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Retrospective Study

Conditional survival probability of distant-metastatic hepatocellular carcinoma: A population-based study

Yang YP *et al*. CS of distant-metastatic HCC

Abstract

BACKGROUND

The prognosis of many patients with distant metastatic hepatocellular carcinoma (HCC) improved after they survived for several months. Compared with traditional survival analysis, conditional survival (CS) which takes into account changes in survival risk could be used to describe dynamic survival probabilities.

AIM

To evaluate CS of distant metastatic HCC patients.

METHODS

Patients diagnosed with distant metastatic HCC between 2010 and 2015 were extracted from the Surveillance, Epidemiology and End Results database. Univariate and multivariate Cox regression analysis were used to identify risk factors for overall survival (OS), while competing risk model was used to identify risk factors for cancer specific survival (CSS). Six-month CS was used to calculate the probability of survival for an additional 6 mo at a specific time after initial diagnosis, and standardized difference (d) was used to evaluate the survival differences between subgroups. Nomograms were constructed to predict CS.

RESULTS

Positive alpha-fetoprotein expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis were independent risk factors for actual OS and CSS through univariate and multivariate analysis. Actual survival rates decreased over time, while CS rates gradually increased. As for the 6-mo CS, the survival difference caused by chemotherapy and radiotherapy gradually disappeared over time, and the survival difference caused by lung metastasis reversed. Moreover, the influence of age and gender on survival gradually appeared. Nomograms were fitted for patients who have lived for 2-, 4-, and 6-mo to predict 6-mo

conditional OS and CSS, respectively. The area under the curve (AUC) of nomograms for conditional OS decreased as time passed, and the AUC for conditional CSS gradually increased.

CONCLUSION

CS for distant metastatic HCC patients substantially increased over time. With dynamic risk factors, nomograms constructed at a specific time could predict more accurate survival rates.

Key Words: Conditional survival; Hepatocellular carcinoma; Distant metastasis; Prognosis; Nomogram

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Core Tip: Distant metastatic hepatocellular carcinoma (HCC) patients demonstrate high hazard ratios for death in the first few months, which made survival estimates at the time of initial diagnosis becoming inaccurate. Conditional survival (CS) which takes into account changes in survival risk could be used to describe dynamic survival probabilities. We conducted a population-based study to assess CS for distant metastatic HCC patients. Compared with actual survival rate for HCC patients which gradually decreased after initial diagnosis, CS rate substantially increased over time. With dynamic risk factors, nomograms were constructed to predict more accurate CS at different time after initial diagnosis.

INTRODUCTION

Primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906000 new cases and

830000 deaths[1]. Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer accounting for 75%-85% of the cases. HCC represents a growing health threat with annual mortality rates increasing by approximately 2%-3% per year from 2003 to 2012 and a 43% increase in the rate of death from 2000 to 2016 in the United States[2,3]. Due to high metastatic potential, 14.0%-36.7% of HCC patients already have extrahepatic metastasis at the time of initial diagnosis, and the incidence of distant metastases in patients with HCC was about 13.5%[4-7]. The prognosis in HCC patients with extrahepatic metastasis was much poorer than the prognosis of early-stage patients. Over the past three decades, the outcome of patients with advanced HCC has substantially improved due to better selection of appropriate treatments and advances in effective treatments[8-10]. For example, small molecule targeted drug of sorafenib had been shown to extend life expectancy by nearly 3 mo[11,12]. But as been reported, extrahepatic metastatic HCC patients still bear poor survival with a median expected survival time of only 6-8 mo or a 25% survival rate at one year[13].

With high mortality rate and poor prognosis, distant metastatic HCC patients would demonstrate high hazard ratios for death in the first few months, which made survival estimates at the time of initial diagnosis becoming inaccurate. Conditional survival (CS) which is a concept that takes into account changes in survival risk could be used to describe dynamic survival probabilities[14]. Previous studies have reported CS of breast cancer, glioma, lung cancer, colorectal cancer and other cancers[15-19]. CS studies of HCC patients have also been published, but these studies didn't categorize the patients according to clinical stage[20-22]. As distant metastatic HCC patients have much poorer survival than those in early stage, the CS estimates would also be much different. Therefore, a study of dynamic CS analysis in patients with distant metastatic HCC is meaningful.

In this study, We calculated the dynamic survival probability for patients with distant metastatic HCC using data from the Surveillance, Epidemiology and End Results (SEER) database. Moreover, nomograms were constructed to predict CS of distant metastatic HCC patients at different time after initial diagnosis.

MATERIALS AND METHODS

Data collection

Data of primary diagnosed HCC patients from 2010 to 2015 were retrieved from the SEER database Program 17 registries (https://seer.cancer.gov/). Data were included following these criteria: (1) Patients aged over 18; (2) Patients were pathologically diagnosed with stage IVB HCC; (3) HCC was the only primary cancer; and (4) Complete follow-up and survival data. Patients were excluded if the diagnosis were made only at autopsy. Those patients with incomplete American Joint Committee on Cancer (AJCC) staging, alpha-fetoprotein (AFP) expression information, and unknown death reason were all excluded. Marital status included married (married and having domestic partner), single (never married), and separated (separated, divorced, and widowed). And the tumor size mentioned in this study referred to the tumor size of the primary tumor. Surgery referred to surgery of the primary site.

Statistical analysis

In this study, overall survival (OS) was defined as the time from the start of randomized treatment to death due to any reason, and cancer specific survival (CSS) was defined as the time from the start of randomized treatment to death due to a specific disease. Univariate and multivariate Cox regression model were built to evaluate associations between features and OS, while Fine-Gray competing risk regression model was used to assess associations between features and CSS. Survival analysis was performed using the Kaplan-Meier method. Cumulative incidence function curves were used to describe difference of mortality probability in subgroups.

CS analysis was applied to assess the possibility of additional survival for patients who have survived for specific months. Here, an additional 6-mo survival (CS6) was calculated as: CS6 = S(x + 6)/S(x), which means CS6 among patients who have survived 2 mo from the date of diagnosis was calculated by dividing the survival at 8 mo by the survival at 2 mo. Based on variables selected by the multivariate Cox regression model

and the competing risk model, nomograms for OS and CSS were fitted to estimate the CS6 of distant metastatic HCC patients, respectively. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to evaluate the performance of these nomograms.

Differences of CS among subgroups were calculated using the standardized differences (d) method, with $d = (P2 - P1)/\sqrt{[P\,(1 - P)]}$ [23]. The value of standardized differences can be divided into four conditions: $|d| < 0.1$ shows no difference in each group; $0.1 \leq |d| < 0.3$ shows a small difference; $0.3 \leq |d| < 0.5$ shows a moderate difference; and $|d| \geq 0.5$ shows a significant difference. A significance level of $P < 0.05$ was used in all analyses. The statistical analysis was conducted using R software (packages: survival, cmprsk, rms, and timeROC).

RESULTS

Clinicopathological characteristics

A total of 1502 patients were included in the study (Table 1). The median age of these patients was 61 years old (interquartile range: 56-68), 81.89% were male patients, and 65.11% of the patients were white. About half of the patients (49.40%) were married. Most patients were diagnosed with positive AFP (84.29%) and had a primary tumor size more than 5 cm (72.70%). As for TNM-staging, over 50% patients were diagnosed in the T3 stage (n = 783, 52.13%), and more the 60% patients were diagnosed without lymph nodes metastasis (N0, n = 1031, 68.64%). Consistent with previous study, lung metastasis (n = 553, 36.82%) was more frequent than other distant metastasis sites included bone (n = 430, 28.63%) and brain (n = 27, 1.80%) metastasis. Over half of the patients received chemotherapy, while relatively few received primary-site surgery (n = 82, 5.46%) and radiotherapy (n = 302, 20.11%). The median survival time was only 4 (range, 1-117) mo, 1457 (97.00%) patients died during the follow-up time and 1379 (94.65%) of them died because of HCC.

Comparison of OS and CSS

The 2-, 6-, and 12-mo OS rates were 64.14%, 32.79%, and 17.48%, while the 2-, 6-, and 12-mo CSS rates were 65.89%, 34.77%, and 19.16%, respectively (Figure 1). From the results of univariate analysis: Positive AFP expression, tumor size (> 5 cm), higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis were risk factors for OS, and these factors were also risk factors for CSS through the Gray's test (Supplementary Table 1; Supplementary Figures 1 and 2). Race was also identified to be associated with CSS through the Gray's test. For multivariate analysis, positive AFP expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, lung metastasis, and bone metastasis were independent risk indicators of OS, and they were also independent risk indicators of CSS through competing risk model (Table 2). Bone metastasis was only identified as a risk factor in multivariate analysis, which may be influenced by the factor of radiotherapy. And patients with bone metastasis who received radiotherapy had better survival rates and less cancer specific mortality rates before 22 mo compared with patients without bone metastasis and bone metastatic patients without radiotherapy (Supplementary Figure 3).

Comparison of actual and CS

Actual OS and CSS rates since initial diagnosis and their corresponding CS were presented in Supplementary Tables 2 and 3. Among patients surviving at 2, 4, and 6 mo after diagnosis, the probability of OS at 12 mo were 27.25%, 39.39%, and 53.31%, respectively. Among patients surviving at 2, 4, and 6 mo after diagnosis, the probability of CSS at 12 mo was 29.08%, 41.20%, and 55.11%, respectively. The actual survival and 6-mo CS are shown in Figures 2A and B. The actual survival rates decreased over time for OS and CSS, while the CS rates had gradually increased.

According to d of conditional OS, risk factors could be categorized into three groups (Table 3): (1) $|d| > 0.1$, which means risk factors remained to be significant over time [AFP expression (negative *vs* positive), tumor size (> 5 cm *vs* ≤ 5 cm), T stage (T3 *vs* T1, T4 *vs* T1), N stage (N1 *vs* N0), and primary-site surgery (Yes *vs* No)]; (2) $|d| > 0.1 \rightarrow$

|d| < 0.1, which means the influence caused by risk factors gradually decreased [race (other race *vs* black race), chemotherapy (Yes *vs* No/unknown), and radiotherapy (Yes *vs* No/unknown)]; and (3) d < -0.1 → d > 0.1, which means the difference in survival caused by risk factors reversed over time [lung metastasis (Yes *vs* No)]. As for conditional CSS, risk factors could be also divided into three group according to *d* value (Table 4): (1) |d| > 0.1, which means risk factors remained to be significant over time [AFP expression (negative *vs* positive), tumor size (> 5 cm *vs* ≤ 5 cm), T stage (T3 *vs* T1, T4 *vs* T1), N stage (N1 *vs* N0), and primary-site surgery (Yes *vs* No)]; (2) |d| > 0.1 → |d| < 0.1, which means the influence caused by risk factors gradually decreased [race (other race *vs* black race), chemotherapy (Yes *vs* No/unknown), and radiotherapy (Yes *vs* No/unknown)]; and (3) d < -0.1 → d > 0.1, which means the difference in survival caused by risk factors reversed over time [lung metastasis (Yes *vs* No)]. In addition, differences in conditional OS and CSS caused by age (55-65 *vs* < 55, ≥ 65 *vs* < 55) and gender (male *vs* female) gradually appeared over time (|d| < 0.1 → |d| > 0.1).

Nomograms for CS

Prognostic relevance of features varied at different time since the initial diagnosis. Based on multivariate Cox regression model at different time points, three nomograms for 6-mo conditional OS were fitted for patients who have lived for 2-, 4-, and 6-mo separately (Supplementary Table 4 and Figure 3). And the value of AUC for these nomograms gradually decreased over time: AUC was 0.679 for patients who have survived 2 mo (Figure 3A); AUC was 0.663 for patients who have survived 4 mo (Figure 3B); AUC was 0.655 for patients who have survived 6 mo (Figure 3C). The characteristics included in the nomogram changed with time, and AFP expression, tumor size, and primary-site surgery were prognostic indicators for all the three models.

Similarly, based on competing risk models at different time points, three nomograms for 6-mo conditional CSS were conducted for patients who have lived for 2-, 4-, and 6-mo separately (Supplementary Table 5 and Figure 4). The value of AUC of the ROC

curves gradually increased over time, and the AUCs for patients who have survived 2-, 4-, and 6-mo were 0.659, 0.663, and 0.664, separately (Figures 4A-C). AFP expression, tumor size, and primary-site surgery were still prognostic indicators which were included in all the models, while T stage was associated with 6-mo conditional CSS for patients who have lived for 2-, 4-mo.

DISCUSSION

As one of the leading causes of cancer-related death worldwide, HCC was usually diagnosed at late and advanced stages[24]. While previous studies have concentrated on predicting prognosis for HCC patients, only a few had focused on distant metastatic HCC patients. Former studies on prognosis of metastatic HCC have identified risk factors including older age, male gender, high T stage, low degree of tumor differentiation, N1 stage, non-primary site surgery, no chemoradiotherapy, larger tumor size, no radiotherapy, and multi-organ metastasis, while high T stage, N1 stage, non-primary site surgery, no chemotherapy, and no radiotherapy were also independent risk factors in our study[25,26].

What's more, attributing to the characteristics of poor prognosis and high mortality rate, the predicting model which was constructed at the time of initial diagnosis would be influenced by patients who died in the first few months. Actual survival didn't reflect how prognosis changed over time. Therefore, CS would provide patients with survival probabilities at a specific time since prognosis was adjusted for the time the patient had already survived[27]. There were several reports regarding CS of HCC, including a study which also used the data from SEER[22]. As reported in this study, the conditional OS improved from 8.4% to 44.1% for the AJCC stage IVB group during the first five years after initial diagnosis, and the conditional CSS improved from 12.1% to 66.7% in the AJCC stage IVB group. However, only 3.1% of distant metastatic HCC patients held a 5-year survival[28]. Thus, a 5-year CS could not reflect the survival situation for distant metastatic HCC patients and these patients should be separated from patients with early-stage HCC. Since one year survival rate was 17.48% for distant

metastatic HCC patients in this study, we adopted 6-mo CS analysis, which was more suitable.

Compared with actual survival which demonstrated a downward trend, conditional OS and CSS demonstrated upward trends over time. Survival rates for patients who had already lived for 6 mo to survive additional 6 mo were 53.31%, while 12-mo OS rate of the whole cohort was only 17.48% calculated at initial diagnosis. In subgroup analysis, risk factors of positive AFP expression, tumor size (> 5 cm), T stage (T3 and T4), N1 stage, and non-primary-site surgery held substantial and stable effect on CS, while survival differences among races, chemotherapy groups, radiotherapy groups decreased over time. Disparities in detection and treatment receipt were linked to survival difference among ethnic groups, but their impact diminished over time[29]. Chemotherapy and radiotherapy were considered to be protective factors for survival at initial diagnosis, and they may provide benefit in the first few months. But as time goes by, their influence would decrease gradually. This may be due to the difference in molecular pathology and resistance which appeared 10 mo following the initial diagnosis. Also, patients who had a poorer condition could not tolerate chemotherapy and radiotherapy at the initial diagnosis and would have a shorter survival time, so poor conditions may explain worse survival for some non-chemotherapy or non-radiotherapy patients. Lung metastasis held reversed effect on CS over time, which was an unfavorable indicator for survival at initial diagnosis and became a protective factor when patients survived for 12 mo. This may partly be because patients with the ability to live beyond 12 mo had better molecular pathological features and health status. The influence of age groups and genders on survival did not appear until 10 mo after initial diagnosis, older patients would have poorer prognosis because of poorer health status. The survival difference was not significant in the first few months for different age groups attributing to the high mortality, but it would become significant after 10 mo. Similarly, females have a higher CS rate than males, and sex disparities may be caused by factors including sex-related biologic factors, gender-related environmental and behavioral factors[30-34]. Patients with bone metastasis had better CS rate compared to

those without bone metastasis before first 12 mo, which may be because a lot of patients with bone metastasis received radiotherapy treatment[35]. The findings which followed the result that patients with bone metastasis received radiotherapy had a better OS and CSS in the first few months compared with patients without bone metastasis also recommended the effective treatment of radiotherapy on HCC patients with bone metastasis.

Nomogram is a useful tool combining tumor - related risk factors to estimate and predict the survival rate of different patients[36]. We constructed nomograms for 6-mo CS at 2, 4, and 6 mo after initial diagnosis separately. These nomograms may help to predict dynamic survival for distant metastatic HCC survivors with greater accuracy. As risk indicators for survival kept changing as time passed, the features fitted in nomograms also changed. AFP expression, tumor size, and primary-site surgery were included in all the nomograms, which were consistent with previous nomogram studies on HCC[37,38]. The value of AUC gradually decreased in nomograms for conditional OS, while the value of AUC showed a gradual and slight increase in models for conditional CSS. This may be explained by the fact that as time goes on, the increased death rate of other causes led to diminished effect of these clinicopathological factors on OS; but they kept their influence on CSS. These nomograms may help assess patients' survival rates at different times. It can be used to remind clinicians and family members that more continued surveillance and care should be given to patients with lower CS rates. Furthermore, if patients have survived for certain number of months, they have more opportunity to have a better prognosis, and the therapeutic goals and strategies can be more positive for them.

There were several limitations to our study. First, the research was a retrospective analysis with higher selection biases. Second, there was a lack of important features such as liver function, carcinoembryonic antigen, and vascular invasion that were not available in the SEER database, especially liver function, which was significant in the survival of HCC patients. Due to incomplete data, grade and fibrosis score were also not included in the analysis pipeline, which limits the ability of the nomogram to assess

relevant survival. Third, the SEER database provided disease information at initial diagnosis, and so the metastasis events occurred in the later survival time cannot be recorded. We used data on HCC patients who were diagnosed from 2010 to 2015; the treatment may have improved in the years since; for example, the occurrence of combo therapy, which includes immune therapy and molecular targeted therapy, limited the use of our CS nomograms on these patients. For example, as the first small oral molecular targeted medicine sorafenib successfully prolonged the OS of advancer HCC patients, and the novel programmed cell death 1 checkpoint inhibitor nivolumab could be used for patients who had disease progression or unacceptable adverse effects with sorafenib[39,40]. These are important factors which should be taken into consideration in the prediction model. Further, due to the time, we used the 7th edition of the AJCC staging system for HCC, as the most up-to-date AJCC staging system for these patients was inaccessible. The Barcelona Clinic Liver Cancer classifications for HCC was also not present in our study. Finally, although the constructed nomograms were internally validated, they also need external validation.

CONCLUSION

Positive AFP expression, higher T stage (T3 and T4), N1 stage, non-primary-site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis were independent risk factors for actual OS and CSS through univariate and multivariate analysis. Actual survival rates decreased over time, while CS rates gradually increased. With dynamic risk factors, nomograms constructed at different time would provide more accurate CS.

ARTICLE HIGHLIGHTS

Research background

Distant metastatic hepatocellular carcinoma (HCC) patients have poor survival rates, while some of them who have survived for several months may have a better prognosis than the prediction at initial diagnosis. Conditional survival (CS) would provide

patients with survival probabilities at a specific time since the prognosis would be adjusted for the time the patient had already survived.

Research motivation

In this study, we evaluated actual survival and CS of distant metastatic HCC patients.

Research objectives

This study aimed to evaluate the CS of distant metastatic HCC patients and construct nomograms to predict CS at different times.

Research methods

We used Cox regression analysis to identify risk factors for overall survival (OS) and the competing risk model to identify risk factors for cancer specific survival (CSS). Six-month CS was used to calculate the probability of survival for an additional 6 mo at a specific time after the initial diagnosis. We used standardized differences to evaluate the survival differences between subgroups. Nomograms were constructed to predict CS.

Research results

Using univariate and multivariate analysis, we found positive alpha-fetoprotein expression, higher T stage (T3 and T4), N1 stage, non-primary site surgery, non-chemotherapy, non-radiotherapy, and lung metastasis to be independent risk factors for actual OS and CSS. We found that actual survival rates decreased over time, while CS rates gradually increased. The influence of chemotherapy and radiotherapy on survival gradually disappeared over time; the influence of age and gender on survival gradually appeared; and the influence of lung metastasis reversed. The area under the curve (AUC) of nomograms for conditional OS decreased as time passed, and the AUC for conditional CSS gradually increased.

Research conclusions

Actual survival rates decreased over time, while CS rates gradually increased. With dynamic risk factors, nomograms constructed at different time would provide more accurate CS.

Research perspectives

CS could be used to evaluate the dynamic survival rates for distant metastatic HCC patients.