Causes of Death in Hepatocellular Carcinoma Patients: A SEER-Based Study

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Abstract

Objective: To identify cancer and non-cancer causes of death in hepatocellular carcinoma (HCC) patients over different time periods after diagnosis and to compare the mortality risk of each cause in HCC patients with the general population.

Methods: In this retrospective cohort study, data of 67,637 HCC patients from 1975 to 2016 were collected from the Surveillance, Epidemiology, and End Results (SEER) database. We investigated the association between different causes of death and the following variables: age, race, tumor stage at diagnosis, and treatment (surgery, chemotherapy, and radiotherapy); each according to the periods of < 1 year, 1–5 years, 5–10 years, and > 10 years following the diagnosis. Standardized mortality ratios (SMRs) and their 95% confidence intervals (CIs) were calculated for cancer and non-cancer deaths in each of the mentioned periods following diagnosis.

Results: Data of 67,637 patients, of whom 50,571 patients died during the follow-up period, were analyzed. Most deaths were due to HCC itself (35,535, 70.3%), followed by other cancers (3,983, 7.9%). Common causes of non-cancer mortality included infectious and parasitic diseases including HIV (2,823 patients, SMR = 105.68, 95% CI: 101.82-109.65), chronic liver disease (2,719 patients, SMR = 76.56, 95% CI: 73.71,79.5), and heart diseases (1,265 patients, SMR = 2.26, 95% CI: 2.14–2.39), with higher mortality risk in HCC patients than in the general population.

Conclusion: Cancers stand for most deaths in patients with HCC. Besides, infectious, and parasitic diseases including HIV represent the commonest non-cancer cause of mortality.

Background

Hepatocellular Carcinoma (HCC) represents the majority of primary liver cancer cases (> 80%) and it arises from hepatocytes (1–3). In 2020, HCC was the sixth most commonest cancer and the third major reason for cancer death (4). The estimated number of new cases of liver cancer and deaths in 2020 was about 906,000 and 830,000 respectively (4). It is expected that, by 2025, more than one million individuals will be affected by liver cancer per year (5).

Unlike other cancers, the causative agent of HCC is usually identifiable. But the etiology of HCC varies across different geographic regions due to the variation in multiple factors. These factors can affect patients' characteristics and the disease course. So, HCC represents a composite condition that has a poor prognosis (6). HCC pathogenesis involves alterations of some metabolic pathways and gene mutations. These changes initiate the malignant transformation of cells and maintain the cancer progression (7–12).

In many cases, HCC develops after a known history of chronic liver disease or cirrhosis (13). HCC may develop as a complication of the chronic hepatitis B, hepatitis C, non-alcoholic steatohepatitis or alcoholic liver disease (14). Other risk factors include diabetes, obesity, some metabolic and hereditary disorders (e.g., hemochromatosis), and aflatoxin toxicity (15, 16).

HCC has a low 5-year relative survival rate at about 18.4% (3). The survival rates also vary depending upon the stage of cancer at diagnosis, underlying extent of liver damage, therapeutic measures or surgical interventions administered and the influence of other risk factors like diabetes, hereditary and metabolic disorders (17). Patients with conserved liver functions, small, localized tumor, and less co-morbid conditions, have better survival rates and are more liable to have a successful curative procedure (e.g., ablation, resection, or transplantation) (18–20).

The overall prognosis however, remains very poor and it is extremely challenging to identify the most dominant factor in the progress of a certain patient to terminal liver failure and death, as each one of the risk factors is an independent death cause (21).

This study, therefore, aims to demonstrate the different cancer- or non-cancer causes of deaths in patients with HCC compared with the general population. Also, it aims to investigate the association between several variables – such as age, race, or treatment – and the cause-specific mortality risk over different intervals after HCC diagnosis.

Methods

We followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines while conducting this retrospective cohort study (22).

Data Collection And Study Subjects

We included patients with hepatocellular carcinoma registered in the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2016. The follow-up period was until the end of 2016 or until death. Patients' data were extracted using the SEER*Stat software version 8.3.9. SEER-registered data are publicly available and are anonymized, so the institutional review board approval was not required.

Study Outcomes

For the included patients, we studied the cancer and non-cancer causes of death, and their possible association with the following variables: age, race, stage at diagnosis, and treatment options (chemotherapy, radiotherapy, or surgery). Races stated as "other" include Asian or Pacific Islander and Indian American/Alaska Native. Death events were categorized into time intervals from HCC diagnosis to death, including < 1 year, 1–5 years, 5–10 years, and > 10 years intervals. We reported the percentage of all deaths and cause-specific deaths in each period. Besides, we calculated the standardized mortality ratios

(SMRs) for cancer and non-cancer cause of death in the studied population compared with the United states (US) general population. Using the SEER*Stat, we got the US general population's death rates, as collected by the National Center for Health Statistics from 1969 to 2016.

Statistical analysis

Analysis was conducted using the SEER*Stat software version 8.3.9. We calculated the SMRs with their 95% confidence intervals (CIs). All performed statistical tests were 2-sided. A significantly increased risk was considered when the observed deaths of a specific cause in the studied population are significantly more than the expected deaths of the same cause in the general population ($P < 0.05$). SEER data are generally available in public, so this study is exempt from institutional review board approval.

Results

We reviewed data of 67,637 HCC patients. The majority of them were aged ≥ 50 years at diagnosis (61,203; 90.5%) and were males (52,212; 77.2%). Most patients were White (45,530; 67.3%) and were diagnosed at a localized disease stage (35,420; 52.4%). Most patients had chemotherapy (42,279; 62.5%), but a minority of patients had radiotherapy (4,935; 7.3%) or underwent surgery (17,373; 25.7%). During the follow-up period, 50,571 patients died (74.77%). Table 1 shows the characters of the included patients.

Table 1
Baseline characteristics of hepatocellular carcinoma patients.

Characteristic	Total	Observed deaths	Percentage
Overall	67,637	50,571	74.77
Age			
< 50	6,434	4,628	71.93
≥ 50	61,203	45,943	75.07
Sex			
Male	52,212	39,374	75.41
Female	15,425	11,197	72.59
Race			
White	45,530	34,408	75.57
Black	9,280	7,363	79.34
Other ^a	12,827	8,800	68.61
Stage			
Localized	35,420	22,767	64.28
Regional	20,602	17,073	82.87
Distant	11,615	10,731	92.39
Grade			
Grade 1	7,679	5,260	68.5
Grade 2	10,552	6,976	66.11
Grade 3	5,379	4,302	79.98
Grade 4	539	449	83.3
Unknown	43,488		0
Surgery			
Yes	17,373	8,879	51.11
No	50,264	41,692	82.95
Chemotherapy			
Yes	42,279	32,850	77.7
No	25,358	17,721	69.88
Radiotherapy			
Yes	4,935	3,503	70.98
No	62,702	47,068	75.07
^a Asian or Pacific Islander and Indian American/Alaska Native females.			

Totally, 50,571 patients died during the follow-up period. The majority of deaths were attributed to HCC (35,535 deaths, 70.3%) and other cancers (3,983 deaths, 7.9%). Leading causes of non-cancer mortality, with higher mortality risk than the general population, included infectious and parasitic diseases (including human retrovirus (HIV)) (2,823 deaths, SMR = 105.68, 95% CI: 101.82-109.65), followed by chronic liver disease (2,719 deaths, SMR = 76.56, 95% CI: 73.71,79.5), and heart diseases (1,265 deaths, SMR = 2.26, 95% CI: 2.14–2.39).

Causes of Death During the first Year After HCC Diagnosis

During the first year after the HCC diagnosis, a total of 33,775 patients died. Among these patients, 24,547 died from HCC, and 2,621 died from other cancers. During this period, the first non-cancer cause of death was chronic liver disease and cirrhosis, accounting for 1,814 deaths, with a significantly higher risk in HCC patients than in the general population (SMR = 147.50, 95% CI: 140.79-154.45). This was followed by other infectious and parasitic diseases including HIV, accounting for 1,699 deaths, (SMR = 177.22, 95% CI: 168.89-185.85), and then heart diseases, accounting for 723 deaths, (SMR = 3.61, 95% CI: 3.35–3.88) (See Table 2).

Table 2
Standardized mortality ratios for each cause of death categorized by timing of deaths after hepatocellular carcinoma diagnosis.

Cause of death	> 1 year		1–5 years		5–10 years		> 10 years		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes	33,775	59.72 (59.09–60.36)*	14,780	25.60 (25.19–26.02)*	1,755	15.64 (14.92–16.39)*	261	17.33 (15.29–19.56)*	50,571	40.19 (39.84–40.55)
Hepatocellular carcinoma	24,547	62.43 (61.65–63.22)*	10,036	29.42 (28.84–30)*	882	19.06 (17.83–20.36)*	70	20.02 (15.61–25.29)	35,535	45.32 (44.85–45.79)
Other cancers	2,621	56.68 (54.53–58.89)*	1,118	22.60 (21.3–293.97)*	200	14.39 (12.46–16.53)*	44	26.12 (18.98–35.06)*	3,983	35.79 (34.69–36.92)
Non-cancer causes										
In situ, benign or unknown behavior neoplasm	92	19.70 (15.88–24.17)*	15	2.45 (1.37–4.05)*	5	2.35 (0.76–5.49)	0	0 (0–6.25)	112	8.30 (6.83–9.98)*
Tuberculosis	6	15.99 (5.87–34.81)*	3	5.68 (1.17–16.6)*	0	0 (0–19.44)	0	0 (0–73.19)	9	7.87 (3.6–14.94)
Syphilis	0	0 (0–231.59)	0	0 (0–183.89)	0	0 (0–596.15)	0	0 (0–2481.55)	0	0 (0–84.49)
Septicemia	141	12.47 (10.5–14.7)*	83	5.65 (4.5–7.01)*	16	3.23 (1.84–5.24)*	6	4.53 (1.66–9.85)*	246	7.62 (6.7–8.64)*
Other Infectious and Parasitic Diseases including HIV	1,699	177.22 (168.89–185.85)*	967	78.83 (73.94–83.96)*	137	34.89 (29.29–41.24)*	20	21.46 (13.11–33.15)*	2,823	105.61 (101.8–109.61)
Diabetes Mellitus	139	5.09 (4.28–6.01)*	92	2.55 (2.05–3.12)*	28	2.26 (1.5–3.27)*	11	3.36 (1.68–6.02)*	270	3.41 (3.02–3.85)*
Alzheimer's (ICD-9 and 10 only)	13	0.77 (0.41–1.31)	14	0.64 (0.35–1.07)	4	0.51 (0.14–1.31)	2	0.79 (0.1–2.85)	33	0.67 (0.46–0.94)*
Diseases of Heart	723	3.61 (3.35–3.88)*	407	1.60 (1.45–1.77)*	114	1.37 (1.13–1.64)*	21	0.96 (0.59–1.46)	1,265	2.26 (2.14–2.39)*
Hypertension without Heart Disease	43	5.21 (3.77–7.02)*	24	2.18 (1.4–3.25)*	8	2.06 (0.89–4.06)	3	2.78 (0.57–8.12)	78	3.22 (2.55–4.02)*
Cerebrovascular Diseases	120	2.91 (2.41–3.48)*	112	2.14 (1.76–2.57)*	32	1.84 (1.26–2.6)*	9	1.88 (0.86–3.56)	273	2.36 (2.09–2.65)*
Atherosclerosis	12	5.67 (2.93–9.9)*	4	1.62 (0.44–4.14)	1	1.34 (0.03–7.45)	0	0 (0–19.09)	17	3.07 (1.79–4.92)*
Aortic Aneurysm and Dissection	6	1.43 (0.52–3.1)	3	0.58 (0.12–1.69)	1	0.61 (0.02–3.4)	0	0 (0–8.96)	10	0.87 (0.42–1.61)
Other Diseases of Arteries, Arterioles, Capillaries	5	1.8 (0.58–4.2)	9	2.57 (1.17–4.87)*	2	1.73 (0.21–6.25)	1	3.21 (0.08–17.89)	17	2.19 (1.28–3.51)*
Pneumonia and Influenza	60	3.57 (2.72–4.59)*	45	2.09 (1.52–2.79)*	12	1.61 (0.83–2.82)	4	1.98 (0.54–5.07)	121	2.53 (2.1–3.02)*
Chronic Obstructive Pulmonary Disease and Allied Cond	122	2.78 (2.31–3.32)*	69	1.22 (0.95–1.54)	26	1.32 (0.87–1.94)	8	1.46 (0.63–2.88)	225	1.79 (1.56–2.04)*

SMR, standardized mortality ratio. *P < 0.05.

Cause of death	> 1 year		1–5 years		5–10 years		> 10 years		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Stomach and Duodenal Ulcers	23	20.38 (12.92–30.57)*	7	4.88 (1.96–10.05)*	1	2.09 (0.05–11.66)	0	0 (0–29.28)	31	9.78 (6.65–13.89)
Chronic Liver Disease and Cirrhosis	1,814	147.50 (140.79–154.45)*	809	49.40 (46.05–52.92)*	80	14.50 (11.5–18.05)*	16	12.12 (6.93–19.67)*	2,719	76.56 (73.71–79.5)*
Nephritis, Nephrotic Syndrome and Nephrosis	93	6.13 (4.95–7.51)*	71	3.60 (2.81–4.54)*	25	3.75 (2.43–5.53)*	9	5.04 (2.3–9.56)*	198	4.57 (3.95–5.25)*
Complications of Pregnancy, Childbirth, Puerperium	2	227.03 (27.49–820.11)*	0	0 (0–275.25)	0	0 (0–745.93)	0	0 (0–2793.63)	2	70.23 (8.51–253.7)
Congenital Anomalies	6	6.83 (2.5–14.86)*	6	5.21 (1.91–11.34)*	0	0 (0–9.75)	0	0 (0–40.79)	12	4.80 (2.48–8.39)*
Certain Conditions Originating in Perinatal Period	1	93.87 (2.38–523.04)*	0	0 (0–211.08)	0	0 (0–2258.56)	0	0 (0–11169.99)	1	33.23 (0.84–185.11)
Symptoms, Signs and Ill-Defined Conditions	92	12.56 (10.13–15.41)*	44	4.69 (3.41–6.3)*	7	2.24 (0.9–4.61)	2	2.44 (0.3–8.82)	145	7.02 (5.93–8.27)*
Accidents and Adverse Effects	116	4.44 (3.66–5.32)*	118	3.45 (2.85–4.13)*	32	2.79 (1.91–3.94)*	3	1.03 (0.21–3)	269	3.60 (3.18–4.05)*
Suicide and Self-Inflicted Injury	16	1.95 (1.12–3.17)*	23	2.12 (1.35–3.19)*	5	1.39 (0.45–3.25)	0	0 (0–4.41)	44	1.88 (1.36–2.52)*
Homicide and Legal Intervention	8	4.53 (1.96–8.92)*	1	0.47 (0.01–2.6)	1	1.58 (0.04–8.79)	1	7.56 (0.19–42.1)	11	2.35 (1.18–4.21)*
Other Cause of Death	1,255	12.47 (11.79–13.17)*	700	5.27 (4.89–5.67)*	136	2.92 (2.45–3.45)*	31	2.34 (1.59–3.33)*	2,122	7.23 (6.93–7.55)*
SMR, standardized mortality ratio. *P < 0.05.										

Infectious and parasitic diseases (including HIV) was the commonest cause of non-cancer mortality in various patients' subgroups such as patients less than 50 years old, females, Blacks, other races, patients with distant tumor stage, patients with grade II or IV tumor, and patients who underwent chemotherapy, radiotherapy or surgery. However, the difference between it and chronic liver disease and cirrhosis was generally small. (See supplementary tables 1 to 13).

Causes of Death Within 1 to 5 Years After HCC Diagnosis

A total of 14,780 patients died during this period, of whom, 10,036 died from HCC, and 1,118 died from other cancers. During this interval, the first non-cancer mortality cause was infectious and parasitic diseases (including HIV), accounting for 967 deaths with significant mortality risk in HCC patients compared with the general population (SMR = 78.83, 95% CI: 73.94–83.96). Other significant non-cancer causes of death included chronic liver disease and cirrhosis (809 patients, SMR = 49.40, 95% CI: 46.05–52.92), heart diseases (407 patients, SMR = 1.60, 95% CI: 1.45–1.77), accidents and adverse effects (118 patients, SMR = 3.45, 95% CI: 2.85–4.13), and cerebrovascular diseases (112 patients, SMR = 2.14, 95% CI: 1.76–2.57). There was no reported death from syphilis, complications of pregnancy, labor, or puerperium, or from conditions related to the perinatal period (See Table 2).

The leading cause of non-cancer mortality in most patients' subgroups was also infectious and parasitic diseases (including HIV). However, in patients with distant disease stage, and in patients with grade I or III at diagnosis, chronic liver disease and cirrhosis was the first cause of non-cancer mortality (See supplementary tables 1 to 13).

Causes of Death Within 5 to 10 Years After HCC Diagnosis

A total of 1,755 patients died during this period, of whom, 882 died from HCC, and 200 died from other cancers. During this period, the first cause of non-cancer mortality was infectious and parasitic diseases (including HIV), that had a high risk of mortality in HCC patients than the US general population (137 deaths, SMR = 34.89, 95% CI: 29.29–41.24), followed by heart diseases (114 deaths, SMR = 1.37, 95% CI: 1.13–1.64), and chronic liver disease and cirrhosis (80 deaths, SMR = 14.50, 95% CI: 11.5–18.05). There was no reported death from syphilis, tuberculosis, congenital anomalies, complications of pregnancy, labor, or puerperium, or from conditions related to the perinatal period (See Table 2).

Infectious and parasitic diseases was the leading cause of non-cancer mortality in different patients' demographic and pathological subgroups. But in patients with grade I or II tumor at diagnosis, heart diseases was the leading cause of non-cancer mortality (See supplementary tables 1 to 13).

Causes of Death after more than 10 Years Following HCC Diagnosis

A total of 261 patients died during this period, of whom, 70 died from HCC, and 44 died from other cancers. During this period, the first cause of non-cancer mortality was heart diseases, but its mortality risk in HCC patients was similar to that in the general population (21 deaths, SMR = 0.96, 95% CI: 0.59–1.46). Other common causes of death included other infectious and parasitic diseases including HIV (20 patients, SMR = 21.46, 95% CI: 13.11–33.15), and chronic liver disease and cirrhosis (16 patients, SMR = 12.12, 95% CI: 6.93–19.67). There was no reported death from syphilis, tuberculosis, suicide and self-inflicted injury, stomach and duodenal ulcers, non-invasive neoplasm, aortic aneurysm and dissection, atherosclerosis, complications of pregnancy or puerperium, and congenital anomalies (See Table 2). The category "other cause of death" was accounted for more deaths than heart diseases with high SMR (31 patients, SMR = 2.34, 95% CI: 1.59–3.33), but the causes of death included in this category was not defined by the SEER database.

Heart diseases was the leading cause of non-cancer death in most patients' subgroups. But infectious and parasitic diseases (including HIV) was the leading cause of non-cancer mortality in many subgroups, including patients with localized tumor or with grade III tumor at diagnosis and patients treated with chemotherapy or surgery. Chronic liver disease and cirrhosis was the leading cause of non-cancer mortality in patients < 50 years at diagnosis, and in females. In blacks, it was cerebrovascular diseases. In other races, both infectious and parasitic diseases (including HIV) and chronic liver disease and cirrhosis were the leading causes of non-cancer mortality.

Discussion

The results show that cancers are the main death cause in HCC patients, and that the highest mortality rates occurred during the first year after diagnosis and declined over the next intervals until reaching the lowest rate after 10 years of diagnosis. The commonest non-cancer cause of death was not the same in all the different intervals, but these intervals had similar top causes including infectious and parasitic diseases (including HIV), chronic liver disease and cirrhosis, and heart diseases.

Cancers remained the general leading cause of death over time. This is contrary to what happened in patients with endometrial cancer, when death from cancer decreased by time, and the death from heart diseases increased (23). Heart diseases have been reported as one of the leading non-cancer causes of death for several cancer patients, such as breast cancer (24) and endometrial cancer patients, and sometimes it even exceeded death from cancer (23, 25).

The high death rates from chronic liver disease and infectious diseases including HIV in HCC patients (exceeding the death rate from heart diseases) may be due to cirrhosis and certain infections that attributed to the HCC development. In the stage of liver cirrhosis, liver architecture is irreversibly impaired, and the condition is challenging to manage or to avoid complications. Death may occur due to complications of cirrhosis, such as liver cell failure or HCC (26). HCC is the leading death cause in patients with cirrhosis (27). Kanwal et al. and Ioannou et al. have observed that 1–8% of patients with cirrhosis develop HCC annually (28, 29). Bilimoria et al. suggested two explanations for the adverse effect of existing fibrosis on survival after 5 years of HCC resection. One of them is that the patients with advanced fibrosis or cirrhosis are more probable to have recurrence of the primary HCC, and consequently the disease causes their death. The other explanation is that the fibrosis and cirrhosis may symbolize a field of cancerization which is associated with the development of a novel metachronous HCC after resection (30).

In hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, the affected cells are damaged, thus releasing oxidative molecules. The increased oxidative stress and the sustained stimulation of the immune system causes inflammation and fibrosis. The disease then advances to cirrhosis with subsequent potential to develop HCC. Cirrhosis raises the risk of HCC even after the successful treatment of the cause that initiated liver disease, because cirrhosis is a premalignant state (26). Pinato et al. concluded that HIV seropositivity was associated with reduced survival in HCC patients, regardless of the stage, the anticancer and the antiretroviral treatment, and the geographical origin (31). Several studies have discussed or investigated the association between parasitic infections and cancers (32–35). Toda et al. have concluded that it was still unclear if the sole schistosoma mansoni infection had carcinogenic potential. However, schistosoma mansoni, in a co-infection with HBV and HCV, can contribute to the liver injury.

In the present study, several deaths fell in the category of "other causes", this shall encourage more efforts to investigate such causes to form better understanding of them, which will result in better targeted management.

Strengths And Limitations

This study relies on the data registered in the SEER database. These data are more generalizable due to their high-quality and accuracy. Also, we included a large sample of HCC patients, and we investigated several cancer and non-cancer causes of death. However, limitations of this study include the retrospective design and the missing of some variables – e.g. genetic and environmental factors – that may have affected the mortality rates. Also, some mortality causes maybe underreported due to missing the diagnosis.

Conclusion

The primary cause of death in HCC patients remains HCC itself over all time intervals after diagnosis. The mortality rates are higher within the first year after the HCC diagnosis. Non-cancer mortality causes are mainly infectious and parasitic diseases (including HIV), chronic liver disease and cirrhosis, and heart diseases. More research is needed to investigate the other causes of death which represented a major cause of non-cancer death.

Abbreviations

HCC, Hepatocellular Carcinoma; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SEER, Surveillance, Epidemiology, and End Results; SMRs, Standardized Mortality Ratios; CIs, Confidence Intervals; US, United states; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; HIV, Human Retrovirus.

Declarations

Ethics approval and consent to participate

The de-identified data that do not contain any personally identifiable information from any sources including the public cBioPortal for Cancer Genomics are not required for approval of the Institutional Review Board (IRB), and the informed consent is not applicable.

Consent for publication

Not applicable for individual patient data. This is a pooled analysis

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the SEER database, [<https://seer.cancer.gov/>].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

[PHK, SSD: Idea conception, study design, data extraction, manuscript drafting; TSB, SJJ : data extraction, analysis; TZ,HUR : data extraction, manuscript drafting, writing; TZ: manuscript drafting, writing, supervision]. All authors reviewed the manuscript and approved it for publication.

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