Heliyon 10 (2024) e28497

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Comparison of metastasis and prognosis between early-onset and late-onset hepatocellular carcinoma: A population-based study

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ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Early-onset
Late-onset
Distant metastasis
Prognosis

ABSTRACT

Background: While hepatocellular carcinoma (HCC) represents a highly heterogeneous disease with variable oncogenesis mechanisms and biological features, little is understood about differences in distant metastasis (DM) and prognosis between early-onset and late-onset HCC. This study defined early-onset disease as cancer diagnosed at age younger than 50 years and aimed to present a comprehensive analysis to characterize these disparities based on age.

Methods: Information of HCC patients was retrospectively collected from the SEER database and our hospital. Patient demographics, tumor characteristics, and survival were compared between the two groups. A 1:1 propensity score matching (PSM) was adopted to adjust confounding factors. Logistic and cox analysis were utilized to explore risk factors of DM and prognosis, respectively. Besides, the survival differences were assessed by the Kaplan–Meier curve and log-rank test.

Results: In total, 19187 HCC patients obtained from the SEER database and 129 HCC patients obtained from our own center were enrolled. Among 19187 patients with HCC, 3376 were identified in the matched cohort, including 1688 early-onset patients and 1688 late-onset patients. Compared with late-onset HCC, early-onset HCC was more likely to occur in female (25.2% vs. 22.9%, P = 0.030), have large tumors (>10.0 cm, 24.1% vs. 14.6%, P = 0.000), harbor poorly differentiated/undifferentiated cancers (17.0% vs. 14.0%, P = 0.003), present advanced clinical stage (T3+T4, 33.7% vs. 28.5%; N1, 9.2% vs. 6.7%; P = 0.000), and develop DM (13.0% vs. 9.5%, P = 0.000). After adjustment for confounders by PSM, we discovered that early-onset HCC

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https://doi.org/10.1016/j.heliyon.2024.e28497
Received 20 January 2024; Received in revised form 9 March 2024; Accepted 20 March 2024
Available online 26 March 2024

remained an independent risk factor for DM. However, combined with Kaplan–Meier curve and cox analysis, early-onset HCC was an independent favorable predictor of survival. We validated these data on an independent cohort from our hospital.
Conclusion: In this population-based study, despite developing DM more frequently, early-onset HCC exhibited a superior prognosis than late-onset HCC. Nevertheless, further research is warranted to understand the underlying aetiologic basis for the disparities.

1. Introduction

Hepatocellular carcinoma (HCC) represents the most common form of primary liver cancer and one of the most prevalent malignancies worldwide [1]. In the latest global cancer report, HCC has risen to the third leading cause of mortality worldwide, with 830,000 deaths each year [2]. Unfortunately, the five-year survival rate remains low at approximately 18% despite advances in diagnostic tools and treatment modalities [3–5]. The incidence of HCC increases with age, with the average age at onset reported to be 50 years [6,7].

Currently, the definition of early-onset HCC alternates between onset before 30 and 50 years of age in the literature [8–10]. Early-onset HCC occupies 15%–20% of all HCC cases in Asia, and the incidence is on the rising [8]. Although it contributes only a minor fraction of the total HCC, studies have indicated that early-onset HCC constitutes a unique subtype with different mechanisms of hepatocarcinogenesis and biological characteristics [11]. For example, hepatitis B virus (HBV) has remarkably diverse genotypes and integration patterns in early-onset and late-onset HCC([8,12,13]). Moreover, compared with late-onset HCC, early-onset HCC is less likely to develop cirrhosis [10,14] and presents later clinical manifestations, but has a higher resectability rate [9].

To date, comparison of distant metastasis (DM) between early-onset and late-onset HCC has not been exhaustively investigated. Recently, a large study only focused on the relationship between tumor size and DM of HCC, while ignored the impact of age-related differences on DM and overall survival (OS) [15]. Regarding long-term prognosis, some prior studies have revealed that the survival rate was similar between early-onset and late-onset HCC [9,11,14]. However, some studies failed to reach the same findings [16,17]. From these, there is limited awareness of differences in DM and prognosis between early-onset and late-onset cases. As such, additional efforts are needed to bridge this knowledge gap. For early-onset HCC with insufficient population and relatively low incidence, we employed a well-structured database named SEER (Surveillance, Epidemiology, and End Results), which can potentially provide more detailed and accurate results. We aimed to conduct a comprehensive analysis that was validated by an independent external cohort comprising 129 HCC patients to better ascertain their association with prognosis.

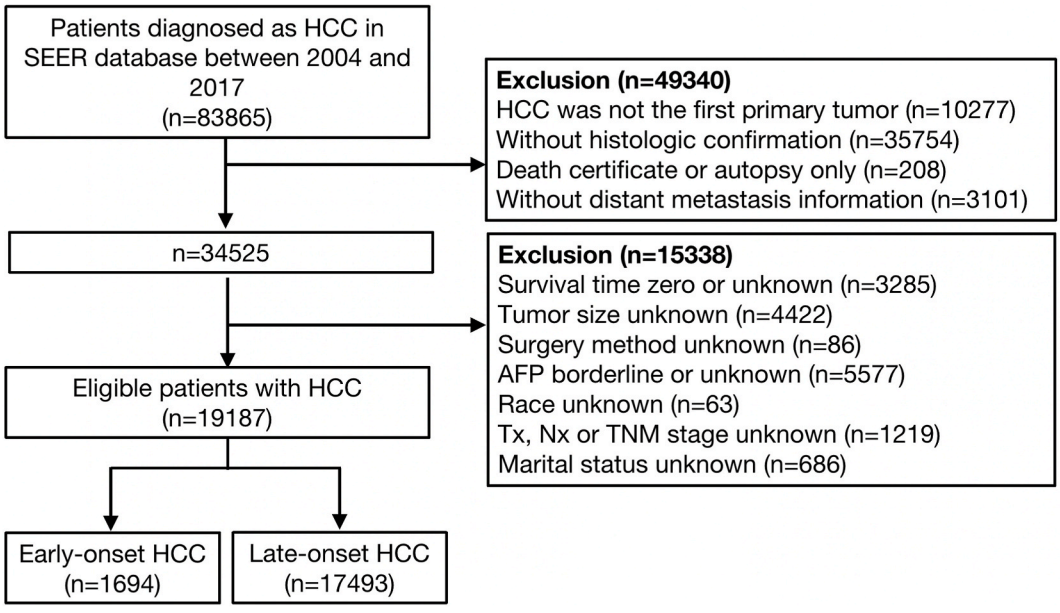

Fig. 1. Flow diagram of eligible patients diagnosed with hepatocellular carcinoma (HCC) from SEER database.

2. Patients and methods

2.1. Database and patient selection

All patients were enrolled from SEER database and Jinling Hospital, Medical School of Nanjing University. Information on patients diagnosed with HCC was retrospectively collected from the SEER database between 2004 and 2017. The SEER database is a large population-based collaboration program that records demographic and clinical information from 19 geographically distinct cancer registries covering approximately 34% of the total US population [18]. Detailed per-patient data was extracted using the SEER*Stat 8.3.9 software (National Cancer Institute, Bethesda, MD, USA). A total of 83865 patients were screened out from the dataset who met the criteria of HCC patients with the concrete histology code (8170, 8171, 8172, 8173, 8174, and 8175) and primary site code C22.0 (liver) based on the third edition of the International Classification of Diseases for Oncology. Subsequently, eligible patients that met the following criteria were enrolled: (a) patients with only one primary malignancy in their lifetime; (b) diagnosis determined by positive histology; (c) cases not diagnosed by autopsy or death certificate; (d) having clear DM information; (e) known survival time and surgery methods; (f) complete data about race, marital status, tumor size, alpha-fetoprotein (AFP), primary tumor (T), regional lymph nodes (N), and TNM staging. In addition, individuals with less than 1-month of follow-up were excluded owing to the limited immortal time bias [19]. The final population for analysis consisted of 19187 HCC patients from the SEER database (1694 early-onset HCC and 17493 late-onset HCC). Fig. 1 demonstrates the specific process of study selection. As for extracting patients from our center, we included 129 patients diagnosed with HCC from June 2018 to May 2020 in Jinling Hospital. The following inclusion criteria were

Table 1
Basic information of patients with hepatocellular carcinoma from 2004 through 2017 in SEER database.

Characteristic (Early-onset/Late-onset)	Total population (19187)	Early-onset HCC (1694)	Late-onset HCC (17493)	P value
Race				0.000
White (7.9%/92.1%)	12639 (65.9%)	1001 (59.1%)	11638 (66.5%)	
Black (7.8%/92.2%)	2602 (13.5%)	202 (11.9%)	2400 (13.7%)	
Other (12.4%/87.6%)	3946 (20.6%)	491 (29.0%)	3455 (19.8%)	
Gender				0.030
Male (8.6%/91.4%)	14757 (76.9%)	1267 (74.8%)	13490 (77.1%)	
Female (9.6%/90.4%)	4430 (23.1%)	427 (25.2%)	4003 (22.9%)	
Marital status				0.000
Married (7.8%/92.2%)	10993 (57.3%)	855 (50.5%)	10138 (58.0%)	
Unmarried (10.2%/89.8%)	8194 (42.7%)	839 (49.5%)	7355 (42.0%)	
Grade				0.003
Well differentiated (8.5%/91.5%)	3958 (20.6%)	338 (20.0%)	3620 (20.7%)	
Moderately differentiated (8.1%/91.9%)	6097 (31.8%)	494 (29.1%)	5603 (32.0%)	
Poorly differentiated/Undifferentiated (10.5%/89.5%)	2744 (14.3%)	288 (17.0%)	2456 (14.0%)	
Unknown (9.0%/91.0%)	6388 (33.3%)	574 (33.9%)	5814 (33.2%)	
Tumor size, cm				0.000
≤3.0 (8.5%/91.5%)	5518 (28.8%)	469 (27.7%)	5049 (28.9%)	
3.1–5.0 (7.2%/92.8%)	5013 (26.1%)	360 (21.3%)	4653 (26.6%)	
5.1–10.0 (8.0%/92.0%)	5688 (29.6%)	456 (26.9%)	5232 (29.9%)	
>10.0 (13.8%/86.2%)	2968 (15.5%)	409 (24.1%)	2559 (14.6%)	
T stage				0.000
T1 (8.2%/91.8%)	8583 (44.7%)	704 (41.6%)	7879 (45.0%)	
T2 (8.3%/91.7%)	5045 (26.3%)	419 (24.7%)	4626 (26.4%)	
T3 (9.9%/90.1%)	4898 (25.5%)	486 (28.7%)	4412 (25.2%)	
T4 (12.9%/87.1%)	661 (3.4%)	85 (5.0%)	576 (3.3%)	
N stage				0.000
N0 (8.6%/91.4%)	17860 (93.1%)	1538 (90.8%)	16322 (93.3%)	
N1 (11.8%/88.2%)	1327 (6.9%)	156 (9.2%)	1171 (6.7%)	
Distant metastasis				0.000
No (8.5%/91.5%)	17299 (90.2%)	1473 (87.0%)	15826 (90.5%)	
Yes (11.7%/88.3%)	1888 (9.8%)	221 (13.0%)	1667 (9.5%)	
AFP				0.378
Normal (9.1%/90.9%)	5991 (31.2%)	545 (32.2%)	5446 (31.1%)	
Elevated (8.7%/91.3%)	13196 (68.8%)	1149 (67.8%)	12047 (68.9%)	
Primary tumor surgery				0.000
None (7.2%/92.8%)	10106 (52.7%)	729 (43.0%)	9377 (53.6%)	
Local tumor destruction (6.1%/93.9%)	2528 (13.2%)	154 (9.1%)	2374 (13.6%)	
Resection (12.4%/87.6%)	6553 (34.1%)	811 (47.9%)	5742 (32.8%)	
Radiation				0.000
No (9.1%/90.1%)	17367 (90.5%)	1574 (92.9%)	15793 (90.3%)	
Yes (6.6%/93.4%)	1820 (9.5%)	120 (7.1%)	1700 (9.7%)	
Chemotherapy				0.761
No/Unknown (8.9%/91.1%)	10863 (56.6%)	965 (57.0%)	9898 (56.6%)	
Yes (8.8%/91.2%)	8324 (43.4%)	729 (43.0%)	7595 (43.4%)	

Other: American Indian/Alaska Native and Asian/Pacific Islander; AFP: alpha-fetoprotein.

adopted: (a) aged more than 18 years; (b) have an ascertained diagnosis of HCC; (c) no severe chronic diseases; (d) no other tumor history; (e) complete case data such as tumor size, AFP, treatment, and so forth; and (f) complete follow-up information. This study was approved by the Ethics Committee of Jinling Hospital, Medical School of Nanjing University.

2.2. Definitions of variables

The obtained clinical covariates included basic demographic characteristics (gender, age, race, and marital status), tumor-related data [histological grading, tumor size, AFP, and American Joint Committee on Cancer (AJCC) TNM staging], type of treatment received (primary tumor surgery, radiation, and chemotherapy), and follow-up information (vital status, and survival time)]. For this study, early-onset HCC was defined as HCC diagnosed before 50 years of age, while late-onset HCC referred to HCC diagnosed at or after the age of 50 years [20]. In the light of the primary tumor resection, participants were classified into three groups: no tumor-directed surgery, local tumor destruction (photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, percutaneous ethanol injection, thermal ablation, ultrasound, and acetic acid), and resection (partial, and total hepatectomy). In cases where tumor resection was not performed, imaging modalities including contrast-enhanced ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT), among others, were utilized to assess the T stage, N stage, and tumor size. Moreover, the variable of AFP was divided into normal and elevated. According to clinical features, tumor size was dichotomized into four categories: ≤3.0 cm, 3.1–5.0 cm, 5.1–10.0 cm, and >10.0 cm. The status of DM was separated into no and yes. The primary outcome measures included DM and OS. The state of DM was identified on initial admission. As for OS, it

Table 2
Basic information of patients with hepatocellular carcinoma from 2004 through 2017 after propensity-score-matching in SEER database.

Characteristic (Early-onset/Late-onset)	Total population (3376)	Early-onset HCC (1688)	Late-onset HCC (1688)	P value
Race				0.839
White (50.4%/49.6%)	1982 (58.7%)	999 (59.2%)	983 (58.2%)	
Black (49.0%/51.0%)	408 (12.1%)	200 (11.8%)	208 (12.3%)	
Other (49.6%/51.4%)	986 (29.2%)	489 (29.0%)	497 (29.4%)	
Gender				0.750
Male (49.8%/50.2%)	2536 (75.1%)	1264 (74.9%)	1272 (75.4%)	
Female (50.5%/49.5%)	840 (24.9%)	424 (25.1%)	416 (24.6%)	
Marital status				0.810
Married (50.2%/49.8%)	1701 (50.4%)	854 (50.6%)	847 (50.2%)	
Unmarried (49.8%/50.2%)	1675 (49.6%)	834 (49.4%)	841 (49.8%)	
Grade				0.904
Well differentiated (49.6%/50.4%)	682 (20.2%)	338 (20.0%)	344 (20.4%)	
Moderately differentiated (50.8%/49.2%)	972 (28.8%)	494 (29.3%)	478 (28.3%)	
Poorly differentiated/Undifferentiated (49.0%/51.0%)	586 (17.4%)	287 (17.0%)	299 (17.7%)	
Unknown (50.1%/49.9%)	1136 (33.6%)	569 (33.7%)	567 (33.6%)	
Tumor size, cm				0.848
≤3.0 (49.9%/50.1%)	939 (27.8%)	469 (27.8%)	470 (27.8%)	
3.1–5.0 (49.5%/50.5%)	728 (21.6%)	360 (21.3%)	368 (21.8%)	
5.1–10.0 (49.3%/50.7%)	922 (27.3%)	455 (27.0%)	467 (27.7%)	
>10.0 (51.3%/48.7%)	787 (23.3%)	404 (23.9%)	383 (22.7%)	
T stage				0.922
T1 (49.5%/50.5%)	1421 (42.1%)	703 (41.6%)	718 (42.5%)	
T2 (50.5%/49.5%)	829 (24.6%)	419 (24.8%)	410 (24.3%)	
T3 (50.0%/50.0%)	968 (28.7%)	484 (28.7%)	484 (28.7%)	
T4 (51.9%/48.1%)	158 (4.7%)	82 (4.9%)	76 (4.5%)	
N stage				0.236
N0 (49.7%/50.3%)	3095 (91.7%)	1538 (91.1%)	1557 (92.2%)	
N1 (53.4%/46.4%)	281 (8.3%)	150 (8.9%)	131 (7.8%)	
Distant metastasis				0.000
No (48.8%/51.2%)	3012 (89.2%)	1470 (87.1%)	1542 (91.4%)	
Yes (59.9%/40.1%)	364 (10.8%)	218 (12.9%)	146 (8.6%)	
AFP				0.322
Normal (48.8%/51.2%)	1107 (32.8%)	540 (32.0%)	567 (33.6%)	
Elevated (50.6%/49.4%)	2269 (67.2%)	1148 (68.0%)	1121 (66.4%)	
Primary tumor surgery				0.979
None (50.2%/49.8%)	1453 (43.0%)	729 (43.2%)	724 (42.9%)	
Local tumor destruction (50.2%/49.8%)	307 (9.1%)	154 (9.1%)	153 (9.1%)	
Resection (49.8%/50.2%)	1616 (47.9%)	805 (47.7%)	811 (48.0%)	
Radiation				0.078
No (49.6%/50.4%)	3161 (93.6%)	1568 (92.9%)	1593 (94.4%)	
Yes (55.8%/44.2%)	215 (6.4%)	120 (7.1%)	95 (5.6%)	
Chemotherapy				0.143
No/Unknown (48.9%/51.1%)	1966 (58.2%)	962 (57.0%)	1004 (59.5%)	
Yes (51.5%/48.5%)	1410 (41.8%)	726 (43.0%)	684 (40.5%)	

Other: American Indian/Alaska Native and Asian/Pacific Islander; AFP: alpha-fetoprotein.

was computed from the date of diagnosis to death or the last follow-up.

2.3. Statistical analysis

To determine the differences in clinicopathological characteristics among the early-onset cohort and the late-onset cohort, the Chi-square test or Fisher's exact test was applied for comparisons of categorical variables. Univariable and multivariable logistic regression models were conducted to identify the potential risk factors correlated with DM, whereas cox regression analyses were used to assess independent predictors on survival, of which all results were expressed as the odd ratio (OR) and hazard ratio (HR) with corresponding 95% confidence interval (CI), respectively. Only factors with P values < 0.05 in univariable analysis were subsequently included in multivariable analysis. Besides, the survival differences between the two groups were estimated visually by the Kaplan–Meier (KM) curve and log-rank test.

Owing to the imbalance of the data from the SEER database, we employed propensity score matching (PSM) to minimize the effects of potential confounders on the outcomes. Patients were matched 1:1 into early-onset and late-onset HCC groups. The nine variables utilized to match were as follows: race, gender, marital status, grade, tumor size, T stage, N stage, primary tumor surgery, and radiation. After PSM, we analyzed the differences of all covariates between the two sets via the Chi-square test.

For the described analysis above, the following software programs were applied: SPSS Statistics software 26.0 (IBM Corporation) for Chi-square test, logistic regression analysis, and cox regression analysis, GraphPad Prism 9.0 (San Diego, CA, USA) for KM analysis and log-rank test, and R software 3.6.2 (https://www.rproject.org/) for PSM. In all analyses, a two-sided P-value <0.05 was recognized as statistically significant.

3. Results

3.1. Clinicopathologic characteristics of early-onset and late-onset HCC

Detailed baseline clinical and pathological features of the patients from the SEER database are exhibited in Table 1, while information of patients extracted from our center were listed in Table S1. For patients from the SEER database, 19187 cases with HCC were considered qualified for this study, of whom 1694 (8.8%) patients were identified with early-onset HCC and 17493 (91.2%) patients

Table 3
Univariable and multivariable logistic regression model for exploring the potential risk factors for distant metastasis in patients from SEER database.

Variables (DM Yes/No)	Univariable analysis OR (95% CI)	P value	Multivariable analysis OR (95% CI)	P value
Race		0.003		0.341
White (1250/11389)	Reference		Reference	
Black (294/2308)	1.161 (1.014–1.328)	0.030	0.984 (0.848–1.142)	0.832
Other (344/3602)	0.870 (0.768–0.986)	0.029	0.903 (0.788–1.035)	0.143
Gender		0.000		0.000
Male (1541/13216)	Reference		Reference	
Female (347/4083)	0.729 (0.645–0.823)	0.000	0.771 (0.676–0.879)	0.000
Marital status		0.000		0.000
Married (983/10010)	Reference		Reference	
Unmarried (905/7289)	1.264 (1.150–1.391)	0.000	1.245 (1.119–1.385)	0.000
Grade		0.000		0.000
Well differentiated (225/3733)	Reference		Reference	
Moderately differentiated (360/5737)	1.041 (0.877–1.236)	0.645	0.895 (0.747–1.071)	0.226
Poorly differentiated/Undifferentiated (365/2379)	2.546 (2.139–3.029)	0.000	1.497 (1.241–1.806)	0.000
Unknown (938/5450)	2.855 (2.454–3.322)	0.000	2.257 (1.923–2.649)	0.000
HCC type		0.000		0.039
Early-onset HCC (221/1473)	Reference		Reference	
Late-onset HCC (1667/15826)	0.702 (0.604–0.816)	0.000	0.839 (0.709–0.991)	0.039
Tumor size, cm		0.000		0.000
≤3.0 (211/5307)	Reference		Reference	
3.1–5.0 (319/4694)	1.709 (1.430–2.043)	0.000	1.503 (1.251–1.805)	0.000
5.1–10.0 (770/4918)	3.938 (3.365–4.608)	0.000	2.267 (1.891–2.717)	0.000
>10.0 (588/2380)	6.214 (5.271–7.325)	0.000	3.256 (2.686–3.946)	0.000
T stage		0.000		0.000
T1 (480/8103)	Reference		Reference	
T2 (298/4747)	1.060 (0.913–1.230)	0.445	1.109 (0.946–1.301)	0.203
T3 (905/3993)	3.826 (3.404–4.301)	0.000	1.838 (1.602–2.108)	0.000
T4 (205/456)	7.589 (6.284–9.166)	0.000	3.617 (2.924–4.473)	0.000
N stage		0.000		0.000
N0 (1337/16523)	Reference		Reference	
N1 (551/776)	8.775 (7.763–9.919)	0.000	5.536 (4.852–6.317)	0.000
AFP		0.000		0.000
Normal (375/5616)	Reference		Reference	
Elevated (1513/11683)	1.939 (1.725–2.181)	0.000	1.462 (1.286–1.661)	0.000

Other: American Indian/Alaska Native and Asian/Pacific Islander; AFP: alpha-fetoprotein; OR: odd ratio; CI: confidence interval.

were diagnosed as late-onset HCC. Detailed baseline clinical and pathological features of the patients from the two groups are exhibited in Table 1. Among the unmatched cohort, the early-onset patients were more frequently female (25.2% vs. 22.9%, P = 0.030), with unmarried status (49.5% vs. 42.0%, P = 0.000) compared to late-onset HCC, while the level of AFP was not significantly different (P = 0.378). Conversely, there were more black patients in the late-onset group than in the early-onset group (13.7% vs. 11.9%, P = 0.000). Surprisingly, patients with early-onset disease were more likely to have large (tumor >10.0 cm, 24.1% vs. 14.6%, P = 0.000) and poorly differentiated/undifferentiated (17.0% vs. 14.0%, P = 0.003) tumors, present advanced T stage (T3+T4, 33.7% vs. 28.5%, P = 0.000) and N stage (N1, 9.2% vs. 6.7%, P = 0.000), develop DM (13.0% vs. 9.5%, P = 0.000). Additionally, we discovered that the proportion of those receiving partial or total hepatectomy for early-onset HCC was dramatically higher than that for late-onset HCC (47.9% vs. 32.8%, P = 0.000). In contrast, late-onset patients were prone to undergo non-cancer-directed surgery (53.6% vs. 43.0%, P = 0.000) or radiation (9.7% vs. 7.1%, P = 0.000). However, the ratio of patients treated with chemotherapy did not differ markedly between groups (P = 0.761). Considering that the non-random allocation of patients might affect our outcome, we then adopted PSM to further match the baseline data between the two groups, and a new cohort early-onset (n = 1688) and late-onset (n = 1688) cohort was generated. All covariates of both sets were balanced after matching, showing no significant difference (P > 0.05). Besides, compared with late-onset HCC, early-onset HCC was still more susceptible to experiencing DM after 1:1 PSM (12.9% vs. 8.6%, P = 0.000). The clinicopathological characteristics of the matched population are illustrated in Table 2. In addition, we ultimately included 129 HCC patients from our hospital, including 36 early-onset patients and 93 late-onset patients. Similarly, we also found that earlyonset HCC had more cases with DM (25.0% vs. 10.8%, P = 0.041).

3.2. Identification of risk factors for DM

To identify the risk factors related to DM, univariable and multivariable logistic regression analyses were performed on patients in

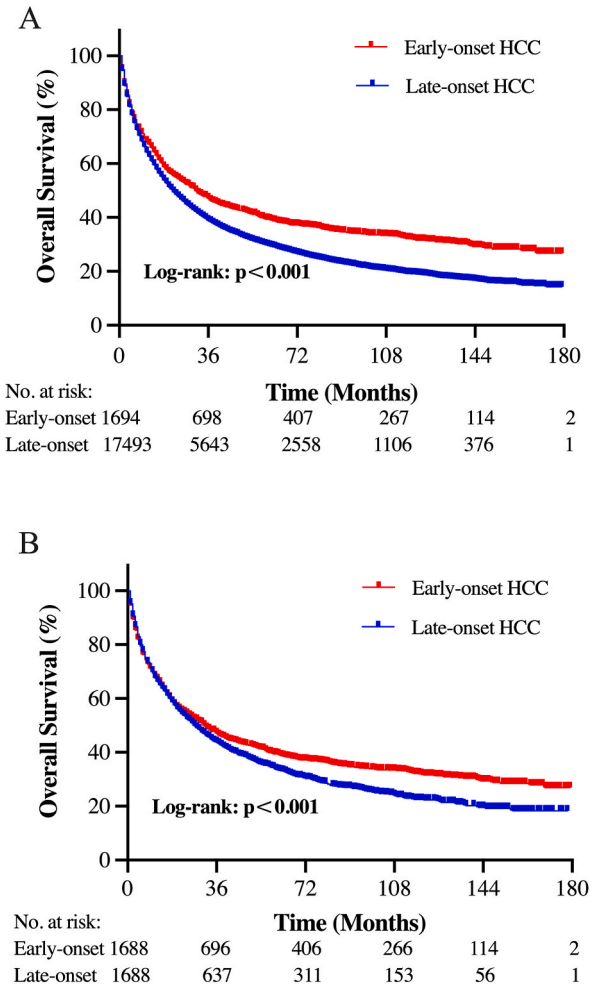

Fig. 2. Comparison of survival between early-onset and late-onset hepatocellular carcinoma (HCC) using SEER data: (A) Kaplan–Meier curve for entire cohort before propensity matching; (B) Kaplan–Meier curve for calibrated cohort after propensity matching.

the SEER database. As shown in Table 3, female gender was a favorable element compared to male gender (OR = 0.771, 95%CI, 0.676–0.879, P = 0.000). Unmarried status had a greater possibility to occur DM than being married (OR = 1.245, 95%CI, 1.119–1.385, P = 0.000). As expected, a higher risk of metastasis was associated with larger tumor size (P = 0.000), as well as worse differentiation grade (P = 0.000), advanced clinical stage including T (P = 0.000) and N stage (P = 0.000). Of note, HCC type was an independent factor for DM (OR = 0.839, 95%CI, 0.709–0.991, P = 0.039) and patients diagnosed with early-onset HCC more commonly experienced metastasis. Besides, elevated AFP levels significantly increased the risk of DM (OR = 1.462, 95%CI, 1.286–1.661, P = 0.000). To exclude effects from potential confounding factors, we also made the above analysis in the post-matched population. From the results of logistic regression models (Table S2), late-onset HCC was less likely to develop metastasis after correction (OR = 0.604, 95%CI, 0.475–0.768, P = 0.000), which was in agreement with that before PSM. Regarding our own patients, we also discovered that late-onset patients had DM less often than early-onset patients (OR = 0.252, 95%CI, 0.071–0.894, P = 0.033 , Table S3).

3.3. Comparison of survival and screening of prognostic factors

We first employed KM curve to compare the survival of the two groups. In analyses of the entire cohort from the SEER database, early-onset patients harbored a superior OS than late-onset patients (P < 0.001), which is depicted in Fig. 2A. Specifically, the median OS time was 31 months in the early-onset group and 22 months in the late-onset group. Likewise, the 3-year and 5-year OS rates for patients with early-onset HCC were 47.0%, and 39.3%, respectively, and 38.7%, and 29.6%, respectively, for patients with late-onset HCC, with significant differences. Further, we investigated the association between HCC type and survival outcomes in the matched population. After controlling for confounding factors, early-onset patients remained connected with improved median survival (31 months vs. 27 months, p < 0.001, Fig. 2B). Moreover, there was a trend for higher 3-year and 5-year OS in early-onset cohort compared to late-onset cohort [3-year OS (47.0% vs. 43.7%, p < 0.001) and 5-year OS (39.3% vs. 33.6%, p < 0.001)]. To verify these findings, we analyzed data from our own hospital and found that early-onset patients had better survival than late-onset patients (P < 0.01, Fig. 3).

Subsequently, univariate and multivariate cox analyses were used to obtain insight into factors related to the prognosis. From Table 4, we observed that late-onset HCC was independently correlated with an increased risk of overall death and decreased OS (HR = 1.280, 95%CI, 1.201–1.365, P = 0.000). Furthermore, worse tumor differentiation (P = 0.000), larger tumor diameter (P = 0.000), higher tumor stage [T stage (P = 0.000), N stage (P = 0.000)], presence of DM (P = 0.000), and positive AFP expression (P = 0.000) substantially increased the hazard of all-cause mortality among patients with HCC. Conversely, the receipt of primary tumor surgery (P = 0.000), chemotherapy (P = 0.000), or radiotherapy (P = 0.000) led to a pronounced improvement in survival of patients. Other independent factors of unfavorable prognosis included white race (P = 0.000), male gender (P = 0.006), and unmarried status (P = 0.000). The results that late-onset HCC represented an independent negative predictor of survival were unchanged after adjustment for potential confounders (HR = 1.195, 95%CI, 1.099–1.301, P = 0.000, Table S4). Consistent with these, our own data also uncovered that late-onset HCC was independently associated with poor prognosis (HR = 5.887, 95%CI, 2.755–12.580, P = 0.000, Table S5).

4. Discussion

Due to its growing incidence, early-onset HCC has drawn increased attention over the last several decades [21]. Even the American Association for the Study of Liver Diseases (AASLD) has recommended that Asian male HBV carriers should conduct examinations for HCC screening at 40 years other than 50 years, indicating that the onset of HCC shows a younger trend [22]. Nevertheless, there are only limited studies focused on early-onset HCC and very few reports comparing the tumor characteristics of early-onset and late-onset HCC. Hence, to more objectively evaluate the disparities between early-onset and late-onset HCC, we performed the study on a propensity-matched population basis.

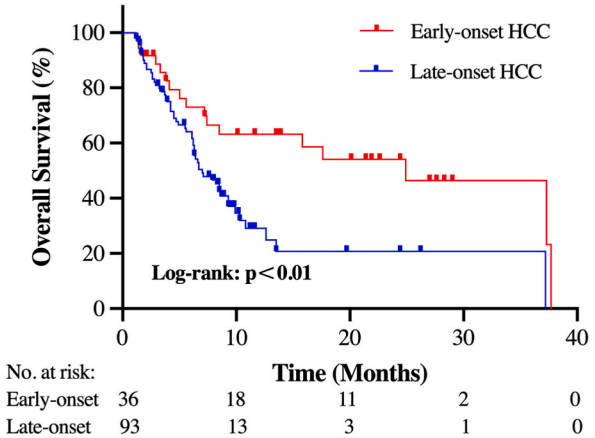

Fig. 3. Kaplan–Meier curve between early-onset and late-onset hepatocellular carcinoma (HCC) was performed with data from our hospital.

Table 4
Univariate and multivariate cox regression model for exploring the potential risk factors. for patient's prognosis in SEER database.

Variables	Univariate analysis HR (95% CI)	P value	Multivariate analysis HR (95% CI)	P value
Race		0.000		0.000
White	Reference		Reference	
Black	1.178 (1.122–1.237)	0.000	1.006 (0.958–1.057)	0.807
Other	0.813 (0.778–0.850)	0.000	0.858 (0.820–0.897)	0.000
Gender		0.000		0.006
Male	Reference		Reference	
Female	0.902 (0.866–0.939)	0.000	0.943 (0.905–0.983)	0.006
Marital status		0.000		0.000
Married	Reference		Reference	
Unmarried	1.277 (1.235–1.321)	0.000	1.104 (1.066–1.144)	0.000
Grade		0.000		0.000
Well differentiated	Reference		Reference	
Moderately differentiated	0.982 (0.934–1.031)	0.459	1.149 (1.093–1.208)	0.000
Poorly differentiated/Undifferentiated	1.540 (1.454–1.631)	0.000	1.560 (1.470–1.655)	0.000
Unknown	1.428 (1.361–1.497)	0.000	1.192 (1.136–1.251)	0.000
HCC type		0.000		0.000
Early-onset HCC	Reference		Reference	
Late-onset HCC	1.309 (1.230–1.394)	0.000	1.280 (1.201–1.365)	0.000
Tumor size, cm		0.000		0.000
≤3.0	Reference		Reference	
3.1–5.0	1.621 (1.542–1.703)	0.000	1.465 (1.393–1.541)	0.000
5.1–10.0	2.677 (2.554–2.805)	0.000	1.835 (1.736–1.939)	0.000
>10.0	3.511 (3.327–3.705)	0.000	2.363 (2.218–2.516)	0.000
T stage		0.000		0.000
T1	Reference		Reference	
T2	1.117 (1.070–1.167)	0.000	1.284 (1.227–1.344)	0.000
T3	2.960 (2.841–3.084)	0.000	1.599 (1.524–1.678)	0.000
T4	2.961 (2.717–3.226)	0.000	1.523 (1.390–1.667)	0.000
N stage		0.000		0.000
N0	Reference		Reference	
N1	2.645 (2.493–2.806)	0.000	1.232 (1.157–1.313)	0.000
Distant metastasis		0.000		0.000
No	Reference		Reference	
Yes	3.441 (3.270–3.620)	0.000	1.762 (1.667–1.863)	0.000
AFP		0.000		0.000
Normal	Reference		Reference	
Elevated	1.561 (1.503–1.622)	0.000	1.330 (1.279–1.383)	0.000
Primary tumor surgery		0.000		0.000
None	Reference		Reference	
Local tumor destruction	0.391 (0.371–0.412)	0.000	0.503 (0.475–0.532)	0.000
Resection	0.211 (0.203–0.221)	0.000	0.227 (0.216–0.238)	0.000
Radiation		0.000		0.000
Yes	Reference		Reference	
No/Unknown	0.709 (0.671–0.750)	0.000	1.381 (1.305–1.462)	0.000
Chemotherapy		0.000		0.000
Yes	Reference		Reference	
No/Unknown	0.885 (0.856–0.916)	0.000	1.518 (1.464–1.573)	0.000

Other: American Indian/Alaska Native and Asian/Pacific Islander; AFP: alpha-fetoprotein; HR: hazard ratio; CI: confidence interval.

To our knowledge, this is the first and largest retrospective study focusing on the DM characteristics and survival outcomes of early-onset and late-onset HCC by the SEER database and validating it in an external cohort. Based on our findings, significant differences in clinical characteristics were observed between the two groups from the SEER database. Early-onset HCC was connected with a higher prevalence of advanced disease, which was evidenced by the higher percentages of DM. There are several potential explanations for this phenomenon. On the one hand, we observed that early-onset patients were inclined to be unmarried, with larger tumor size and worse histological grade than late-onset patients. Furthermore, it has been demonstrated that unmarried status [23], large tumor diameter [24], and poor tumor differentiation [25] were considered independent risk factors for HCC metastasis, which could partially explain why early-onset HCC was prone to experience DM. On the other hand, the lack of suspicion of HCC in the younger patient population has led to delays in seeking medical attention and diagnosing the condition. As the unbalanced distribution of these covariates might result in bias that disturbs the comparison of outcomes, PSM was applied in this study. The results of logistic regression analysis revealed a significant positive correlation between early-onset HCC and DM in the entire cohort and the PSM cohort. As for the survival analysis, early-onset HCC displayed a more favorable prognosis than late-onset HCC in both cohorts. Besides, multivariate cox regression analysis of the unmatched and PSM cohorts also revealed that early-onset disease was independently relevant to improved OS. Analogously, the results of our own data were in line with the above analysis with SEER data.

So far, there are still limited data on the comparison of metastasis between early-onset and late-onset HCC. Previously, two publications [23,24] using the SEER database explored risk factors of pulmonary metastasis in patients with HCC and discovered that

early-onset HCC was linked to a higher risk of lung metastasis. Moreover, a retrospective study by Yan et al. [15] simultaneously demonstrated that HCC type had a significant impact on the occurrence of DM. Nevertheless, these studies did not include other sites of DM and/or did not exclude potential confounding factors. Interestingly, the same outcome that DM was more common in early-onset HCC was obtained in our large population-based PSM cohort study (12.9% vs. 8.6%, P = 0.000), and HCC type was also found to be an important risk factor by multivariate analysis (OR = 0.604, 95%CI, 0.475–0.768, P = 0.000), as demonstrated by SEER data and our own data. Notably, conflicting views also exist. For instance, Chen et al. [26] reported that HCC type was not associated with the risk of brain metastasis. Another piece of literature also showed the same result [27]. One possible explanation for this contradiction, compared with our study, could be the inconsistent classification criteria for early-onset HCC between studies. In this research, we adopted the definition of early-onset tumors, defined as cancers diagnosed in adults under 50 years of age [21], which could provide more scientific and reasonable evidence for comparative analysis. We acknowledge that simply applying a cutoff value (50 years) as the boundary of early-onset HCC also has certain limitations, as the nature of tumor is unlikely to undergo significant changes at certain timepoint. Besides, many other factors, such as genetics, environmental factors, the etiology of HCC, the initiation of liver damage or liver dysfunction, and antiviral therapies can all affect the onset of HCC([28,29]). Yet, due to the inherent limitations of retrospective studies, we cannot define early-onset HCC by combining other factors, which makes the comparison inherently flawed and carries a high risk for confounding factor. So we adopted PSM to further reduce the impact of confounding factors and conducted external data validation. All these results were in agreement with the results before PSM. We have reason to believe that the differences in DM between early-onset and late-onset HCC are mainly caused by age itself rather than by the confounder alone. Further studies in the form of multicenter prospective randomized controlled trials (RCTs) are desperately required to prove our results.

For survival analysis, there were some paradoxical results between previous reports. On the one hand, in a single center, retrospective study of 1863 patients with HCC, 121 early-onset and 1742 late-onset HCC patients had median OS of 6.6 months and 8.3 months, respectively (P = 0.77) [9]. Likewise, another single-institution study of 278 HCC patients undergoing surgical excision reached a similar conclusion, emphasizing comparable survival rates between early-onset and late-onset HCC [14]. Besides, Katsuta et al. [11] further confirmed that no significant differences were noticed in prognostic outcomes across the groups. On the other hand, one study from China with small numbers of patients indicated that children (3–17 years) suffering from HCC experienced a worse prognosis [16]. Analogously, another report suggested that early-onset HCC was correlated with poor outcome [17]. Of note, inconsistent with our hypothesis, we observed that despite developing DM more frequently, early-onset HCC exhibited a tendency of relatively better survival, with a median survival duration of 31 months for early-onset HCC and 27 months for late-onset HCC. This was further supported by the results of the multivariate cox analysis from SEER data and our own data. The reasons for this seemingly incompatible phenomenon are undoubtedly complex and multi-factorial. It is well known that HCC is a group of heterogeneous diseases with distinct pathogenesis, involving genetic, hormonal, immunological, environmental, and other factors [30–32]. Additionally, heterogeneity also exists between studies in terms of research design, objectives, and populations, which leads to incomparable study findings. These arguments may account for the observed differences. In line with our results, a recent study investigated that young HCC patients showed a trend toward favorable survival duration than their older counterparts [23]. Perhaps the underlying causes were better physical and functional status in the early-onset group. Moreover, early-onset patients often held more positive attitudes toward treatment and better compliance with therapy, all of which can favor a better outcome. But these characteristics were not included in our analysis due to the inherent deficiency of the database. Of course, many important prognostic factors were also not analyzed in our study. For example, tumor number is the core component of prognostic system of HCC [33]. In a large cohort of Western patients, investigators verified the performance of new liver cancer prognostic system, which indicated that OS deteriorated with increasing tumor number [34]. Furthermore, different etiologies also affect the survival and mortality risk of HCC. Based on SEER-Medicare data, results showed that HCC associated with alcohol (HR = 1.49, 95%CI, 1.25–1.77) or metabolic disorders (HR = 1.25, 95%CI, 1.07–1.47) had a higher mortality compared to HBV-related HCC [35]. Accordingly, therapies aimed at etiology could improve the prognosis of HCC. Given these issues, further well-designed prospective clinical studies of high quality are warranted to verify our observations in the future.

Inevitably, our present work has some limitations that should be acknowledged. First, given the retrospective cohort study design, the sample sizes varied considerably between both groups. Although we conducted PSM to reduce the difference, this approach would exclude a substantial proportion of cases in the late-onset cohort and might introduce sampling bias. Besides, information about performance status, comorbidity, and tumor recurrence was unavailable in the SEER database, which impacted clinical treatment decisions and might be a confounder in this study. Third, the administrative database lacked data concerning the etiologies of HCC, such as hepatitis B or C virus, alcohol consumption, and non-alcoholic fatty liver disease; these causes may have an effect on tumor biological characteristics, metastatic behavior, and clinical outcome. Fourth, given that pathological T, N, and M status of unresected HCC were not available, it was possible that information of DM were not well documented in some cases, which might influence the reliability of results. Lastly, our analysis was limited to patients within the SEER database and thus may not be generalizable to the entire population.

5. Conclusion

In summary, our study demonstrated that early-onset HCC is more likely to experience DM compared with late-onset HCC; however, early-onset HCC harbored a superior prognosis. This provides an opportunity to better understand age-related hepatocarcinogenesis, which might be exploited during HCC screening, diagnosis, and management. Nevertheless, further investigation is necessary to elucidate the underlying aetiologic basis for these disparities.

Funding

This study is supported by the National Natural Science Foundation of China (Grant number 82170574), Youth Fund of National Natural Science Foundation of China (Grant number 82100621), and Youth funding projects of Jiangsu Provincial Natural Science Foundation (Grant number BK20210147). All authors are very appreciative of the financial support.

Ethics approval and consent to participate

Ethics approval and written consent to participate in the study were obtained prior to start of the study.

Consent for publication

Not applicable.

Data availability statement

Data are available in a public, open access repository (https://seer.cancer.gov).

CRediT authorship contribution statement

Hanlong Zhu: Writing – original draft, Software, Methodology, Conceptualization. **Si Zhao:** Validation, Resources, Investigation. **Tianming Zhao:** Formal analysis, Data curation. **Lu Chen:** Formal analysis, Data curation. **Shupei Li:** Formal analysis, Data curation. **Kun Ji:** Investigation. **Kang Jiang:** Formal analysis, Data curation. **Hui Tao:** Visualization. **Ji Xuan:** Investigation. **Miaofang Yang:** Supervision. **Bing Xu:** Supervision. **Mingzuo Jiang:** Writing – review & editing, Validation. **Fangyu Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We sincerely thank the Surveillance, Epidemiology, and End Results (SEER) program for the efforts in providing high-quality open resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28497.

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