Retrospective Cohort Study

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

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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

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

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.

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%

annually[8], mainly due to the decrease in mortality of leukemia, non-Hodgkin' 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
		n = 12721	*n* = 366 (2.9%)	*n* = 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.
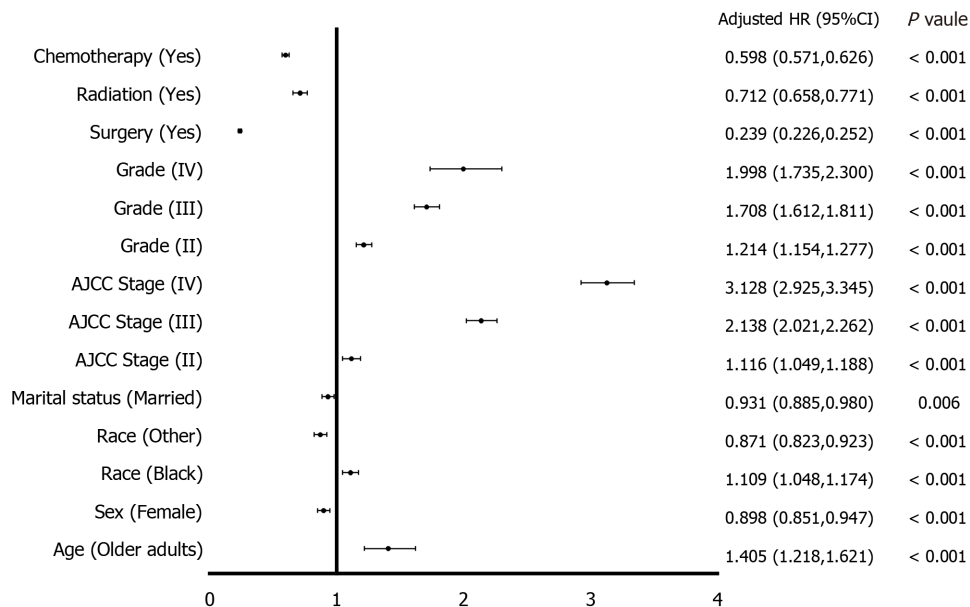

Figure 1 Forest map of multivariate analysis of overall survival in patients with hepatocellular carcinoma. All variables were statistically significant. Advanced age, black ethnicity, advanced American Joint Committee on Cancer stage, and advanced grade are risk factors for OS of HCC patients; female 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,

A

Number at risk					
AYA	366	112	48	3	0
Older adults	12355	2485	771	42	0

B

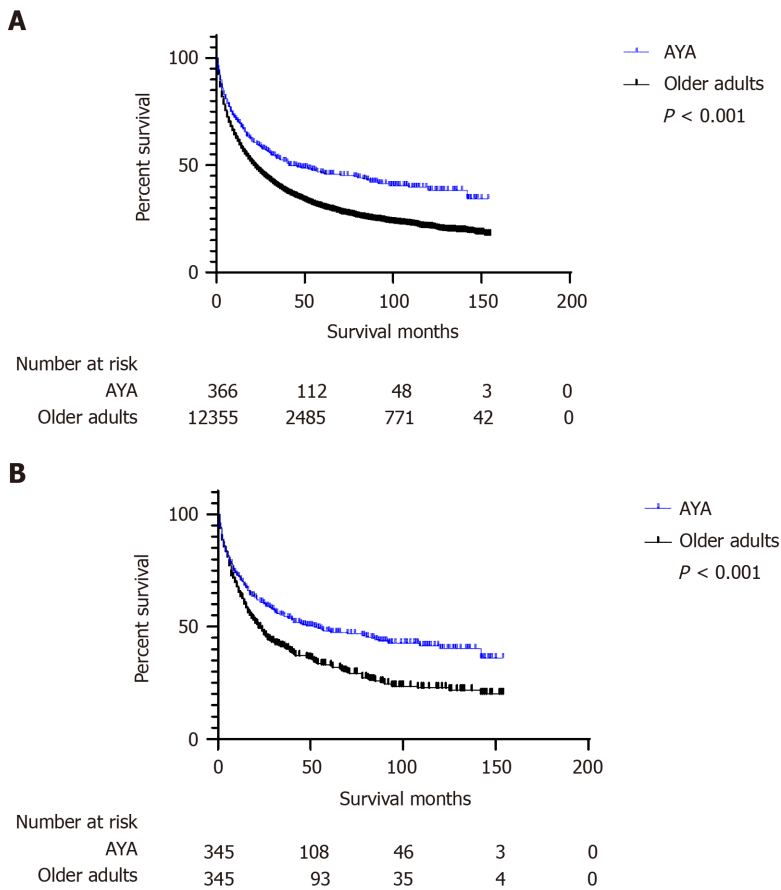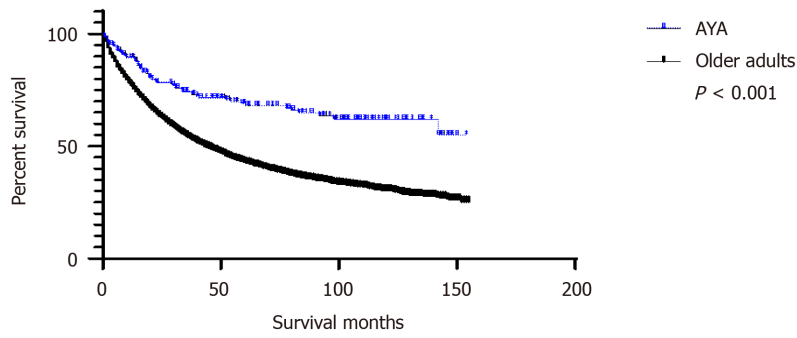| Number at risk					
AYA	345	108	46	3	0
Older adults	345	93	35	4	0

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.
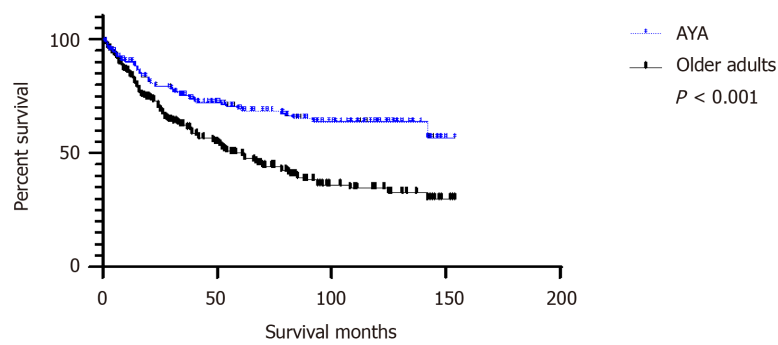
CONCLUSION

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.
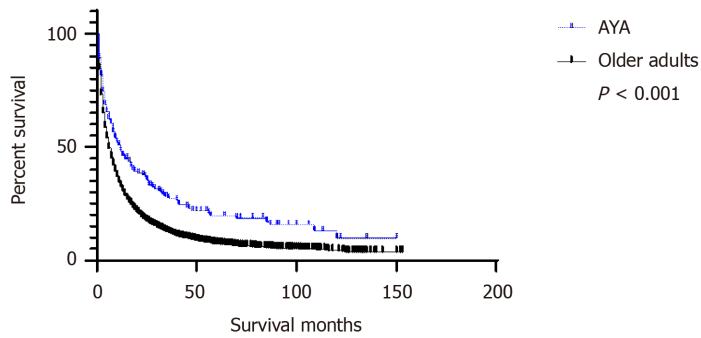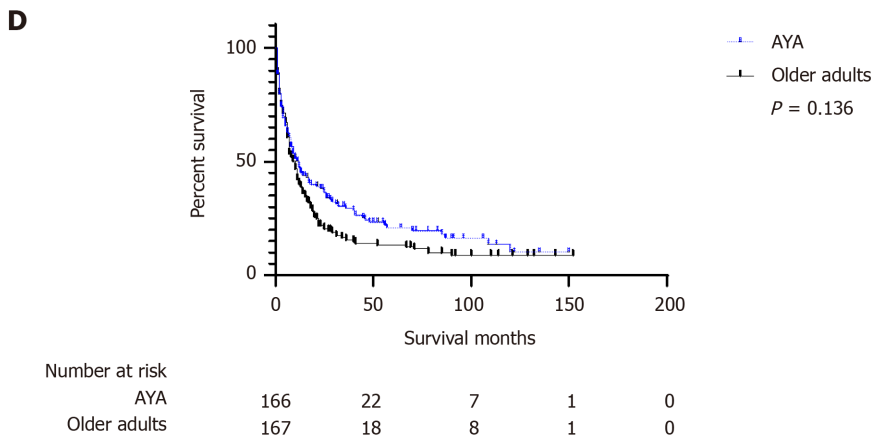
D

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.

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