

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2020 December 15; 12(12): 1381-1463



ORIGINAL ARTICLE

Retrospective Cohort Study

- 1381** Cholecystectomy reduces subsequent cholangiocarcinoma risk in choledocholithiasis patients undergoing endoscopic intervention

Wang CC, Tseng MH, Wu SW, Yang TW, Chen HY, Sung WW, Su CC, Wang YT, Lin CC, Tsai MC

- 1394** Comparison of survival between adolescent and young adult *vs* older patients with hepatocellular carcinoma

Ren J, Tong YM, Cui RX, Wang Z, Li QL, Liu W, Qu K, Zhang JY, Liu C, Wan Y

Retrospective Study

- 1407** Robotic resection of liver focal nodal hyperplasia guided by indocyanine green fluorescence imaging: A preliminary analysis of 23 cases

Li CG, Zhou ZP, Tan XL, Wang ZZ, Liu Q, Zhao ZM

- 1416** Clinicopathological characteristics and prognosis of 77 cases with type 3 gastric neuroendocrine tumours

Li YL, Qiu XD, Chen J, Zhang Y, Li J, Xu JM, Wang C, Qi ZR, Luo J, Tan HY

Observational Study

- 1428** Outcomes of neoadjuvant chemoradiotherapy followed by radical resection for T4 colorectal cancer

Huang CM, Huang CW, Ma CJ, Tsai HL, Su WC, Chang TK, Huang MY, Wang JY

META-ANALYSIS

- 1443** Prognostic impact of at least 12 lymph nodes after neoadjuvant therapy in rectal cancer: A meta-analysis

Tan L, Liu ZL, Ma Z, He Z, Tang LH, Liu YL, Xiao JW

CASE REPORT

- 1456** Pancreatic mucinous cystadenocarcinoma in a patient harbouring *BRCA1* germline mutation effectively treated with olaparib: A case report

Di Marco M, Carloni R, De Lorenzo S, Mosconi C, Palloni A, Grassi E, Filippini DM, Ricci AD, Rizzo A, Di Federico A, Santini D, Turchetti D, Ricci C, Ingaldi C, Alberici L, Minni F, Golfieri R, Brandi G, Casadei R

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Dr. Lin is a distinguished professor at the Hebei Medical University in Shijiazhuang, China. Dr. Lin received his Bachelor's degree from Tianjin Medical University in 1998 and undertook his postgraduate training at Hebei Medical University, receiving his PhD in 2007. He rose to Chief Oncologist in the Department of Oncology, North China Petroleum Bureau General Hospital Affiliated to Hebei Medical University in 2013 and has held the position since. Further, he has served as one of the academic leaders of the five Key Developing Disciplines (Oncology) in Hebei Province since 2017. He also currently serves as Secretary General of the Clinical Committee of Anticancer Drugs, China Pharmaceutical Industry Research and Development Association. His ongoing research interests involve the application of evidence-based medicine in digestive oncology and thoracic oncology. (L-Editor: Filipodia)

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INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJGO as 2.898; IF without journal self cites: 2.880; 5-year IF: 3.316; Ranking: 143 among 244 journals in oncology; Quartile category: Q3; Ranking: 55 among 88 journals in gastroenterology and hepatology; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rosa M Jimenez Rodriguez, Pashtoon Kasi, Monjur Ahmed

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

December 15, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Retrospective Cohort Study

Comparison of survival between adolescent and young adult vs older patients with hepatocellular carcinoma

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Author contributions: Ren J, Tong YM, and Cui RX contributed equally to this work; Ren J participated in the research design, data analysis, and writing of the paper; Tong YM and Cui RX participated in the data analysis; Wang Z, Liu W, and Li QL participated in revising of the paper; Qu K participated in research design and revising of the paper; Zhang JY, Liu C, and Wan Y provided substantial advice in designing the study, assisting in the division of labor, and writing and revising the paper; all authors have read and approved the final manuscript.

Institutional review board

statement: The IRB has reviewed this information and found that this protocol does not fall under the purview of the IRB as it does not meet the definition of human subject research.

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Abstract

BACKGROUND

Due to the special clinical features and biologic characteristics of adolescent and young adult (AYA) cancers, AYA cancers are different from cancers in children and elderly individuals. However, there are few reports on AYA hepatocellular carcinoma (HCC).

AIM

To investigate the overall survival (OS) of AYA (15-39 years) and elderly (40-74 years) patients with HCC.

METHODS

The data of all the HCC cases were extracted from the Surveillance, Epidemiology, and End Results database from 2004 to 2015 and were then divided into two groups based on age: AYA group (15-39 years) and older group (40-74 years). Kaplan-Meier curves and log-rank tests were used to compare the OS of the two groups. Propensity score matching (PSM) was employed to analyze the OS difference between the two groups. The Cox proportional hazards regression model was used to perform multivariate analysis to explore the risk factors for OS of HCC patients.

RESULTS

Compared to elderly cancer patients, AYA patients with HCC had a worse

Informed consent statement: As the data used was accessed *via* a public national database with deidentified patients, there was no need for informed consent.

Conflict-of-interest statement: The authors have no conflict of interest to report.

Data sharing statement: Data from this manuscript will be available upon request.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Oncology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 31, 2020

Peer-review started: August 31, 2020

First decision: September 12, 2020

Revised: September 20, 2020

Accepted: October 26, 2020

Article in press: October 26, 2020

Published online: December 15,

Surveillance, Epidemiology, and End Results stage, including the distant stage (22.1% *vs* 15.4%, $P < 0.001$), and a more advanced American Joint Committee on Cancer (AJCC) stage, including AJCC III and IV (49.2% *vs* 38.3%, $P < 0.001$), and were more likely to receive surgery (64.5% *vs* 47.5%, $P < 0.001$). Before PSM, the AYA group had a longer survival in months (median: 20.00, interquartile range [IQR]: 5.00-62.50) than the older group (median: 15.00, IQR: 4.00-40.00) ($P < 0.001$). After PSM, the AYA group still had a longer survival in months (median: 21.00, IQR: 5.00-64.50) than the older group (median: 18.00, IQR: 6.00-53.00) ($P < 0.001$). The Cox proportional hazards regression model showed that advanced age (hazard ratio [HR] = 1.405, 95%CI: 1.218-1.621, $P < 0.001$) was a risk factor for OS of HCC patients. In the subgroup analysis, the Cox proportional hazards regression model showed that in AJCC I/II HCC patients, advanced age (HR = 1.749, 95%CI: 1.352-2.263, $P < 0.001$) was a risk factor for OS, while it was not a risk factor in AJCC III/IV HCC patients (HR = 1.186, 95%CI: 0.997-1.410, $P = 0.054$) before PSM. After PSM, advanced age (HR = 1.891, 95%CI: 1.356-2.637, $P < 0.001$) was still a risk factor for OS in AJCC I/II HCC patients, but was not a risk factor for OS in AJCC III/IV HCC patients (HR = 1.192, 95%CI: 0.934-1.521, $P = 0.157$) after PSM.

CONCLUSION

AYA patients with HCC have different clinical characteristics from older adults. In different AJCC stages, the two groups of patients have different OS: In AJCC I/II HCC patients, advanced age is a risk factor for OS, but it is not a risk factor for OS in the AJCC III/IV HCC patient group.

Key Words: Adolescent and young adults; Older adults; Hepatocellular carcinoma; Overall survival; Propensity score matching; Risk factor

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Core Tip: Adolescent and young adult (AYA) population refer to people aged 15-39 years old in the United States, and AYA has become a special age phase in oncology research in recent years. We aimed to investigate overall survival (OS) of AYA and older hepatocellular carcinoma patients. Our study confirmed that in different American Joint Committee on Cancer (AJCC) stages, the two groups of patients had different OS: In the AJCC I/II group, advanced age was a risk factor for OS, but it was not a risk factor for OS in the AJCC III/IV group.

Citation: Ren J, Tong YM, Cui RX, Wang Z, Li QL, Liu W, Qu K, Zhang JY, Liu C, Wan Y. Comparison of survival between adolescent and young adult *vs* older patients with hepatocellular carcinoma. *World J Gastrointest Oncol* 2020; 12(12): 1394-1406

URL: <https://www.wjgnet.com/1948-5204/full/v12/i12/1394.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v12.i12.1394>

INTRODUCTION

Adolescent and young adult (AYA) population refer to people aged 15-39 years old in the United States^[1,2]. With advancements in cancer diagnosis and treatment, people have increasingly realized that AYA cancer survivors have some unique challenges in the diagnosis and treatment process^[3-5]. Due to specific socioeconomic factors, *i.e.*, AYA cancer survivors experience graduations, new careers, and marriages^[3,4], and in certain specific biologic characteristics^[5], AYA cancers are different from those in children and older individuals. Therefore, AYA has become a special age phase in oncology research in recent years^[2]. The number of AYA cancer survivors has been estimated to be 678420, accounting for approximately 5% of all cancer survivors, while there were 70000 new cancer cases in the United States by January 1, 2019^[6-8]. From the time of cancer diagnosis, the 5-year survival rate rose from 71% in the mid-1970s to 86% during 2008-2014^[9,10]. Between 2007 and 2016, the death rate declined by 0.8%

2020

P-Reviewer: MD SW**S-Editor:** Zhang L**L-Editor:** Wang TQ**P-Editor:** Li JH

annually^[8], mainly due to the decrease in mortality of leukemia, non-Hodgkin's lymphoma, melanoma of the skin, and ovarian cancer, as these tumors account for a large proportion of AYA cancers^[8].

Liver cancer is the sixth most common malignant cancer in the world and the fourth cancer-related cause of death. Hepatocellular carcinoma (HCC) is the most common pathological type of liver cancer, accounting for approximately 90% of liver cancers^[11-13]. Current research shows that advanced age is a risk factor for HCC^[11-13]. Research performed by Yang *et al*^[14] shows that the age at which HCC is likely to occur is different in different regions of the world. Although childhood liver cancer is rare, some studies have reported the clinical features and diagnosis of and treatment options for childhood liver cancer^[15,16]. However, there are few reports on AYA HCC research.

Therefore, this study aimed to: Describe the clinical characteristics of AYA HCC, and compare OS between AYA (15-39 years) and older (40-74 years) HCC patients.

MATERIALS AND METHODS

Statistics extraction

The Surveillance, Epidemiology, and End Results (SEER) database incorporates cancer information from the populations of 18 regions in the United States; these 18 regions comprise approximately 28% of the population of the United States. The general data, clinical data, pathological data, and follow-up data of all HCC patients in the SEER database were extracted from 2004 to 2015, including age, gender, race, marital status, histology, tumor stage, tumor grade, therapies, survival status, cause of death, survival months, sequence number, and International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code.

Inclusion and exclusion criteria

The inclusion criteria were: (1) Patients older than 18 years of age; (2) "Positive histology" to ensure correct diagnosis; (3) Data with complete survival time for the survival month flag; and (4) "Active follow-up" to ensure the effectiveness of follow-up. The exclusion criteria were: (1) Cases obtained from autopsies and only death reports; and (2) Patients with multiple primary malignancies.

Statistical analysis

In the baseline data comparison between AYA and older HCC patients, the *t* test or Mann-Whitney *U* test was used for measurement data, the Chi-square test or Mann-Whitney *U* test was used for count data, and the Mann-Whitney *U* test was used for ranked data. Kaplan-Meier curves and the log-rank tests were used to compare the overall survival (OS) of AYA and older patients. OS was defined as the time interval from cancer diagnosis to death due to any cause. Variables with statistical significance in univariate analysis were subjected to multivariate analysis. The Cox proportional hazards regression model was used for multivariate analysis to identify the risk factors for OS of HCC patients. After 1:1 propensity score matching (PSM) of the baseline data, the OS difference between the two groups was analyzed again. Subsequently, a subgroup analysis was carried out. After the two groups of patients were stratified according to American Joint Committee on Cancer (AJCC) stage, the Cox proportional hazards regression model was used to analyze the OS difference. SPSS 22.0 (IBM Corp, Armonk, NY, United States) was used for statistical analyses, the test was two-sided, and *P* < 0.05 was considered statistically significant.

RESULTS

Patient baseline statistics

A total of 12721 patients were included in the study, including 366 (2.9%) AYA HCC patients and 12355 (97.1%) patients in the older group. Compared to older patients, AYA HCC patients had a worse SEER stage, including the distant stage (22.1% *vs* 15.4%, *P* < 0.001); a more advanced AJCC stage, including AJCC stages III and IV (49.2% *vs* 38.3%, *P* < 0.001); and were more likely to receive surgery (64.5% *vs* 47.5%, *P* < 0.001) (Table 1).

Table 1 Baseline characteristics of adolescent and young adult and older hepatocellular carcinoma patients

Characteristic	Total	AYA	Older	P value
	<i>n</i> = 12721	<i>n</i> = 366 (2.9%)	<i>n</i> = 12355 (97.1%)	
Sex				< 0.001
Male	10075	249 (68.0%)	9826 (79.5%)	
Female	2646	117 (32.0%)	2529 (20.5%)	
Race				< 0.001
White	8323	190 (51.9%)	8133 (65.8%)	
Black	1990	59 (16.1%)	1931 (15.6%)	
Other	2408	117 (32.0%)	2291 (18.5%)	
Marital status				< 0.001
Not married	2818	197 (53.8%)	2621 (21.2%)	
Married	9903	169 (46.2%)	9734 (78.0%)	
SEER stage				< 0.001
Localized	7264	178 (48.6%)	7086 (57.4%)	
Regional	3476	107 (29.2%)	3396 (27.3%)	
Distant	1981	81 (22.1%)	1900 (15.4%)	
AJCC stage				< 0.001
I	5063	118 (32.2%)	4945 (40.0%)	
II	2744	68 (18.6%)	2676 (21.7%)	
III	3036	105 (28.7%)	2931 (23.7%)	
IV	1878	75 (20.5%)	1803 (14.6%)	
Grade				0.158
I	3913	114 (31.3%)	3799 (30.7%)	
II	5719	141 (38.5%)	5578 (45.1%)	
III	2848	102 (27.9%)	2746 (22.2%)	
IV	241	9 (2.5%)	232 (1.9%)	
Surgery				< 0.001
No	6622	130 (35.5%)	6492 (52.5%)	
Yes	6099	236 (64.5%)	5863 (47.5%)	
Radiation				0.319
No	11862	346 (94.5%)	11516 (93.2%)	
Yes	859	20 (5.5%)	839 (6.8%)	
Chemotherapy				0.306
No	8074	223 (60.9%)	7851 (63.5%)	
Yes	4647	143 (39.1%)	4504 (36.5%)	

AYA: Adolescent and young adult; HCC: Hepatocellular carcinoma; SEER: Surveillance, Epidemiology, and End Results; AJCC: American Joint Committee on Cancer; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.

Univariate and multivariate analyses of OS in HCC patients

In the univariate analysis of OS of HCC patients, age, sex, race, marital status, AJCC stage, grade, surgery, radiation, and chemotherapy were all statistically significant ($P < 0.05$), although AJCC stage II was not ($P = 0.376$, taking AJCC stage I as the reference). In the multivariate analysis using the Cox proportional hazard regression model, advanced age, black ethnicity, advanced AJCC stage (II-IV), and advanced

grade (II-IV) were risk factors for OS of HCC. Female gender, other races, being married, surgery, radiation, and chemotherapy were protective factors for OS of HCC patients (Table 2). Figure 1 shows the results of the multivariate analysis.

Propensity score matching

After PSM was performed on sex, race, marital status, AJCC stage, grade, surgery, radiation, and chemotherapy, the differences were balanced in the AYA and the older groups: Sex ($P = 0.934$), race ($P = 0.985$), marital status ($P = 1.000$), AJCC stage ($P = 0.974$), grade ($P = 0.887$), surgery ($P = 1.000$), radiation ($P = 1.000$), and chemotherapy ($P = 0.937$) (Table 3).

Comparison of OS between AYA and older HCC patients

Kaplan-Meier curves were used to compare OS of AYA and older patients. Before PSM, the AYA group had a longer survival in months (median: 20.00, IQR: 5.00-62.50) than the older group (median: 15.00, IQR: 4.00-40.00) ($P < 0.001$). After PSM, the AYA group still had a longer survival in months (median: 21.00, IQR: 5.00-64.50) than the older group (median: 18.00, IQR: 6.00-53.00) ($P < 0.001$) (Table 4). Figure 2 shows the difference in OS between the two groups.

Subgroup analysis stratified by AJCC stage

To compare the survival difference between AYA and older patients in different AJCC stages, we divided the AJCC stage into two levels. Figure 3 shows the difference in OS between the two groups of patients in different AJCC stages before and after PSM using Kaplan-Meier curves and the log-rank tests. AYA patients had a better OS ($P < 0.001$) in the stage AJCC I/II and AJCC stage III/IV groups before PSM; after PSM, AYA patients had a better OS than older patients ($P < 0.001$) in the AJCC stage I/II group, while in the AJCC stage III/IV group, the difference in OS between AYA and older patients was not statistically significant ($P = 0.136$). Then, we performed multivariate analysis of different AJCC stages to compare the survival difference between the two groups of patients. After joint adjustment of age, sex, race, marital status, AJCC stage, grade, surgery, radiation, and chemotherapy, we found that before PSM, advanced age was a risk factor for OS in the AJCC stage I/II group, but in the AJCC stage III/IV group, it was not observed that advanced age was a risk factor. After PSM, in the AJCC stage I/II group, advanced age was a risk factor for OS. In the AJCC stage III/IV group, advanced age was not a risk factor for OS (Table 5).

DISCUSSION

AYA cancer survivors have an inferior 5-year OS compared with the general population, while the long-term survival of AYA cancer survivors has improved^[17]. However, the improvements of the survival rate and mortality of AYA cancer patients are not as good as those of younger or older patients, mainly because past oncologists and researchers did not pay attention to AYA cancer patients and there are few clinical studies on them^[18,19]. With the emphasis on AYA cancer, recent studies have analyzed the reasons for the low participation rate of AYA cancer survivors in clinical trials, which may be related to the low availability of medical insurance for patients of this age group and to tumor type and stage^[20,21]. A previous study tried to explore methods to improve the participation rate and accuracy of clinical trials for AYA cancer survivors^[22]. Therefore, it is particularly significant to explore the clinical characteristics and prognosis of AYA HCC patients.

After comparing the baseline data, we found that compared to older patients, AYA HCC patients had a worse SEER stage and more advanced AJCC stage and were more likely to receive surgery. These findings were consistent with the finding of a previous study that cancer in AYA patients was often in advanced stages and showed more aggressiveness^[23]. The research by Bleyer *et al*^[23] showed that young women with breast cancer were more likely to develop larger, higher-grade tumors that were less sensitive to hormones than older women, and most Burkitt lymphomas were at stage III/IV according to another study^[24]. Research involving acute lymphocytic leukemia (ALL) showed that compared with children, AYA patients with ALL were more likely to have unfavorable biological characteristics^[25], which may be related to the poor prognosis of AYA cancer patients.

The hospitalization rate of AYA cancer survivors increased by 56% compared with noncancer patients of the same age, and they had a longer hospital stay^[26,27]. Zhi *et al* showed that an appropriate and active exercise intervention had a positive effect in

Table 2 Univariate and multivariate analyses of overall survival in patients with hepatocellular carcinoma

Characteristic		Univariate analysis, HR (95%CI)	P value	Multivariate analysis, HR (95%CI)	P value
Age	AYA	Reference		Reference	
	Older	1.504 (1.307-1.732)	< 0.001	1.405 (1.218-1.621)	< 0.001
Sex	Male	Reference		Reference	
	Female	0.817 (0.775-0.861)	< 0.001	0.898 (0.851-0.947)	< 0.001
Race	White	Reference		Reference	
	Black	1.293 (1.223-1.368)	< 0.001	1.109 (1.048-1.174)	< 0.001
	Other	0.812 (0.767-0.860)	< 0.001	0.871 (0.823-0.923)	< 0.001
Marital status	Not married	Reference		Reference	
	Married	0.805 (0.767-0.846)	< 0.001	0.931 (0.885-0.980)	0.006
AJCC stage	I	Reference		Reference	
	II	1.028 (0.967-1.093)	0.376	1.116 (1.049-1.188)	< 0.001
	III	2.810 (2.662-2.966)	< 0.001	2.138 (2.021-2.262)	< 0.001
	IV	5.629 (5.290-5.990)	< 0.001	3.128 (2.925-3.345)	< 0.001
Grade	I	Reference		Reference	
	II	1.068 (1.016-1.123)	0.010	1.214 (1.154-1.277)	< 0.001
	III	1.856 (1.754-1.964)	< 0.001	1.708 (1.612-1.811)	< 0.001
	IV	2.270 (1.974-2.610)	< 0.001	1.998 (1.735-2.300)	< 0.001
Surgery	No	Reference		Reference	
	Yes	0.223 (0.213-0.234)	< 0.001	0.239 (0.226-0.252)	< 0.001
Radiation	No	Reference		Reference	
	Yes	1.428 (1.321-1.544)	< 0.001	0.712 (0.658-0.771)	< 0.001
Chemotherapy	No	Reference		Reference	
	Yes	1.053 (1.009-1.099)	0.018	0.598 (0.571-0.626)	< 0.001

OS: Overall survival; HCC: Hepatocellular carcinoma; HR: Hazard ratio; CI: Confident interval; AYA: Adolescent and young adult; AJCC: American Joint Committee on Cancer; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.

improving the quality of life of AYA cancer survivors^[28]. However, Rabin *et al*^[29] found that more than half of AYA cancer survivors remained sedentary and did not undergo scientific exercise interventions. AYA cancer survivors were more likely to have negative life narratives and more disease-related future thoughts than noncancer patients of the same age, which greatly increased their risk of mental illness^[30]. In the field of psycho-oncology, age-appropriate interventions are also needed for AYA cancer survivors^[31]. In terms of comorbidities, studies have shown that AYA cancer survivors have an increased risk of comorbidities compared with the general

Table 3 Baseline characteristics of adolescent and young adult and older hepatocellular carcinoma patients after propensity score matching

Characteristic	Total, n = 690	AYA, n = 345 (50%)	Older, n = 345 (50%)	P value
Sex				0.934
Male	475	238 (69.0%)	237 (68.7%)	
Female	215	107 (31.0%)	108 (31.3%)	
Race				0.985
White	371	185 (53.6%)	186 (53.9%)	
Black	117	58 (16.8%)	59 (17.1%)	
Other	202	102 (29.6%)	100 (29.0%)	
Marital status				1.000
No married	356	178 (51.6%)	178 (51.6%)	
Married	334	167 (48.4%)	167 (48.4%)	
AJCC stage				0.974
I	230	115 (33.3%)	115 (33.3%)	
II	127	64 (18.6%)	63 (18.3%)	
III	197	98 (28.4%)	99 (28.7%)	
IV	136	68 (19.7%)	68 (19.7%)	
Grade				0.887
I	217	109 (31.6%)	108 (31.3%)	
II	271	136 (39.4%)	135 (39.1%)	
III	188	93 (27.0%)	95 (27.5%)	
IV	14	7 (2.0%)	7 (2.0%)	
Surgery				1.000
No	250	125 (36.2%)	125 (36.2%)	
Yes	440	220 (63.8%)	220 (63.8%)	
Radiation				1.000
No	666	333 (96.5%)	333 (96.5%)	
Yes	24	12 (3.5%)	12 (3.5%)	
Chemotherapy				0.937
No	437	219 (63.5%)	218 (63.2%)	
Yes	253	126 (36.5%)	127 (36.8%)	

AYA: Adolescent and young adult; HCC: Hepatocellular carcinoma; PSM: Propensity score matching; AJCC: American Joint Committee on Cancer; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated.

population. Different cancer treatments and exposures can cause different complications^[32]. The study by Kaul *et al*^[33] showed that AYA cancer survivors had a higher percentage of smoking than noncancer patients of the same age after 5 years of receiving a cancer diagnosis; had more comorbidities, such as asthma and diabetes; and had worse health conditions. Insufficient exercise, mental illness, bad living habits, and comorbidities may not be conducive to the OS of AYA cancer patients^[28-33].

After using Kaplan-Meier curves to compare the OS of the two groups of patients, we found that before and after PSM, advanced age was a risk factor for OS in AYA patients with HCC. This result was consistent with the results of the multivariate analysis and seemed to indicate that AYA patients with HCC had a better prognosis than older patients. In a further subgroup analysis, we found that in the AJCC stage I/II group, advanced age was a risk factor; combined with previous research, this may be because compared with older patients, AYA patients with HCC had worse

Table 4 Comparison of overall survival between adolescent and young adult and older groups

	Characteristics	Survival months (Median, IQR)	P value
Before PSM	AYA	20.00 (5.00-62.50)	< 0.001
	Older adults	15.00 (4.00-40.00)	
After PSM	AYA	21.00 (5.00-64.50)	< 0.001
	Older adults	18.00 (6.00-53.00)	

OS: Overall survival; AYA: Adolescent and young adult; PSM: Propensity score matching; IQR: Interquartile range.

Table 5 Subgroup multivariate analysis stratified by American Joint Committee on Cancer stage

	Characteristics (AYA vs Older adults)	Multivariate analysis HR (95%CI)	P value
Before PSM	AJCC stage I/II	1.749 (1.352-2.263)	< 0.001
	AJCC stage III/IV	1.186 (0.997-1.410)	0.054
After PSM	AJCC stage I/II	1.891 (1.356-2.637)	< 0.001
	AJCC stage III/IV	1.192 (0.934-1.521)	0.157

Incorporating “age, sex, race, marital status, AJCC stage, grade, surgery, radiation, and chemotherapy” into Cox proportional hazard regression model, with AYA group as the reference. AJCC: American Joint Committee on Cancer; AYA: Adolescent and young adult; HR: Hazard ratio; CI: Confident interval; PSM: Propensity score matching.

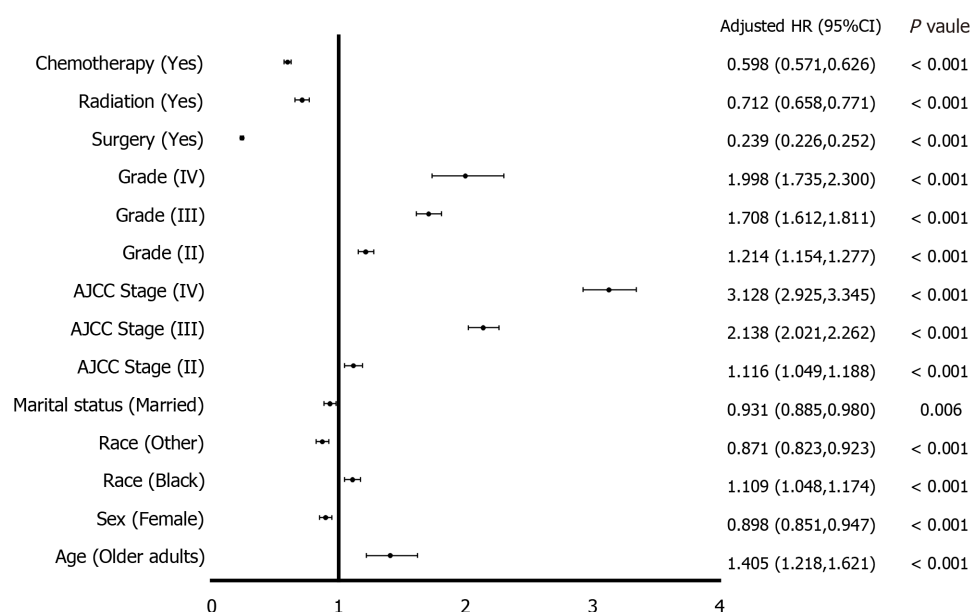


Figure 1 Forest map of multivariate analysis of overall survival in patients with hepatocellular carcinoma. All variables were statistically significant. Advanced age, black ethnicity, advanced American Joint Committee on Cancer stage, and advanced grade are risk factors for OS of HCC patients; female gender, other races, married status, surgery, radiation, and chemotherapy are protective factors for OS of HCC patients. AJCC: American Joint Committee on Cancer; Grade I: Well differentiated; Grade II: Moderately differentiated; Grade III: Poorly differentiated; Grade IV: Undifferentiated; OS: Overall survival; HCC: Hepatocellular carcinoma.

biological characteristics and were more likely to receive surgery, which was a strong protective factor for OS. Therefore, AYA patients with HCC had a better OS than older patients. In the AJCC stage III/IV group, advanced age was not a risk factor because for this stage of HCC, even if surgery was performed, it did not help improve the prognosis.

This study has some limitations. First, the data in this study came from a database,

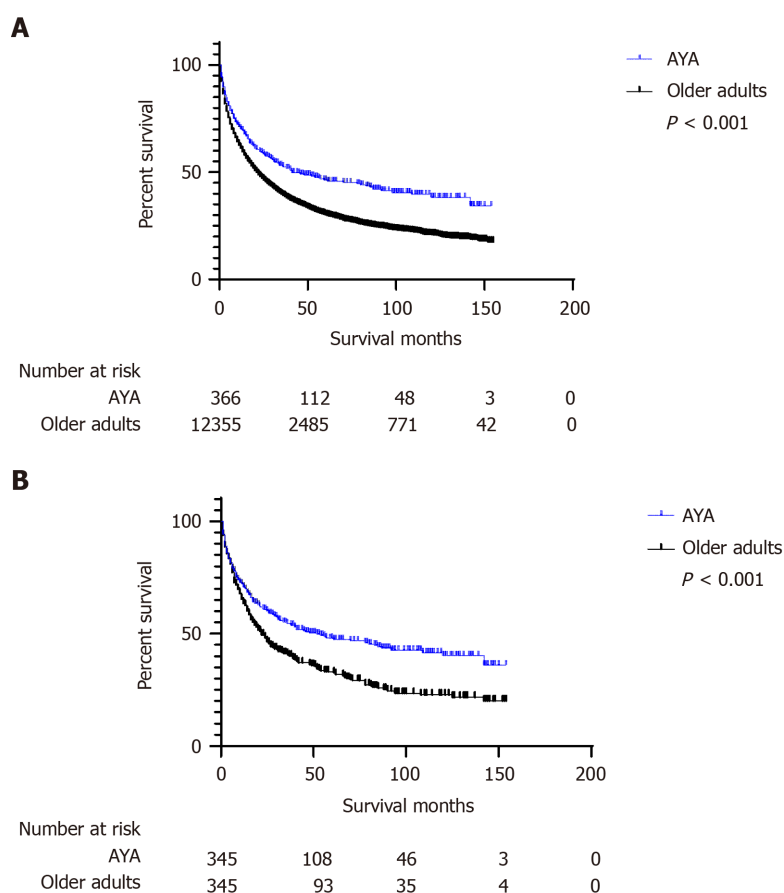
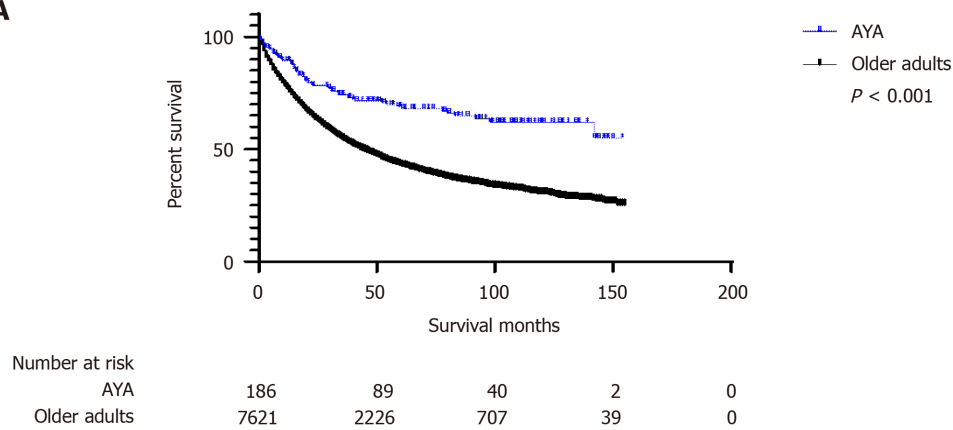
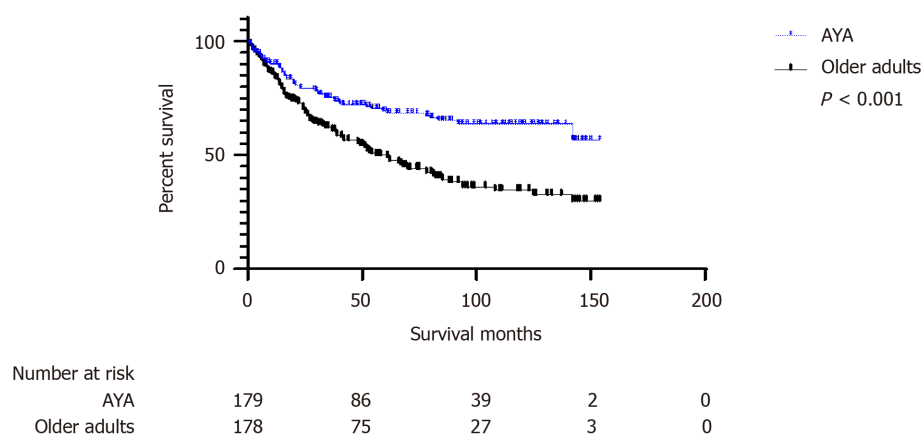
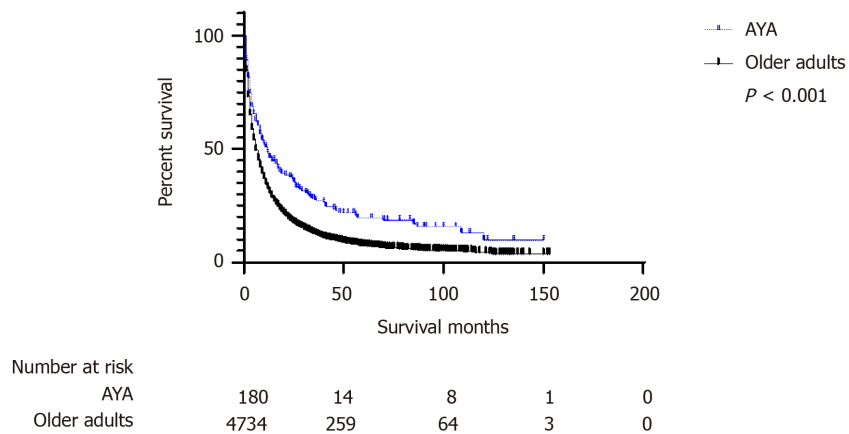


Figure 2 Comparison of overall survival in hepatocellular carcinoma patients between adolescent and young adult and older groups before and after propensity score matching (A and B). AYA: Adolescent and young adult; OS: Overall survival.

and variable inclusion was limited to that database. Thus, information such as laboratory examinations, combined diseases, and economic status could not be obtained. Second, this study was a retrospective case-control study, which may have an inherent bias. Finally, more samples were needed to verify our findings.

CONCLUSION

AYA HCC patients have different clinical characteristics from older adults. In different AJCC stages, the two groups of patients have different OS: In the AJCC stage I/II group, advanced age is a risk factor for OS, while advanced age is not a risk factor in the AJCC stage III/IV group. More basic studies are needed to explore this mechanism.

A**B****C**

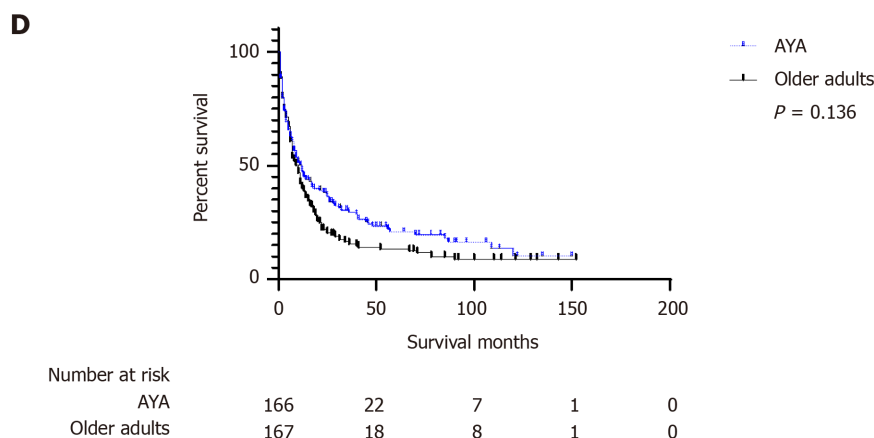


Figure 3 Difference in overall survival between the two groups of patients in different American Joint Committee on Cancer stages before and after propensity score matching using Kaplan-Meier curves and the log-rank tests. A and B: Comparison of overall survival between adolescent and young adult and older hepatocellular carcinoma patients in AJCC stage I/II before and after propensity score matching; C and D: Comparison of overall survival between adolescent and young adult and older hepatocellular carcinoma patients in AJCC stage III/IV before and after propensity score matching (C and D). AYA: Adolescent and young adult.

ARTICLE HIGHLIGHTS

Research background

Adolescent and young adult (AYA) population refer to people aged 15-39 years old. AYA cancers are different from those in children and elderly individuals due to their special clinical features and biologic characteristics. Liver cancer is the sixth most common malignant cancer in the world and the fourth cancer-related cause of death. Hepatocellular carcinoma (HCC) is the most common pathological type of liver cancer. Age-related studies of HCC are needed to guide the diagnosis and treatment of this malignancy.

Research motivation

There have been studies on liver cancer among children and elderly individuals. However, there are few studies on AYA HCC.

Research objectives

First, this study aimed to describe the clinical characteristics of AYA HCC. Second, this study intended to compare overall survival (OS) between AYA (15-39 years) and older (40-74 years) HCC patients.

Research methods

A total of 12721 patients were included in the study, including 366 (2.9%) AYA HCC patients and 12355 (97.1%) patients in the older group. Kaplan-Meier curves and the log-rank tests were used to compare OS of the AYA and older patients. The Cox proportional hazards regression model was used for multivariate analysis to identify the risk factors for OS of HCC patients. After a 1:1 PSM of the baseline data, the OS difference between the two groups was analyzed again. Subsequently, a subgroup multivariate analysis was carried out, and patients were stratified according to American Joint Committee on Cancer (AJCC) stage.

Research results

Compared to older patients, AYA HCC patients had a worse SEER stage, including distant stage (22.1% *vs* 15.4%, $P < 0.001$); a more advanced AJCC stage, including AJCC stages III and IV (49.2% *vs* 38.3%, $P < 0.001$); and were more likely to receive surgery (64.5% *vs* 47.5%, $P < 0.001$). Before PSM, the AYA group had a longer survival in months (median: 20.00, IQR: 5.00-62.50) than the older group (median: 15.00, IQR: 4.00-40.00) ($P < 0.001$). After PSM, the AYA group still had a longer survival in months (median: 21.00, IQR: 5.00-64.50) than the older group (median: 18.00, IQR: 6.00-53.00) ($P < 0.001$). The Cox proportional hazards regression model showed that advanced age (HR = 1.405, 95%CI: 1.218-1.621, $P < 0.001$) was a risk factor for OS of HCC. In the subgroup analysis, the Cox proportional hazards regression model showed that in

AJCC stage I/II patients, advanced age (HR = 1.749, 95%CI: 1.352-2.263, $P < 0.001$) was a risk factor for OS, while advanced age (HR = 1.186, 95%CI: 0.997-1.410, $P = 0.054$) was not a risk factor in AJCC stage III/IV patients before PSM. Advanced age (HR = 1.891, 95%CI: 1.356-2.637, $P < 0.001$) was a risk factor for OS in AJCC stage I/II patients, while it (HR = 1.192, 95%CI: 0.934-1.521, $P = 0.157$) was not a risk factor for OS in AJCC stage III/IV patients after PSM.

Research conclusions

AYA HCC patients have different clinical characteristics from older adults. In different AJCC stages, the two groups of patients have different OS: In the AJCC stage I/II group, advanced age was a risk factor for OS, while it was not a risk factor for OS in the AJCC stage III/IV group.

Research perspectives

The data in this study came from a database; thus, variable inclusion was limited to the database, and information such as laboratory examinations, combined diseases, and economic status could not be obtained. More samples are needed to verify our research results, and more basic studies are needed to explore the molecular mechanism of this research result.

ACKNOWLEDGEMENTS

We are indebted to all individuals who participated in or helped with this research project.

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