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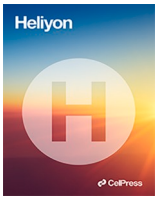

Research article

Survival and cardiovascular disease mortality among primary liver cancer patients: A population-based study

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A B S T R A C T

Background: The prognosis of primary liver cancer (PLC) was influenced by death due to non-cancer causes, particularly death related to cardiovascular disease (CVD). This study aimed to analyze mortality of non-cancer causes and identify the independent risk factors associated with CVD-related deaths in PLC patients.

Methods: In total, 112140 patients were enrolled from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2019). Independent risk factors for death from CVD in patients with PLC were identified by Cox proportional hazards model.

Results: The median follow-up time of all PLC patients was 76 months (interquartile range (IQR): 36–129). The median overall survival (OS) was 12 months (IQR: 3–40). Patients with intrahepatic cholangiocarcinoma (ICC) had shorter OS than patients with hepatocellular carcinoma (HCC) (8 vs. 14 months; $P < 0.001$). A total of 87299 deaths were observed, among which 61477 (70.42 % of all deaths) were from PLC, and 12727 (14.58 % of all deaths) were from other cancers. Of all non-cancer deaths (9276, 10.63 %), 2860(30.86 %) were results of CVD. PLC patients had higher risks on CVD-related deaths, compared with general population (standard mortality ratio, SMR, 2.20; 95 % confidence interval, CI, 2.12–2.28). Typically, the highest SMRs appeared in the first year following cancer diagnosis. The multivariable analysis revealed the characteristics listed as followed to be independently risk factors of CVD: age, male (hazard ratio, HR: 1.248, 95%CI: 1.147–1.359), black race (HR: 1.334, 95%CI: 1.195–1.490), year 2016–2019 of diagnosis (HR 0.758, 95%CI: 0.671–0.856), ICC (HR: 1.202, 95%CI: 1.086–1.330), without surgery (HR: 2.479, 95%CI: 2.266–2.711) and without chemotherapy (HR: 2.211, 95%CI: 2.033–2.403).

Conclusion: It is essential to take cardiovascular health into consideration at the time of diagnosis for PLC patients as the risk of CVD mortality is significantly higher than that of general population.

1. Introduction

As a global health challenge, primary liver cancer (PLC) is the sixth most frequently diagnosed cancer and the third leading cause of cancer mortality [1,2]. Newly diagnosed cases of PLC and deaths associated with PLC have increased worldwide in the past few years, despite significant public health efforts [3–5]. The number of liver cancer diagnoses and deaths worldwide in 2022 is estimated to be 865,269 and 757,948, respectively [1,3]. Hepatocellular carcinoma (HCC) is the most dominant pathological type of liver cancer, which accounts for approximately 75–85 % of all liver malignancies, followed by intrahepatic cholangiocarcinoma (ICC), accounting for about 10–15 % [1].

In recent years, emerging therapies, such as immunotherapies and targeted therapies have improved the prognosis of PLC [6–8]. However, cancer survivors are at risk of recurrence, as well as potential life-threatening complications, including cardiovascular disease (CVD) [9]. Elgenidy A et al. reported that about 34 % patients died from non-ICC causes among ICC patients and CVD was the

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main non-cancer-cause [10]. Wang J et al. revealed that patients with cancer had a seriously higher risk of cardiovascular events causing deaths [11]. Among cancer patients, CVD plays an vital role in prognosis and results in extremely poor outcomes [12]. Therefore, for a further improvement in survival and treatments of PLC, more attention should be paid to learn about the proportion and the risk factors of non-cancer causes of death after PLC diagnosis. The Surveillance, Epidemiology, and End Results (SEER) database was used here to assess risks and trends for deaths caused by non-cancer causes and to identify independent predictors of CVD-related deaths.

PLC and cardiovascular events, including heart and cerebrovascular diseases, have been studied in few large-scale population-based studies. Thus, our study focused on analyzing the risks of CVD among PLC patients and identifying potential risk factors related to CVD death.

2. Methods

2.1. Data sources

The SEER database was used in this retrospective cohort study. SEER is a population-based cancer registry that contains the information on mortality, morbidity, and survival, covering about 27.8 % of US population.

Since SEER is a population-based program, the data selected from it is comparable with that of the general population, allowing estimation of cancer incidence and mortality. In our study, we extracted PLC patients diagnosed between 2000 and 2019 from SEER*stat software. Public information from the SEER program did not require ethical approval. The data was collected from the time of PLC diagnosis to the earliest time of the following dates: death, loss to follow-up, or the end of follow-up period (Dec. 31, 2019).

Calculated standardized mortality ratios (SMR) are based on the following cases from Incidence SEER Research Plus Data, 17 Registries (excl AK), Nov. 2021 Sub (2000–2019) for SMRs. Patients' data for the prognosis associated with cardiovascular mortality (CVM) were collected from Incidence SEER Research Plus Data, 17 Registries, Nov. 2021 Sub (2000–2019).

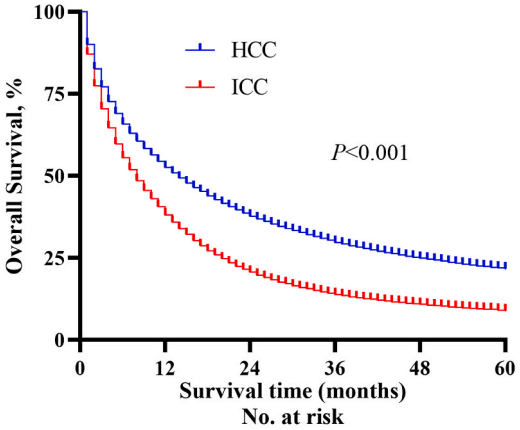
2.2. Variables

Cases of ICC were classified according to International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes (site: C22.0, C22.1, AND histology/behavior: 8160/3). Cases of HCC were classified according to ICD-O-3 codes (site: C22.0 AND histology: 8170–8175). Exclusion criteria were listed below: [1]: The cause of death remained unknown [2]. Death certificate or autopsy was the only diagnostic basis [3]. Liver cancer was not the first cancer diagnosed. The study variables included age, sex, race, era of diagnosis, stage, types of treatment, outcome and cause of death. Metastatic stage of HCC and ICC was defined by SEER Summary Stage 2000.

2.3. Classification of cause of death

Cause of death categories were classified with International Classification of Diseases, Version 9 (ICD-9) and Version 10 (ICD-10). Cause of death categories for general population came from the Wide-ranging Online Data for Epidemiologic Research tool from the Centers for Disease Control and Prevention.

Using standard and systematic procedures in data collection, SEER ensures the precision of cause of death determinations, thus reducing the impact of possible biases [13]. Non-cancer death was classified into following seven categories: cardiovascular diseases, respiratory diseases, renal diseases, gastrointestinal diseases, infectious diseases, external injuries, and other causes. CVD consisted of



No. at risk

HCC	77012	38612	25072	17706	13183	10024
ICC	17323	6354	3010	1748	1199	865

Fig. 1. OS of HCC and ICC patients.

the following six categories: disease of heart, cerebrovascular diseases, hypertension without heart disease, atherosclerosis, aortic aneurysm and dissection, and other diseases of arteries, arterioles, capillaries [14].

2.4. Statistical analysis

CVM risks for PLC patients vs. US general populations could be assessed by SMRs. Using SEER*Stat software (version 8.1.5), SMRs were calculated as the ratio of observed deaths to expected deaths. Poisson exact method was used to compute 95 % CIs and corresponding p values for SMRs, and significant difference was defined as 95 % CIs excluding 1 with a p value < 0.05. Absolute excess risk (AER) was defined as the excess deaths (i.e. observed deaths–expected deaths) per 10,000 persons at risk per year. Based on univariable and multivariable Cox proportional hazards models, the hazard ratios (HRs) and 95 % CIs were calculated to analyze the correlation between patients' characteristics and CVD-related deaths.

In survival analysis, individuals who lacked a follow-up period post-diagnosis, or were diagnosed solely by death certificate, or were newly diagnosed on the basis of autopsy were excluded from the study. GraphPad Prism 8 was used to conduct survival analysis, and all missing data was excluded from calculations and analysis automatically. The one-, three-, and five-year overall survival (OS) rates of ICC and HCC cases were calculated using the Kaplan Meier method. The cutoff date of follow up was 60 months in Fig. 1. Furthermore, the survival curves were compared through the utilization of the log-rank test. Multivariable subgroup analyses were performed among subgroups by different age, gender, race, stage, treatment type and causes of death to estimate OS of HCC compared to ICC. The proportional hazards ratio was calculated by log-rank test using GraphPad Prism 8 [13,14].

3. Results

3.1. Patients' characteristics

112140 patients were included in our study during 2000–2019, including 20801 ICC and 91339 HCC patients (Table 1). Age at diagnosis was distributed as follows: <50 years, 8.44 %; 50–64 years, 44.77 %; >65 years, 46.80 %. Majority of the ICC patients were diagnosed at the age of above 65 years old., which was much older than patients with HCC. The majority of patients were male (72.05 %), especially in patients with HCC (76.99 %). The predominant race was white (70.05 %) both in patients with ICC (77.07 %) and HCC (68.46 %). About one quarter patients were in localized stage. About 22.32 % patients underwent surgery and 36.26 % patients received chemotherapy.

Table 1
Demographics and clinical characteristics of the patients.

Characteristic	Cases, No.	%	Cases, No. (ICC)	%	Cases, No. (HCC)	%
Overall	112140		20801		91339	
Age at diagnosis, years						
<50	9460	8.44	1740	8.36	7720	8.45
50-64	50201	44.77	6409	30.81	43792	47.94
65+	52479	46.80	12652	60.82	39827	43.60
Sex						
Male	80801	72.05	10476	50.36	70325	76.99
Female	31339	27.95	10325	49.64	21014	23.01
Race						
White	78559	70.05	16032	77.07	62527	68.46
Black	13072	11.66	1728	8.31	11344	12.42
Other/Unknown	20509	18.29	3041	14.62	17468	19.12
Era of diagnosis, y						
2000–2005	21407	19.09	3738	17.97	17669	19.34
2006–2010	26091	23.27	4405	21.18	21686	23.74
2011–2015	34586	30.84	6311	30.34	28275	30.96
2016–2019	30056	26.80	6347	30.51	23709	25.96
Stage						
Localized	39843	35.53	2388	11.48	37455	41.01
Regional	24107	21.50	2960	14.23	21147	23.15
Distant	15610	13.92	3742	17.99	11868	12.99
Unknown	32580	29.05	11711	56.30	20869	22.85
Surgery						
Yes	25026	22.32	3923	18.86	21103	23.10
No/Unknown	87114	77.68	16878	81.14	70236	76.90
Chemotherapy						
Yes	40663	36.26	8861	42.60	31802	34.82
No/Unknown	71477	63.74	11940	57.40	59537	65.18

3.2. Survival

The median follow-up time of all PLC patients was 76 months (IQR: 36–129). The median overall survival (OS) of all PLC patients was 12 months (IQR: 3–40), with 1-, 3-, and 5-year survival rate of 40.10 %, 17.35 %, and 9.71 %, respectively. The median OS in ICC patients was 8 months (IQR: 2–19) with 1-, 3-, and 5-year survival rate of 30.5 %, 8.40 %, and 4.16 %, respectively. HCC patients had longer median OS at 14 months (IQR: 3–47), with 1-, 3-, and 5-year survival rates of 42.27 %, 19.38 %, and 11.00 %, respectively (Fig. 1). Subgroup analyses were performed in the comparison of OS between HCC and ICC stratified by age, gender, race, stage, therapy and causes of death. OS was shorter in ICC patients than HCC patients among all subtypes (Fig. 2).

3.3. Cause-specific mortality compared with general population

Among all patients with liver cancer, 87299 deaths were observed overall including 69712 in HCC and 17587 in ICC (Table 2). About 2/3 patients (61477) died from liver cancer. In all non-cancer-related deaths (9276), 2863 (30.86 %) were a result of CVD. Other non-cancer-related deaths included infectious diseases (693, 7.47 %), external injuries (544, 5.86 %), endocrine diseases (440, 4.74 %), respiratory diseases (402, 4.33 %), renal diseases (339, 3.65 %) and gastrointestinal diseases (54, 0.58 %). The AER of CVM among patients with liver cancer per 10,000 person-years was 78.73. In comparison to the general population, PLC patients had higher risk of deaths from cardiovascular diseases (SMR, 2.20; 95 % CI, 2.12–2.28), pneumonia and influenza (SMR, 2.68, 95 % CI, 2.35–3.05), septicemia (SMR, 7.75; 95 % CI, 7.05–8.51), tuberculosis (SMR 5.88, 95 % CI, 2.93–10.52), chronic obstructive pulmonary disease (COPD) (SMR, 1.74 95 % CI, 1.58–1.92), stomach and duodenal ulcers (SMR, 9.63; 95 % CI, 7.23–12.56), nephritis, nephrotic syndrome, and nephrosis (SMR, 4.31; 95 % CI, 3.87–4.80), suicide and self-inflicted injury (SMR, 2.81; 95 % CI, 1.84–4.12), along with other causes. Significantly increased mortality was observed in both HCC and ICC patients. Among all CVD-related deaths, the highest

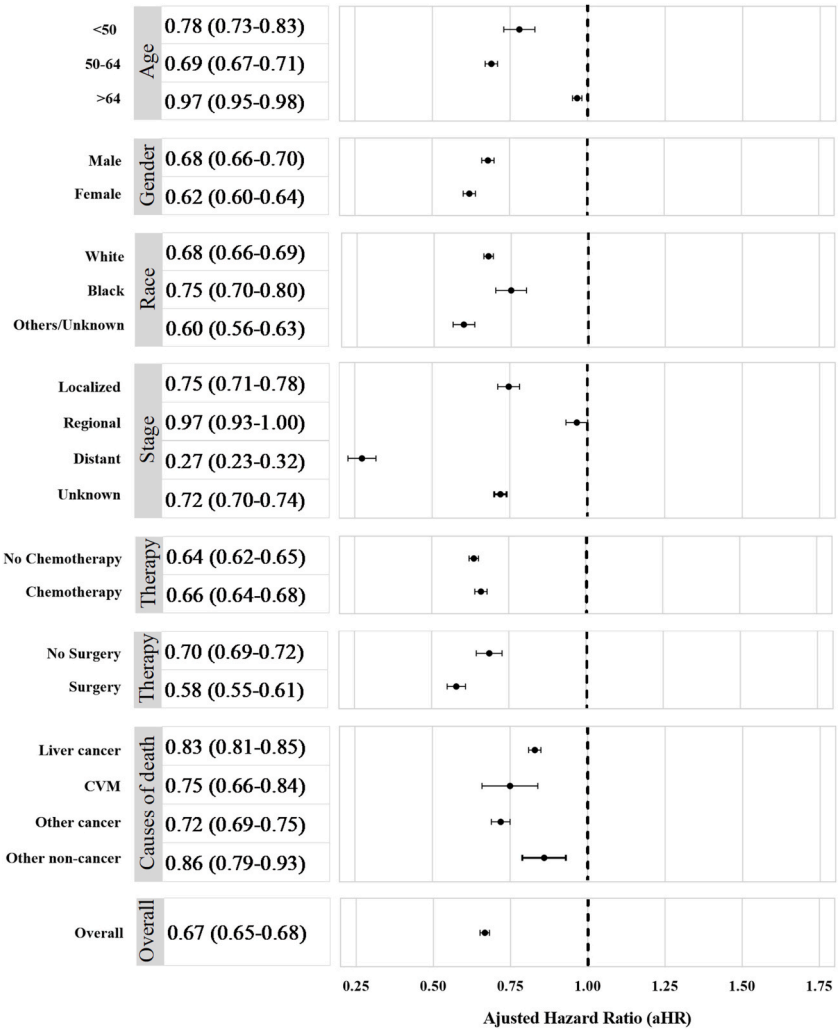


Fig. 2. OS of HCC compared with ICC in subgroups of patients with different age, gender, race, stage, treatment type and causes of death.

Table 2
Standardized mortality ratios for each cause of death among patients with liver cancer.

Causes of Death	Total			HCC			ICC		
	No.	SMR (95 % CI)	AER	No.	SMR	AER	No.	SMR	AER
Overall	87299	22.02 (21.87–22.17)	4203.63	69712	20.77 (20.62–20.93)	3,796.54	17587	28.89 (28.47–29.32)	7,236.03
Died from liver cancer	61477	1057.22 (1048.88–1065.61)	3098.14	50389	1081.79 (1072.37–1091.28)	2539.41	11088	958.28 (940.53–976.29)	558.73
Non–cancer-related deaths									
Cardiovascular diseases	2863	2.20 (2.12–2.28)	78.73	2378	2.17 (2.09–2.26)	73.49	485	2.33 (2.12–2.54)	117.83
Disease of the heart	2169	2.17 (2.08–2.26)	58.98	1803	2.14 (2.04–2.24)	54.97	366	2.32 (2.09–2.58)	88.89
hypertension without heart disease	155	3.28 (2.79–3.84)	5.44	127	3.20 (2.67–3.81)	5.00	28	3.73 (2.48–5.39)	8.74
cerebrovascular diseases	457	2.15 (1.96–2.36)	12.33	387	2.20 (1.98–2.43)	12.07	70	1.92 (1.49–2.42)	14.27
atherosclerosis	33	3.51 (2.41–4.92)	1.19	24	3.20 (2.05–4.76)	0.94	9	4.70 (2.15–8.92)	3.02
aortic aneurysm and dissection	15	0.79 (0.44–1.3)	−0.2	12	0.74 (0.38–1.29)	−0.24	3	1.07 (0.22–3.12)	0.08
other diseases of the arteries, arterioles, and capillaries	34	2.39 (1.66–3.34)	1	25	2.11 (1.36–3.11)	0.75	9	3.84 (1.76–7.29)	2.84
Infectious diseases									
Pneumonia and influenza	233	2.68 (2.35–3.05)	7.37	194	2.69 (2.33–3.1)	6.98	39	2.63 (1.87–3.6)	10.31
Tuberculosis	11	5.88 (2.93–10.52)	0.46	10	5.97 (2.86–10.97)	0.48	1	5.11 (0.13–28.48)	0.34
Septicemia	449	7.75 (7.05–8.51)	19.73	383	7.81 (7.05–8.64)	19.11	66	7.43 (5.74–9.45)	24.34
Syphilis	0	NA	NA	NA					
Respiratory diseases									
Chronic obstructive pulmonary disease and allied conditions	402	1.74 (1.58–1.92)	8.64	343	1.78 (1.6–1.98)	8.59	59	1.56 (1.19–2.01)	9.05
Gastrointestinal diseases									
Stomach and Duodenal Ulcers	54	9.63 (7.23–12.56)	2.44	46	9.64 (7.06–12.86)	2.36	8	9.57 (4.13–18.85)	3.05
Renal diseases									
Nephritis, nephrotic syndrome, and nephrosis	339	4.31 (3.87–4.8)	13.14	312	4.70 (4.2–5.25)	14.05	27	2.20 (1.45–3.21)	6.29
Endocrine diseases									
Diabetes mellitus	440	3.10 (2.81–3.4)	15.03	386	3.14 (2.83–3.47)	15.05	54	2.83 (2.12–3.69)	14.87
External injuries									
Accidents and Adverse Effects	470	3.44 (3.14–3.77)	16.82	424	3.57 (3.24–3.93)	17.47	46	2.56 (1.88–3.42)	11.95
Suicide and self-inflicted injury	74	1.86 (1.46–2.34)	1.73	66	1.85 (1.43–2.36)	1.74	8	1.99 (0.86–3.91)	1.69

SMR was seen in atherosclerosis (SMR, 3.51 95 % CI, 2.41–4.92), followed by hypertension without heart disease (SMR, 3.28, 95 % CI, 2.79–3.84), other diseases of the arteries, arterioles, and capillaries (SMR, 2.39 95 % CI, 1.66–3.34) and disease of the heart (SMR, 2.17 95 % CI, 2.08–2.26).

3.4. Cardiovascular disease mortality among liver cancer patients

The SMR of CVD-related deaths was higher in younger patients and decreased in patients who were diagnosed at an advanced age. (Table 3). As was shown, the SMR of CVM in patients younger than 50y was 4.40 (95 % CI, 3.60–5.20), while the SMR of CVM in patients diagnosed at the age >65y was 1.93 (95 % CI, 1.84–2.02). The SMR of CVM in young patients with ICC was 7.74 (95 % CI, 4.43–12.58), compared with 4.09 (95 % CI, 3.29–5.02) in young HCC patients, which indicated higher CVM in ICC, especially in the young patients. The highest SMR for CVM appeared in the first year after diagnosis (3.34, 95 % CI, 3.18–3.51) and decreased over the follow-up period. During the year 2016–2019, the SMR of CVM was 2.58(95 % CI, 2.35–2.81), which was higher than that in the previous eras. In non-Hispanic AI/AN patients with ICC, the SMR of CVM was extremely high (SMR 8.03, 95 % CI, 2.61–18.75). No significant difference was found in SMR of CVM when it was compared between male and female.

Table 3
Standardized mortality ratios of cardiovascular disease mortality among liver cancer patients according to baseline characteristics.

Characteristics	Total			HCC			ICC		
	No.	SMR (95 % CI)	AER	No.	SMR	AER	No.	SMR	AER
Total cardiovascular disease deaths	2863	2.20 (2.12–2.28)	78.73	2378	2.17 (2.09–2.26)	73.49	485	2.33 (2.12–2.54)	117.83
Age, y									
<50	106	4.40 (3.60–5.20)	34.73	90	4.09 (3.29–5.02)	33.16	16	7.74 (4.43–12.58)	45.18
50-64	952	2.78 (2.61–2.96)	59.02	319.32	2.73 (2.56–2.92)	58.56	79	3.43 (2.72–4.28)	63.90
65+	1,805	1.93 (1.84–2.02)	121.83	752.27	1.88 (1.78–1.98)	110.94	390	2.13 (1.92–2.35)	177.82
Sex									
Male	2,088	2.21 (2.12–2.31)	79.72	1810	2.17 (2.08–2.28)	74.19	278	2.48 (2.20–2.79)	142.1
Female	775	2.17(2.02–2.32)	76.15	568	2.17 (2.00–2.36)	71.32	207	2.15 (1.86–2.46)	93.8
Race									
Non-Hispanic White	1,536	2.18 (2.08–2.29)	84.98	1226	2.18 (2.06–2.30)	79.51	310	2.20 (1.96–2.46)	116.51
Non-Hispanic Black	377	2.55 (2.30–2.82)	119.53	335	2.53 (2.27–2.82)	116.27	42	2.70 (1.95–3.66)	152.14
Non-Hispanic AI/AN	23	3.82 (2.42–5.74)	87.05	18	3.34 (1.98–5.27)	70.69	5	8.03 (2.61–18.75)	260.81
Non-Hispanic API	451	1.98 (1.80–2.17)	53.54	388	1.90 (1.71–2.09)	47.88	63	2.77 (2.13–3.54)	116.01
Hispanic (All Races)	476	2.19 (2.00–2.40)	69.17	411	2.18 (1.97–2.4)	65.72	65	2.28 (1.76–2.91)	101.64
Latency periods, m									
0-11	1,531	3.34 (3.18–3.51)	161.91	1214	3.39 (3.2–3.59)	154.84	317	3.17 (2.83–3.54)	197.46
12-59	941	1.69 (1.59–1.8)	43.39	811	1.68 (1.57–1.8)	41.32	130	1.77 (1.48–2.1)	61.24
60-119	270	1.34 (1.18–1.51)	21.31	245	1.37 (1.21–1.56)	22.62	25	1.06 (0.68–1.56)	5.58
120+	121	1.40 (1.16–1.67)	30.7	108	1.44 (1.18–1.74)	31.57	13	1.13 (0.6–1.94)	19.21
Era of diagnosis, y									
2000–2005	669	1.98 (1.83–2.14)	74.03	551	2.00 (1.84–2.18)	69.44	118	1.88 (1.55–2.25)	110.82
2006–2010	821	2.25 (2.09–2.40)	77.3	681	2.18 (2.02–2.35)	69.68	140	2.66 (2.24–3.14)	143.15
2011–2015	876	2.16 (2.02–2.31)	71.53	750	2.15 (2.00–2.31)	69.12	126	2.20 (1.83–2.62)	89.83
2016–2019	497	2.58 (2.35–2.81)	105.35	396	2.52 (2.28–2.78)	98.98	101	2.82 (2.3–3.42)	137.84

AI: American Indian. AN: Alaska Native. API: Asian or Pacific Islander.

3.5. Risk factor of CVD related death

Since the vast majority of non-cancer deaths was CVD-related deaths, we used a univariable and multivariable cox regression analyses to identify predictors for CVD-related death in patients with liver cancer. As were shown in Table 4, the multivariable analysis revealed the following characteristics to be independently associated with CVD risk: age, male (hazard ratio, HR: 1.248, 95%CI: 1.147–1.359), black race (HR: 1.334, 95%CI: 1.195–1.490), year 2016–2019 of diagnosis (HR 0.758, 95%CI: 0.671–0.856), ICC (HR: 1.202, 95%CI: 1.086–1.330), without surgery (HR: 2.479, 95%CI: 2.266–2.711) and without chemotherapy (HR: 2.211, 95%CI: 2.033–2.403). HR increased rapidly as the age grew, which meant CVM increased significantly (50–64 years old (HR: 1.998, 95%CI (1.634–2.443)), >65 years old (HR: 4.833, 95%CI (3.966–5.889)). Moreover, compared to patients diagnosed between 2000 and 2005, patients who were diagnosed between 2016 and 2019 had a 24.2 % decrease in CVM (HR: 0.758 CI: (0.671–0.856). Patients without surgery or chemotherapy had a significantly higher risk of CVD-related death.

4. Discussion

To the best of our knowledge, this study represented the initial large-scale population-based investigation into the survival, causes of death, and associated factors of CVM in patients with PLC. The median OS of the entire cohort of PLC patients was 12 months, with ICC demonstrating a shorter OS than HCC across all subsets. The most prevalent non-PLC cause of death following diagnosis was cardiovascular disease, which is consistent with prior research indicating that CVD-related death is the primary cause of mortality in cancer survivors [11,15–17]. ICC is associated with the risk factors of metabolic diseases and endocrine disorders, including type II diabetes, obesity, dyslipidemia and non-alcoholic fatty liver disease (NAFLD), which will cause CVD as well [18,19]. CVD will further worsen the OS of ICC patients.

Some studies have indicated that older patients are more susceptible to mortality from CVD [11,17,20]. However, our study found that the SMR of CVM was 2.20 (2.12–2.28), which was higher at a younger age of diagnosis. We postulate that this may be due to the lower prevalence of CVD in younger individuals, as it is typically diagnosed in the elderly. It is important to note that SMRs are a standardized population measure. Additionally, older patients may succumb to their underlying primary illness before developing CVD in the long run [21]. Moreover, older patients with severe comorbidities may develop various adverse health outcomes, including infections, which may not be directly attributable to heart-specific diseases [22].

Table 4
Univariate and multivariate analysis for associations between patient characteristics and heart-specific mortality in liver cancer patients (2000–2019).

Variable	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P	HR (95 % CI)	P
Age, y				
<50	Ref	Ref	Ref	Ref
50-64	1.989(1.628–2.430)	0.000	1.998(1.634–2.443)	0.000
65+	4.946(4.063–6.021)	0.000	4.833(3.966–5.889)	0.000
Sex				
Female	Ref	Ref	Ref	Ref
Male	–	0.415	1.248(1.147–1.359)	0.000
Race				
White	Ref	Ref	Ref	Ref
Black	1.250(1.120–1.395)	0.000	1.334(1.195–1.490)	0.000
Other	0.795(0.720–0.878)	0.000	0.753(0.681–0.833)	0.000
Unknown	0.431(0.193–0.960)	0.039	0.449(0.201–1.000)	0.050
Era of diagnosis, year				
2000–2005	Ref	Ref	Ref	Ref
2006–2010	0.952(0.857–1.057)	0.354	1.058(0.952–1.175)	0.298
2011–2015	0.822(0.740–0.913)	0.000	0.866(0.778–0.963)	0.008
2016–2019	0.802(0.710–0.905)	0.000	0.758(0.671–0.856)	0.000
Stage				
Localized	Ref	Ref	–	0.312
Regional	1.016(0.918–1.125)	0.760	–	0.293
Distant	1.366(1.188–1.570)	0.000	–	0.091
Unknown	1.361(1.236–1.499)	0.000	–	0.649
Surgery				
Yes	Ref	Ref	Ref	Ref
No/Unknown	2.229(2.043–2.432)	0.000	2.479(2.266–2.711)	0.000
Chemotherapy				
Yes	Ref	Ref	Ref	Ref
No	2.004(1.848–2.173)	0.000	2.211(2.033–2.403)	0.000
Tumor type				
HCC	Ref	Ref	Ref	Ref
ICC	1.269(1.150–1.400)	0.000	1.202(1.086–1.330)	0.000

HR, hazard ratio; CI, confidence interval.

Among all categories of CVD death, the highest SMR was found as atherosclerosis (SMR, 3.51 95 % CI, 2.41–4.92), followed by hypertension without heart disease (SMR, 3.28, 95 % CI, 2.79–3.84), other diseases of the arteries, arterioles, and capillaries (SMR, 2.39 95 % CI, 1.66–3.34) and diseases of the heart (SMR, 2.17 95 % CI, 2.08–2.26).

The findings of our study indicated that the incidence of CVM deaths was highest during the initial year following PLC diagnosis, and was lowest after a decade of diagnosis. These results were in line with prior research that suggested non-cancer related causes, such as CVM, were more prevalent in the first year post-cancer diagnosis, potentially due to treatment-related factors [15,23–25]. Furthermore, for the type of CVD deaths, atherosclerosis probably gives significant effect to death of PLC patients, with the highest SMR (3.51 95 % CI, 2.41–4.92). Our investigation also revealed that male cancer patients exhibit a greater susceptibility to CVD-related mortality compared to their female counterparts, which may be attributed to hormonal disparities [11,26]. Another plausible explanation is that men tend to exhibit poorer lifestyle habits, such as alcohol consumption and tobacco use, which have been identified as autonomous risk factors for CVD in previous research [27–29]. Additionally, prior studies have indicated that individuals of African descent are at a heightened risk of mortality from CVD compared to other ethnic groups [30,31], potentially due to the elevated incidence of venous thromboembolism in black cancer patients [16]. Our investigation yielded comparable findings.

Numerous studies have established a positive correlation between surgery and an elevated risk of venous thromboembolism [32,33]. However, Trinh V. Q. et al.'s investigation has revealed a decrease in the incidence of venous thromboembolic-related mortality subsequent to major cancer surgery [34]. Our own study has revealed that cancer patients who have not undergone surgery exhibit a significantly heightened risk of cardiovascular disease-related death (HR = 2.479, $P < 0.001$). This may be attributed to the fact that patients without surgery are typically those with advanced tumor progression, and such individuals inherently face a greater risk of mortality. Khorana posited that thromboembolism is the primary cause of mortality among cancer patients who underwent chemotherapy [35]. Our study revealed that patients who did not receive chemotherapy alone exhibited a greater risk of death related to cardiovascular disease compared to those who received chemotherapy (HR = 2.211; $P < 0.001$). It is suggested that anticoagulant therapy can extend the life span of cancer patients, and low molecular weight heparin and warfarin have become increasingly prevalent in cancer patients undergoing chemotherapy recently, thereby reducing the likelihood of thromboembolism in cancer patients [36–38]. Furthermore, patients who receive regular chemotherapy may benefit from improved health monitoring during treatment and follow-up. Therefore, thromboembolism can be diagnosed and treated in time, thereby reducing the likelihood of subsequent adverse events. These factors may account for the lower incidence of cardiovascular disease-related mortality observed in patients with primary liver cancer who receive chemotherapy alone.

However, it is essential to note that this study has certain limitations. Firstly, the research data utilized in this study is derived solely from the SEER database. Secondly, due to the study's cutoff date of 2019, patients who were recently diagnosed may not have had enough time to follow up. Thirdly, the absence of individual-level information pertaining to alcohol consumption, smoking, diabetes, obesity, hyperlipidemia and history of cardiovascular diseases may be linked to an elevated risk of cardiovascular mortality. Additionally, it is noteworthy that mortality resulting from venous thromboembolism is a significant contributor to cardiac mortality, yet no instances of venous thromboembolism were documented in SEER.

In the future, a nested case-control or cohort study can be conducted to examine CVD risk factors in detail using individual patient data. Moreover, a prospective cohort study could better establish causality and assess interventions to lower CVD risk in PLC patients. Artificial intelligence techniques like machine learning algorithms can also be applied in the surveillance of cardiovascular diseases. For example, Support Vector Machine algorithm model invented by Khazaal SM was able to predict coronary artery disease accurately and effectively, as was reported [39].

In Conclusion: Our cohort study based on population data revealed that CVM is the predominant cause of death among non-PLC causes during the follow-up period subsequent to a cancer diagnosis. The present study aimed to explore the association between various patient-specific covariates and CVM in individuals diagnosed with PLC, while also investigating the underlying mechanisms that influence survival. The highest SMRs of CVM occurred within the first year following a cancer diagnosis, which was consistent with previous studies. Our findings hold considerable significance for healthcare providers in terms of counseling PLC survivors and addressing the clinical challenges associated with prognosticating future health risks.

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Availability of data and materials

The data were obtained from the SEER database (https://seer.cancer.gov/seerstat/), which is freely accessible to the public.

CRediT authorship contribution statement

Lidong Wang: Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Ting Wang:** Formal analysis, Data curation. **Wu Zhang:** Writing – review & editing, Supervision. **Shusen Zheng:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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