the white group. Furthermore, pathological grade I PCCCL was more likely to present AJCC stage I (P=0.005, OR=-1.062).

Conclusion: PCCCL patients had a poor outcome. PCCCL was inclined to be localized, male-prevalent and lower pathological grade. Insurance, tumor size, and marital status were independent prognostic factors for OS and DSS, whereas race affected only OS. Surgery could improve OS and DSS. Moreover, highly differentiated PCCCL was susceptible to early AJCC stage.

Introduction

Liver cancer is the third most common cause of cancer-related mortality and ranks fifth in cancer incidence, and > 90% of the cases are hepatocellular carcinoma (HCC) [1]. HCC could be subdivided into clear cell, spindle cell, fibrolamellar, scirrhous, and pleomorphic types, and combined HCC with cholangiocarcinoma [2]. The primary clear cell carcinoma of the liver (PCCCL) is a specific and rare histological subtype of HCC accounting for 7.5–12.5% of all liver cancers [3]. PCCCL cells do not stain with hematoxylin and eosin due to the prominent cytoplasmic accumulation of lipid droplets and glycogens [4]. Decreased number and size of organelles, and metabolic impairment can be observed in these cells [5]. HCC with > 50% clear cells is generally diagnosed as PCCCL [6].

The clinical and pathological characteristics of PCCCL have been controversial for long. It is generally accepted that PCCCL has a favorable clinical outcome [4, 7, 8], except for several reports [9, 10]. In fact, PCCCL prognosis and prognostic factors largely remain unknown due to the limited number of cases. Additionally, studies have suggested that PCCCL mainly occurs in patients > 50 years old and has a relatively high association with hepatitis C infection [11]. Moreover, PCCCL has been shown to be more common in females and conducive to capsule formation [12] and cirrhosis development [13]. It tends to have less vascular infiltration [14], moderate degree of
differentiation, and low-grade malignancy [15]. However, due to the lack of effective large case studies, the clinical and pathological features remain unclear.

As a rare HCC variant, PCCCL has its unique clinicopathological features, which may contribute to the survival of patients. Thus, characterization of these features is crucial for the management of PCCCL. However, owing to its rarity, PCCCL has largely been described in case reports or by small, single-institution studies, rendering the conclusions questionable. Hence, in this study, we expanded the number of the study cases by utilizing the "Surveillance, Epidemiology, and End Results" (SEER) database to clarify the tumor features, epidemiology, therapies, and prognostic factors.

**Material And Methods**

**Study population**

The SEER database was supported by the National Cancer Institute and contained the information of 18 population based registered cancer institutes. The US population accounts for 28.0% of the SEER database. SEER program was established to collect cancer patients information including cancer incidence, prevalence, treatments, clinicopathological features and survival data from U.S. cancer registries, which is broadly represents the population of the US population. It serves to minimize the potential biases, reduce the cancer burden and provide first-hand evidence for clinicians to perform studies focusing on oncologic disease[16]. As the patients data in the SEER dataset are publicly available, therefore, no approval was required from any institutional review board [17].

The study we designed was a population based longitudinal cohort study. And we utilized the SEER database to identify patients diagnosed with PCCCL (SEER codes 8174/3) from 2004 to 2016 according to the 3rd edition of International Classification of Disease for Oncology (ICD-0-3) and the 6th edition of American Joint Committee on Cancer (AJCC). The patient information including diagnostic confirmation, Histology/behavior (ICD-O-3), SEER Combined Summary Stage, AJCC Stage (6th), AJCC T stage (6th), AJCC M stage (6th), AJCC N stage (6th), Surgery Primary Site (1998+), radiation therapy, tumor size, CS extension, CS lymph nodes (2004–2015), CS metastasis at distance (2004–2015), SEER cause-specific death classification, survival months, sequence number, age at diagnosis, gender, race, marital status and pathological grade were extracted from the database. The details of chemotherapy was not included in the SEER database. No private identity information were acquired from the SEER database.

**Statistical analysis**

The demographic, clinical, and pathological characteristics of PCCCL patients were analyzed with basic statistics. The primary endpoints were overall survival (OS) and disease-specific survival (DSS). OS and DSS were defined as the time intervals from diagnosis to death by any cause and PCCCL-related reasons, respectively. The Kaplan-Meier method and log-rank test were used to validate the prognostic factors and statistical significance for the OS and DSS. The univariate and multivariable Cox proportional hazards regression were performed to identify the independent prognostic variables. The hazard ratio (HR) and 95% confidence interval (95% CI) were measured for assessing the correlation strength between each variable and survival. Additionally, we performed multivariable ordinal logistic regression to validate the association between grade, sex, race, or age and AJCC stage. The odds ratios (ORs) shown in the ordinal regression analysis could be perceived as the increased odds of presenting with an AJCC stage higher by one level. The GraphPad Prism 6 software was applied to draw the figures and charts.
SPSS 19.0 (SPSS, Inc., Chicago, IL) was for data analysis. SEER*STAT version 8.3.5 (Surveillance Research Program, NCI, Bethesda, MD, USA) was utilized to extract patient information from the SEER database [18]. \( P < .05 \) was considered statistically significant.

More detailed Material and Methods were showed in the supplementary file.

Results

Patient Population

PCCCL cases during 2004–2016 (\( n = 499 \)) were extracted from the SEER database. Subsequently, 248 cases were recruited to our study cohort according to the inclusion and exclusion criteria as shown in supplementary Fig. 1.

Patient-related general information, including sex, age, marital status, race, tumor size, T and N stages, and other variables are listed in supplementary Table 1. The average age at diagnosis was 64.1 ± 12.3 years with 58.8% male; 63.3%, 23.4%, and 13.3% were white, black, and of other ethnicity, respectively. Married, divorced, single, and separated patients accounted for 60.1%, 8.5%, 15.3%, and 3.2% of the sample size. Tumor was present in 68.1% (< 1 cm) and 23% (\( \geq 1 \) cm) of the patients. Nearly half the patients (49.6%) were diagnosed at T1, 19.4% at T2, 24.2% at T3, and 6.8% at T4 stages. The overwhelming majority of the patients (N0, 95.2%) had no regional lymph node or tumor distant metastasis (M0, 85.9%). The patients diagnosed as early AJCC stage I, or stages II, IIIA, IIIB, IIIC, and IV accounted for 44%, 17.7%, 18.5%, 4%, 1.6%, and 14.2% of the sample size, respectively. Regarding SEER staging, 61.3%, 33.6%, and 16.4% of the patients had localized, regional, and distant extent of PCCCL, respectively. The patients with no vascular invasion or distant lymph node metastasis corresponded to 61.3% and 85.9%, respectively. Regarding the pathological grade, most patients were diagnosed as low grade (Grade I, 16.1%; and Grade II, 34.3%). Over half the patients (56%) had health insurance. Only a few people (2.8%) underwent radiotherapy. Approximately half the patients (51.6%) had no surgical treatment; 8.5% and 20.2% received local tumor destruction and local tumor excision, respectively; 11.3% underwent wedge or segmental resection/partial proctosigmoidectomy; 0.4%, 1.2%, and 6.8% underwent total proctectomy, total colectomy, and a combination of both, respectively. The great majority (92.3%) had no lymph node surgery.

Clinical prognosis and survival analysis

To understand whether these variables would affect the survival of patients, we first analyzed the association strength between each variable and survival. The Kaplan-Meier survival analysis showed that the 5-year OS and DSS rates were 23.2% and 28.3%, respectively, and thus indicated a poor clinical (Figs. 1A-B). The median OS and DSS were 19 and 24 months, respectively (Table 1). The Kaplan-Meier analysis results showed that the patients ≥ 75 years old exhibited a poorer outcome than that of the younger patients, with a median OS of 13 vs. 21 months (log-rank \( P = 0.029 \)). However, age had no statistically significant effect on the DSS (log-rank \( P = 0.1032 \)) (Figs. 2A-B, Table 1). Additionally, later summary stage (distant) correlated with decreased survival (median OS and DSS, both 4 months) compared with localized stage (median OS and DSS: 34 and 41 months, respectively) and regional stage (median OS and DSS, both 13 months) (OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 2C-D, Table 1). The patients with health insurance (median OS and DSS: 25 and 30 months, respectively) showed a better survival than those without health insurance (median OS and DSS, both 1 month) or with any medicaid (median OS and DSS: 10 and 11 months, respectively) (OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 2E-F, Table 1). Higher pathological grade (Grade IV) correlated with decreased OS and DSS (log-ranks \( P = 0.000, 11 \) months for both) (Figs. 3A-B, Table 1). The widowed patients showed worse prognosis than the married ones.
(median OS: 9 vs. 25 months; median DSS: 9 vs. 33 months) (OS log-rank \( P = 0.002 \), DSS log-rank \( P = 0.009 \)) (Figs. 3C-D, Table 1). Shorter survival could be observed in patients with gallbladder extension (median OS and DSS, both 9 months), parenchyma surface extension (median OS and DSS, both 11 months), major vascular invasion (median OS and DSS: 9 and 12 months, respectively), hepatic artery or vena cava invasion (median OS and DSS, both 4 months), or coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension (median OS and DSS, both 9 months) compared with those without vascular invasion (median OS and DSS: 30 and 40 months, respectively) (OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 3E-F, Table 1). The median OS and DSS of the patients with tumor size \(< 1 \text{ cm} \) were 33 and 36 months, respectively, which were longer than those of the patients with tumors \( \geq 1 \text{ cm} \) (median OS and DSS, both 12 months) (OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 4A-B, Table 1). However, no statistically significant differences in OS and DSS could be observed in patients of both genders (OS log-rank \( P = 0.446 \), DSS log-rank \( P = 0.82 \)) and different races. (OS log-rank \( P = 0.08 \), DSS log-rank \( P = 0.411 \)) (supplementary Figs. 2A-D). Additionally, higher T stage correlated with decreased OS and DSS (log-ranks \( P = 0.000 \) for both) with patients at T4 or T3 stage having a dismal prognosis (T4 median OS and DSS, both 5 months; T3 median OS and DSS, both 12 months) (Figs. 4C-D, Table 1). Poor prognosis could be observed in the patients with M1 stage (OS log-rank \( P = 0.000 \), median OS: 4 months; DSS log-rank \( P = 0.000 \), median DSS: 6 months) and N1 stage (OS log-rank \( P = 0.003 \), median OS: 5 months; DSS log-rank \( P = 0.000 \), median DSS: 5 months) (Figs. 4E-F, Figs. 5A-B, Table 1). Regarding AJCC stage, shorter survival was observed in the stage IV patients (median OS and DSS: 4 and 6 months, respectively) and stage III patients (median OS and DSS: 12 and 13 months, respectively), while, the opposite trend could be observed in those with stage II (median OS: 26 months; median DSS: 30 months) and stage I (median OS: 34 months; median DSS: 46 months) (OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 5C-D, Table 1). With reference to different surgery methods, a median OS and DSS of 37 and 42 months, respectively, were observed for patients receiving local tumor destruction, 55 (OS) and 56 months (DSS) for patients accepting wedge or segmental resection/partial proctosigmoidectomy, 84 months (OS) for those having total colectomy, and 124 months (OS) for those with total proctectomy along with total colectomy. Conversely, the clinical outcome of the patients without any surgery was poor (median OS and DSS: 7 and 9 months, respectively; OS and DSS log-ranks, both \( P = 0.000 \)) (Figs. 5E-F, Table 1). It should be noted that there was no significant difference in OS (log-rank, \( P = 0.096 \)) or DSS (log-rank, \( P = 0.139 \)) regardless of regional lymph node removal (supplementary Figs. 2E-F, Table 1). A similar trend could be observed in patients with or without radiation (OS and DSS log-ranks, \( P = 0.858 \) and \( P = 0.588 \), respectively) (supplementary Figs. 3A-B, Table 1).
Table 1  
Results of univariate Cox regression analysis of potential characteristics influencing DFS and OS.

| Parameter | Subgroup     | Overall survival | Disease-free survival | MST (m) | Hazard ratio (95% CI) | P value | MST (m) | Hazard ratio (95% CI) | P value |
|-----------|--------------|------------------|-----------------------|---------|-----------------------|---------|---------|-----------------------|---------|
|           |              | MST (m)          | P value               |         |                       |         | MST (m) | Hazard ratio (95% CI) | P value |
|           | Whole group  | 19               | **0.033**             | 24      | **0.033**             | 0.11    |         |                       |         |
|           | Age          |                  |                       |         |                       |         |         |                       |         |
|           | <75          | 21               | 1                     | 26      | 1                     |         |         |                       |         |
|           | ≥75          | 13               | 1.477 (1.03,2.11)     | 0.033   | 18                    | 1.38 (0.93,2.04) | 0.11    |                     |         |
|           | Summary      |                  | **0.000**             | **0.000** |                     |         |         |                       |         |
|           | Stage        |                  |                       |         |                       |         |         |                       |         |
|           | Localized    | 34               | 1                     | 41      | 1                     |         |         |                       |         |
|           | Regional     | 13               | 1.861 (1.31,2.63)     | **0.01** | 13                    | 2.078 (1.43,3.01) | **0.000** |                     |         |
|           | Distant      | 4                | 3.823 (2.56,5.69)     | **0.000** | 4                     | 4.19 (2.73,6.43) | **0.000** |                     |         |
|           | Insurance    |                  | **0.000**             | **0.000** |                     |         |         |                       |         |
|           | Insured      | 25               | 1                     | 30      | 1                     |         |         |                       |         |
|           | Uninsured    | 1                | 5.466 (2.51,11.9)     | **0.000** | 1                     | 5.774 (2.49,13.4) | **0.000** |                     |         |
|           | Any Medicaid | 10               | 1.669 (1.15,2.42)     | **0.007** | 11                    | 1.861 (1.26,2.75) | **0.002** |                     |         |
|           | Insurance status unknown | 5 | 1.257 (0.40,3.99) | 0.698 | 5                     | 1.101 (0.27,4.50) | 0.893 |                     |         |
|           | Blank(s)     | 24               | 1.061 (0.73,1.55)     | 0.757   | 29                    | 1.137 (0.76,1.71) | 0.539 |                     |         |
|           | M stage      |                  | **0.000**             | **0.000** |                     |         |         |                       |         |
|           | M0           | 24               | 1                     | 30      | 1                     |         |         |                       |         |
|           | M1           | 4                | 2.992 (2.02,4.42)     | **0.000** | 6                     | 3.096 (2.04,4.7) | **0.000** |                     |         |
|           | N stage      |                  | **0.004**             | **0.001** |                     |         |         |                       |         |
|           | N0           | 20               | 1                     | 26      | 1                     |         |         |                       |         |
|           | N1           | 5                | 2.463 (1.32,4.58)     | **0.004** | 5                     | 2.919 (1.56,5.46) | **0.001** |                     |         |
|           | T stage      |                  | **0.000**             | **0.000** |                     |         |         |                       |         |
|           | T1           | 34               | 1                     | 45      | 1                     |         |         |                       |         |
| Parameter      | Subgroup | Overall survival | Disease-free survival |
|----------------|----------|------------------|-----------------------|
|                |          | 26               | 26                    |
| Overall survival | T2       | 1.014 (0.67,1.53) | 0.946                 |
| Disease-free survival |          | 1.169 (0.74,1.85) | 0.503                 |
|                | T3       | 2.449 (1.72,3.48) | 0.000                 |
|                | T4       | 2.619 (1.50,4.57) | 0.001                 |
|                | Race     |                  |                       |
|                | White    | 19               | 21                    |
|                | Black    | 9                | 20                    |
|                | Others   | 24               | 34                    |
| Tumor size, (cm) |         |                  |                       |
|                | < 1 cm   | 33               | 36                    |
|                | □ 1 cm   | 12               | 12                    |
|                | Unknown  | 3                | 4                     |
| Pathological grade |        |                  |                       |
|                | Grade I  | 23               | 45                    |
|                | Grade II | 28               | 30                    |
|                | Grade III| 26               | 34                    |
|                | Grade IV | 11               | 11                    |
|                | Unknown  | 9                | 12                    |
| Marital status |          |                  |                       |
|                | Married  | 25               | 33                    |
|                | Divorced | 12               | 12                    |
|                | Widowed  | 9                | 19                    |
|                | Single   | 15               | 26                    |


| Parameter | Subgroup | Overall survival | Disease-free survival |
|-----------|----------|------------------|----------------------|
|           |          |                  |                      |
|           | Separated 9 | 3.406 (1.24,9.38) | 0.18 |
|           | Unknown 26 | 0.968 (0.39,2.38) | 0.943 |
|           | Sex       |                  |                      |
|           | Male 15 1 |                  |                      |
|           | Female 24 | 0.895 (0.67,1.20) | 0.454 |
|           | Extension |                  |                      |
|           | No vascular invasion 30 1 |                  | 0.92 |
|           | Intrahepatic vascular invasion 26 | 1.027 (0.62,1.71) | 0.043 |
|           | Gallbladder extension 9 | 3.315 (1.04,10.6) | 0.015 |
|           | Intrahepatic vascular invasion + Gallbladder extension NA | 0.000 (0.000,1.18E+151) | 0.959 |
|           | Surface of parenchyma extension 11 | 1.993 (1.29,3.08) | 0.002 |
|           | Major vascular invasion: major branch of portal or hepatic vein(s) 9 | 3.138 (1.90,5.19) | 0.000 |
|           | Hepatic artery or vena cava invasion 4 | 2.789 (1.02,7.64) | 0.046 |
|           | Coronary, Falciform, Hepatoduodenal, Hepatogastric, Round (of liver), Triangular, Perforation of visceral peritoneum, Parietal peritoneum, Pancreas, Pleura, Stomach extension 9 | 2.235 (1.16,4.29) | 0.016 |
|           | Unknown 3 | 1.367 (0.34,5.57) | 0.662 |
|           | Radiation |                  |                      |
|           | No 19 1 |                  |                      |
|           | Yes 17 | 1.076 (0.48,2.43) | 0.861 |
|           | Surgery |                  |                      |
|           | None 7 |                  |                      |
| Parameter | Subgroup                                      | Overall survival | Disease-free survival |
|-----------|-----------------------------------------------|------------------|-----------------------|
|           |                                               |                  |                       |
| Local tumor destruction | 37 | 0.38 (0.22, 0.65) | 0.000 | 42 | 0.325 (0.18, 0.60) | 0.000 |
| Local tumor excision     | 55 | 0.233 (0.15, 0.36) | 0.000 | 56 | 0.222 (0.14, 0.36) | 0.000 |
| Wedge or segmental resection/partial proctosigmoidectomy | 34 | 0.246 (0.15, 0.42) | 0.000 | 34 | 0.276 (0.16, 0.47) | 0.000 |
| Total proctectomy        | 41 | 0.385 (0.05, 2.77) | 0.343 | 41 | 0.441 (0.06, 3.18) | 0.417 |
| Total colectomy          | 84 | 0.211 (0.05, 0.86) | 0.03 | NA | 0.122 (0.02, 0.88) | 0.037 |
| Total proctectomy + Total colectomy | 124 | 0.104 (0.05, 0.23) | 0.000 | NA | 0.072 (0.03, 0.2) | 0.000 |
| AJCC stage               |     | 0.000 | 0.000 |
| I                     | 34 | 1   | 46 | 1 |
| II                    | 26 | 1.052 (0.68, 1.64) | 0.823 | 30 | 1.167 (0.71, 1.92) | 0.541 |
| III                   | 12 | 2.519 (1.75, 3.63) | 0.000 | 13 | 3.167 (2.14, 4.68) | 0.000 |
| IV                    | 4  | 4.103 (2.66, 6.32) | 0.000 | 6  | 4.785 (2.98, 7.67) | 0.000 |

**Uni- and multivariate analyses**

To further dissect the independent predictors for OS and DSS of the PCCCL patients, we performed uni- and multivariate analyses. Insurance, marital status, extension, surgery, tumor size, pathological grade, and M, N, T, AJCC, and summary stages were markedly correlated with both the OS and DSS (Table 1). Moreover, age and race had obvious associations with the OS. The univariate analysis showed that patients ≥ 75 years old had a higher risk of death (HR = 1.477, 95%CI = 1.03–2.11) than the younger patients. Additionally, the summary stage was a significant predictor of OS and DSS (P < 0.001 for both). Relative to patients with localized stage, increased HR could be observed in the patients with distant stage (OS: HR = 3.823, 95%CI = 2.56–5.69; DSS: HR = 4.19, 95%CI = 2.73–6.43) or regional stage (OS: HR = 1.861, 95%CI = 1.31–2.63; DSS: HR = 2.078, 95%CI = 1.43–3.01). Univariate analysis indicated a higher mortality among patients without insurance (OS: HR = 5.466, 95%CI = 2.51–11.92; DSS: HR = 5.774, 95%CI = 2.49–13.41) or with any medicaid (OS: HR = 1.669, 95%CI = 1.15–2.42; DSS: HR = 1.861, 95%CI = 1.26–2.75) than those with insurance. Lower survival occurred in M1 stage (OS: HR = 2.992, 95%CI = 2.02–4.42; DSS: HR = 3.096, 95%CI = 2.04–4.7), N1 stage (OS: HR = 2.463, 95%CI = 1.32–4.58; DSS: HR = 2.919, 95%CI = 1.56–5.46), and T3 (OS: HR = 2.449, 95%CI = 1.72–3.48; DSS: HR = 3.144, 95%CI = 2.16–4.58) and T4 stages (OS: HR = 2.619, 95%CI = 1.5–4.57; DSS: HR = 3.498, 95%CI = 1.98–6.19) than in M0, N0, and T1 stages, respectively. The black patients had higher risks in OS (OS: HR = 1.531, 95%CI = 1.01–2.31) than the white patients. The patients with tumors < 1 cm had poorer prognosis (OS: HR = 1.882, 95%CI = 1.3–2.56; DSS: HR = 1.3–2.56;
2.007, 95% CI = 1.4–2.87) than those with tumors ≥ 1 cm. The pathological grade IV patients showed shorter survival than those with pathological grade I (OS: HR = 3.541, 95% CI = 1.06–11.69; DSS: HR = 3.976, 95% CI = 1.18–13.38). Relative to the married patients, the widowed patients exhibited a higher death rate (OS: HR = 2.242, 95% CI = 1.44–3.5; DSS: HR = 2.236, 95% CI = 1.38–3.63). PCCCL extended in the gallbladder (OS: HR = 3.315, 95% CI = 1.04–10.58; DSS: HR = 4.244, 95% CI = 1.32–13.63), parenchyma surface (OS: HR = 1.993, 95% CI = 1.29–3.08; DSS: HR = 2.411, 95% CI = 1.52–3.82), major branches of portal or hepatic vein(s) (OS: HR = 3.318, 95% CI = 1.9–5.19; DSS: HR = 3.574, 95% CI = 2.09–6.13), hepatic artery or vena cava (OS: HR = 2.789, 95% CI = 1.02–7.64; DSS: HR = 3.522, 95% CI = 1.28–9.7), or with coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, or stomach extension (OS: HR = 2.235, 95% CI = 1.16–4.29; DSS: HR = 2.826, 95% CI = 1.46–5.47) had higher risks than those without vascular invasion. Compared with patients without surgery, those who underwent local tumor destruction (OS: HR = 0.38, 95% CI = 0.22–0.65; DSS: HR = 0.325, 95% CI = 0.18–0.6), local tumor excision (OS: HR = 0.233, 95% CI = 0.15–0.36; DSS: HR = 0.222, 95% CI = 0.14–0.36), wedge or segmental resection/partial proctosigmoidectomy (OS: HR = 0.246, 95% CI = 0.15–0.42; DSS: HR = 0.276, 95% CI = 0.16–0.47), total colectomy (OS: HR = 0.211, 95% CI = 0.05–0.86; DSS: HR = 0.122, 95% CI = 0.02–0.88), or total proctectomy along with total colectomy (OS: HR = 0.104, 95% CI = 0.05–0.23; DSS: HR = 0.072, 95% CI = 0.03–0.2) had reduced risks of death. Patients diagnosed as AJCC III (OS: HR = 2.519, 95% CI = 1.75–3.63; DSS: HR = 3.167, 95% CI = 2.14–4.68) or AJCC IV (OS: HR = 4.103, 95% CI = 2.66–6.32; DSS: HR = 4.785, 95% CI = 2.98–7.67) showed significantly reduced risks of death than those with AJCC I or II. However, sex and radiotherapy had no impacts on the hazard rate.

Next step, to determine the independent prognostic factors, we performed multivariate cox proportional analysis model of OS and DSS (Table 2) for those variables whose P value < 0.05 according to the univariate analyses results in Table 1. As shown in Table 2, for the whole cohort, insurance, race, tumor size, marital status and surgery were independent determinants of OS, while insurance, tumor size, marital status and surgery were independent predictors of DSS. Compared to the patients with insurance, those without insurance (OS: HR = 2.668, 95% CI = 1.1-6.47) and with any medicaid (OS: HR = 1.757, 95% CI = 1.09-2.83; DSS: HR = 2.133, 95% CI = 1.29–3.52) showed a higher risk of death. Relative to the patients with tumor < 1 cm, those with lesion ≥ 1 cm possessed shorter survival (OS: HR = 1.825, 95% CI = 1.22-2.74; DSS: HR = 1.958, 95% CI = 1.27–3.02). Respect to the while patients, the black one had a diminished OS (HR = 1.903, 95% CI = 1.12-3.22). Comparison of married patients, the widowed one were proved to be with higher mortality rate (OS: HR = 1.85, 95% CI = 1.08-3.16; DSS: HR = 2.656, 95% CI = 1.54–4.58). Receiving surgery had improved OS and DSS. Using no surgery as a reference, patients accepting local tumor excision (OS: HR = 0.399, 95% CI = 0.25–0.65; DSS: HR = 0.423, 95% CI = 0.25–0.71), wedge or segmental resection/partial proctosigmoidectomy (OS: HR = 0.355, 95% CI = 0.18–0.68; DSS: HR = 0.358, 95% CI = 0.18–0.71) and total proctectomy plus total colectomy (OS: HR = 0.082, 95% CI = 0.03–0.21; DSS: HR = 0.068, 95% CI = 0.02–0.21) had a bad clinical outcome. In the final model, tumor size, marital status, and surgery had impacts on the OS and DSS, whereas race had impact only on the OS; however, insurance had no significant effect on clinical prognosis (supplementary Table 2). Being married, having a small tumor (< 1 cm), or undergoing surgery was correlated with a better OS and DSS. Moreover, the while patient exhibited low risk of death than those black patients.
Table 2
Results of multivariate Cox regression analysis of potential characteristics influencing DFS and OS.

| Parameter       | Subgroup | Overall survival | Disease-free survival |
|-----------------|----------|------------------|----------------------|
|                 |          | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| Age             | < 75     | 1                |          | 0.067                |         |
|                 | ≥ 75     | 1.498 (0.97,2.31) | 0.067    | 1                    |         |
| Summary Stage   |          | 0.303             | 0.075    | 0.029                | 0.017   |
| Stage           | Localized| 1                | 1        |                      |         |
|                 | Regional | 0.983 (0.38,2.52) | 0.972    | 0.845 (0.31,2.3)     | 0.741   |
|                 | Distant  | 3.24 (0.59,17.71) | 0.175    | 4.64 (0.84,25.7)     | 0.079   |
| Insurance       | Insured  | 1                | 1        |                      |         |
|                 | Uninsured| 2.668 (1.1,6.47) | **0.03** | 2.558 (0.95,6.9)     | 0.064   |
|                 | Any Medicaid| 1.757 (1.09,2.83) | **0.02** | 2.133 (1.29,3.52)    | **0.003** |
|                 | Insurance status unknown| 0.602 (0.15,2.43) | 0.477    | 0.764 (0.15,3.96)    | 0.748   |
|                 | Blank(s) | 1.336 (0.85,2.09) | 0.205    | 1.5 (0.93,2.41)      | 0.094   |
| M stage         | M0       | 1                | 1        |                      |         |
|                 | M1       | 1.076 (0.18,6.42) | 0.936    | 0.75 (0.12,4.7)      | 0.758   |
| N stage         | N0       | 1                | 1        |                      |         |
|                 | N1       | 1.535 (0.69,3.4)  | 0.291    | 1.655 (0.74,3.69)    | 0.219   |
| T stage         | T1       | 1                | 1        |                      |         |
|                 | T2       | 0.68 (0.17,2.81)  | 0.595    | 0.699 (0.16,3.05)    | 0.634   |
|                 | T3       | 0.737 (0.24,2.31) | 0.601    | 0.893 (0.26,3.06)    | 0.857   |
|                 | T4       | 2.006 (1,42.52)   | 0.655    | 4.26 (0.19,95.2)     | 0.361   |
| Race            | White    | 0.056             | 1        |                      |         |
| Parameter                      | Subgroup | Overall survival  | Disease-free survival |
|-------------------------------|----------|-------------------|-----------------------|
|                               |          | (95% CI)          |                       |
|                                |          | \( p \)           |                       |
| Black                         | 1.903    | (1.12, 3.22)      | \( 0.017 \)           |
| Others                        | 1.13     | (0.74, 1.72)      | \( 0.568 \)           |
| Tumor size, (cm)              |          | \(0.001\)         | \(0.002\)             |
| < 1 cm                        | 1        |                   |                       |
| \(\geq 1\) cm                | 1.825    | (1.22, 2.74)      | \(0.004\)             | 1.958 | (1.27, 3.02) | \(0.002\) |
| Unknown                       | 2.711    | (1.38, 5.32)      | \(0.004\)             | 2.279 | (1.08, 4.81) | \(0.031\) |
| Pathological grade            |          | \(0.021\)         | \(0.05\)              |
| Grade I                       | 1        |                   |                       |
| Grade II                      | 0.912    | (0.55, 1.51)      | 0.722 | 0.961 | (0.56, 1.66) | 0.886 |
| Grade III                     | 0.732    | (0.38, 1.42)      | 0.358 | 0.765 | (0.37, 1.57) | 0.465 |
| Grade IV                      | 2.448    | (0.65, 9.27)      | 0.188 | 3.149 | (0.86, 11.5) | 0.083 |
| Unknown                       | 1.562    | (0.97, 2.53)      | 0.069 | 1.551 | (0.92, 2.61) | 0.099 |
| Marital status                |          | \(0.271\)         | \(0.022\)             |
| Married                       | 1        |                   |                       |
| Divorced                      | 1.114    | (0.62, 2.01)      | 0.719 | 1.318 | (0.72, 2.41) | 0.369 |
| Widowed                       | 1.85     | (1.08, 3.16)      | \(0.024\)             | 2.656 | (1.54, 4.58) | \(0.000\) |
| Single                        | 1.135    | (0.71, 1.82)      | 0.599 | 1.278 | (0.77, 2.12) | 0.34  |
| Separated                     | 1.276    | (0.40, 4.03)      | 0.678 | 0.889 | (0.25, 3.2)  | 0.858 |
| Unknown                       | 0.667    | (0.25, 1.79)      | 0.422 | 0.818 | (0.29, 2.3)  | 0.697 |
| Extension                     |          | \(0.878\)         | \(0.748\)             |
| No vascular invasion          | 1        |                   |                       |
| Intrahepatic vascular invasion| 0.883    | (0.39, 2.01)      | 0.767 | 0.888 | (0.37, 2.13) | 0.79  |
| Gallbladder extension         | 1.622    | (0.36, 7.23)      | 0.526 | 2.274 | (0.51, 10.1) | 0.28  |
| Intrahepatic vascular invasion + Gallbladder extension | 0.000 | (0.000, 3.46E + 162) | 0.955 | 0.000 | (0.000, 3.46E + 194) | 0.963 |
| Surface of parenchyma extension | 1.848    | (0.65, 5.29)      | 0.253 | 2.083 | (0.68, 6.38) | 0.199 |
| Unknown                       | 0.553    | (0.06, 5.13)      | 0.602 | 0.632 | (0.07, 6.05) | 0.69  |
| Parameter                           | Subgroup                                                                 | Overall survival | Disease-free survival |
|------------------------------------|---------------------------------------------------------------------------|------------------|-----------------------|
|                                    | Major vascular invasion: major branch of portal or hepatic vein(s)        | 1.694 (0.57,5.04) | 0.344 (0.53,5.55)    |
|                                    | Hepatic artery or vena cava invasion                                      | 0.32 (0.13,7.72) | 0.483 (0.01,6.84)    |
|                                    | Coronary, Falciform, Hepatoduodenal, Hepatogastric, Round of liver, Triangular, Perforation of visceral peritoneum, Parietal peritoneum, Pancreas, Pleura, Stomach extension | 0.379 (0.16,8.91) | 0.547 (0.01,5.16)    |
| Surgery                            |                                                                           |                  |                       |
| None                               |                                                                           | 0.000            | 0.000                 |
| Local tumor destruction            |                                                                           | 0.588 (0.33,1.06) | 0.077 (0.25,0.96)    |
| Local tumor excision               |                                                                           | 0.399 (0.25,0.65) | **0.000** (0.25,0.71) |
| Wedge or segmental resection/partial proctosigmoidectomy |                                                                           | 0.355 (0.18,0.68) | **0.002** (0.18,0.71) |
| Total proctectomy                  |                                                                           | 1.096 (0.14,8.72) | 0.931 (0.17,10.5)    |
| Total colectomy                    |                                                                           | 0.54 (0.12,2.42) | 0.42 (0.06,3.32)     |
| Total proctectomy + Total colectomy|                                                                           | **0.082** (0.03,0.21) | **0.000** (0.02,0.21) |
| AJCC stage                         |                                                                           | 0.139 (0.18,6.42) | 0.936 (0.12,4.7)     |
| I                                  |                                                                           | 1                | 1                     |
| II                                 |                                                                           | 3.492 (0.86,14.2) | 0.08 (0.78,15.0)     |
| III                                |                                                                           | 2.738 (0.91,8.26) | 0.074 (0.87,9.45)    |
| IV                                 |                                                                           | 1.076 (0.18,6.42) | 0.936 (0.12,4.7)     |

**Association of the pathological grade with T stage**

According to the multivariate ordinal logistic regression analysis results (supplementary Table 3), patients with pathological grade I (P = 0.005, OR=-1.062; 95% CI=-1.8–-0.33) were less likely to develop PCCCL with a higher T stage (T4), which was used as the reference. The distribution of AJCC stage at presentation significantly varied according to the pathological grade (Fig. 6). Patients with pathological grade I more frequently developed tumors with AJCC I (57%) than the grade II (45%), III (32%), or IV (0%) patients. Conversely, grade IV patients were more likely to develop tumors with AJCC IV (33.33%) than the grade III (14.3%), II (14.1%), or I (0%) patients.
Discussion

Due to the glycogen accumulation and fat storage in the cytoplasm, cytoplasmic clearing to the hematoxylin-eosin staining is a distinguishing feature of PCCCL [19]. Owing to the relative rareness, most studies regarding PCCCL have been case reports or small, single-institution studies, rendering the epidemiology, etiology, and pathogenesis poorly understood [20]. To the best of our knowledge, the present study included the largest published cohort of PCCCL patients and was the first to characterize the clinicopathologic properties, demographic features, treatment outcomes, and prognostic factors.

PCCCL has previously been reported to have low mortality and incidence (< 10% of HCC cases) [12, 13, 21–23]. A morbidity of 8.7% has been observed in America [22]. Additionally, PCCCL has been detected in 9.3% [9], and 6.7–13.3% [4, 24] of the HCC patients in Japan and China, respectively. As expected, our results confirmed the rarity of PCCCL; we found that, between 2004 and 2016, 33345 cases (data not shown) were diagnosed as single primary HCC with positive histology confirmation, and 349 of them (1.05%) were PCCCL.

In this study, the average age of PCCCL patients was 64.1 years (range: 18–94 years), which was older than those reported by Qing-Yu Liu et al [14] (52 years) and Jung Hee Lee [25] (58.8 years). Regarding sex, our study indicated a male-to-female ratio of 1.43, indicating that males were more prone than females. This observation is in agreement with previous reports [4] [6]. Additionally, most patients (63.3%) were of white ethnicity, reflecting the race distribution of western population. We also observed that the tumors were mostly (68.1%) < 1 cm. This observation differed from the previous observations of the high prevalence of big tumors (> 2.1 cm [9] or 7.28 cm [14] on average). This difference was likely due to the relatively small numbers of cases in these two previous studies (20 cases per study). Furthermore, the observations of Kazutoshi Kida et al are in agreement with ours [12, 26].

In this study, more PCCCL patients were diagnosed as T1 (49.6%), N0 (95.2%), or M0 (85.9%) stage, in addition to more AJCC stage I (44%) or localized stage (61.3%) patients, in accordance with several studies that have shown that PCCCL tends to have less vascular invasion[4, 12], lymph node metastases [14], and extra- or intrahepatic metastasis [3]. This may be attributable to the high incidence of tumor capsule formation [11, 27], presumably caused by the stable expression of type I and III procollagen [4, 28]. In line with this, our study showed that the patients without vascular invasion accounted for 61.3% of the sample size.

PCCCL has hitherto been considered a highly differentiated subtype of HCC [29]. Our results were confirmative, showing that high and moderate differentiation were present in 16.1% and 34.3% of the patients, respectively.

The clinical prognosis of PCCCL patients remains disputed. Most studies have indicated that patients with PCCCL had better outcome than those with other subtypes of HCC [10, 22, 30, 31]. Zhisheng Liu et al [4] have reported that PCCCL patients had a 5-year OS rate of 39% and a median OS of 40 months. Wei XU et al [5] have suggested a good prognosis, with a 5-year OS and DSS of 58.5% of 48.6%, respectively, whereas another study [11] has estimated 35.9% and 28.1%. Even the spontaneous regression of primary and metastatic PCCCL lesions occasionally occur [19]. Meanwhile, several studies have claimed that the prognosis of PCCCL is poor [9]. However, the limited numbers of cases render these conclusions unreliable. Here, we observed a 5-year OS and DSS of 23.2% and 28.3%, respectively, and a median OS and DSS of 19 and 24 months. Accordingly, our findings support the former view that PCCCL patients have a bad clinical outcome. Although our results are inconsistent
with the mainstream, we have included 248 cases of PCCCL patients in the cohort study, reinforcing the reliability of our conclusions.

Kaplan-Meier and Cox regression analyses revealed that the increased tumor size was independently correlated with low OS and DSS rates in PCCCL patients. This association agreed with the conclusion of Zu-Shun Chen et al [11] that tumor size was a prognostic indicator for OS, disagreeing with Wei XU et al [5], who have claimed that the Edmondson grade is the only independent risk. This difference may be attributable to the involvement of a small patient cohort (38 cases in the study of Wei XU et al), hindering an accurate estimation.

Different socioeconomic factors, such as marital status, have increasingly been identified as having obvious impacts on oncologic prognosis [32, 33]. Marriage has been shown to be correlated with improved clinical outcome in testicular [34], colon [35], and epithelial ovarian [36] cancers. However, the association between marital status and PCCCL prognosis has never been validated. Here, we found that marriage was independently associated with significant improvement in the OS and DSS. Accordingly, the clinical significance of this study is that it highlights the impact of marriage on the survival of PCCCL patients. Therefore, our study results may draw public attention to increase the social support for vulnerable populations, such as widow(er)s, thereby markedly maximizing the survival.

Insurance status is another important socioeconomic factor affecting the prognosis of cancer patients. Receiving a continuous and high-quality treatment by means of insurance significantly improves the survival of patients with cancer, such as small intestine adenocarcinoma [37] and colorectal cancer [38]. To our knowledge, this is the first study that has explored the correlation between PCCCL outcome and insurance status in a population-based study. We found that the patients without insurance but with any medicaid had worse outcome than those with insurance. Similarly, Na Wang et al [37] have reported that patients with small intestine adenocarcinoma with insurance coverage have a significantly better OS than those with medicaid or without insurance. Moreover, Rosenberg AR et al [39] have suggested that patients uninsured or under medicaid coverage had 2.4 and 3.2 times higher risks to present stage IV disease, respectively, than insured patients. Accordingly, this study highlights the significance of governmental support on health insurance coverage.

Surgery may be the most important factor affecting the survival. Since PCCCL is more prone to forming capsules, surgical resection is an effective way to eliminate lesions containing intact capsules, thereby improving the survival [40]. Surgery has been suggested to provide a long-term survival for PCCCL patients [27]. Here, we found that the PCCCL patients who received no surgery had a shorter survival (median OS: 7 months; median DSS: 9 months) than those who underwent surgeries. We observed that total proctectomy and colectomy combination offered the longest survival (median OS: 124 months) for the PCCCL patients, followed by local tumor excision (median OS: 55 months; median DSS: 56 months), and wedge or segmental resection/partial proctosigmoidectomy (median OS and DSS: both 34 months). Therefore, surgical interventions should be used as the first-line treatment.

Although surgical resection is effective in treating PCCCL, adjuvant treatments, such as radiation therapy, has increasingly been receiving attention. Radiation therapy has been reported as an important clinical application in various tumors [41]. However, our results showed that radiotherapy had no significant effect on the prognosis of PCCCL patients. This observation may be due to the special pathological type of PCCCL. Similarly, traditional chemo- and radio-therapy are largely ineffective in treating any renal cell carcinoma subtype, and the underlying mechanistic reasons need to be further explored [42].
In this study, we also reported a correlation between the pathological grade and AJCC stage of PCCCL. Kaplan-Meier analysis results showed that a higher AJCC stage or pathological grade was associated with decreased survival. Moreover, the grade I PCCCL patients were found more likely to present with AJCC stage I, implying that the patients with higher pathological grades should receive a systemic examination for metastases.

Similar with other retrospective studies using data from the SEER database, there are some limitations in our research. Firstly, the detailed chemotherapy information was not available in the database. Lack of these data is not conducive to our understanding of the treatments for PCCCL. Secondly, the patient data mainly illustrated the clinical characteristics of PCCCL in America and might not be globally applicable. Thirdly, we failed to collect the data about the proportion of clear cells and capsule formation. However, most studies indicated that capsule formation or high proportion of clear cells is beneficial to prolong the survival time [5]. Fourthly, there are no data about any PCCCL-related genetic abnormalities in the SEER database. As known, oncogenic mutations or DNA abnormalities play an important role in the progression and chemo- and radio-sensitivities of various tumors [43]. Aggressive morphologic features and aneuploidy have been reported to be associated with the prognosis of PCCCL [44]. Clear cell HCC shows a higher frequency of IDH1 mutation, which is associated with shorter survival times [25]. Lack of such information limits our full understanding of PCCCL.

In conclusion, in our exploratory research on PCCCL patients, we used the SEER dataset to characterize the demographic, clinical, survival, and therapeutic features of PCCCL patients. Our study showed a poor outcome of PCCCL, which was more common in males and prone to be localized. Moreover, insurance, tumor size, and marital status were independent prognostic factors for the OS and DSS of the PCCCL patients, whereas race was only correlated with the OS. Surgery intervention could improve the outcome; however, radiotherapy failed to lengthen the survival time. Additionally, grade I PCCCL patients were found more likely to present AJCC stage I.

**Abbreviations**

Epidemiology and End Results; OS: overall survival; DSS: disease-specific survival; PCCCL: primary clear cell carcinoma of the liver; SEER: Surveillance, HR: The hazard ratio; OR: odds ratio; MST: median survival time

**Declarations**

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**Competing interests**

The authors declare that they have no conflict of interest.

**Author contribution Statement**
Jie Wen: research concept and design, acquisition and analysis of data, and drafting the work; Abudureyimujiang Aili and Xueyan Yao: data analysis and revising it critically; Abudureyimujiang Aili, Lixiang Xue and Junjie Wang: funding critical revision.

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**Availability of data and materials**

The data were abstracted from an open database, the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov).

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

As the patients' data in the SEER dataset are publicly available, therefore, no approval was required from any institutional review board.

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Figures

![Figure 1](image-url)

Kaplan–Meier analysis: overall survival curves and disease-specific survival of PCCCL for the entire cohort. 3-, 5-, and 10-year OS rates were 33.8%, 23.2%, and 12.2%, respectively. 3-, 5-, and 10-year DSS rates were 39.8%, 28.3%, and 19.1%, respectively. Median OS and DSS were 19 and 24 months, respectively.
Figure 2

Kaplan–Meier analysis of the variables. Kaplan-Meier estimates of the OS and DSS stratified by (A-B) age, (C-D) extent of disease, (E-F) insurance status.
Figure 3

Kaplan–Meier analysis of the variables (Continued from Fig. 2). Kaplan-Meier estimates of the OS and DSS stratified by (A-B) pathological grade, (C-D) marital status, (E-F) invasion status.
Figure 4

Kaplan–Meier analysis of the variables (Continued from Fig. 3). Kaplan-Meier estimates of the OS and DSS stratified by (A-B) tumor size, (C-D) AJCC T stage, (E-F) AJCC M stage.
Figure 5

Kaplan–Meier analysis of the variables (Continued from Fig. 4). Kaplan-Meier estimates of OS and DSS stratified by (A-B) AJCC N stage, (C-D) AJCC stage, (E-F) surgery.
Figure 6

Distribution of the AJCC stage at the presentation of PCCCL according to the pathological grade. Patients with lower pathological grades were more likely to present with earlier AJCC stage tumors.

Supplementary Files

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