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***Retrospective Cohort Study***

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

Ren J *et al.* HCC in AYA and older individuals

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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

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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.

**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* shows that the age at which HCC is likely to occur is different in different regions of the world[14]. 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***

TheSurveillance, 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. OSwas 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).

***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 thatcompared 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 improving the quality of life of AYA cancer survivors[28]. However, Rabin *et al* found that more than half of AYA cancer survivors remained sedentary and did not undergo scientific exercise interventions[29]. 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 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 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, 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.

**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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**REFERENCES**

1 **Coccia PF**, Pappo AS, Beaupin L, Borges VF, Borinstein SC, Chugh R, Dinner S, Folbrecht J, Frazier AL, Goldsby R, Gubin A, Hayashi R, Huang MS, Link MP, Livingston JA, Matloub Y, Millard F, Oeffinger KC, Puccetti D, Reed D, Robinson S, Rosenberg AR, Sanft T, Spraker-Perlman HL, von Mehren M, Wechsler DS, Whelan KF, Yeager N, Gurski LA, Shead DA. Adolescent and Young Adult Oncology, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018; **16**: 66-97 [PMID: 29295883 DOI: 10.6004/jnccn.2018.0001]

2 **Sender L**, Zabokrtsky KB. Adolescent and young adult patients with cancer: a milieu of unique features. *Nat Rev Clin Oncol* 2015; **12**: 465-480 [PMID: 26011488 DOI: 10.1038/nrclinonc.2015.92]

3 **Overholser L**, Kilbourn K, Liu A. Survivorship Issues in Adolescent and Young Adult Oncology. *Med Clin North Am* 2017; **101**: 1075-1084 [PMID: 28992855 DOI: 10.1016/j.mcna.2017.06.002]

4 **Thomas DM**, Albritton KH, Ferrari A. Adolescent and young adult oncology: an emerging field. *J Clin Oncol* 2010; **28**: 4781-4782 [PMID: 20733122 DOI: 10.1200/JCO.2010.30.5128]

5 **Tricoli JV**, Bleyer A. Adolescent and Young Adult Cancer Biology. *Cancer J* 2018; **24**: 267-274 [PMID: 30480571 DOI: 10.1097/PPO.0000000000000343]

6 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

7 **Miller KD**, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL, Siegel RL. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin* 2019; **69**: 363-385 [PMID: 31184787 DOI: 10.3322/caac.21565]

8 **Close AG**, Dreyzin A, Miller KD, Seynnaeve BKN, Rapkin LB. Adolescent and young adult oncology-past, present, and future. *CA Cancer J Clin* 2019; **69**: 485-496 [PMID: 31594027 DOI: 10.3322/caac.21585]

9 **Liu L**, Moke DJ, Tsai KY, Hwang A, Freyer DR, Hamilton AS, Zhang J, Cockburn M, Deapen D. A Reappraisal of Sex-Specific Cancer Survival Trends among Adolescents and Young Adults in the United States. *J Natl Cancer Inst* 2019; **111**: 509-518 [PMID: 30321398 DOI: 10.1093/jnci/djy140]

10 **Keegan TH**, Ries LA, Barr RD, Geiger AM, Dahlke DV, Pollock BH, Bleyer WA; National Cancer Institute Next Steps for Adolescent and Young Adult Oncology Epidemiology Working Group. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer* 2016; **122**: 1009-1016 [PMID: 26848927 DOI: 10.1002/cncr.29869]

11 **Villanueva A**. Hepatocellular Carcinoma. *N Engl J Med* 2019; **380**: 1450-1462 [PMID: 30970190 DOI: 10.1056/NEJMra1713263]

12 **Kulik L**, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. *Gastroenterology* 2019; **156**: 477-491.e1 [PMID: 30367835 DOI: 10.1053/j.gastro.2018.08.065]

13 **Fujiwara N**, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol* 2018; **68**: 526-549 [PMID: 28989095 DOI: 10.1016/j.jhep.2017.09.016]

14 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0186-y]

15 **Kelly D**, Sharif K, Brown RM, Morland B. Hepatocellular carcinoma in children. *Clin Liver Dis* 2015; **19**: 433-447 [PMID: 25921672 DOI: 10.1016/j.cld.2015.01.010]

16 **Reuben A**. Hepatocellular carcinoma in adults and children. *Clin Liver Dis* 2015; **19**: xiii-xxvi [PMID: 25921673 DOI: 10.1016/j.cld.2015.02.001]

17 **Berkman AM**, Livingston JA, Merriman K, Hildebrandt M, Wang J, Dibaj S, McQuade J, You N, Ying A, Barcenas C, Bodurka D, DePombo A, Lee HJ, de Groot J, Roth M. Long-term survival among 5-year survivors of adolescent and young adult cancer. *Cancer* 2020; **126**: 3708-3718 [PMID: 32484922 DOI: 10.1002/cncr.33003]

18 **Tai E**, Beaupin L, Bleyer A. Clinical trial enrollment among adolescents with cancer: supplement overview. *Pediatrics* 2014; **133 Suppl 3**: S85-S90 [PMID: 24918212 DOI: 10.1542/peds.2014-0122B]

19 **Bleyer A**, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. *Cancer* 2006; **107**: 1645-1655 [PMID: 16906507 DOI: 10.1002/cncr.22102]

20 **Parsons HM**, Harlan LC, Seibel NL, Stevens JL, Keegan TH. Clinical trial participation and time to treatment among adolescents and young adults with cancer: does age at diagnosis or insurance make a difference? *J Clin Oncol* 2011; **29**: 4045-4053 [PMID: 21931022 DOI: 10.1200/JCO.2011.36.2954]

21 **Kirchhoff AC**, Lyles CR, Fluchel M, Wright J, Leisenring W. Limitations in health care access and utilization among long-term survivors of adolescent and young adult cancer. *Cancer* 2012; **118**: 5964-5972 [PMID: 23007632 DOI: 10.1002/cncr.27537]

22 **Fern LA**, Bleyer A. Dynamics and Challenges of Clinical Trials in Adolescents and Young Adults with Cancer. *Cancer J* 2018; **24**: 307-314 [PMID: 30480575 DOI: 10.1097/PPO.0000000000000347]

23 **Bleyer A**, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B; Biology and Clinical Trials Subgroups of the US National Cancer Institute Progress Review Group in Adolescent and Young Adult Oncology. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer* 2008; **8**: 288-298 [PMID: 18354417 DOI: 10.1038/nrc2349]

24 **Hochberg J**, El-Mallawany NK, Abla O. Adolescent and young adult non-Hodgkin lymphoma. *Br J Haematol* 2016; **173**: 637-650 [PMID: 27071675 DOI: 10.1111/bjh.14074]

25 **Möricke A**, Zimmermann M, Reiter A, Gadner H, Odenwald E, Harbott J, Ludwig WD, Riehm H, Schrappe M. Prognostic impact of age in children and adolescents with acute lymphoblastic leukemia: data from the trials ALL-BFM 86, 90, and 95. *Klin Padiatr* 2005; **217**: 310-320 [PMID: 16307416 DOI: 10.1055/s-2005-872515]

26 **Printz C**. Adolescent and young adult cancer survivors appear to have higher hospitalization risk. *Cancer* 2020; **126**: 2509 [PMID: 32396697 DOI: 10.1002/cncr.32952]

27 **Anderson C**, Kaddas HK, Ou JY, Ramsay JM, Trogdon JG, Kirchhoff AC, Nichols HB. Hospitalization after Adolescent and Young Adult (AYA) Cancer: A Population-Based Study in Utah. *Cancer Epidemiol Biomarkers Prev* 2020; **29**: 336-342 [PMID: 31959598 DOI: 10.1158/1055-9965.EPI-19-1229]

28 **Zhi X**, Xie M, Zeng Y, Liu JE, Cheng ASK. Effects of Exercise Intervention on Quality of Life in Adolescent and Young Adult Cancer Patients and Survivors: A Meta-Analysis. *Integr Cancer Ther* 2019; **18**: 1534735419895590 [PMID: 31845599 DOI: 10.1177/1534735419895590]

29 **Rabin C**, Pinto B, Fava J. Randomized Trial of a Physical Activity and Meditation Intervention for Young Adult Cancer Survivors. *J Adolesc Young Adult Oncol* 2016; **5**: 41-47 [PMID: 26812450 DOI: 10.1089/jayao.2015.0033]

30 **Sansom-Daly UM**, Wakefield CE, Robertson EG, McGill BC, Wilson HL, Bryant RA. Adolescent and young adult cancer survivors' memory and future thinking processes place them at risk for poor mental health. *Psychooncology* 2018; **27**: 2709-2716 [PMID: 30109738 DOI: 10.1002/pon.4856]

31 **Richter D**, Koehler M, Friedrich M, Hilgendorf I, Mehnert A, Weißflog G. Psychosocial interventions for adolescents and young adult cancer patients: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2015; **95**: 370-386 [PMID: 25922217 DOI: 10.1016/j.critrevonc.2015.04.003]

32 **Chao C**, Bhatia S, Xu L, Cannavale KL, Wong FL, Huang PS, Cooper R, Armenian SH. Chronic Comorbidities Among Survivors of Adolescent and Young Adult Cancer. *J Clin Oncol* 2020; **38**: 3161-3174 [PMID: 32673152 DOI: 10.1200/JCO.20.00722]

33 **Kaul S**, Veeranki SP, Rodriguez AM, Kuo YF. Cigarette smoking, comorbidity, and general health among survivors of adolescent and young adult cancer. *Cancer* 2016; **122**: 2895-2905 [PMID: 27286172 DOI: 10.1002/cncr.30086]

**Footnotes**

**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.

**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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**Figure Legends**



**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.

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**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.



**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.

**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.

**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.

**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.

**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.