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## Risk factors associated with suicide among hepatocellular carcinoma patients: A surveillance, epidemiology, and end results analysis



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### ABSTRACT

**Background:** Throughout the world, hepatocellular carcinoma (HCC) remains the primary type of liver cancer. The suicide risk was higher among patients with HCC than the general population. Hence, the purpose of this study was to confirm the suicide rates, standardized mortality ratios (SMRs), and the potential risk factors associated with suicide among HCC patients.

**Methods:** HCC patients were collected from the Surveillance, Epidemiology, and End Results (SEER) database during 1975–2016. Suicide rates and SMRs among these patients were calculated, and the general population of the United States (U.S.) during 1975–2016 was used as a reference. Univariable and multivariable Cox regression were taken to find out the underlying risk factors of suicide in HCC patients.

**Results:** There were 70 suicides identified among 102,567 individuals with HCC observed for 160,500.88 person years. The suicide rate was 43.61 per 100,000 person-years, and SMR was 2.26 (95% CI: 1.78–2.84). On Cox regression, year of diagnosis (1975–1988 vs. 2003–2016, HR: 3.00, 95% CI: 1.01–8.89,  $P = 0.047$ ; 1989–2002 vs. 2003–2016, HR: 1.92, 95% CI: 1.10–3.34,  $P = 0.021$ ), gender (male vs. female, HR: 8.72, 95% CI: 2.73–27.81,  $P < 0.001$ ), age at diagnosis (63–105 years old vs. 0–55 years old, HR: 2.28, 95% CI: 1.21–4.31,  $P = 0.011$ ), race (white race vs. American Indian/Alaska Native, Asian/Pacific Islander, HR: 3.02, 95% CI: 1.35–6.76,  $P = 0.007$ ) were independent risk factors of suicide among HCC patients.

**Conclusions:** Diagnosed in the early years (1975–2002), male sex, the older age (63–105 years old), white race, survival months (< 2 months) were significantly associated with suicide among HCC patients. For the sake of preventing suicide behaviors, the government, clinicians, and family members should take adequate measures to decrease the rate of suicide, especially in patients with high-risk factors of suicide.

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### Introduction

Suicide is a global public health problem, a complex behavior influenced by physical, psychological, social, environmental, and cultural factors [1]. Additionally, suicide is the leading cause of death worldwide among persons 15–24 years of age and the 10th leading cause of death in North America [2]. Globally, 817,000

persons died of suicide in 2016, comprising 1.49% of total deaths [3]. The World Health Organization (WHO) estimated that the suicide rate in 2016 was 10.6 suicides per 100,000 people, of which 80% occurred in low- and middle-income countries [4]. Although suicide rates had an approximate 18% reduction from 2000 to 2016 in most WHO regions [2], the United States (U.S.) had a suicide rate increasing annually by 1.5% since 2000 [5]. Besides, the data from Centers for Disease Control and Prevention had released that the suicide rate for men aged 45 to 64 had increased from 21 suicides among 100,000 in 1999 to 30 suicides among 100,000 in 2017 [6].

In recent years, studies have reported a significant correlation between depression and suicide, and the suicide rate of depression patients is much higher than that of the average population [7–9].

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Furthermore, during the COVID-19 outbreak and the outcomes of isolation and quarantine, a rapidly increasing in suicide ideation and behavior may be witnessed among at-risk populations, such as the unemployed [10], the bereaved [11], the debtor [12]. Many previous proofs also indicated that patients with poor prognosis diseases (especially cancer) are more likely to feel desperate, suffer from depression and subsequently commit suicide [13–16]. Additionally, some evidence from systematic reviews has also shown an increased risk of suicide among patients with cancer [17–19]. Surprisingly in the U.S., the suicide rate of patients with cancer was almost twice than that of the general population [20]. Moreover, one of the most recent studies conducted by Zaorsky et al. showed that the standardized mortality rate (SMR) of suicide among cancer patients is 4.44 compared to the general population [21]. Since suicidal behavior is potentially recognizable and preventable, identifying patients with high-risk factors for suicide is particularly important [22].

Similarly, primary liver cancer is the 7th most common cancer in the world and the second leading cause of cancer mortality [23]. Throughout the world, hepatocellular carcinoma (HCC) was the primary type of liver cancer, accounting for nearly 75% of the total [24], and prognosis of HCC were inferior [25]. In 2019, Chelsea Anderson et al. reported that the suicide rate of patients with digestive system cancer was higher than that of the general population. The SMR of the liver and intrahepatic bile duct was 2.14 (95% CI: 1.58–2.85) relative to the general U.S. population (2000–2014), with adjustment for age, sex, and race [26]. However, risk factors and SMR for suicide in patients with HCC were not involved in the study.

To our knowledge, a comprehensive study of suicide rates in patients with liver cancer has not been investigated before. Additionally, few studies explored the risk factors for suicide in patients with HCC based on a large representative sample. Thus, the goal of our research was to calculate the suicide rate and SMRs compared to the U.S. general population and to identify potential risk factors related to suicide based on the SEER database.

## Methods

### Data source

Patients with HCC, diagnosed between 1975 and 2016, were abstracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER Program of the National Cancer Institute (NCI) is an authoritative source of data not only covering approximately 34.6% of the U.S. population, but also including cancer incidence, survival, and treatment (e.g., surgery, radiation therapy, and chemotherapy) [27]. The Public Use version of data collected from the SEER18 registries from 1975 to 2016 was used for this study [28]. The data of the total U.S. population, including the cause of death, was obtained by the National Center for Health Statistics spanning 1975 to 2016 and accessed through the SEER program [29,30]. The permission to access the database was achieved after we signed and submitted a SEER Research Data Agreement form through email. Moreover, it is unnecessary to ask for the patient's informed consent because the data of patients in the SEER database were anonymized and de-identified before release. The SEER database can be accessed publicly available, and this study was exempted from seeking informed consent by the institutional research committee of the Dongfang Hospital, Xiamen University.

The software of SEER\*Stat (version 8.3.6) was used to identify the patients [31].

### Study population

Patients were identified using the primary site codes (C22.0) for liver and morphology codes (8170/3, 8171/3, 8172/3, 8173/3, 8174/3, and 8175/3) based on International Classification of Diseases for Oncology codes (3rd edition) for HCC [32].

### Measurements of variables

Demographic and clinical variables of interest were accessed through the software of SEER\*Stat, such as (1) Year of diagnosis; (2) Gender; (3) Age at diagnosis; (4) Marital status; (5) the Purchased/Referred Care Delivery Area (PRCDA) Region; (6) Histologic grade; (7) SEER histologic stage; (8) Surgery performed; (9) Radiotherapy performed; (10) Chemotherapy performed; (11) Survival months. Furthermore, the following cases were excluded: (1) Unknown age or race; (2) No active follow up; (3) All autopsy or death certificate cases. The steps of patient selection were depicted in Fig. 1.

### Ascertainment of the outcome

The primary outcome of this study was suicidal death, which was identified by cause of death code (suicide and self-inflicted injury) in the software of SEER\*Stat [33].

### Statistical analysis

Suicide rates among patients with HCC were calculated as the number of observed suicides per 100,000 person-years of follow-up. To compare suicide rates in our cohort with those of the general population, we used U.S. population suicide rates from the National Center for Health Statistics, available through the SEER program. Data were characterized with SMRs adjusted by age, race, and sex to the U.S. population over the same time. Five-year age categories were used for standardization using SEER\*Stat 8.3.6 and Microsoft Excel 16.0.12730.20188 (Microsoft, Redmond, WA) [34,35]. SMRs were calculated as the ratio of observed suicides among HCC patients to the number of expected suicides in the general population. The number of expected suicides was figured out by multiplying the general population suicide rate by the person-time in our cohort, calculated across strata of age, race, and sex. For SMRs calculations, individuals of unknown race were excluded, since general population rates are not applicable for the unknown race. Ninety-five percent of confidence interval (CI) for the SMRs were calculated by the mid-P test [36]. Besides, the

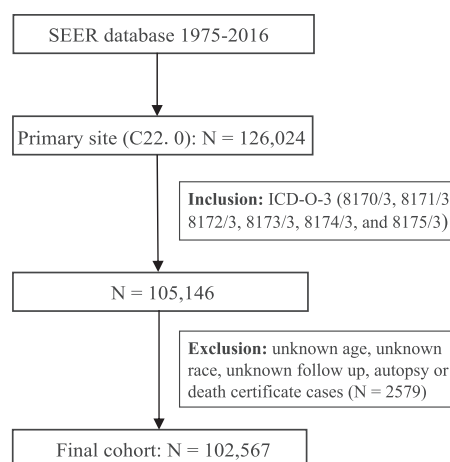


Fig. 1. The flow diagram of patient selection.

suicide rates between groups were compared with the chi-square test, and the Bonferroni-corrected P-value was applied for multiple comparisons. Furthermore, we estimated SMRs according to survival months (<2 months, 2 months - 11months, 12 months–59 months, ≥ 60 months), selecting the initial 2-month cutoff as our best estimate of a reasonable window between diagnosis and the start of cancer treatment, this period which we hypothesized would be associated with the highest suicide rates. Univariable and multivariable Cox regression were used to generate crude and adjusted hazard ratios (HRs) and 95% CI for revealing potential risk factors of suicide. Only variables with  $P < 0.1$  in the univariate Cox regression models can be included in multivariate Cox regression models. For these analyses, patients with 0 completed months of follow-up were assigned a value of 0.5 months [35]. Age at diagnosis was the unique continuous variable. To investigate the risk of suicide among patients of different ages, X-tile software was applied to discover the optimal cutoffs for stratifying age (Fig. 2) [37]. All statistical tests were two-sided, with  $P < 0.05$  considered to be indicative of statistical significance. Statistical analyses were performed using SPSS (version 25.0, SPSS, Chicago, IL, USA) and Microsoft Excel 16.0.12730.20188 (Microsoft, Redmond, WA). The X-tile program was implemented using X-tile software (<http://tissuearray.org/>).

**Ethical considerations**

This study did not involve the use of human participants or access to personal identifying information. Therefore, approval by an institutional review board was not required. Informed consent was also waived for this anonymous survey.

**Results**

*Patient baseline characteristics*

Overall, 102,567 patients with HCC were identified from the SEER database in 1975–2016, including 77,630 male patients and 24,937 female patients. Of these, 70 patients (0.07%) died of suicide, 82,616 patients (80.55%) died of other causes, and 19,881 patients (19.38%) were alive (Table 1).

- (1) Among all patients, 53,790 (52.4%) of them were married or domestic partners, while 24,686 (24.1%) of them were previously married (divorced, widowed and separated), and 19,467 (19%) of them were single (never married). Caucasian (67.4%) was the predominant race. A total of 22,620 (22.1%)

- patients underwent cancer-directed surgery, and 6806 (6.6%) patients receive radiotherapy.
- (2) For the patients who committed suicide, 67 (95.7%) of them were males, and 3 (4.3%) of them were females. Concerning marital status, 43 (61.4%) of them were married or domestic partners, while 11 (15.7%) of them were previously married, and 10 (14.3%) of them were single. Similarly, Caucasian (80%) was also the predominant race. 24 (34.3%) patients received cancer-directed surgery, and only 3 (6.6%) patients received radiotherapy.

Patient demographics and clinical characteristics were summarized in Table 1.

*Difference in suicide rates and SMRs*

*Suicide rates*

From 1975 to 2016, there were 70 suicides among 102,567 patients with HCC observed for 160500.88 person-years, yielding a suicide rate of 43.61 per 100,000 person-years. The suicide rate of the U.S. general population reported by the Centers for Disease Control and Prevention was only 12.14 per 100,000 person-years between 2001 and 2016 [38], which was significantly lower than that of the HCC patients in our cohort (Table 2).

- (1) The results showed that higher suicide rates in patients with HCC were associated with male sex (vs. female sex,  $P < 0.0001$ ) and no surgery performed ( $P = 0.014$ );
- (2) The result of the chi-square test for linear trend showed that suicide rates among HCC patients increased with SEER histologic stage ( $P < 0.01$ ) and survival months ( $P < 0.01$ );
- (3) No statistical differences in suicide rates were found concerning the year of diagnosis, age at diagnosis, marital status, race, PRCA region, histologic type, radiotherapy performed, chemotherapy performed.

*Standardized mortality rate (SMR)*

SMRs were used to compare suicide mortality in the study population with that in the general population (Table 2).

- (1) A SMR of 2.26 (95% CI: 1.78–2.84) was noted between HCC patients and the U.S. general population, with 2.37 (95% CI: 1.85–2.99) for males, 1.15 (95% CI: 0.29–3.13) for females, 2.19 (95% CI: 1.67–2.82) for the white race, 5.14 (95% CI: 2.25–10.17) for the black race, and 1.76 (95% CI: 0.77–3.49)

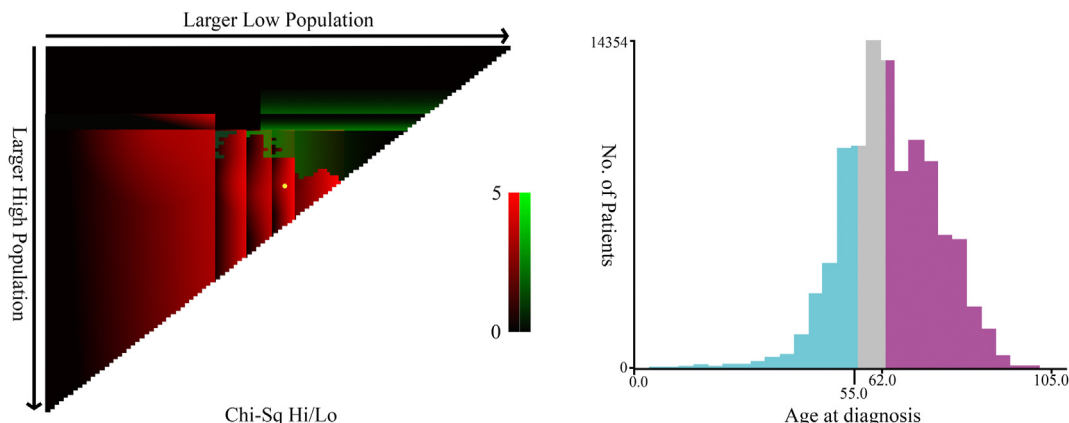


Fig. 2. Age at diagnosis stratification by X-tile software.

**Table 1**  
Baseline characteristics of patients with hepatocellular carcinoma stratified by suicidal death, nonsuicidal death and alive patients (1975–2016).

Variables	Overall	Suicidal death	Nonsuicidal death	Alive Patients
	N (%)	N (%)	N (%)	N (%)
Patients	102,567	70	82,616	19,881
Year of diagnosis				
1975–1988	4441 (4.3%)	4 (5.7%)	4392 (5.3%)	45 (0.2%)
1989–2002	20,227 (19.7%)	18 (25.7%)	19,323 (23.4%)	886 (4.5%)
2003–2016	77,899 (75.9%)	48 (68.6%)	58,901 (71.3%)	18,950 (95.3%)
Sex				
Male	77,630 (75.7%)	67 (95.7%)	62,836 (76.1%)	14,727 (74.1%)
Female	24,937 (24.3%)	3 (4.3%)	19,780 (23.9%)	5154 (25.9%)
Age at diagnosis				
0–55	24,073 (23.5%)	13 (18.6%)	19,095 (23.1%)	4965 (25%)
56–62	24,279 (23.7%)	15 (21.4%)	18,436 (22.3%)	5828 (29.3%)
63–105	54,215 (52.9%)	42 (60%)	45,085 (54.6%)	9088 (45.7%)
Marital status				
Married/ Domestic Partner	53,790 (52.4%)	43 (61.4%)	42,648 (51.6%)	11,099 (55.8%)
Previously Married <sup>a</sup>	24,686 (24.1%)	11 (15.7%)	20,849 (25.2%)	3836 (19.3%)
Single <sup>b</sup>	19,467 (19%)	10 (14.3%)	15,616 (18.9%)	3841 (19.3%)
Unknown	4614 (4.5%)	6 (8.6%)	3503 (4.2%)	1105 (5.6%)
Race				
White	69,178 (67.4%)	56 (80%)	55,930 (67.7%)	13,192 (66.4%)
Black	13,433 (13.1%)	7 (10%)	11,166 (13.5%)	2260 (11.4%)
American Indian/Alaska Native, Asian/Pacific Islander	19,956 (19.5%)	7 (10%)	15,520 (18.8%)	4429 (22.3%)
PRCDA Region				
Pacific Coast	59,169 (57.7%)	42 (60%)	47,242 (57.2%)	11,885 (59.8%)
East	29,428 (28.7%)	16 (22.9%)	23,531 (28.5%)	5881 (29.6%)
Northern Plains	9203 (9%)	5 (7.1%)	7894 (9.6%)	1304 (6.6%)
Southwest	4625 (4.5%)	7 (10%)	3848 (4.7%)	770 (3.9%)
Alaska	142 (0.1%)	0 (0%)	101 (0.1%)	41 (0.2%)
Histologic grade				
Grade I	11,665 (11.4%)	12 (17.1%)	8751 (10.6%)	2902 (14.6%)
Grade II	14,647 (14.3%)	12 (17.1%)	10,434 (12.6%)	4201 (21.1%)
Grade III	8034 (7.8%)	6 (8.6%)	6829 (8.3%)	1199 (6%)
Grade IV	870 (0.8%)	1 (1.4%)	765 (0.9%)	104 (0.5%)
Unknown	67,351 (65.7%)	39 (55.7%)	55,837 (67.6%)	11,475 (57.7%)
SEER disease stage				
Localized	46,252 (45.1%)	45 (64.3%)	31,798 (38.5%)	14,409 (72.5%)
Regional	27,688 (27%)	14 (20%)	23,963 (29%)	3711 (18.7%)
Distant	16,221 (15.8%)	6 (8.6%)	15,396 (18.6%)	819 (4.1%)
Unknown/unstaged	12,406 (12.1%)	5 (7.1%)	11,459 (13.9%)	942 (4.7%)
Surgery performed				
Yes	22,620 (22.1%)	24 (34.3%)	12,758 (15.4%)	9838 (49.5%)
No/unknown	79,947 (77.9%)	46 (65.7%)	69,858 (84.6%)	10,043 (50.5%)
Radiotherapy performed				
Yes	6806 (6.6%)	3 (4.3%)	5074 (6.1%)	1729 (8.7%)
No/unknown	95,671 (93.3%)	67 (95.7%)	77,542 (93.9%)	18,152 (91.3%)
Chemotherapy performed				
Yes	34,083 (33.2%)	28 (40%)	25,373 (30.7%)	8682 (43.7%)
No/unknown	68,484 (66.8%)	42 (60%)	57,243 (69.3%)	11,199 (56.3%)

Abbreviations SEER = the surveillance, epidemiology, and end results program; PRCDA = the purchased/referred care delivery area.

<sup>a</sup> Included divorced, widowed and separated.

<sup>b</sup> Included never married.

for other races (American Indian/Alaska Native, Asian/Pacific Islander).

- (2) A general decline of suicide rates from 1975 to 2016 (1975–1988, SMR: 7.05, CI: 2.24–17.00; 1989–2002, SMR: 3.12, CI: 1.91–4.48; 2003–2016, SMR: 1.95, CI: 1.45–2.57), though a statistical trend was not found ( $P = 0.173$ ).
- (3) Significantly increased suicide rates among HCC patients were found in the initial five years after cancer diagnosis (<2 months, SMR: 26.78, 95% CI: 13.06–49.15; 2 months–11 months, SMR: 7.22, 95% CI: 4.73–10.58; 12 months–59 months, SMR: 2.20, 95% CI: 1.51–3.10).

*Associations of risk factors with suicide*

- (1) The result of univariable analysis presented that significant associations with high risk of suicide were obtained according to year of diagnosis (1975–1988 vs. 2003–2016, HR:

- 2.60, 95% CI: 0.88–7.70,  $P = 0.086$ ; 1989–2002 vs. 2003–2016, HR: 1.76, 95% CI: 1.02–3.04,  $P = 0.041$ ), gender (male vs. female, HR: 7.89, 95% CI: 2.48–25.11,  $P < 0.001$ ), age at diagnosis (63–105 years old vs. 0–55 years old, HR: 2.00, 95% CI: 1.06–3.76,  $P = 0.032$ ), race (white race vs. American Indian/Alaska Native, Asian/Pacific Islander, HR: 2.70, 95% CI: 1.23–5.93,  $P = 0.013$ ), PRCDA Region (Southwest vs. Pacific Coast, HR: 2.46, 95% CI: 1.10–5.49,  $P = 0.028$ ) (Table 3).
- (2) On multivariable Cox regression, the results showed that year of diagnosis (1975–1988 vs. 2003–2016, HR: 3.00, 95% CI: 1.01–8.89,  $P = 0.047$ ; 1989–2002 vs. 2003–2016, HR: 1.92, 95% CI: 1.10–3.34,  $P = 0.021$ ), gender (male sex vs. female sex, HR: 8.72, 95% CI: 2.73–27.81,  $P < 0.001$ ), age at diagnosis (63–105 years old vs. 0–55 years old, HR: 2.28, 95% CI: 1.21–4.31,  $P = 0.011$ ), race (white race vs. American Indian/Alaska Native, Asian/Pacific Islander, HR: 3.02, 95% CI: 1.35–6.76,  $P = 0.007$ ) were predictive of suicide. Conversely,

**Table 2**  
Suicide rates and SMRs among patients with hepatocellular carcinoma by demographic and clinic characteristics (1975–2016).

Variables	Suicidal death	Person-years	Suicide rate per 100,000 person-years	P	SMR <sup>a</sup>	95% CI	
						Lower	Upper
Total	70	160,500.88	43.61		2.26	1.78	2.84
Year of diagnosis							
1975–1988	4	3892.67	102.76	0.173 <sup>§</sup>	7.05	2.24	17.00
1989–2002	18	32,309.88	55.71		3.12	1.91	4.84
2003–2016	48	124,298.33	38.62		1.95	1.45	2.57
Sex							
Male	67	117,926.96	56.81	< 0.0001****	2.37	1.85	2.99
Female	3	42,573.92	7.05		1.15	0.29	3.13
Age at diagnosis							
0–55	13	50,067.50	25.96	0.221 <sup>§</sup>	1.39	0.77	2.32
56–62	15	41,419.33	36.21		1.90	1.10	3.06
63–105	42	69,014.04	60.86		3.07	2.24	4.11
Marital status							
Married/ Domestic Partner	43	94,285.96	45.61	reference	2.27	1.66	3.03
Previously Married <sup>b</sup>	11	31,952.04	34.43	0.079 <sup>#</sup>	1.96	1.03	3.40
Single <sup>c</sup>	10	27,383.46	36.52		1.99	1.01	3.54
Unknown	6	6879.42	87.22		4.55	1.84	9.45
Race							
White	56	105,483.00	53.09	reference	2.19	1.67	2.82
Black	7	16,594.42	42.18	0.268 <sup>#</sup>	5.14	2.25	10.17
American Indian/Alaska Native, Asian/Pacific Islander	7	38,423.46	18.22		1.76	0.77	3.49
Region							
Pacific Coast	42	97,614.17	43.03	reference	2.34	1.71	3.13
East	16	43,474.83	36.80	0.363 <sup>#</sup>	1.76	1.04	2.80
Northern Plains	5	12,845.79	38.92		2.00	0.73	4.43
Southwest	7	6179.42	113.28		5.15	2.25	10.19
Alaska	0	386.67	0.00		0.00	0.00	82.83
Histologic grade							
Grade I	12	29,204.88	41.09	0.064 <sup>§</sup>	2.05	1.11	3.49
Grade II	12	33,562.96	35.75		1.84	1.00	3.13
Grade III	6	10,526.83	57.00		3.20	1.30	6.66
Grade IV	1	1108.50	90.21		4.87	0.24	24.04
Unknown	39	86,097.71	45.30		2.36	1.71	3.20
SEER histologic stage							
Localized	45	109,254.33	41.19	< 0.01**,\$	2.14	1.58	2.84
Regional	14	31,741.92	44.11		2.27	1.29	3.72
Distant	6	7689.17	78.03		4.00	1.62	8.32
Unknown/unstaged	5	11,815.46	42.32		2.20	0.80	4.87
Surgery performed							
Yes	24	83,037.13	28.90	0.014	1.55	1.01	2.27
No/unknown	46	77,463.75	59.38		2.99	2.21	3.95
Radiotherapy performed							
Yes	3	8196.29	36.60	0.429	1.72	0.44	4.68
No/unknown	67	152,304.58	43.99		2.30	1.79	2.90
Chemotherapy performed							
Yes	28	65,143.13	42.98	0.229	2.20	1.49	3.14
No/unknown	42	95,357.75	44.04		2.30	1.68	3.08
Survival months							
< 2 months	9	1577.21	570.63	< 0.01**,\$	26.78	13.06	49.15
2 months–11 months	24	15,937.50	150.59		7.22	4.73	10.58
12 months–59 months	30	67,577.33	44.39		2.20	1.51	3.10
≥ 60 months	7	75,408.83	9.28		0.51	0.22	1.02

Abbreviations SMR = standardized mortality ratio; SEER = the surveillance, epidemiology, and end results program; PRCDA = the purchased/referred care delivery area; 95% CI = 95% confidence interval.

# The Bonferroni-corrected P-value was used for multiple comparisons.

\$ The chi-square test for linear trend was used for ordinal multi-categorical variables.

The P values in the bold are statistically significant.

\*\*P < 0.01, \*\*\*\*P < 0.0001.

<sup>a</sup> SMR was adjusted by age, race, and sex to the US population over the same time. Five-year age categories were used for standardization using SEER\*Stat 8.3.6 and Microsoft Excel 16.0.12730.20188 (Microsoft, Redmond, Wa<sup>h</sup>ington).

<sup>b</sup> Included divorced, widowed and separated.

<sup>c</sup> Included never married.

apparent associations of suicide with the PRCDA region were not found. Table 3 presented further details about the predictors of suicide in the entire cohort.

### Discussion

According to relevant investigations, the risk of suicide among

cancer patients in different countries has increased [19,20,39–42]. In a UK population-based study of 4,722,099 adult patients with cancer, Henson, K. E. et al. reported that the elevated risk of suicide (SMR: 1.20, 95%CI: 1.16–1.25) in patients with cancers is a concern, compared to the general population [39]. Based on data from the Italian Romagna Cancer Registry and 19 selected studies, a data analysis conducted by Ravaioli, A. et al. confirmed that cancer

**Table 3**  
Univariable and multivariable analysis for the suicide of hepatocellular carcinoma patients.

Variables	Univariable analysis				Multivariable analysis			
	HR	95% CI		P	HR	95% CI		P
		Lower	Upper			Lower	Upper	
Year of diagnosis								
1975–1988	2.60	0.88	7.70	<b>0.086</b>	3.00	1.01	8.89	<b>0.047</b>
1989–2002	1.76	1.02	3.04	<b>0.041</b>	1.92	1.10	3.34	<b>0.021</b>
2003–2016	Reference			<b>0.046</b>	Reference			<b>0.020</b>
Sex								
Male	7.89	2.48	25.11	<b>&lt;0.001***</b>	8.72	2.73	27.81	<b>&lt;0.001***</b>
Female	Reference				Reference			
Age at diagnosis								
0–55	Reference			<b>0.062</b>	Reference			<b>0.021</b>
56–62	1.28	0.61	2.70	0.520	1.34	0.63	2.85	0.443
63–105	2.00	1.06	3.76	<b>0.032</b>	2.28	1.21	4.31	<b>0.011</b>
Marital status								
Married/ Domestic Partner	Reference			0.233				
Previously Married <sup>a</sup>	0.69	0.35	1.34	0.269				
Single <sup>b</sup>	0.74	0.37	1.48	0.397				
Unknown	1.79	0.76	4.21	0.182				
Race								
White	2.70	1.23	5.93	<b>0.013</b>	3.02	1.35	6.76	<b>0.007</b>
Black	2.00	0.70	5.70	0.196	2.67	0.90	7.87	0.076
American Indian/Alaska Native, Asian/Pacific Islander	Reference			<b>0.041</b>	Reference			<b>0.027</b>
PRCDA Region								
Pacific Coast	Reference			0.183	Reference			0.217
East	0.83	0.46	1.47	0.515	0.70	0.39	1.27	0.240
Northern Plains	0.89	0.35	2.24	0.798	0.67	0.26	1.73	0.410
Southwest	2.46	1.10	5.49	<b>0.028</b>	1.98	0.88	4.47	0.098
Alaska	0.00	0.00	2.15E+129	0.959	0.00	6.22E-140	1.37E+133	0.965
Histologic grade								
Grade I	Reference			0.875				
Grade II	0.85	0.38	1.88	0.680				
Grade III	1.23	0.46	3.30	0.674				
Grade IV	2.09	0.27	16.06	0.480				
Unknown	0.94	0.49	1.79	0.841				
SEER disease stage								
Localized	Reference			0.890				
Regional	0.91	0.50	1.67	0.760				
Distant	1.30	0.54	3.11	0.560				
Unknown/unstaged	0.86	0.34	2.18	0.755				
Surgery performed								
Yes	Reference				Reference			
No/unknown	1.60	0.95	2.68	<b>0.077</b>	1.41	0.83	2.38	0.202
Radiotherapy performed								
Yes	Reference							
No/unknown	1.42	0.44	4.52	0.554				
Chemotherapy performed								
Yes	Reference							
No/unknown	1.06	0.66	1.71	0.811				

Abbreviations SMR = standardized mortality ratio; SEER = the surveillance, epidemiology, and end results; PRCDA = the purchased/referred care delivery area; HR=Hazard Ratio; 95% CI = 95% confidence interval.

# The Bonferroni-corrected P-value was used for multiple comparisons.

\$ The chi-square test for linear trend was used for ordinal multi-categorical variables.

The P and HR values in the bold were statistically significant or considered to be analyzed in multivariate regression models.

\*\*P < 0.01, \*\*\*P < 0.001.

<sup>a</sup> Included divorced, widowed and separated.

<sup>b</sup> Included never married.

patients are at increased risk for suicide (pooled SMR: 1.7; 95% CI: 1.5–1.9) [19]. A historical cohort study involving 6,073,240 Swedes, written by Fang, Fang., concluded that the patients who had recently received a cancer diagnosis had increased risks of both suicides and death from cardiovascular causes, compared with cancer-free persons [42]. Apart from these, the researchers from Norway (HR: 2.5; 95% CI: 1.7–3.8) [40], Lithuania (SMR:1.62; 95% CI: 1.27–2.06) [41], and the United States (SMR: 2.06; 95% CI: 2.00–2.12) also reported the similar results in recent decades., [20].

In this population-based study, the results indicated that the suicide rate of HCC patients was 43.61 per 100,000 person-years, and total SMR was 2.26 (95% CI: 1.78–2.84). Diagnosed in early

years (1975–2002), male sex, diagnosed at an older age (63–105 years old), and white race were significant predictors of suicide in the result of multivariable Cox regression. Noteworthy, through the chi-square test for linear trend variables, we found that suicide rates among HCC patients also significantly increased with SEER histologic stage (P < 0.01) and survival months (P < 0.01) (Table 2). Therefore, the increasing suicide rate of patients with HCC may be influenced by various demographic characteristics, histopathologic features, and follow-up features.

### Year of diagnosis

In reviewing the results, the patients diagnosed in 1975–2002 were more likely to commit suicide in comparison with those diagnosed in 2003–2016, which may be due to the emergence of new and effective therapeutic regimens and better quality of life. Moreover, the risk of suicide in patients with bladder cancer in the early years (1973–1983) was also significantly higher than in recent years (2004–2010) [43]. However, another research conducted by Damien Urban in 2013 reported that the rate of suicide in the patients diagnosed with lung cancer did not change considerably over time, with 8.83 compared with 7.17 suicides per 10,000 person-years in 1973–1979 and 2000–2009, respectively [44].

### Gender

In the present study, the suicide rate of males (56.81 per 100,000 person-years) was nearly eight times higher than that of females ( $P < 0.0001$ ) (Table 2). Additionally, males were more dangerous than females to commit suicide with an HR of 8.72, which was corresponding to the findings in the general population [45], and patients with other types of cancer, such as lung cancer (SMR for males: 4.61, 95% CI: 4.34–4.90; SMR for females: 3.02, 95% CI: 2.53–3.58) [44], gastric carcinomas (SMR for males: 4.85, 95% CI: 3.89–5.98; SMR for females: 3.74, 95% CI: 1.94–6.48) [20,21]. Even though male and female cancer patients experienced similar pressure [46,47], smoking [48], alcohol consumption [49–51], sharp reduction in household income may prompt males to experience increased suicidal thoughts and behavior [52].

### Age at diagnosis

In our study, the older age (63–105 years old vs. 0–55 years old, HR: 2.28, 95% CI: 1.21–4.31,  $P$  for linear trend = 0.011) was also observed with a tendency of significantly increasing suicide rate (Table 3). Some recent publications also indicated that older age was a risk factor of suicide for cancer patients and the general population [42,53]. For example, a similar conclusion corroborated that the suicide incidence rates increased with increasing age, regardless of a cancer diagnosis [42]. In the same way, the incidence of death from suicide was elevated in cancer survivors, between the individuals diagnosed in childhood (0–14 years old, HR: 2.3, 95% CI: 1.2–4.6) and during adolescence and young adulthood (15–24 years old, HR: 2.6, 95% CI: 1.5–4.2) [53]. Nevertheless, there were exceptions, reported by Gaitanidis A et al. and Kroenke CH et al., that younger patients were more likely to commit suicide comparing to older breast cancer patients [54,55]. One convincing explanation was that young women might be more likely to get worse than middle-aged or older women in both physical and psychosocial status after the breast cancer diagnosis, which prompted them to have more suicidal behaviors and suicide attempts [54].

### Race

Moreover, we further analyzed the risk factors for suicide among patients in terms of race. The results of the current work inferred that the white race was another factor associated with suicide. Our study showed that the suicide rates of the white race (vs. American Indian/Alaska Native, Asian/Pacific Islander, HR: 3.02, 95% CI: 1.35–6.76) were 53.09 per 100,000 person-years. As was released by the Centers for Disease Control and Prevention, the white race had a higher suicide rate than the black race in the US [56]. In a retrospective study, the predominant patients who committed suicide were whites (12,258, 92.1%), with HR of suicide for black

race vs. white race among cancer patients is 0.31 (95% CI: 0.29–0.35,  $P < 0.0001$ ), which suggested that white race may be significant predictors of suicide in the cancer population. Furthermore, the white race also has been corroborated to be a risk factor of suicide in many previous investigations [55,57]. Regarding the low suicide rate of the non-white ethnicity, the most reasonable explanation of that may be attributed to being impacted by religious beliefs, family support and a culture of refusing suicide [58–60].

### SEER disease stage

As shown in Table 2, the current study proved the finding that the risk of suicide significantly increased with increasing stage of HCC (Localized, SMR: 2.14, 95% CI: 1.58–2.84; Regional, SMR: 2.27, 95% CI: 1.29–3.72; Distant, SMR: 4.00, 95% CI: 1.62–8.32;  $P$  for linear trend  $< 0.01$ ). Besides, an international population-based study of 723,810 women, conducted by Catherine Schairer et al., also verified that breast cancer patients' risk of suicide increased as cancer stage increasing [61]. In 915,303 Austrian cancer patients, studied by Benjamin Vyssoki et al., high suicide risk was found for patients with locally advanced (SMR: 1.59; 95% CI: 1.47–1.71) or metastasized cancer (SMR: 4.07; 95% CI: 3.58–4.61) [62]. Interestingly, a cohort, comprising patients from the Cancer Registry of Norway 1960 to 1997, confirmed that the relative suicide risk was higher for male patients with nonlocalized cancers than for males with localized cancers ( $P < 0.001$ ). Contrary to men, the difference was not significant for women ( $P = 0.67$ ) [63].

### Survival months

In Table 2, our findings showed that survival months was another increasing risk of suicide in patients with HCC cancer, particularly within two months after diagnosis (SMR: 26.78, 95% CI: 13.06–49.15). As previously reported in other cancers, the risk of suicide in cancer patients was generally higher in the early stage after diagnosis than other periods of the disease [21,42,64,65]. For example, Fang Fang et al. identified relative risk of suicide among patients after being diagnosed with cancer was 12.6 (95% CI: 8.6–17.8) during the first week (incidence rate, 2.50 per 1000 person-years) and proved that the risk elevations decreased rapidly during the first year after diagnosis, compared with cancer-free persons [42]. Similarly, it was reported by Lu, D. et al. that adolescents and young adults getting a cancer diagnosis were at immediately increased risk of suicidal behaviors, particularly during the first year after diagnosis (RR: 2.5, 95% CI 1.7–3.5) [64]. Moreover, the research of Zaorsky, N.G., and Bolton, J.M. also obtained the results consistent with the above research, which both suggested the need to support and carefully monitor cancer patients at these special periods [21,65].

Beyond these risk factors, suicide is a very complicated behavior, which may be affected by the interaction of physical, psychological, and socioeconomic factors at the same time. Thus, more factors should be taken into accounts, such as posttraumatic stress disorder (PTSD) [66], depression [13,14], cardiovascular disease [67], opioid prescriptions [68], education level [69], or even genetic level [70,71].

### Limitations

Our research has several unavoidable limitations, including those inherent to the use of abundant retrospective data sources from SEER. In 2012, the limitations and biases of the SEER database had been comprehensively described by Park.H.S [72]. One of the limitations was reported that misclassifications of the cause of



death (specifically, suicide) might cause an underrepresentation of that outcome in our analysis [73]. However, rather high sensitivity and specificity have been proved for the coding of suicide on death certificates with a physician review panel engaged in providing the gold standard for the cause of death determination [74]. Furthermore, potential confounders such as psychiatric conditions, comorbidities, cancer recurrences, substance abuse, and details of therapeutic interventions could not be analyzed because that data was not available in the SEER program. Finally, limited by its retrospective design, some ratings are difficult to explain while the anonymization of information makes it impossible to verify whether respondents' descriptions accurately signified what had actually occurred.

## Conclusions

In summary, we found an elevated risk of suicide in patients with HCC, which is mainly distributed among people with the following characteristics: diagnosed in early years (1975–2002), male sex, the older age (63–105 years old), white race, survival months (< 2 months). Nevertheless, marital status, PRCDA Region, histologic grade, surgery, radiotherapy, and chemotherapy did not show a strong association with the HCC patients relate to suicide in our analysis. Hence, the government, clinicians, and family members should periodically evaluate whether patients with HCC have suicide attempts or behaviors and take appropriate measures to reduce the risk of suicide, especially in white males over 62 years old with HCC diagnosed within two months [75]. Additionally, further investigating the validity of the interventions for decreasing the suicide rate is urgently needed among HCC patients.

## Data availability statement

The data analyzed during the current study are available from the corresponding author on reasonable request.

## Author contributions

Conception and design: Huapeng Lin, Chongfa Chen, Yi Jiang; Collection and assembly of data: Chongfa Chen, Yi Jiang, Jianyong Liu; Data analysis and interpretation: Chongfa Chen, Fang Yang, Yushen Wu; Manuscript writing: Chongfa Chen, Huapeng Lin, Qicheng Cai; Final approval of manuscript: Huapeng Lin, Yushen Wu, Yi Jiang.

## Declaration of competing interest

The authors declare that they have no conflicts of interests.

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