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Retrospective Study**Risk of cardiovascular death in patients with hepatocellular carcinoma based on the Fine-Gray model**

Zhang YL *et al.* CVD death risk in HCC patients

Abstract**BACKGROUND**

Hepatocellular carcinoma (HCC) is one of the most common types of cancers worldwide, ranking fifth among men and seventh among women, resulting in more than 7 million deaths annually. With the development of medical technology, the 5-year survival rate of HCC patients can be increased to 70%. However, HCC patients are often at increased risk of cardiovascular disease (CVD) death due to exposure to potentially cardiotoxic treatments compared with non-HCC patients. Moreover, CVD and cancer have become major disease burdens worldwide. Thus, further research is needed to lessen the risk of CVD death in HCC patient survivors.

AIM

To determine the independent risk factors for CVD death in HCC patients and predict cardiovascular mortality (CVM) in HCC patients.

METHODS

This study was conducted on the basis of the Surveillance, Epidemiology, and End Results (SEER) database and included HCC patients with a diagnosis period from 2010 to 2015. The independent risk factors were identified using the Fine-Gray model. A

nomograph was constructed to predict the CVM in HCC patients. The nomograph performance was measured using Harrell's concordance index (C-index), calibration curve, receiver operating characteristic (ROC) curve, and area under the ROC curve (AUC) value. Moreover, the net benefit was estimated *via* decision curve analysis (DCA).

RESULTS

The study included 21,545 HCC patients, of whom 619 died of CVD. Age (<60) [1.981 (1.573-2.496), $P < 0.001$], marital status(married) [unmarried: 1.370 (1.076-1.745), $P = 0.011$], alpha fetoprotein(AFP)(normal) [0.778 (0.640-0.946), $P = 0.012$], tumor size (≤ 2 cm) [(2, 5] cm: 1.420 (1.060-1.903), $P = 0.019$; >5 cm: 2.090 (1.543-2.830), $P < 0.001$], surgery (no) [0.376 (0.297-0.476), $P < 0.001$], and chemotherapy(none/unknown) [0.578 (0.472-0.709), $P < 0.001$] were independent risk factors for CVD death in HCC patients. The discrimination and calibration of the nomograph were better. The C-index values for the training and validation sets were 0.736 and 0.665, respectively. The AUC values of the ROC curves at 2, 4 , and 6 years were 0.702, 0.725, 0.740 in the training set and 0.697, 0.710, 0.744 in the validation set, respectively. The calibration curves showed that the predicted probabilities of the CVM prediction model in the training set *vs* the validation set were largely consistent with the actual probabilities. DCA demonstrated that the prediction model has a high net benefit.

CONCLUSION

Risk factors for CVD death in HCC patients were investigated for the first time. The nomograph served as an important reference tool for relevant clinical management decisions.

Key Words: HCC; CVD deaths; Fine-Gray model; Risk factor; Nomograph; Predict

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Core Tip: Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. Studies have shown that HCC patients have chance to improve 5-year survival rate to 70%. How to avoid cardiovascular disease(CVD) death in HCC patients has become a problem worth exploring due to the course of treatment and the manifestation of certain paraneoplastic syndromes. In this study, we used Fine-Gray model to identify the independent risk factors for CVD death in HCC patients and constructed a predictive nomograph with high performance.

INTRODUCTION

HCC is one of the most common cancers worldwide, ranking fifth among men and seventh among women, resulting in more than 7 million deaths annually^{1, 2}. CVD, which includes heart disease and stroke, is the most prevalent noncommunicable disease(NCD)³. CVD is also the major cause of morbidity and mortality around the world, representing approximately one-third of all deaths⁴. As the report goes, CVD and cancer are the major causes of death around the world, while being a major burden of disease in the world³.

In the last decade, CVD has been recognized as one of the most frequent advanced comorbidities of cancer treatment⁵. Advances in therapeutic approaches, especially the advent of immunotherapies, have revolutionized cancer treatment, allowing the lifespan of cancer patients to be extended, but at the same time leading to millions of cancer survivors currently at risk of developing CVD⁶⁻⁸. In recent years, studies have found that the 5-year survival rate for HCC patients can increase to 70%, if an early diagnosis or some potential treatment is received⁹. Cancer patients are at an elevated risk of CVD death from exposure to potentially cardiotoxic therapies compared with noncancer persons¹⁰. Furthermore, in addition to cardiotoxicity from treatment, HCC

patients often exhibit various paraneoplastic syndromes, including hypercholesterolemia, thrombocytosis, and hypercalcemia^{11, 12}. All of this may lead to an increased risk of cardiovascular death in HCC patients¹³⁻¹⁵. All of this may lead to an increased risk of cardiovascular death in HCC patients¹³⁻¹⁵. Therefore, how to prevent death from CVD in cancer survivors is a question worth exploring. Although several studies have addressed this field, they mainly focused on breast, colorectal, prostate, and other cancers¹⁶⁻¹⁸, and studies focusing on CVD outcomes in HCC patients have not been reported.

Traditional survival analyses typically focus on only one outcome event, and ignoring observational endpoints in medical research is often not unique. This omission of observations for other endpoints is prone to bias and, in turn, produces an overestimation of the model's predictive ability¹⁹. Competing risks refer to events whose occurrence excludes the incidence of the major event of interest, and NCD deaths are a competing risk if the major event of interest is CVD death²⁰. This study chose to construct a prediction model *via* the Fine-Gray model with the aim of separating competing events from the outcome event of interest, eliminating the effect of competing events on the study.

¹ The Surveillance, Epidemiology, and End Results (SEER) database is a publically accessible, federally funded cancer reporting system that represents the collaboration between the Centers for Disease Control and Prevention, the National Cancer Institute, and regional and state cancer registries and serves as the authoritative cancer statistics database in the United States²¹. The SEER database contains data extracted from 18 different geographic populations, representing rural, urban, and regional populations²². ⁹ The aim of this study was to investigate the independent influencing factors of CVD death in HCC patients and to construct a predictive model by analyzing HCC patients (age ≥ 18 years) diagnosed between 2010 and 2015 in the SEER database to assess the probability of CVD death in HCC patients while effectively avoiding death due to CVD, improving prognosis, and improving the quality of life of HCC patients.

MATERIALS AND METHODS

Data sources and population selection

HCC patient information was extracted from the SEER database *via* SEER*stat 8.4.0.1 with the liver site code C22.0, excluding Fibrolamellar histology (8171/3)²³. The inclusion criteria were as follows: (1) patients aged 18 years or older and pathologically diagnosed with HCC; (2) Diagnosed between 2010 and 2015; and (3) Complete follow-up data. The patient information collected includes age, sex, race, marital status, year of diagnosis, pretreatment alpha fetoprotein(AFP) level, AJCC stage group, T stage, N stage, M stage, surgery, radiotherapy, and chemotherapy status, survival time, and cause of death. This study used the 7th edition of the AJCC staging. Data on patients with any of the abovementioned missing information were excluded.

Outcome Assessment

Death due to CVD was the primary observational endpoint. According to the SEER database, causes of death due to CVD include hypertension without heart disease, heart diseases, cerebrovascular diseases, aortic aneurysm and dissection, atherosclerosis, and other diseases of arteries, arterioles, and capillaries. Death from other causes was considered a competing event, and survival at the end of the study was considered a censored event.

Statistical analysis

In this study, categorical information was statistically described by number and percentage. The R software was used to divide all the study subjects into two parts in a ratio of 7:3, which were the training set and the validation set. The balance test between the two sets was performance using χ^2 test. In the training test, the Fine-Gray model was used for univariate and multivariate analyses. Multivariate analysis of statistically significant indicators in univariate analysis to explore risk factors for CVD death in HCC patients, which was measured as the adjusted hazard ratio (HR) and 95% confidence interval(CI), and a nomograph was established to predict the AUC and the

probability of survival at 2, 4, and 6 years in HCC patients. Harrell's concordance C-index was calculated using bootstrap resampling(1,000 replications) to measure the discriminatory ability of the nomograph. Consistency was gauged by calibration curves, while the predictive effect of the model was verified using the ROC curve and AUC^{24, 25}. In addition, the net clinical benefit of the nomograph was estimated *via* DCA.

All statistical analyses for this study were conducted using SPSS 25.0 and the R software (version 4.2.2). The packages used included survival, caret, risk, regression, foreign, state, pROC, ggDCA, and pe. Furthermore, all tests were bilateral, and statistical significance was set at a P value of <0.05.

RESULTS

Patient Selections and Baseline Characteristics

In this study, 40,401 HCC patients from the SEER database were included. Moreover, 45 patients under the age of 18; 39 patients with a T stage of T0; 5,306 patients with missing or zero survival time; and 8,966 patients with missing clinical data were excluded. Finally, 21,545 HCC patients were included in the statistical analysis. Table 1 shows the detailed characteristics of the case arm, where DSW represents divorce, separation, or widowhood.

Balance test between the training and validation sets

As shown in Table 2, no significant differences in basic characteristics were observed between the HCC patients in the training and validation sets ($P > 0.05$). The results revealed that the distributions of each feature of the HCC patients in the training and validation sets were the same and the resulting nomogram prediction model in the training set could be validated in the validation set.

Univariate analysis of CVD-related death in HCC patients

As shown in Table 3, the HCC patients in the entire cohort were randomly assigned to the training set ($N_1 = 15,081$) vs the validation set ($N_2 = 6,464$) in a 7:3 ratio. The

univariate analysis of the training set data revealed that age (HR, 2.054; 95%CI, 1.637–2.576), race (other [HR, 0.653; 95%CI, 0.493–0.864]), marital status (unmarried [HR, 1.322; 95%CI, 1.042–1.678]; DSW [HR, 1.377; 95%CI, 1.099–1.726]), AFP (HR, 0.786; 95%CI, 0.647–0.954), AJCC stage group (Grad II [HR, 0.775; 95%CI, 0.611–0.982]), tumor size ((2, 5] cm [HR, 1.361; 95%CI, 1.018–1.821]; >5 cm [HR, 2.254; 95%CI, 1.667–3.048]), T stage (T2 [HR, 0.761; 95%CI, 0.602–0.960]; T4 [HR, 1.806; 95%CI, 1.033–3.159]), surgery (HR, 0.447; 95%CI, 0.359–0.557), and chemotherapy (HR, 0.770; 95%CI, 0.637–0.931) were risk factors of CVD death in HCC patients.

Multifactorial analysis of CVD-related death in HCC patients

As shown in **Figure 1**, the variables that were statistically significant in the univariate analysis were included in the multivariate analysis. After adjustment of the model, the following independent risk factors for CVD death in HCC patients were finally obtained, including age (HR, 1.981; 95%CI, 1.573–2.496), marital status (unmarried [HR, 1.370; 95%CI, 1.076–1.745]; DSW [HR, 1.240; 95%CI, 0.988–1.556]), AFP (HR, 0.778; 95%CI, 0.640–0.946), tumor size ((2, 5] cm [HR, 1.420; 95%CI, 1.060–1.903]; >5 cm [HR, 2.090; 95%CI, 1.543–2.830]), surgery (HR, 0.376; 95%CI, 0.297–0.476), and chemotherapy (HR, 0.578; 95%CI, 0.472–0.709).

Construction of the predictive model

Based on the results of the multifactorial analysis, the six variables of age, marital status, AFP, tumor size, surgery, and chemotherapy were incorporated into the prediction model of CVD death in HCC patients, and a nomograph was constructed to predict the probability of CVD death at 2, 4, and 6 years in HCC patients by summing the factor scores according to the individual condition of the patients (**Figure 2**).

Validation of the prediction model

This study used the data from both the training and validation sets to estimate the constructed nomogram model in terms of discrimination and calibration. The

evaluation of the degree of discrimination was performed using the C-index obtained from bootstrap resampling, plotting the ROC curve, and calculating the AUC value. The C-index values were 0.736 and 0.665 in the training and development sets, respectively. **Figure 3** shows the ROC curves of the nomogram model to predict the 2-, 4-, and 6-year CVMs in HCC patients, with AUC values of 0.702, 0.725, and 0.740 in the training set and 0.697, 0.710, and 0.744 in the validation set. The AUC values were generally greater than 0.7, which indicated that the discrimination of the nomogram model was good. The calibration was evaluated by plotting the calibration curves of the training and development sets. If the predicted probability is close to the actual probability, the fitted line after the predicted probability that corresponds to the actual probability will be close to the reference line or overlap with the reference line. As shown in **Figure 4**, the predicted probabilities of CVMs at 2, 4, and 6 years were highly consistent with the actual probabilities, suggesting that the calibration of this nomogram model was good. Finally, in order to determine whether the nomogram prediction model was clinically useful, the net benefit of the model was evaluated using the DCA. As shown in **Figure 5**, in all plots, the nomogram showed a high net benefit.

DISCUSSION

Currently, CVD and cancer are the primary causes of premature death in 127 countries²⁶. Research has shown that the risk of CVD among cancer survivors is associated with common lifestyles or the toxicity of cancer treatment²⁷. For cancer patients, increasingly refined treatment options have greatly extended their survival. Therefore, cardiovascular care for cancer survivors should be emphasized to meet their clinical needs and improve their quality of life. This study is based on the SEER database and used the data of HCC patients with a diagnosis period from 2010 to 2015, which has a high clinical application value.

The factors associated with the CVD outcomes in HCC patients included age, marital status, pretreatment AFP level, tumor size, surgical status, and chemotherapy status. Consistent with the majority of most studies, we observed that the risk of CVD

death in HCC patients increased with age^{6, 28, 29}. The American College of Cardiology (ACC/AHA) revealed that advancing age can seriously affect its estimated 10-year CVD event risk²⁹. This may be associated with poorer physical fitness and longer acting time of lifestyle risk factors in elderly patients³⁰. Moreover, the present study revealed that unmarried people have a significantly increased risk of CVD death compared with married people, which is consistent with previous research results³¹⁻³³. It was revealed that marriage can have a beneficial effect on health by providing social support³⁴⁻³⁶. The higher risk for unmarried individuals compared with married individuals may be due to a combination of lifestyle, body hormones, and stress. Numerous studies have also revealed that unmarried individuals have higher levels of loneliness, lower life satisfaction, and higher mortality from physical illness³⁷. Moreover, it is currently well documented that all different unmarried states are associated with an elevated risk of mortality³⁸. The findings of the present study revealed that the HCC patients with pretreatment AFP levels above normal had a reduced risk of CVD death. This may be due to the combined effects of interventions taken earlier when AFP positivity is present and the participants' spontaneous health behavior changes that are effective in protecting their cardiovascular health, which in turn reaches the death-lowering effect of CVD. Studies assessing the link between AFP and CVD are limited, but an inverse association between AFP and CVD prevalence was proven in the study by Bracun V *et al*³⁹, which is consistent with the results of the present study. Therefore, when the AFP levels are at normal levels in HCC patients, the importance of cardiovascular system care should be increased to avoid the occurrence of CVD death in HCC patients as much as possible. When categorizing tumor size, the risk of CVD death in HCC patients increases as tumor size increases. Recent studies have shown an inverse association between tumor size and CVD death^{40, 41}. The findings of this analysis suggest that HCC patients undergoing surgery have a significantly lower risk of CVD death. This finding is in agreement with those of previous studies^{5, 17, 42}. It is worth noting that chemotherapy usually increases the risk of CVD because of the cardiotoxicity associated with this treatment modality⁴³. Transcatheter arterial chemoembolization (TACE) is the

most common first-line treatment, while doxorubicin (DOX) is the most frequently used chemotherapy drug⁴⁴. Moreover, the clinical efficacy of DOX is often limited by its cardiotoxicity, nephrotoxicity and hepatotoxicity⁴⁵. Although TACE can improve the safety of the drug and minimize the incidence of adverse events, it can only reduce the toxicity of the drug, but not completely eliminate it. However, the results showed a lower risk of CVD death in HCC patients treated with chemotherapy, which is inconsistent with the cardiotoxic effects of chemotherapy. The reason for this result needs to be further investigated because of the lack of chemotherapy drug-related information in the SEER database. Several studies have suggested that this situation may result from the shorter survival time of this group of people who receive chemotherapy because of CVD death⁵. In the supplemental analysis, we discussed the proportion of patients who received both chemotherapy and radiotherapy. We found that the higher the grade, the higher the proportion of patients receiving both radiotherapy and chemotherapy. Therefore, it should be considered that patients at higher grades who receive potentially cardiotoxic treatment are also more likely to die earlier due to their underlying HCC disease before they might develop a heart-specific disease in the long term⁴⁶. Another reason could be that differences in baseline conditions between the patients who receive chemotherapy and those who do not were observed, such as younger age at diagnosis, higher grading, and no CVD⁴⁶. Although the drugs that block the vascular endothelial growth factor signaling pathway (VSP) have been shown to expand the treatment options for HCC, the use of such drugs also contributes to the increased risk of CVD death in HCC patients⁴⁷. However, the limitations of the data prohibit further discussion.

Most previous studies on the relationship between cancer and CVD death have used traditional survival analysis methods, such as Cox proportional-hazards regression models. The model does not well distinguish between the effects of competing events and often overestimates the risk of outcome events. In this study, we used the Fine-Gray model to exploit the independent hazard factors for CVD death in HCC patients and to construct a related predictive model. Based on the literature, the present study is

the first to investigate the relationship between HCC and CVD death. The prediction model has high C-index and AUC values and high discrimination, and all variables are easily accessible, which provides convenience for clinical management. Based on the calibration curve, the model simultaneously has a high calibration level. Meanwhile, the DCA showed that the model can bring higher net benefits. The high degree of discrimination, calibration, and net benefit provided a solid foundation for the application of this prediction model.

The strengths of this study are as follows: (1) adequate sample size, (2) less missing information, and (3) its emphasis on the association between HCC and CVD. However, this study has several limitations. First, this study has a retrospective design, which will inevitably produce bias. Second, the database does not include baseline information (e.g., BMI, diabetes, and hypertension) or other factors associated with CVD. Third, the absence of information on chemotherapy regimens and therapeutic drugs in the SEER database prevented further investigation of the relationship between chemotherapy and CVD death. Finally, more external data are needed to validate the predictive power of the model.

CONCLUSION

Overall, this is the first study to investigate the independent risk factors for CVD death in HCC patients using data from the SEER database and construct a relevant prediction model. With high discrimination, calibration, and net benefit, the model effectively assessed CVMs in HCC patients and was able to serve as an important reference tool for relevant clinical management decisions in HCC patients. However, based on the lack of external data validation, the model remains to be further verified by further research.

3

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma(HCC) is one of the most common tumors today. It is known that patients with HCC will have a higher risk of cardiovascular disease(CVD) death compared to non-HCC patients.

Research motivation

CVD is recognized as one of the most common complications of cancer treatment. As medical technology continues to mature, studies have found that the 5-year survival rate for HCC patients can be increased to 70% with early diagnosis and some potential treatments. Just because there are some unique treatment modalities (e.g. Transcatheter arterial chemoembolization(TACE)) for HCC patients that have some limitations on the potential cardiotoxicity of drugs, it does not mean that we can ignore the potential cardiovascular burden of HCC patients.

Research objectives

The aim of this study was to identify the independent risk factors for CVD death in HCC patients, and to further provide a reference tool for the relevant clinical management decisions of HCC patients by constructing a prediction model for CVD death in HCC patients.

Research methods

In this study, data related to adult hepatocellular carcinoma patients with diagnosis years 2010-2015 in the Surveillance, Epidemiology, and End Results(SEER) database were collected. In order to better eliminate the influence of competing events on the study, we utilized the Fine-Gray model to carry out the analysis and constructed a predictive model.

Research results

The study included 21,545 patients with HCC, of whom 619 died of CVD. Age, marital status, alpha fetoprotein(AFP), tumor size, surgery, and chemotherapy were

independent risk factors for CVD death in HCC patients. The discrimination as well as the calibration of the nomograph was better. Decision curve analysis(DCA) demonstrated that the prediction model has a high net benefit.

Research conclusions

This study focuses on the cardiovascular risk of HCC patients for the first time. Meanwhile, the independent risk factors for CVD deaths in HCC patients were explored for the first time based on the Fine-Gray model, and a prediction model was constructed, which will serve as a reminder for future clinical work.

Research perspectives

Focusing on the burden of CVD in HCC patients and further exploring the impact of different drugs and routes of administration on CVD death in HCC patients.

ACKNOWLEDGEMENTS

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The data of this study are obtained from the SEER database. The patient's data are public and anonymous. The statements contained herein are solely those of the authors.

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