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ORIGINAL RESEARCH

# Clinical Implications and Novel Insights into Adolescent Primary Liver Cancer: A Nightmare for Adolescents?

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**Objective:** This study retrospectively analyzed clinical data from adolescent primary liver cancer (PLC) cases over the past decade, summarizing clinical characteristics, diagnostic approaches, and prognostic outcomes to provide guidance for prevention, early diagnosis, and timely treatment of adolescent PLC.

**Methods:** Clinical data of 497 cases of adolescent PLC patients were collected from January 1, 2014, to December 31, 2024. The baseline demographic data, general condition, imaging, laboratory findings, and pathological features of these patients were described, and the diagnostic and therapeutic processes were analyzed, univariate and multivariate Cox regression analyses were conducted to identify significant prognostic factors.

**Results:** The age of onset for patients was 13.75 (10.25–19.00) years, with 311 males (62.58%) and 186 females (37.42%), yielding a male-to-female ratio of 1.67:1. Elevated ALT and GGT levels were observed in most patients, while all patients exhibited elevated ChE. Among all patients included in this study, 320 cases (64.39%) were infected with HBV, 469 cases (94.36%) were diagnosed with hepatocellular carcinoma (HCC), 14 cases (2.82%) with intrahepatic cholangiocarcinoma, and 14 cases (2.82%) with mixed hepatocellular-intrahepatic cholangiocarcinoma. The follow-up results showed the 1-year, 2-year, and 3-year survival rates in adolescent PLC patients were 45.27%, 20.32%, and 8.45%, respectively. The univariate Cox regression analysis revealed that adolescent PLC patients who accompanied with portal vein tumor thrombus, ascites, advanced CNLC stage, abnormalities in AFP, ALT, AST, AST/ALT ratio, GGT, ALP and TBIL, high ECOG score and non-surgical treatment had shorter OS ($P < 0.05$). Multivariate Cox regression analysis showed that portal vein tumor thrombus, advanced CNLC stage, abnormalities in AFP, GGT, and non-surgical treatment were independent prognostic factors influencing the OS of adolescent PLC patients ($P < 0.05$).

**Conclusion:** Clinical manifestations and symptoms of adolescent PLC patients lack specificity, and portal vein tumor thrombus, advanced CNLC stage, abnormalities in AFP, GGT, and non-surgical treatment were independent prognostic factors influencing OS in adolescent PLC.

**Keywords:** adolescents, primary liver cancer, clinical characteristics, prognosis, risk factors, special population, malignant tumor

## Introduction

Primary liver cancer (PLC) is one of the most lethal malignancies globally, with increasing incidence and mortality rates among adults, drawing significant attention.[1–3] However, adolescent PLC remains a rare but highly invasive disease, with many unresolved questions regarding its epidemiological patterns, pathogenic mechanisms, and clinical management

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strategies.[4,5] Recent lifestyle and environmental changes have led to a younger onset age for liver cancer in adolescents, with rising case numbers in certain regions, suggesting unique carcinogenic risks and pathophysiological features in this group.

According to the World Health Organization (WHO), adolescence spans ages 10–19.[6,7] This developmental stage is critical for self-exploration, education, social skills, emotional maturity, responsibility, ethics, future planning, and independence.[8,9] Developing PLC during this period represents a severe life challenge, imposing substantial burdens on families and society. Unfortunately, adolescent PLC exhibits greater heterogeneity compared to adult cases.[10,11] Its etiology often involves inherited metabolic disorders (eg, tyrosinemia, Wilson's disease), chronic hepatitis virus infections, or specific gene mutations (eg, CTNNB1, TERT promoter variants).[12–14] Clinical manifestations are typically non-specific, including abdominal pain, bloating, and jaundice. Diagnosis is frequently delayed due to overlapping symptoms with other conditions, leading to missed or misdiagnoses. Additionally, traditional treatments such as surgical resection, liver transplantation, or targeted therapies lack robust evidence for efficacy and safety in adolescents.[15–17] Current research on adolescent PLC is limited to small-sample retrospective analyses, lacking systematic molecular profiling and prospective clinical trial data, resulting in insufficient evidence for guideline recommendations.[11]

Therefore, this study aims to systematically investigate and elucidate the clinical characteristics of adolescent primary liver cancer by integrating multi-center clinical data and conducting comprehensive data analysis. The findings are anticipated to provide a robust scientific foundation for enhancing early diagnosis rates, refining treatment decisions, and improving long-term prognosis in adolescent liver cancer patients. Furthermore, they may offer novel perspectives on the age-specific mechanisms underlying hepatocarcinogenesis.

# Materials and Methods

## Research Subjects

From January 1, 2014, to December 31, 2024, a total of 497 adolescents clinically and pathologically diagnosed with PLC were recruited from four major medical centers: the First Affiliated Hospital of Gannan Medical University, the Third Affiliated Hospital of Naval Medical University (Eastern Hepatobiliary Surgery Hospital), the Affiliated Hospital of Putian University, and the Fujian Medical University Union Hospital. All patients underwent complete treatment courses (diagnosis, treatment, and rehabilitation) within these hospitals, ensuring comprehensive data collection. Ethical approval was obtained from medical ethics committee of each centers, adhering to the Declaration of Helsinki. Informed consent was provided by all patients or their guardians, and the study protocol received official ethical clearance. The scientific research technology roadmap for this study is presented in detail in Figure 1.

## Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age between 10 and 19 years. (2) Compliance with the "Standards for Diagnosis and Treatment of Primary Liver Cancer"[18–20], and also meets the Child-Pugh classification criteria (Table 1). (3) First-time confirmation of PLC via hospital-based departments. (4) Patients initially diagnosed elsewhere but untreated and subsequently admitted for treatment. (5) Complete clinical and course data.

Exclusion criteria: (1) Lost to follow-up. (2) Death within one full treatment cycle post-diagnosis. (3) Presence of other malignancies or metastatic liver cancer. (4) Significant data deficiencies or non-standardized diagnosis/treatment. (5) Refusal to participate due to privacy concerns or psychological/mental issues.

## Diagnostic Criteria

Referencing the Chinese version of the "Standards for Diagnosis and Treatment of Primary Liver Cancer".[18–20] Pathological diagnostic criteria (gold standard): Biopsy or surgical excision of hepatic lesions or extrahepatic metastases confirmed histopathologically/cytologically as PLC. Clinical diagnostic criteria: PLC can be clinically diagnosed when (1) + (2) a or (1) + (2) b+ (3) of the following conditions are met:

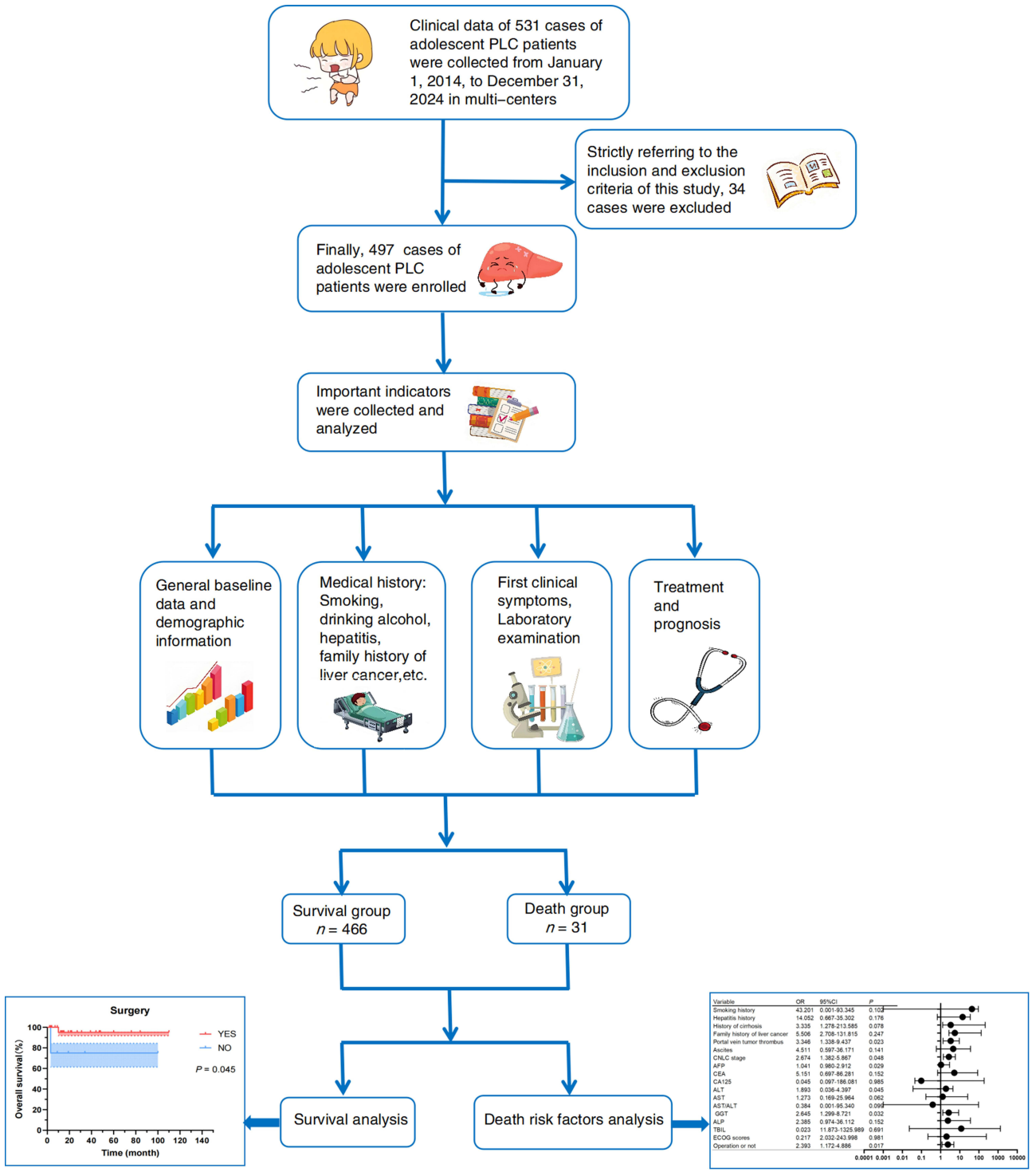


**Figure 1** The scientific research technology roadmap for this study.

1. Patients with a history of viral hepatitis B or C, or cirrhosis of any etiology;
2. Typical imaging features: Dynamic enhanced MRI, enhanced CT, contrast-enhanced ultrasound, or hepatocellular-specific gadolinium-based contrast agent-enhanced MRI showing significant arterial phase enhancement of the lesion(s), followed by washout in the portal venous or equilibrium phase, indicative of the "fast-in and fast-out" characteristic. a. If the diameter of the intrahepatic nodule exceeds 2 cm and only one of the four aforementioned


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**Table 1** Child-Pugh Classification of Liver Function

| Parameters | Child-Pugh Classification | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Total bilirubin | <34 | 34-51 | >51 |
| Serum albumin (g/L) | >35 | 28-35 | <28 |
| Prothrombin time (s) | 1-3 | 4-6 | >6 |
| Ascites | Absent | Mild | Moderate |
| Hepatic encephalopathy | Absent | 1-2 | 3-4 |

**Notes**: A level, 5–6 scores; B level, 7–9 scores; C level, 10–15 scores.

imaging modalities demonstrates typical PLC features, a diagnosis of PLC can be made. b. If the diameter of the intrahepatic nodule is less than 2 cm, at least two of the four imaging modalities must demonstrate typical features for a diagnosis of PLC to be established.

3. Alpha-fetoprotein (AFP) ≥ 400 μg/L, particularly in cases of continuous elevation, after excluding pregnancy, chronic or active liver disease, gonadal embryonal tumors, and digestive tract malignancies.

The conceptual diagram illustrating the clinical diagnosis and staging of PLC patients in this study is elaborated in Figure 2.

## Relevant Definitions of Lifestyle Habits

Smoking history: Defined per WHO guidelines, individuals smoking continuously for ≥6 months are classified as smokers; those without smoking/passive smoking histories are non-smokers.[21,22] Besides, drinking history: Based on the "Guidelines for Prevention and Treatment of Non-Alcoholic Fatty Liver Disease",[23,24] patients are categorized into no-drinking, moderate

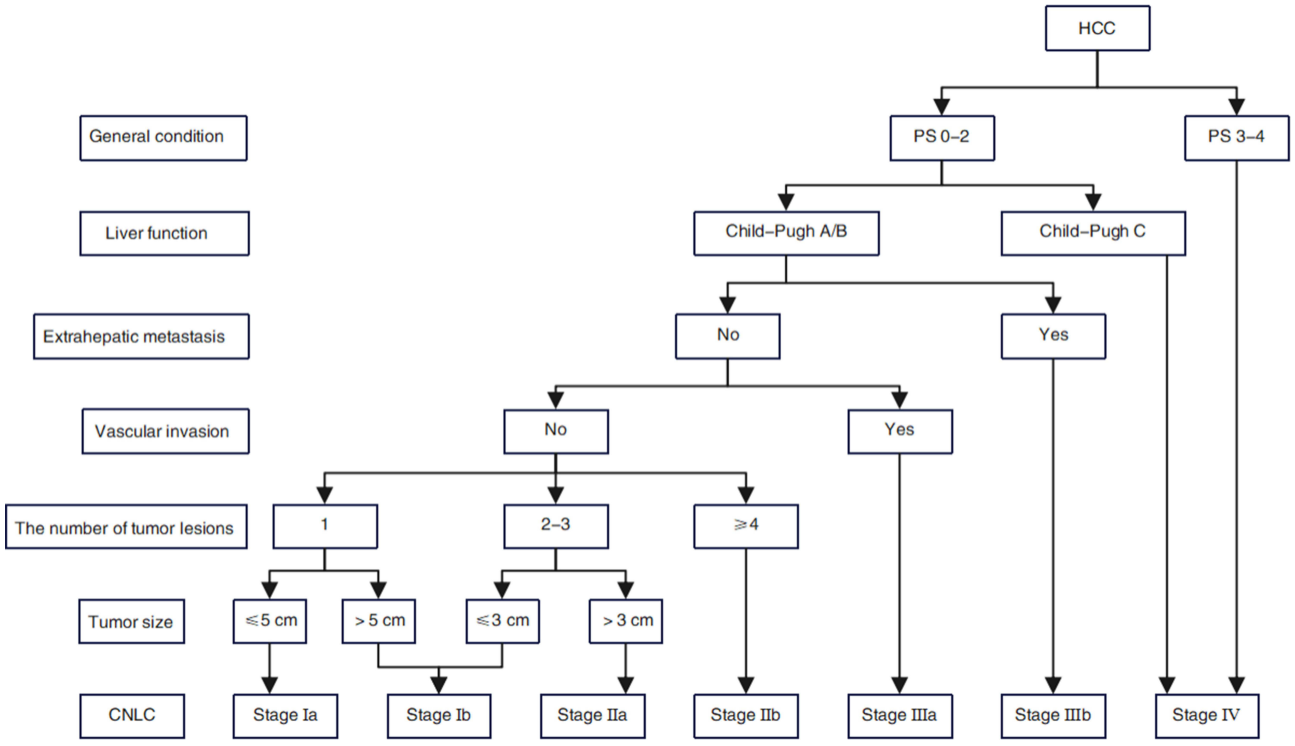


**Figure 2** CNLC staging criteria for primary liver cancer.

drinking (≤5 years, ≤40 g/day for men or ≤20 g/day for women), and excessive drinking (>5 years, >40 g/day for men or >20 g/day for women). Ethanol content = alcohol consumption (mL) × ethanol percentage (%) × 0.8.

## Collection and Organization of Clinical Data

Demographic characteristics of patients across multiple centers were systematically collected and organized: age, sex, living environment, personal history (smoking, drinking), hepatitis history, family liver cancer history, initial symptoms, main clinical manifestations, detection methods; Laboratory tests: neutrophil-to-lymphocyte ratio (NLR), liver function markers (ALT, AST, AST/ALT, ALP, GGT, ChE, TBIL, ALB), prothrombin time, Child-Pugh grade, CNLC stage, tumor markers (AFP, CEA, CA199, CA125, SF); Imaging findings: tumor size, ascites, portal vein thrombosis, extrahepatic metastasis, cirrhosis status, metastatic involvement (intrahepatic/extrahepatic); Child-Pugh classification, CNLC stage, treatment modalities, and survival duration. Besides, we conducted a retrospective study and analysis of the clinico-pathological classification and molecular biology (mutated genes) detection results of the enrolled patients.

## PCR Detection and Sequencing of HBV Gene

The HBV gene S was amplified using the nested PCR method as described before,[25] and positive PCR product was recovered, purified and sent for sequencing. The primers used for amplification included a pair of outer primers for amplification, including forward, 5′-ACCWTATWCYTGGGAACAA-3′; and reverse, 5′-TCAGCAAAYACTYGGCA-3′. Besides, two pairs of inner primers, Ia forward, 5′ACCWTATWCYTGGGAACAA-3′; and reverse, 5′-GAYGAYGGGATGGGAATACA-3′, and Ib forward, 5′-GACTYGTGGTGGACTTCTC-3′; and reverse, 5′-TCAGCAAAYACTYGGCA-3′. The PCR amplification reaction mixture contained 5 μL 5X KAPA2G buffer A, 5 μL 5X KAPA enhancer, 0.1 μL of KAPA2G RobustHotStart DNA polymerase, 0.5 μL of 10 μM dNTP Mix (TaKaRa, Japan), 1 μL of a 10M solution of each primer, 3 μL DNA template and water for PCR to fill up to a final volume of 25 μL in each 25 μL reaction tube. The first round of amplification included: pre-denaturation at 95°C for 3 min; followed by 5 cycles of denaturation at 95°C for 30s, annealing at 57 to 53°C for 30s and extension at 72°C for 30s; followed by 30 cycles of denaturation at 95°C for 30s, annealing at 53°C for 30s and extension at 72°C for 30s; and a final extension at 72°C for 2 min. The PCR products from the first round of amplification were used as the DNA template in the second round of amplification, which was performed using the same amplification conditions and reaction system as in the first round. The primers used for amplification were also used as the primers for sequencing. The information obtained from sequencing was assembled using the subprogram SeqMan of Lasergene software (DNAstar 7.1, USA) followed by a comparison of the sequences using BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

## Detection of Laboratory Indices and Normal Reference Value Ranges

Hepatitis B serology was assessed using an automated immunoanalyzer and corresponding reagents, including hepatitis B surface antigen (HBsAg, normal reference value < 0.05 IU/mL), hepatitis B surface antibody (HBsAb, normal reference value < 10 mIU/mL), hepatitis B e antigen, e antibody, and core antibody (qualitative detection).

Hepatitis B virus DNA (HBV-DNA, lower limit of detection $3.0\times10^1$ IU/mL) and hepatitis C virus RNA (HCV-RNA, lower limit of detection $5.0\times10^1$ IU/mL) were quantified using an automated nucleic acid workstation and corresponding reagents. Liver function biochemical indices were measured using an automated biochemical analyzer and corresponding reagents, including alanine aminotransferase (ALT, normal reference value 9–50 U/L), aspartate aminotransferase (AST, normal reference value 15–40 U/L), alkaline phosphatase (ALP, normal reference value 45–125 U/L), γ-glutamyltransferase (GGT, normal reference value 10–60 U/L), cholinesterase (ChE, normal reference value 4.6–11.5 kU/L), total bilirubin (TBIL, normal reference value 5–21 μmol/L), and serum albumin (ALB, normal reference value 40–55 g/L).

Tumor markers were detected using an immunoanalyzer and corresponding reagents, including alpha-fetoprotein (AFP, normal reference value < 20 ng/mL), carcinoembryonic antigen (CEA, normal reference value: non-smokers < 3.0 μg/L, smokers < 5.0 μg/L), serum ferritin (SF, normal reference value: females 11.0–306.8 μg/L, males 23.9–336.2 μg/L), carbohydrate antigen 19–9 (CA19-9, normal reference value < 35 kU/L), and carbohydrate antigen 125 (CA125, normal reference value < 35 kU/L). Positive values were defined as exceeding or falling below the upper limit of the normal reference range.

Peripheral blood neutrophil and lymphocyte percentages ranged from 50% to 70% and 20% to 40%, respectively. The neutrophil-to-lymphocyte ratio (NLR) in peripheral venous blood ranged from 1.25 to 3.5, with a mean of 2.375. An NLR cutoff of 2 was used for evaluation, where NLR ≤ 2 indicated the low NLR group and NLR > 2 indicated the high NLR group. Alcohol exposure criteria were defined as consuming alcohol more than twice per month for over one year.

## Treatment Strategies and Methods

Transarterial Chemoembolization (TACE) Treatment Group (Interventional Therapy): Prior to the procedure, all necessary equipment, materials, and patient preparations were completed. The femoral or radial artery was selected for puncture, followed by catheter sheath insertion. Arteriography was then performed to identify the tumor's blood supply artery. Superselective catheterization was conducted into the tumor-feeding arterial branch, and chemotherapy agents were slowly administered. These agents were subsequently mixed with iodized oil to form an emulsion, which was then injected. The injection was terminated in a timely manner based on the procedural requirements. Granular embolic agents were then administered until the embolization endpoint was achieved. Upon completion of the procedure, the catheter and sheath were removed, and manual pressure was applied to achieve hemostasis, followed by wound dressing. Patients were instructed to remain in a supine position with immobilization of the lower limb on the punctured side for 6 hours. Electrocardiogram monitoring and symptomatic management were conducted for 2 days postoperatively. Strict adherence to aseptic principles was required throughout the entire procedure. Close monitoring of the PLC patient's condition was essential, and any complications were to be addressed promptly.

TACE Combined with Immunotherapy and Targeted Therapy: Interventional procedures such as TACE can destroy tumor lesions and promote the release of numerous tumor-associated antigens. Additionally, TACE can modulate the immunosuppressive tumor microenvironment, enabling immune checkpoint inhibitors and the host immune system to effectively recognize tumor cells. Immune checkpoint inhibitors, such as PD-1/PD-L1 antibodies, can alleviate tumor ischemia and necrosis induced by TACE, facilitate antigen release, enhance T-cell cytotoxic activity, and generate an "in situ vaccine" effect. Anti-angiogenic targeted agents, including lenvatinib and bevacizumab, inhibit tumor neovascularization, block residual tumor blood supply post-TACE, improve the tumor microenvironment, and promote immune cell infiltration. While TACE targets the primary tumor lesion, immunotherapy and targeted agents address potential micrometastases, achieving comprehensive "local + systemic" disease control.

Conservative Treatment Group: Patients with impaired liver function received supportive therapies, including hepatoprotection, enzyme reduction, and albumin supplementation. Hepatoprotective agents primarily included anti-inflammatory, antioxidant, and hepatocyte membrane-stabilizing medications. Concurrently, general supportive measures such as anti-tumor proliferation therapy, immune modulation, and nutritional support were implemented.

## Prognostic Follow-Up

Follow-up was conducted via telephone, outpatient visits, or inpatient assessments. The time of diagnosis served as the starting point, and the endpoint was defined as either death or the conclusion of follow-up. Median survival was calculated in months. The follow-up period for this study extended until January 1, 2025. By the end of the follow-up period, 31 out of 497 enrolled subjects had died, while 466 remained alive. The 497 patients included in this study were categorized into two groups: the death group, comprising patients who died by the end of follow-up, and the survival group, consisting of patients who were still alive at that time.

## Statistical Methods

Clinical data were organized using Excel tables and analyzed using SPSS 26.0 statistical software. Normally distributed measurement data were expressed as *mean ± standard deviation* ($X \pm SD$), and intergroup comparisons were performed using the *T*-test. Non-normally distributed measurement data were expressed as median (interquartile range, $P_{25}$–$P_{75}$), and intergroup comparisons were conducted using the Mann–Whitney *U*-test. Counting data were compared between groups using the chi-square test, corrected chi-square test, or Fisher's exact probability method. Univariate analysis was performed using the Kaplan-Meier method, and differences were tested using the log-rank method. Survival and

prognosis analyses were conducted using the COX multi-factor risk regression model. $p$-value < 0.05 was considered statistically significant.

# Results

## Demographic Baseline Data

As presented in Table 2, an analysis of age, gender, and residential background among all patients revealed that the mean age of onset was 13.75 years (interquartile range: 10.25–19.00 years). Of the total cohort, 311 were male (62.58%) and 186 were female (37.42%), yielding a male-to-female ratio of 1.67:1. Additionally, 257 cases (51.71%) resided in rural areas, while 240 cases (48.29%) lived in urban areas.

**Table 2** General Baseline Data of Adolescent Patients with Primary Liver Cancer

| **Categories** | **n (%)** |
|---|---|
| Age (years) | |
| 10~14 (≤14) | 98 (19.72%) |
| 14 (>14) ~19 | 399 (80.28%) |
| Gender | |
| Male | 339 (68.21%) |
| Female | 158 (31.79%) |
| Life background | |
| Village | 257 (51.71%) |
| City | 240 (48.29%) |
| History of viral hepatitis | |
| Yes | 356 (71.63%) |
| No | 141 (28.37%) |
| Received anti-hepatitis virus therapy | |
| Yes | 320 (64.39%) |
| No | 177 (35.61%) |
| Family history of hepatitis B | |
| Yes | 78 (15.69%) |
| No | 419 (84.31%) |
| Family history of cirrhosis | |
| Yes | 19 (3.82%) |
| No | 478 (96.18%) |
| Family history of liver cancer | |
| Yes | 16 (3.22%) |
| No | 481 (96.78%) |

(*Continued*)


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**Table 2** (Continued).

| Categories | n (%) |
|---|---|
| History of drinking | |
| Yes | 42 (8.45%) |
| No | 455 (91.55%) |
| History of smoking | |
| Yes | 29 (5.84%) |
| No | 468 (94.16%) |

Medical History analysis revealed that among all patients included in this study, 356 cases (71.63%) had a history of viral hepatitis, of which 320 cases (89.89%) had a history of hepatitis B and 36 cases (10.11%) had a history of hepatitis C. Among all patients with viral hepatitis, 320 received antiviral therapy (241 cases with regular antiviral therapy and 79 cases with irregular antiviral therapy), while the remaining 58 cases of patients either did not receive or were unaware of receiving antiviral therapy.

Additionally, family history analysis showed that 97 cases (19.51%) had a clear family history of hepatitis B or post-hepatitis B cirrhosis. 16 cases (3.22%) had a clear family history of liver cancer. Personal history data indicated that 42 cases (8.45%) had a history of alcohol consumption, all of whom were male, while none of the female patients reported alcohol consumption. In this study, a total of 29 patients (5.84%) had a smoking history, and the rest denied any smoking history.

## First Clinical Symptoms

As shown in Figure 3, among adolescent patients with PLC included in this study, the most common first-visit symptom was abdominal pain (215 cases [43.26%]), followed by physical examination findings (127 cases [25.55%]), fatigue and poor appetite (46 cases [9.26%]), and jaundice (33 cases [6.64%]). Additionally, a total of 37 cases (7.44%) presented

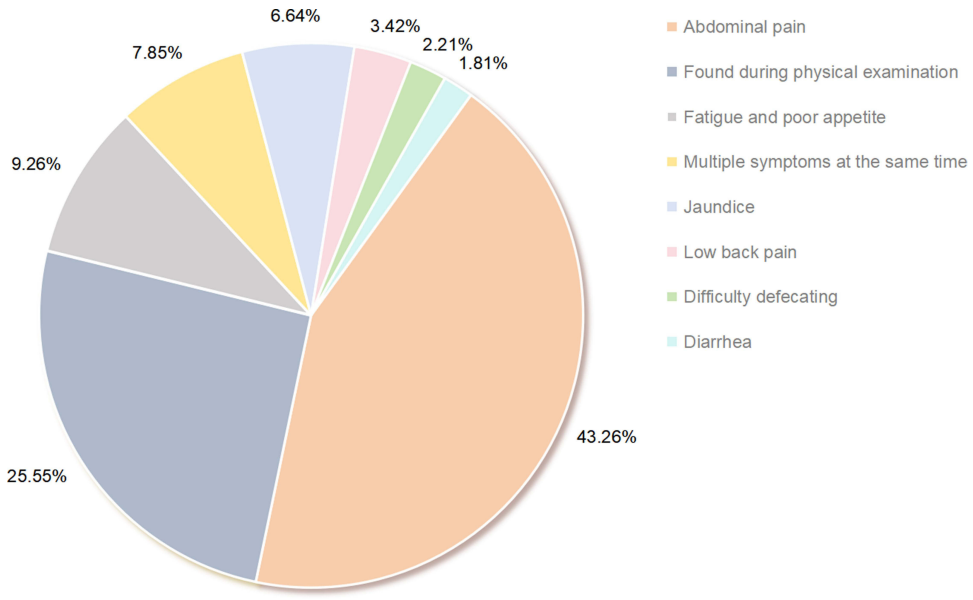


**Figure 3** Distribution of first clinical symptoms in adolescent patients with PLC.

with other less frequent symptoms, including diarrhea (9 cases [1.81%]), low back pain (17 cases [3.42%]), difficulty in defecation (11 cases [2.21%]), and multiple symptoms (39 cases [7.85%]).

## Analysis of Biochemical Liver Function Results

Biochemical tests of liver function were performed on all adolescent patients with primary liver cancer included in this study, including ALT, AST, AST/ALT ratio, GGT, ALP, ChE, TBIL, and ALB. As shown in Table 3, 171 cases (34.41%) had elevated ALT (> 50 U/L), of which 57 cases (11.47%) exceeded twice the upper limit of the normal value. There were 155 cases (31.19%) with elevated AST (> 40 U/L), of which 57 cases (11.47%) exceeded twice the upper limit of the normal range. The AST/ALT ratio was greater than 1 in 43 cases (8.65%). GGT increased in 227 patients (45.67%) (> 60 U/L), of which 98 patients (19.72%) exceeded twice the normal reference value range. There were 84 cases (16.90%) with increased ALP (> 125 U/L). ChE was elevated in all 497 patients (100.00%). There were 85 cases (17.10%) with elevated TBIL (> 21 μmol/L), of which 29 cases (5.84%) exceeded twice the normal value. Seventy cases (14.08%) had decreased ALB (< 40 g/L).

## Analysis of Hepatitis Markers and Virology

All patients included in this study underwent testing for hepatitis B markers, as detailed in Table 4. The specific findings were as follows: A total of 320 cases (64.39%) were infected with HBV, of whom 43 cases (13.44%) tested positive for HBeAg and 277 cases (86.56%) tested negative, indicating a predominance of HBeAg-negative cases. Among these, 172 patients (53.75%) exhibited HBsAg(+)/HBeAb(+)/HBcAb(+), which constituted the majority of positive cases. In contrast, 35 patients (10.94%) tested HBsAg(+)/HBeAg(+)/HBcAb(+). The ratio of HBsAg(+)/HBeAb(+)/HBcAb(+) to HBsAg(+)/HBeAg(+)/HBcAb(+) was 4.91:1. Furthermore, 12 patients (3.75%) tested negative for all five hepatitis B markers, while 8 patients (2.50%) tested positive for surface antigen, e antigen, anti-HBe, and anti-HBc. Four patients (1.25%) tested positive for surface antigen + core antibody, and another four patients (1.25%) tested positive for surface

**Table 3** Test Results of Each Liver Function Index

| Test Items | Indicator Situation | n (%) |
|---|---|---|
| ALT | Normal | 326 (65.59%) |
| | Abnormal rise | 171 (34.41%) |
| AST | Normal | 342 (68.81%) |
| | Abnormal rise | 155 (31.19%) |
| AST/ALT ratio | >1 | 169 (34.00%) |
| | ≤1 | 328 (66.00%) |
| GGT | Normal | 270 (54.33%) |
| | Abnormal rise | 227 (45.67%) |
| ALP | Normal | 413 (83.10%) |
| | Abnormal rise | 84 (16.90%) |
| ChE | Normal | 0 (0.00%) |
| | Abnormal rise | 497 (100.00%) |
| TBIL | Normal | 412 (82.90%) |
| | Abnormal rise | 85 (17.10%) |
| ALB | Normal | 427 (85.92%) |
| | Abnormal decreased | 70 (14.08%) |


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**Table 4** Hepatitis B Marker Test Results in Adolescents with PLC

| Category | Hepatitis B Markers of Detection Items | | | | | n (%) |
|---|---|---|---|---|---|---|
| | HBsAg | HBsAb | HBeAg | HBeAb | HBcAb | |
| Type 1 | (+) | Negative | (+) | (+) | (+) | 8 (2.50%) |
| Type 2 | (+) | Negative | (+) | Negative | (+) | 35 (10.94%) |
| Type 3 | Negative | Negative | Negative | Negative | Negative | 12 (3.75%) |
| Type 4 | (+) | Negative | (+) | (+) | (+) | 172 (53.75%) |
| Type 5 | Negative | (+) | Negative | Negative | (+) | 4 (1.25%) |
| Type 6 | (+) | Negative | Negative | Negative | (+) | 4 (1.25%) |
| Type 7 | Negative | (+) | Negative | (+) | (+) | 3 (0.94%) |
| Type 8 | (+) | (+) | (+) | Negative | (+) | 3 (0.94%) |
| Type 9 | Negative | (+) | Negative | Negative | Negative | 3 (0.94%) |
| Type 10 | Negative | Negative | Negative | Negative | (+) | 1 (0.31%) |
| Type 11 | (+) | (+) | Negative | (+) | (+) | 1 (0.31%) |

**Notes**: The standard of HBV infection is one or more positive items of HBsAg, HBeAg, HBeAb and HBcAb.

antibody + core antibody. Three cases (0.94%) exhibited positivity for three antibodies (HBeAb, HBsAb, HBcAb), two antigens (HBsAg, HBeAg), and two antibodies (anti-HBs, anti-HBc), respectively. While one case (0.31%) respectively, was positive for surface antigen + three antibodies (anti-HBs, anti-HBc, anti-HBe) and only one core antibody was positive.

## Analysis of Tumor Markers

Among all patients included in this study, tumor markers detected included AFP, CEA, SF, CA199, and CA125, with actual detection cases for these indicators being 497, 497, 129, 229, and 213, respectively. A total of 328 cases (66.00%) were positive for AFP (≥9 μg/L), of which 258 cases (51.91%) were positive for AFP (≥400 μg/L). In the AFP-positive group, there were 252 males and 76 females. In the AFP-negative group, there were 87 males and 82 females. There was no significant difference in AFP expression between sexes ($P > 0.05$). All enrolled patients were tested for CEA; however, only 14 patients (2.82%) had positive results (non-smokers ≥3 μg/L, smokers ≥5 μg/L). Among the whole group, 129 patients had SF test results, and 52 cases (40.31%) were positive (male > 336.2 μg/L, female > 306.8 μg/L). There were 229 cases of CA199, and 85 cases (37.12%) were positive (≥35 kU/L). CA125 was detected in 213 cases, and 127 cases (59.62%) were positive (≥35 kU/L).

As shown in Table 5, 497 adolescent PLC patients were stratified into two groups based on the presence of jaundice, portal vein tumor thrombus, ascites, and clinical outcomes. A chi-square test was conducted for each tumor marker. The results demonstrated that, in the factor of jaundice, the expression levels of AFP, CEA, CA199, and CA125 were significantly different between the two groups ($P < 0.05$), the positive rates of AFP, CEA, CA199 and CA125 were higher in the jaundice group ($P < 0.05$); in the factor of portal vein cancer thrombus presence, significant differences were observed in the expression levels of AFP and CA125 between the two groups ($P < 0.05$), the positive rates of AFP and CA125 in the portal vein tumor thrombus group were higher ($P < 0.05$). Regarding the factor of ascites, significant differences in the expression levels of CEA and CA125 were noted between the two groups ($P < 0.05$), the positive rates of CEA and CA125 in the ascites group were higher ($P < 0.05$); and in terms of clinical outcome, a significant difference in the expression level of AFP was identified between the two groups ($P < 0.05$), that is the positive rate of AFP was higher in the death group ($P < 0.05$).

**Table 5** Comparison of Tumor Markers Among Groups in Adolescent Patients with PLC

| **Group 1** | **AFP (n = 497)** | | **CEA (n = 497)** | | **SF (n = 129)** | | **CA199 (n = 229)** | | **CA125 (n = 213)** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) |
| Without jaundice | 314 | 150 | 13 | 451 | 52 | 58 | 124 | 76 | 103 | 77 |
| Jaundice | 14 | 19 | 1 | 32 | 11 | 8 | 11 | 18 | 12 | 21 |
| $\chi^2$ | 8.752 | | 0.939 | | 0.732 | | 8.046 | | 10.837 | |
| *P* | 0.003 | | 0.006 | | 0.392 | | 0.005 | | 0.001 | |
| **Group 2** | **AFP (n = 497)** | | **CEA (n = 497)** | | **SF (n = 129)** | | **CA199 (n = 229)** | | **CA125 (n = 213)** | |
| | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) |
| Without portal vein tumor thrombus | 288 | 169 | 14 | 441 | 53 | 42 | 94 | 102 | 114 | 61 |
| Portal vein tumor thrombus | 40 | 2 | 0 | 42 | 17 | 17 | 21 | 12 | 11 | 27 |
| $\chi^2$ | 17.864 | | 1.330 | | 0.338 | | 2.777 | | 16.870 | |
| *P* | <0.001 | | 0.249 | | 0.561 | | 0.096 | | <0.001 | |
| **Group 3** | **AFP (n = 497)** | | **CEA (n = 497)** | | **SF (n = 129)** | | **CA199 (n = 229)** | | **CA125 (n = 213)** | |
| | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) |
| Without ascites | 325 | 167 | 13 | 479 | 70 | 57 | 113 | 113 | 63 | 148 |
| Ascites | 3 | 2 | 1 | 4 | 0 | 2 | 2 | 1 | 2 | 0 |
| $\chi^2$ | 0.081 | | 5.448 | | 2.410 | | 0.329 | | 4.597 | |
| *P* | 0.776 | | 0.020 | | 0.121 | | 0.566 | | 0.032 | |
| **Group 4** | **AFP (n = 497)** | | **CEA (n = 497)** | | **SF (n = 129)** | | **CA199 (n = 229)** | | **CA125 (n = 213)** | |
| | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) | **(+)** | (-) |
| Survival | 300 | 166 | 32 | 434 | 88 | 85 | 106 | 107 | 76 | 134 |
| Death | 28 | 3 | 0 | 31 | 12 | 4 | 9 | 7 | 1 | 2 |
| $\chi^2$ | 8.719 | | 0.998 | | 3.423 | | 0.250 | | 0.010 | |
| *P* | 0.003 | | 0.318 | | 0.064 | | 0.617 | | 0.919 | |

## Results of Pathological Analysis

All patients enrolled in this study underwent histopathological examination. Among them, 469 cases (94.36%) were diagnosed with hepatocellular carcinoma (HCC), 14 cases (2.82%) with intrahepatic cholangiocarcinoma (ICC), and 14 cases (2.82%) with mixed hepatocellular-intrahepatic cholangiocarcinoma (HIC). As depicted in Figure 4, the pathological microscopy of HCC patients revealed tumor cells arranged in fine trabecular and coarse trabecular patterns, characterized by large polygonal cells. A small degree of fibrous tissue hyperplasia and lymphocyte infiltration was observed in the interstitium. As shown in Figure 5, the pathological microscopy of ICC patients demonstrated tumor cells presenting as small glandular tubular, sieve-like porous, and complex glandular tubular structures. The cells were cuboidal, with significant fibrous tissue hyperplasia and lymphocyte infiltration noted in the interstitium. As illustrated in Figure 6, the pathological microscopy of mixed-cell hepatocellular carcinoma patients exhibited coarse trabecular or small glandular tubular arrangements, with cells being either large polygonal or cuboidal. Extensive fibrous tissue hyperplasia and minimal lymphocyte infiltration were evident in the interstitium. In summary, from a histopathological perspective, positive Hep-1, GS, and CD34 indicate that the tumor originates from hepatocytes; positive CK7 and CK19

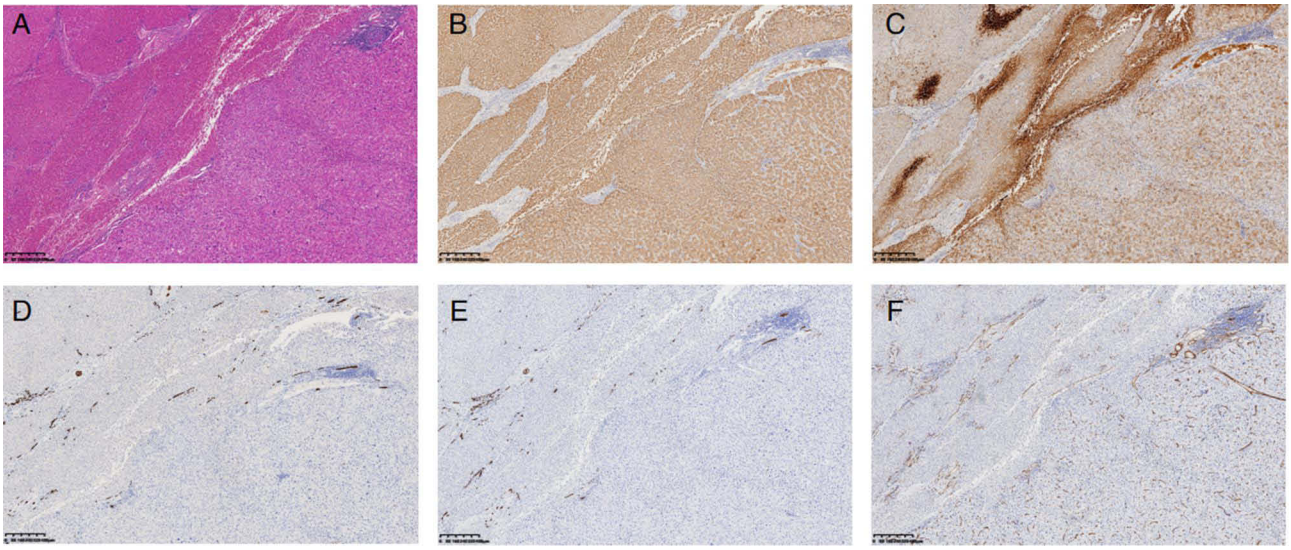


**Figure 4** Pathological examination of HCC patients included in this study ((**A**) HE staining ×40; (**B**) Hep-1 positive, ×40; (**C**) Diffuse positive for GS, ×40; (**D**) CK7 negative, ×40; (**E**) CK19 negative, ×40; (**F**) CD34 shows rich blood vessels (sinusoidal vascularization), ×40).

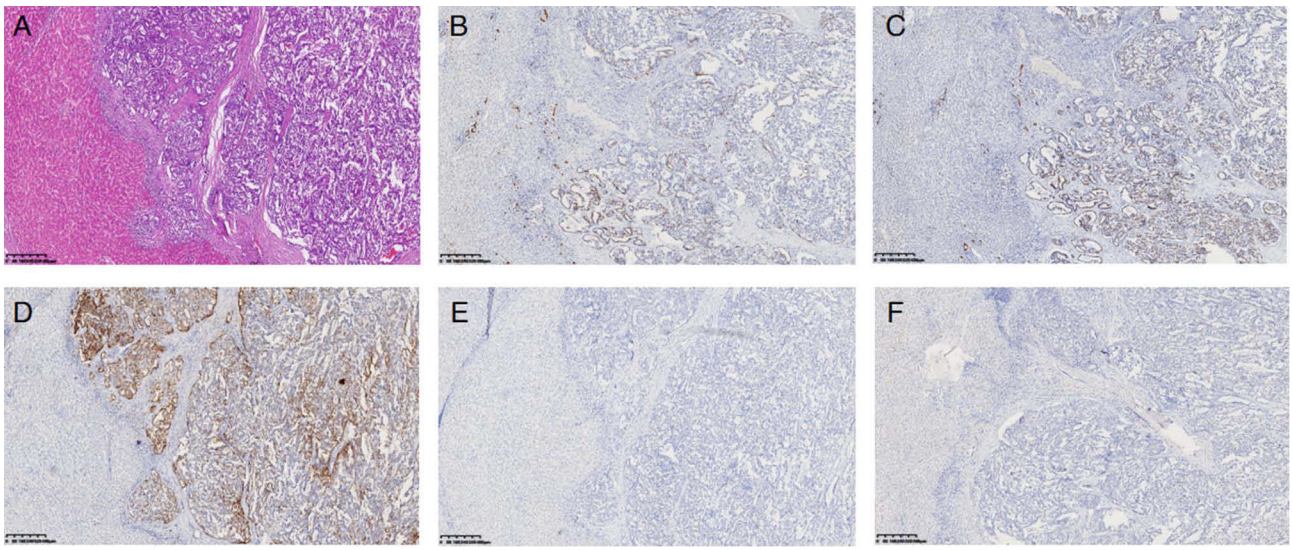


**Figure 5** Pathological examination of ICC patients included in this study ((**A**) HE staining ×40; (**B**) CK7 positive, ×40; (**C**) CK19 positive, ×40; (**D**) Muc-1 positive, ×40; (**E**) Muc-5 negative, ×40; (**F**) CK20 negative, ×40).

suggest bile duct cell origin. When all these markers are positive, combined with morphological characteristics, a diagnosis of mixed-cell liver cancer can be established. Furthermore, Muc-1 marks small bile ducts, Muc-5 marks large ducts, and a positive CK20 indicates intestinal differentiation or, when negative, rules out metastatic adenocarcinoma of intestinal origin.

## Results of Molecular Biology Detection

Among the 497 patients included in this study, molecular biological testing was performed on liver cancer specimens from 384 patients. Of these, 130 patients exhibited molecular biological abnormalities. As detailed in Figure 7, among the molecular abnormalities identified, mutations in nine genes were predominant, with *KRAS* being the most frequently mutated gene.

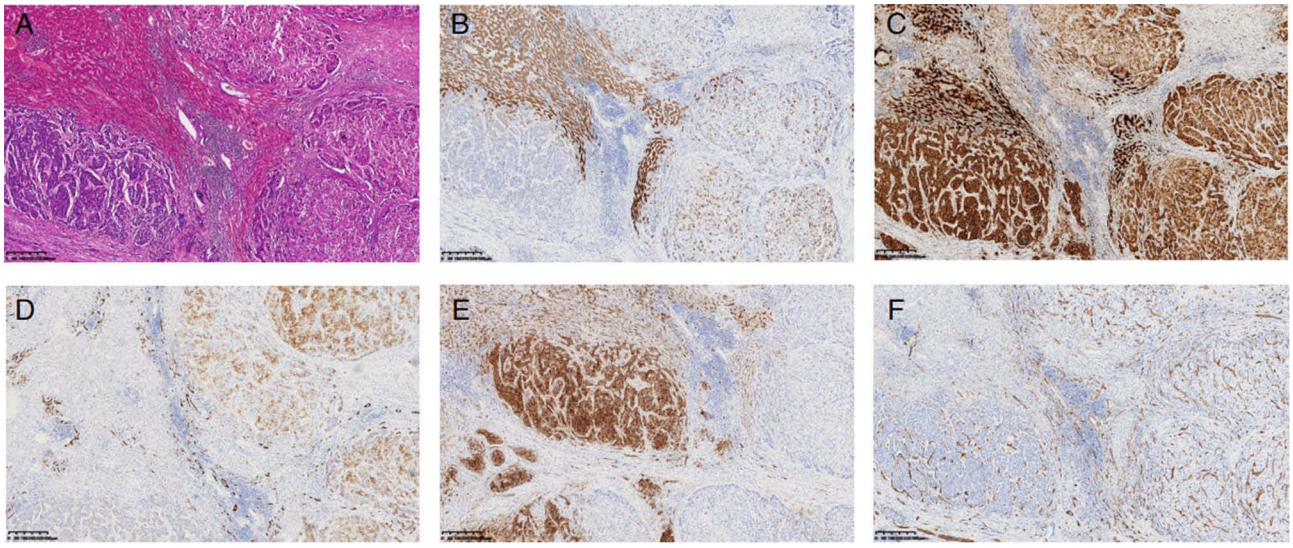


**Figure 6** Pathological examination of mixed-cell hepatoma patients included in this study ((**A**) HE staining ×40; (**B**) Partially positive for Hep-1, ×40; (**C**) Diffuse positive for GS, ×40; (**D**) Partially positive for CK7, ×40; (**E**) Partially positive for CD10, ×40; (**F**) CD34 shows rich blood vessels (sinusoidal vascularization), ×40).

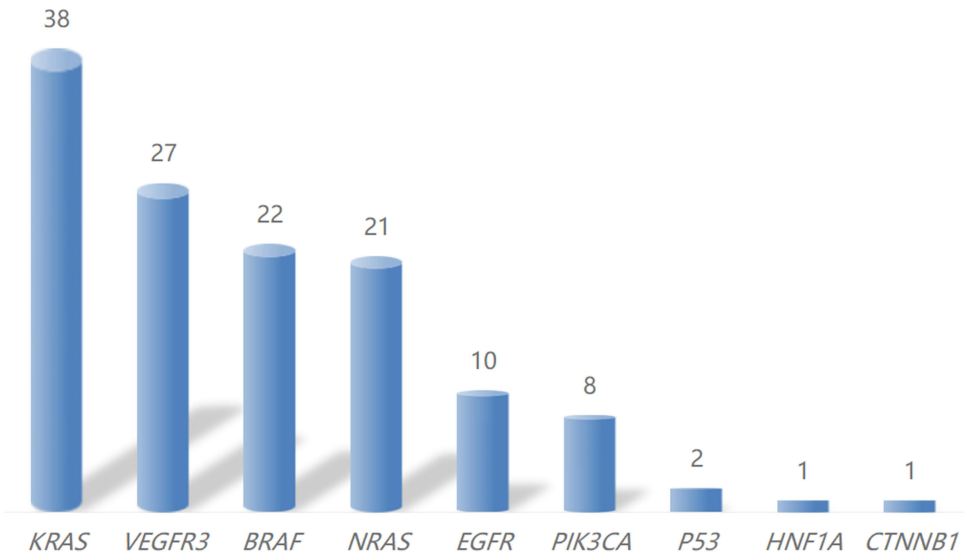


**Figure 7** The molecular biological detection results of adolescent PLC in this study.

## Imaging Results

Abdominal enhanced CT and/or MRI were performed in all patients, with specific analyses as follows: according to imaging results, the Image types could be classified as massive liver cancer, diffuse liver cancer, and nodular liver cancer, accounting for 210 cases (42.25%), 71 cases (14.29%), and 216 cases (43.46%), respectively. It is noteworthy that regarding the size of resected PLC tumors, the maximum diameter distribution among the PLC patients enrolled in this study was categorized as follows: 141 cases had tumors ≤5 cm in diameter, 137 cases fell within the 5–10 cm range, and 219 cases exceeded 10 cm. Among these patients, 134 cases exhibited baseline lymph node metastasis. Based on the abdominal enhanced CT results of all patients included in this study, 258 patients (51.91%) formed portal vein cancer thrombus. As shown in Table 6, out of the 497 patients included in the study, abdominal contrast-enhanced CT scans revealed that 258 cases (51.91%) were diagnosed with portal vein tumor thrombus. Specifically, among the patients with massive-type liver cancer, 152 cases were accompanied by portal vein tumor thrombus and 58 were not. For the nodular


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**Table 6** Relationship Between Image Type and Portal Vein Cancer Thrombus

| Image Type | Portal Vein Cancer Thrombus (Total n = 258) | | Incidence of Portal Vein Cancer Thrombus | $^{a}P$ | $^{b}P$ | $^{c}P$ | $P$ |
|---|---|---|---|---|---|---|---|
| | Yes | No | | | | | |
| Massive PLC (n = 210) | 152 | 58 | 72.38% | 0.587 | <0.001 | <0.001 | <0.001 |
| Diffuse PLC (n = 71) | 49 | 22 | 69.01% | | | | |
| Nodular PLC (n = 216) | 57 | 159 | 26.39% | | | | |

**Notes**: $P < 0.05$, the difference was statistically significant; the comparison between the two groups was corrected by Bonferroni method. $^{a}P$: the comparison between massive and diffuse type; $^{b}P$: the comparison between massive and nodular type; $^{c}P$: the comparison between diffuse and nodular type; $P$: the comparison between massive, diffuse and nodular type.

type, 57 cases were associated with portal vein tumor thrombus, whereas 159 cases were not. In the diffuse-type group, 49 cases were complicated by portal vein tumor thrombus, compared to 22 cases without such complications. Statistical analysis indicated no significant difference in the presence of portal vein tumor thrombus between the massive and diffuse types ($P>0.05$). However, significant differences were observed between the massive and nodular types, as well as between the diffuse and nodular types ($P<0.05$). These findings suggest that both the massive and diffuse types are more prone to developing portal vein tumor thrombus in adolescent PLC patients compared to the nodular type. Ascites, extrahepatic metastasis, and the number of tumors were as follows: 265 cases (53.32%) formed ascites, and 156 cases (31.39%) had extrahepatic metastasis, mainly to the lungs, thoracolumbar vertebrae, and adrenal glands. There were 303 (60.97%) cases with single liver cancer and 194 (39.03%) cases with multiple liver cancers.

## CNLC Stage of Clinical Condition

According to the CNLC staging plan, it can be divided into CNLC phases Ia, Ib, IIa, IIb, IIIa, IIIb, and IV. As shown in Table 7, among all adolescent patients with PLC included in this study, stage I patients accounted for the majority, totaling 360 cases (72.43%), including 175 cases of stage Ia and 185 cases of stage Ib. There were 45 cases (9.05%) in stage II, including 17 cases in stage IIa and 28 cases in stage IIb. There were 84 cases (16.90%) in stage III, including 28 cases in stage IIIa and 56 cases in stage IIIb. There were 8 cases (1.61%) in stage IV.

## Treatment Regimens and Classifications

As illustrated in Figure 8, among the 497 adolescent PLC patients included in this study, treatment modalities were distributed as follows: 298 patients (59.96%) underwent simple surgery, 72 patients (14.48%) received a combination of

**Table 7** CNLC Staging Statistics of Adolescent Patients with PLC

| Clinical Stage | | n (%) |
|---|---|---|
| Stage I | Ia | 175 (35.21%) |
| | Ib | 185 (37.22%) |
| Stage II | IIa | 17 (3.42%) |
| | IIb | 28 (5.63%) |
| Stage III | IIIa | 28 (5.63%) |
| | IIIb | 56 (11.28%) |
| Stage IV | IV | 8 (1.61%) |

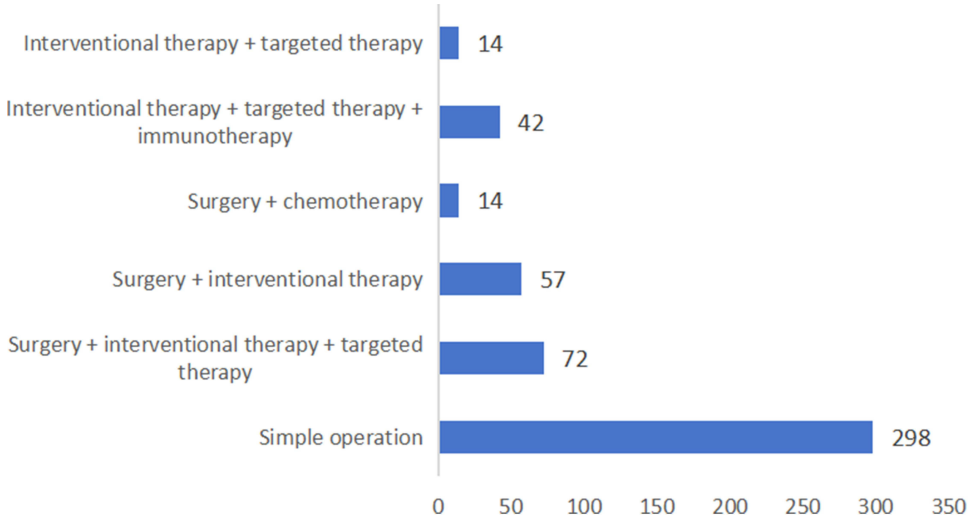


**Figure 8** Treatment regimens of adolescent patients with PLC.

surgery, intervention, and targeted therapy, 57 patients (11.47%) underwent surgery + intervention, 14 patients (2.82%) received surgery + chemotherapy, 42 patients (8.45%) were treated with intervention + targeted therapy + immunotherapy, and 14 patients (2.82%) received intervention + targeted therapy.

## Prognosis and Survival Analysis

In terms of overall survival, as of January 1, 2025, the follow-up time of this study ranged from 2 to 110 months, with a median survival time of 14 months, and the shortest and longest survival times were 2 months and 110 months, respectively. The 1-year survival rate of 497 patients was 45.27%, the 2-year survival rate was 20.32%, and the 3-year survival rate was 8.45%. Regarding the influence of clinical factors on prognosis, 466 patients survived and 31 died in this study. Factors potentially affecting prognosis were included (considering that CNLC staging comprehensively considered Child-Pugh grade, tumor number, and extrahepatic metastasis, these three influencing factors were excluded to avoid collinearity), as shown in Table 8. No significant differences were observed in age, sex, alcohol consumption history, tumor size, HBsAg, SF, CA199, ALB, ChE, LDH, and imaging type between the survival group and the death group ($P > 0.05$). While the smoking history, hepatitis history, cirrhosis history, family history of liver cancer, portal vein

**Table 8** Influence of Clinical Factors on Prognosis of Adolescent PLC

| Parameters | Variables/Groupings | Survival Group n (%) | Death Group n (%) | $Z/\chi^2$ | *P* |
|---|---|---|---|---|---|
| | | n = 466 | n = 31 | | |
| Age | 10~14 (≤14) | 184 | 14 | 0.391 | 0.532 |
| | 14 (>14) ~19 | 282 | 17 | | |
| Gender | Male | 288 | 23 | 1.906 | 0.167 |
| | Female | 178 | 8 | | |
| Drinking history | No | 424 | 31 | 3.052 | 0.081 |
| | Yes | 42 | 0 | | |
| Smoking history | No | 423 | 17 | 36.964 | <0.001 |
| | Yes | 43 | 14 | | |

(*Continued*)


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**Table 8** (Continued).

| Parameters | Variables/Groupings | Survival Group n (%) | Death Group n (%) | $Z/\chi^2$ | *P* |
|---|---|---|---|---|---|
| | | n = 466 | n = 31 | | |
| Hepatitis history | No | 139 | 2 | 7.816 | 0.005 |
| | Yes | 327 | 29 | | |
| History of cirrhosis | No | 464 | 14 | 234.030 | <0.001 |
| | Yes | 2 | 17 | | |
| Family history of liver cancer | No | 463 | 18 | 159.061 | <0.001 |
| | Yes | 3 | 13 | | |
| Portal vein cancer thrombus | No | 452 | 3 | 286.453 | <0.001 |
| | Yes | 14 | 28 | | |
| Ascites | No | 444 | 28 | 23.802 | <0.001 |
| | Yes | 2 | 3 | | |
| CNLC staging | Stage I | 360 | 0 | 149.528 | <0.001 |
| | Stage II | 45 | 0 | | |
| | Stage III | 57 | 27 | | |
| | Stage IV | 4 | 4 | | |
| Tumor size (cm) | <5 | 215 | 13 | 3.289 | 0.193 |
| | 5-10 | 227 | 14 | | |
| | >10 | 24 | 4 | | |
| HBsAg | Positive | 326 | 23 | 0.249 | 0.617 |
| | Negative | 140 | 8 | | |
| AFP | 550.80 [2.48–15,438.00] | 243.00 [2.48–9900.30] | 68,094.50 [62,971.00–73,218.00] | 6.242 | <0.001 |
| CEA | 0.94 [0.64–1.33] | 0.89 [0.64–1.32] | 1.67 [1.21–2.12] | 5.030 | <0.001 |
| SF | 321.00 [6.97–996.34] | 216.00 [6.97–567.00] | 593.00 [446.52–1476.17] | 8.243 | 0.592 |
| CA199 | 17.23 [1.92–59.88] | 13.46 [1.92–34.78] | 43.20 [19.56–101.10] | 9.47 | 0.845 |
| CA125 | 10.50 [7.61–13.90] | 9.55 [7.61–13.90] | 22.10 [13.70–30.50] | 6.185 | <0.001 |
| ALT (U/L) | 41.00 [29.00–61.00] | 40.00 [29.00–56.00] | 112.50 [61.00–164.00] | 6.616 | 0.001 |
| AST (U/L) | 30.00 [22.00–52.00] | 28.00 [22.00–41.00] | 106.00 [55.00–157.00] | 7.007 | 0.001 |
| AST/ALT | ≤1 | 299 | 27 | 6.634 | 0.010 |
| | >1 | 165 | 4 | | |
| GGT (U/L) | 47.00 [28.00–82.00] | 47.00 [28.00–78.00] | 346.50 [133.00–560.00] | 7.841 | 0.001 |
| ALP (U/L) | 91.00 [67.00–112.00] | 88.00 [67.00–111.00] | 320.50 [103.00–538.00] | 6.244 | <0.001 |
| ALB (g/L) | 41.50 [36.00–44.60] | 41.50 [37.80–44.60] | 37.55 [32.80–42.30] | 3.150 | 0.122 |
| TBIL (mol/L) | 10.60 [8.40–16.20] | 10.40 [8.40–14.00] | 157.15 [23.40–290.90] | 8.084 | <0.001 |

(*Continued*)

**Table 8** (Continued).

| Parameters | Variables/Groupings | Survival Group n (%) | Death Group n (%) | $Z/\chi^2$ | P |
|---|---|---|---|---|---|
| | | n = 466 | n = 31 | | |
| ChE (kU/L) | 8601.00 [6491.00–9997.00] | 8697.00 [7022.00–9997.00 | 6492.50 [5985.00–7000.00] | 5.407 | 0.111 |
| LDH | 197.00 [137.00–1056.00] | 194.00 [137.00–1056.00] | 227.00 [212.00–753.00] | 4.619 | 0.346 |
| ECOG scores | 0 | 453 | 14 | 176.704 | <0.001 |
| | 1 | 11 | 5 | | |
| | 2 | 2 | 12 | | |
| Image type | Massive type | 196 | 14 | 0.067 | 0.796 |
| | Nodular type | 212 | 4 | | |
| | Diffuse type | 58 | 13 | | |
| Operation or not | Operation | 425 | 16 | 45.564 | <0.001 |
| | non-surgical | 41 | 15 | | |
| Anti-HBV treatment | ETV | 123 | 9 | 0.161 | 0.984 |
| | TAF, TDF | 99 | 7 | | |
| | LAM | 56 | 4 | | |
| | PEG-INFα | 21 | 1 | | |

**Abbreviations**: ETV, Entecavir; TAF, Tenofovir alafenamide fumarate; TDF, Tenofovir disoproxil fumarate; LAM, Lamivudine; PEG-INFα, Peginterferon α.

cancer thrombus, ascites, advanced CNLC stage, abnormalities in the indicators of AFP, CEA, CA125, ALT, AST, AST/ALT, GGT, ALP and TBIL, high ECOG score, and non-surgical treatment were positively correlated with mortality ($P < 0.05$). As shown in Figure 9, factors with $P < 0.05$ in the univariate analysis were included in multivariate analysis,

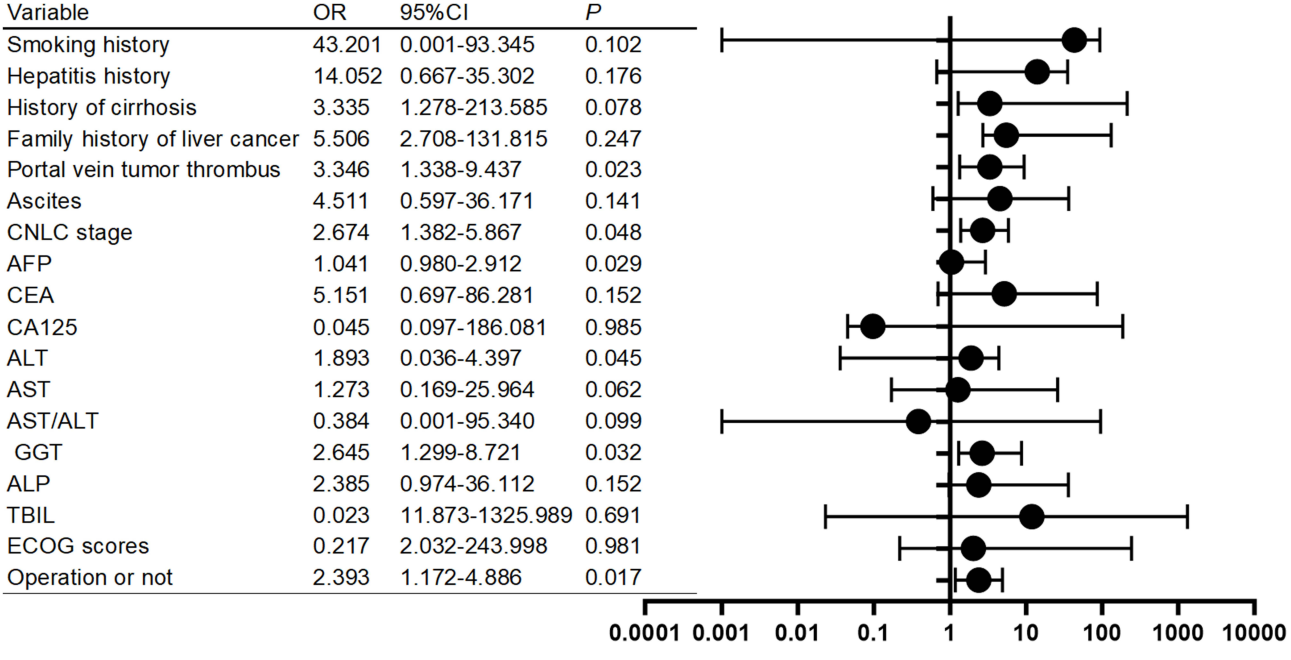


**Figure 9** Multivariate logistic regression analysis of risk factors for death in adolescent patients with primary liver cancer.
**Notes**: The bold numerical text on the horizontal coordinate represents the OR value. Since some values are too large, the interval between the horizontal coordinates is 10 times.

revealing that portal vein cancer thrombus, advanced CNLC stage, abnormalities in AFP, ALT and GGT, and non-surgical treatment were independent risk factors for mortality.

## Prognostic Univariate Analysis

A COX regression univariate analysis was performed on the included indicators, as presented in Table 9. Age, sex, drinking history, smoking history, hepatitis history, cirrhosis history, family history of liver cancer, tumor size, HBsAg,

**Table 9** Univariate Analysis Results for Adolescent PLC

| Parameters | Variables/Groupings | Median Survival (months) | $\chi^2$ | *P* |
|---|---|---|---|---|
| Age | 10~14 (≤14) | 14 | 13.879 | 0.051 |
| | 14 (>14) ~19 | 15 | | |
| Gender | Male | 10 | 19.396 | 0.064 |
| | Female | 44 | | |
| Drinking history | No | 100 | 2.841 | 0.092 |
| | Yes | 31 | | |
| Smoking history | No | 15 | 37.073 | 0.691 |
| | Yes | 10 | | |
| Hepatitis history | No | 9 | 17.615 | 0.060 |
| | Yes | 21 | | |
| History of cirrhosis | No | 17 | 14.615 | 0.073 |
| | Yes | 8 | | |
| Family history of liver cancer | No | 15 | 216.692 | 0.237 |
| | Yes | 3 | | |
| Portal vein cancer thrombus | No | 15 | 296.063 | <0.001 |
| | Yes | 20 | | |
| Ascites | No | 14 | 56.608 | 0.011 |
| | Yes | 3 | | |
| CNLC staging | Stage I | 19 | 167.569 | <0.001 |
| | Stage II | 7 | | |
| | Stage III | 10 | | |
| | Stage IV | 4 | | |
| Tumor size (cm) | <5 | 19 | 2.261 | 0.323 |
| | 5~10 | 21 | | |
| | >10 | 7 | | |
| HBsAg | Positive | 9 | 28.515 | 0.101 |
| | Negative | 15 | | |

(*Continued*)

**Table 9** (Continued).

| Parameters | Variables/Groupings | Median Survival (months) | $\chi^2$ | *P* |
|---|---|---|---|---|
| AFP (g/L) | Normal | 13 | 13.802 | <0.001 |
| | Elevated | 14 | | |
| CEA | Normal | 15 | 0.443 | 0.506 |
| | Elevated | 4 | | |
| ALT (U/L) | Normal | 19 | 59.512 | <0.001 |
| | Elevated | 14 | | |
| AST (U/L) | Normal | 21 | 76.334 | <0.001 |
| | Elevated | 9 | | |
| AST/ALT | ≤1 | 13 | 16.281 | 0.004 |
| | >1 | 15 | | |
| GGT (U/L) | Normal | 13 | 34.872 | 0.031 |
| | Elevated | 19 | | |
| ALP (U/L) | Normal | 14 | 20.456 | 0.044 |
| | Elevated | 10 | | |
| ALB (g/L) | Normal | 12 | 0.936 | 0.333 |
| | Reduced | 19 | | |
| TBIL (mmol/L) | Normal | 19 | 154.006 | 0.011 |
| | Elevated | 10 | | |
| LDH | Normal | 15 | 17.225 | 0.213 |
| | Elevated | 4 | | |
| ECOG score | 0 | 19 | 4.493 | 0.013 |
| | 1 | 12 | | |
| | 2 | 10 | | |
| Image type | Massive type | 19 | 11.778 | 0.234 |
| | Nodular type | 31 | | |
| | Diffuse type | 14 | | |
| Number of lesions | Single shot | 21 | 39.886 | 0.875 |
| | Multiple | 14 | | |
| Remote metastasis | Yes | 15 | 114.573 | 0.099 |
| | No | 20 | | |
| Operation or not | Operation | 15 | 0.715 | 0.045 |
| | Non-surgical | 10 | | |

(*Continued*)


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**Table 9** (Continued).

| Parameters | Variables/Groupings | Median Survival (months) | $\chi^2$ | *P* |
|---|---|---|---|---|
| Anti-HBV treatment | ETV | 23 | 0.142 | 0.986 |
| | TAF, TDF | 22 | | |
| | LAM | 15 | | |
| | PEG-INFα | 14 | | |

CEA, ALB, LDH, imaging type, number of lesions, and distant metastasis did not exhibit statistically significant effects on the overall survival of adolescent patients with PLC ($P > 0.05$). In contrast, adolescent patients with PLC who have portal vein tumor thrombus, ascites, advanced CNLC stage, abnormalities in the indicators of AFP, ALT, AST, AST/ALT ratio, GGT, ALP and TBIL, high ECOG score and non-surgical treatment have shorter overall survival (OS) ($P < 0.05$). The survival curves for portal vein tumor thrombus, ascites, CNLC staging, AFP, ALT, AST, AST/ALT ratio, GGT, ALP, TBIL, ECOG score, and whether surgery was performed are illustrated in Figures10–12.

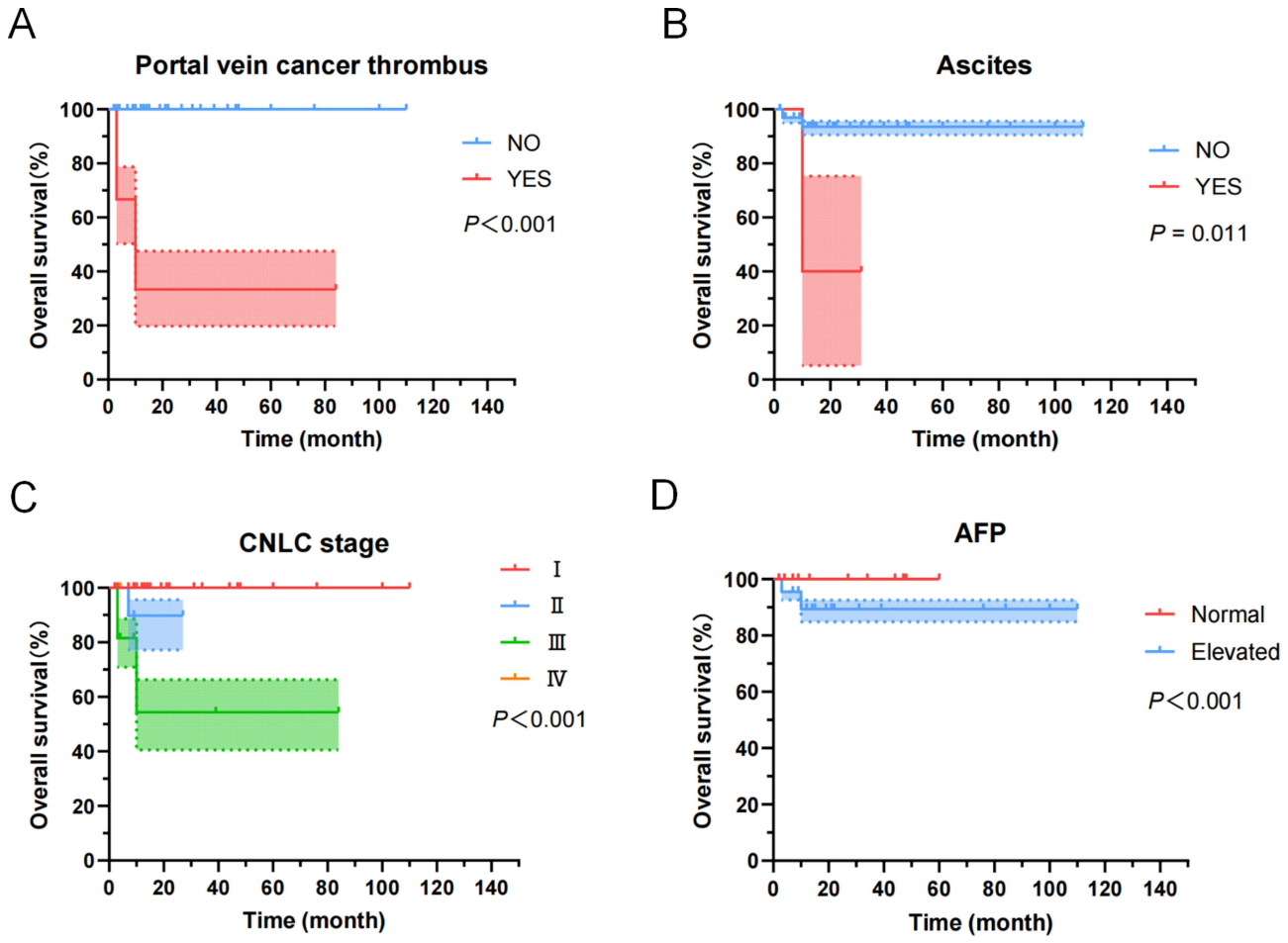


**Figure 10** Kaplan-Meier OS curves for adolescent liver cancer patients. (**A**) The overall survival curves of portal vein cancer thrombus of adolescent PLC patients. (**B**) The overall survival curves of ascites of adolescent PLC patients. (**C**) The overall survival curves of CNLC stage of adolescent PLC patients. (**D**) The overall survival curves of AFP of adolescent PLC patients.

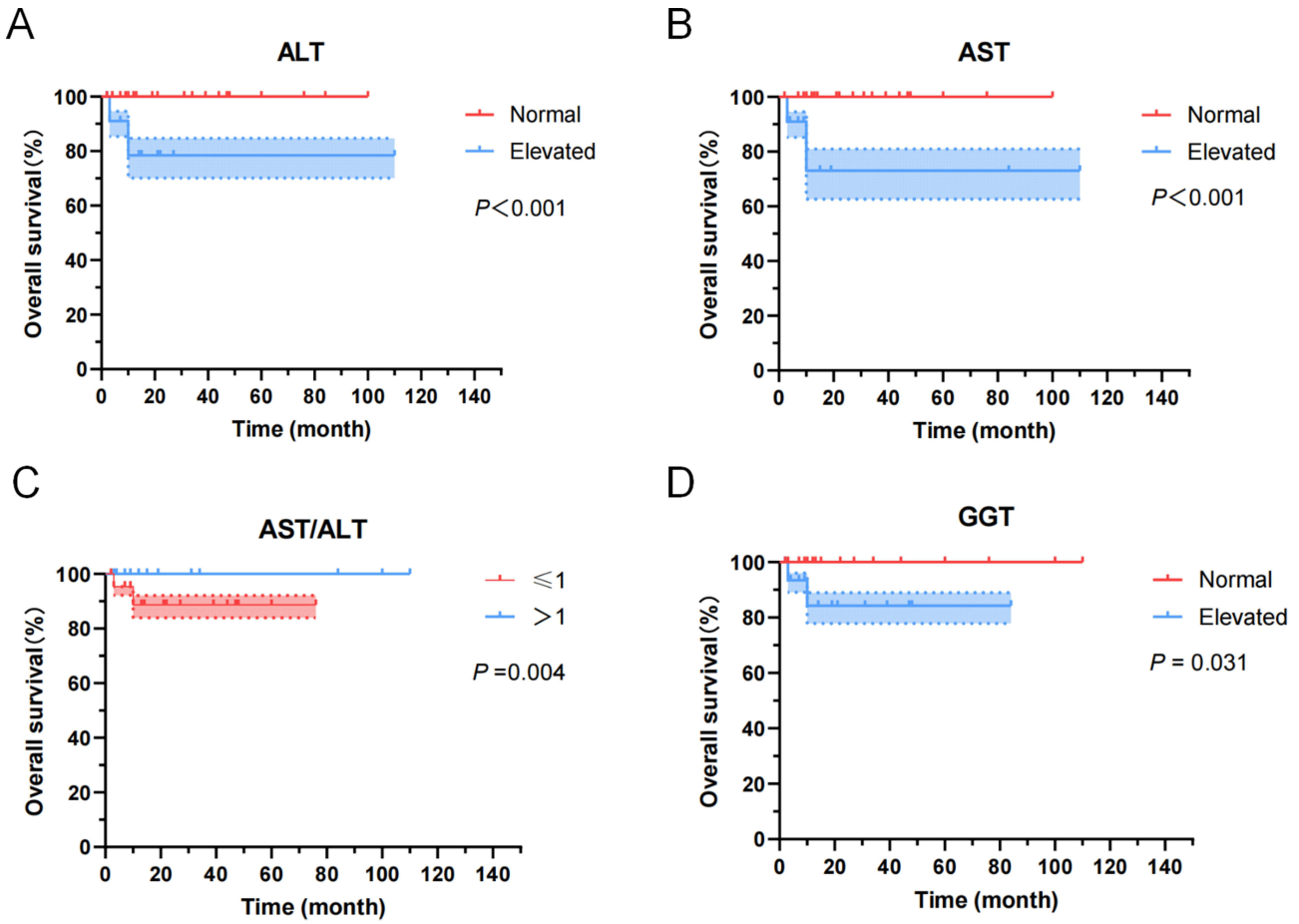


**Figure 1** Kaplan-Meier OS curves for adolescent liver cancer patients. (**A**) The overall survival curves of ALT of adolescent liver cancer patients. (**B**) The overall survival curves of AST of adolescent PLC patients. (**C**) The overall survival curves of AST/ALT of adolescent PLC patients. (**D**) The overall survival curves of GGT of adolescent PLC patients.

## Cox Regression Multivariate Analysis

As shown in Table 10, twelve indicators that exhibited statistical significance ($P < 0.05$) in the univariate analysis—namely, portal vein tumor thrombus, ascites, CNLC stage, AFP, ALT, AST, AST/ALT ratio, GGT, ALP, TBIL, ECOG score, and whether surgery was performed—were incorporated into the COX regression model for multivariate survival analysis. Multivariate analysis revealed that portal vein tumor thrombus, advanced CNLC stage, abnormalities in AFP, GGT, and non-surgical treatment was performed were independent prognostic factors influencing the OS of adolescent patients with PLC ($P < 0.05$).

# Discussion

PLC is one of the most prevalent malignant tumors globally. According to the 2018 Global Cancer Statistics, PLC ranks as the seventh most common malignant tumor worldwide and the second leading cause of cancer-related mortality globally.[4,5] Notably, approximately 72% of PLC cases occur in Asia, with China accounting for half of the global burden. Due to its high malignancy and mortality rates, PLC has predominantly been associated with middle-aged and elderly populations in both academic and clinical contexts.[13,26] Consequently, there is a paucity of research on adolescent PLC, with most studies being limited to individual case reports or single-center analyses, which restricts their generalizability, readability, and scientific rigor. Given the increasing incidence and high mortality rate of adolescent PLC, this condition has garnered increasing attention. Adolescents represent the future of a nation and society and constitute a vital force for national development, while the rise in adolescent PLC poses a significant challenge to countries, societies, and families. Therefore, exploring the disease characteristics of adolescent PLC, analyzing and evaluating its epidemiology, clinical


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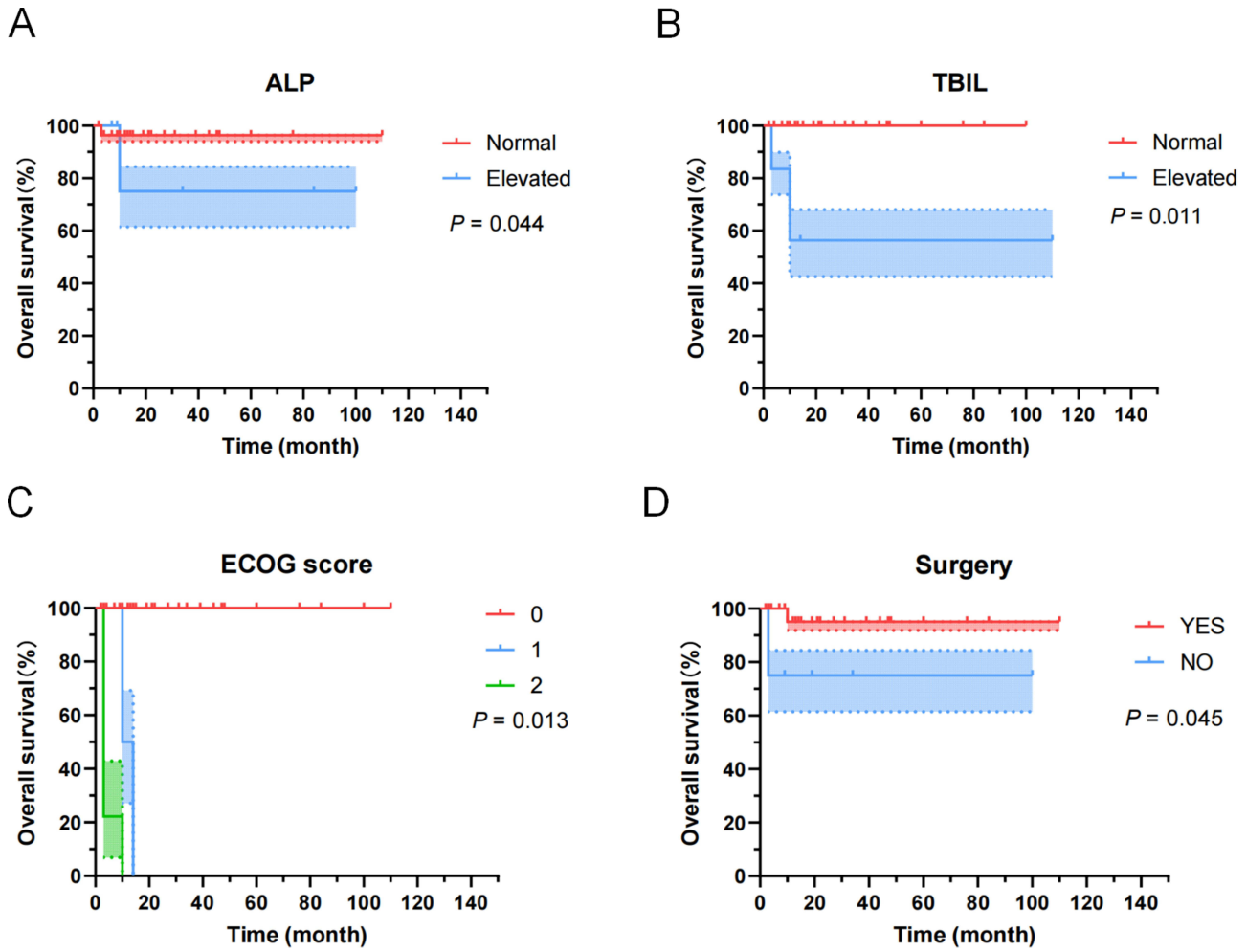


**Figure 12** Kaplan-Meier OS curves for adolescent liver cancer patients. (**A**) The overall survival curves of ALP of adolescent PLC patients. (**B**) The overall survival curves of TBIL of adolescent PLC patients. (**C**) The overall survival curves of ECOG score of adolescent PLC patients. (**D**) The overall survival curves of surgery of adolescent PLC patients.

molecular features, risk factors, and other aspects through systematic summaries and analyses, and further investigating the unique morbidity patterns and risk factors of adolescent PLC are essential. These efforts are crucial for early detection, accurate diagnosis, timely treatment, and prognostic assessment of adolescent PLC.

**Table 10** Multivariate Regression Analysis Results

| Variables | *B* | *SE* | *Wald* | *df* | *P* | *Exp (B)* | *95.0% CI for Exp(B)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Lower* | *Upper* |
| Portal vein tumor thrombus | 3.680 | 4.096 | 0.492 | 1 | 0.043 | 29.967 | 0.001 | 22.883 |
| Ascites | 5.863 | 2.535 | 5.350 | 1 | 0.021 | 0.003 | 0.000 | 0.469 |
| CNLC stage | 2.997 | 1.467 | 0.007 | 3 | 0.028 | 1.615 | 0.002 | 28.134 |
| AFP | 0.424 | 3.398 | 0.016 | 1 | 0.019 | 1.529 | 0.002 | 9.213 |
| ALT | 0.304 | 3.610 | 0.007 | 1 | 0.933 | 0.738 | 0.001 | 872.488 |

(*Continued*)

**Table 10** (Continued).

| Variables | *B* | *SE* | *Wald* | *df* | *P* | *Exp (B)* | *95.0% CI for Exp(B)* | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Lower* | *Upper* |
| AST | 0.598 | 5.931 | 0.010 | 1 | 0.920 | 1.818 | 0.000 | 2031.158 |
| AST/ALT | 0.192 | 3.593 | 0.003 | 1 | 0.957 | 1.212 | 0.001 | 1385.219 |
| GGT | 0.201 | 2.958 | 0.005 | 1 | 0.046 | 1.223 | 0.004 | 12.509 |
| ALP | 1.209 | 4.020 | 0.090 | 1 | 0.764 | 3.350 | 0.001 | 884.848 |
| TBIL | 1.742 | 3.799 | 0.210 | 1 | 0.647 | 0.175 | 0.000 | 299.971 |
| ECOG | 2.542 | 4.123 | 0.541 | 1 | 0.476 | 1.175 | 0.400 | 7.137 |
| Whether surgery | 2.114 | 3.986 | 0.667 | 1 | 0.005 | 0.426 | 0.312 | 8.919 |

**Notes**: *B* represents the regression coefficient; *SE* denotes the standard error; *df* indicates the degree of freedom. $P < 0.05$ signifies a statistically significant difference.

Nowadays, numerous studies have demonstrated that the infection rate of hepatitis B virus (HBV) in adolescent liver cancer patients is relatively high, reaching up to approximately 90%, compared to less than 60% in middle-aged and elderly patients. This suggests a potential close association between HBV infection and the early onset of adolescent liver cancer.[27,28] As indicated by the findings of this study, the initial clinical symptoms of adolescent PLC patients often lack specificity. Among all the patients included in this study, 356 cases (71.63%) had a history of viral hepatitis, predominantly hepatitis B, and this observation aligns closely with the conclusions of previous studies. Additionally, adolescent liver cancer is characterized by larger tumor diameters, higher alpha-fetoprotein (AFP) levels, greater portal vein involvement, and a higher likelihood of metastasis, indicating that tumors in younger patients may exhibit greater activity and aggressiveness. Advanced tumor stages generally imply limited treatment options and poorer survival outcomes.[29] Furthermore, adolescent liver cancer patients often lack early specific clinical symptoms or manifestations, with abdominal pain and distension being the initial symptoms in most cases. By the time of treatment initiation, liver damage is typically severe, and the disease is often in an advanced stage.[7] Combined with the physiological advantages of younger patients, we speculate that more aggressive surgical and adjuvant treatment strategies, such as guideline-overriding, indication-expanding therapies, and personalized treatments, may be suitable Nevertheless, further studies are required to confirm this hypothesis.

From a pathogenic perspective, there are significant differences in the expression of molecules related to adolescent liver cancer. For instance, in HBV-related aspects, adolescent liver cancer exhibits distinct molecular characteristics, particularly in HBV-infected patients. This study, through the analysis of blood biochemical and virological indicators, found that the adolescent PLC patients included in this study could present abnormal liver function biochemical indicators including ALT, AST, AST/ALT ratio, GGT, ALP, ChE, TBIL, ALB, etc. Moreover, hepatitis markers and virological analysis indicated that More than half of the adolescent patients with PLC present with HBsAg(+)/HBeAb (+)/HBcAb(+), and one tenth of the patients present with HBsAg(+)/HBeAg(+)/HBcAb(+). The above undoubtedly indicates that HBV plays an especially important role in the carcinogenicity and disease progression of PLC. From the perspective of tumor markers, this study found that the expression levels of tumor markers such as AFP, CEA, and CA125 were associated with adverse indicators such as jaundice, portal vein tumor thrombus, ascites, and poor prognosis.

Studies have reported that TP53 mutations are more prevalent in young liver cancer patients compared to middle-aged and elderly patients.[30] Other studies[31,32] have shown that TP53 mutations are more frequent in Asian liver cancer populations, closely linked to aflatoxin exposure and HBV infection. This aligns with the higher HBV infection rate observed in adolescent liver cancer patients in this study. Moreover, metabolic pathways offer a promising avenue for exploring the molecular characteristics of young liver cancer. Research[33] indicates that metabolic genes associated with

hepatocellular carcinoma (HCC) suppression, such as the androgen receptor and adrenergic receptor α1A, are under-expressed in adolescent patients. Accordingly, transcriptome sequencing of young and elderly liver cancer patients revealed relatively low expression of lipid metabolism-related genes, with fatty acid metabolism disorders being closely associated with poor prognosis and high recurrence rates in young liver cancer.[34] Additional studies[35,36] demonstrate that UDP glucuronosyltransferase family 2 member B28 (UGT2B28), a heterologous metabolic enzyme encoding bile acid and sex hormone metabolism, exhibits a high mutation rate in adolescent liver cancer patients. Patients with this mutation often experience poor outcomes, such as early recurrence, metastasis, or death post-surgery. It is worth noting that tumor differences in special-age HCC patients may also manifest in their gene expression profiles. Studies[37,38] indicate that adolescent HCC patient tumors possess more pronounced tumor stem cell characteristics and dedifferentiation degrees, along with high cytokeratin 19 (CK19) expression. This renders adolescent liver cancer tumors highly invasive, prone to recurrence, and associated with poor prognosis. Furthermore, allelic mutations in the SPRTN gene and specific methylation changes in CNKSR1, IFI44L, and PENK in early-onset HCC reflect genomic instability and unique molecular biological differences in adolescent HCC patients. However, the most common mutant gene in the liver cancer tissues of adolescent PLC patients in this study was KRAS. Future investigations with larger sample sizes and deeper analyses are necessary to refine the molecular epidemiology of adolescent liver cancer and identify potential therapeutic targets.

Due to the insidious nature of adolescent liver cancer onset, most patients progress to intermediate or late stages at initial diagnosis, potentially missing opportunities for radical treatment.[39] Thus, identifying high-risk groups and developing efficient screening strategies and monitoring methods are critical for improving the survival of adolescent liver cancer patients. High-risk liver cancer groups can be broadly categorized into cirrhosis and non-cirrhosis groups. Considering social cost implications, many guidelines recommend screening only for non-cirrhosis individuals aged over 40 years.[40] Combining clinical and epidemiological data on adolescent liver cancer, this strategy reduces the detection rate in younger populations, leading to delayed diagnoses. Furthermore, many guidelines suggest that high-risk groups undergo liver cancer screening every six months, primarily via liver ultrasound and AFP testing.[41] It is undeniable that currently, abdominal enhanced CT and/or MRI and other medical imaging examinations are one of the important tools for diagnosing adolescent PLC patients. According to the imaging results, the imaging types can be classified into massive liver cancer, nodular liver cancer and diffuse liver cancer. Moreover, although this study found that more than half of adolescent PLC patients were accompanied by portal vein tumor thrombus through imaging examinations, in addition, This study also found that both the massive type and the diffuse type are more likely to form portal vein tumor thrombus in adolescent PLC patients than the nodular type. Liver ultrasound offers advantages such as non-invasiveness, real-time imaging, and portability, making it the most commonly used imaging modality in screening protocols. Conventional grayscale ultrasound imaging demonstrates excellent detection rates for liver cancer. However, detecting early small liver cancers using ultrasound is limited and heavily reliant on operator experience.[42] Serum AFP serves as an important serological marker for liver cancer screening and monitoring but remains negative in approximately one-third of liver cancer patients, with insufficient sensitivity potentially leading to missed diagnoses.[43] An ideal auxiliary screening method for adolescent liver cancer should prioritize high sensitivity for accurate identification and minimize missed diagnoses. While ensuring high sensitivity, specificity should also be maximized, and the method should remain as simple and objective as possible. In the era of precision medicine, diagnostic models have increasingly been utilized for early auxiliary diagnosis and risk stratification of liver cancer. However, existing models predominantly focus on population-wide prediction effects and are unsuitable for heterogeneous adolescent liver cancer patients. Therefore, targeted auxiliary diagnostic models are urgently needed to enhance monitoring efficiency for adolescent patients.

It is important to dialectically address the controversial nature of the prognosis of adolescent PLC patients. Some scholars have identified untimely diagnoses in young patients, associating later-stage and less resectable tumors with poorer survival outcomes compared to older patients, along with higher recurrence rates even after partial surgical treatment. Conversely, other studies have found no significant difference in survival outcomes between young and elderly patients, with some reporting higher survival rates in younger patients. This may result from younger patients' better physical function, shorter duration of liver disease, fewer postoperative complications, and faster recovery, offsetting the advanced tumor status at presentation.[44,45] Generally, the age at diagnosis holds important prognostic value for certain cancers, but survival outcomes

for young liver cancer remain controversial across reports. This may stem from difficulties in collecting young liver cancer data and the lack of representativeness in previous single-center studies. Therefore, high-quality studies are necessary to elucidate the prognostic characteristics of adolescent PLC patients. It is worth noting that among all the patients included in this study, the majority were stage I patients, and the treatment methods respected individualized plans, including surgery, interventional therapy, targeted therapy, chemotherapy, immunotherapy, or the combination of multiple treatment methods. However, our study found that portal vein tumor thrombus, advanced CNLC, abnormalities in AFP, ALT and GGT, and non-surgical treatment are independent risk factors for mortality in adolescent PLC. Correspondingly, the multivariate analysis of this study revealed that portal vein tumor thrombosis, advanced CNLC, abnormalities in AFP and GGT, and non-surgical treatment were independent prognostic factors affecting OS in adolescent PLC patients.

In all, despite the lack of specificity in clinical manifestations and symptomatology and delayed diagnoses, adolescent PLC patients possess better liver function and other physiological advantages. Timely diagnosis and active treatment at early onset may yield considerable survival benefits. To improve the current situation for adolescent PLC patients, the following issues must be addressed: First, early screening and diagnosis are key to improving prognosis, with accurate risk stratification being an essential component of early screening. More sensitive diagnostic methods and screening strategies are needed to identify high-risk groups among younger populations. Second, whether young liver cancer patients can be treated with guideline-overriding or indication-expanding therapies remains unclear, necessitating further clinical studies. Additionally, clinical and molecular pathological studies of adolescent PLC patients are imperative. However, current research on adolescent PLC patients remains one-sided, lacking systematic clinical and molecular epidemiological studies and consequently missing potential therapeutic targets and treatment methods. In summary, the diagnosis and treatment of older liver cancer patients cannot simply be extrapolated to younger patients, who require targeted approaches based on their unique characteristics to significantly improve survival and prognosis.

## Conclusion

Adolescent PLC patients differ from other age groups in terms of treatment, care, psychological, and social support needs. Considering adolescents' optimal physiological state, societal roles, and immense work-life pressures, the early onset of adolescent PLC may present unique clinical characteristics and disease patterns, accompanied by substantial psychological burdens. Clarifying the pathogenesis and risk factors of young liver cancer will facilitate early identification, diagnosis, and treatment, as well as adequate and effective psychological counseling and nursing, thereby improving the prognosis of adolescent PLC patients.

## Data Sharing Statement

The datasets presented in the current study are available from the corresponding author (Prof. Yanquan Liu, doctorliuyanquan@gdmu.edu.cn) on reasonable request.

## Ethics Approval

This multi-institutional retrospective study was conducted in accordance with the ethical standards set forth by the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University (LLSC2015113), the Third Affiliated Hospital of Naval Medical University (Eastern Hepatobiliary Surgery Hospital) (EHBHKY20-2205071), the Affiliated Hospital of Putian University (PYFL-2025139), and the Fujian Medical University Union Hospital (2015KY01903B).

## Patient Consent

Informed consent was provided by the parents or their guardians for participants below 18 years. For participants above 18 years, informed consent was obtained from the individual participants included in the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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