Japanese Journal of Gastroenterology and Hepatology

Clinical Paper

ISSN: 2435-1210 | Volume 8

Gender Difference in Clinical Outcomes of Hepatocellular Carcinoma: Prognostic Analysis Based on Propensity Score Matching and Nomogram Model

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Keywords:

Gender; HCC; Prognosis; Nomogram

Received: 23 Mar 2022
Accepted: 08 Apr 2022
Published: 14 Apr 2022
J Short Name: JJGH

Citation:

Chuangye Han, Gender Difference in Clinical Outcomes of Hepatocellular Carcinoma: Prognostic Analysis Based on Propensity Score Matching and Nomogram Model.. J Gstro Hepato.. V8(12): 1-6

1. Abstract

1.1. Background: Whether male sex has disadvantageous effects on the prognosis for survival in hepatocellular carcinoma (HCC) remains controversial. In this retrospective study, we explored the effect of sex on HCC prognosis. We used sex as a predictor to construct prognostic models to predict HCC-related survival (HRS) and relapse free survival (RFS).

1.2. Methods: A total of 1,024 patients with HCC (161 women and 863 men) who underwent hepatectomy were included in the study. Through Propensity Score Matching (PSM), the relationship between sex and HCC prognosis was investigated. Finally, we constructed prognostic models in which sex was a predictor of HRS and RFS.

1.3. Results: We observed that male sex was an unfavorable factor for HRS (pre-PSM: P = 0.049, HR = 1.442; post-PSM: P = 0.037, HR = 1.596) and RFS (pre-PSM: P = 0.015, HR = 1.531; post-PSM: P = 0.029, HR = 1.542). Subsequently, we used sex and other risk factors to construct models to predict HRS and RFS. The concordance index of the prognostic model for HRS was 0.714(95%CI= 0.683-0.745), and that of the prognostic model for RFS was 0.620(95%CI= 0.588-0.652). By comparing areas under the receiver operating characteristic curve with the Barcelona Clinic Liver Cancer staging system, China Liver Cancer staging system and Hong Kong Liver Cancer staging system, our prognostic models exhibited equal or better discriminatory ability, and nomograms for the models were provided.

1.4. Conclusion: Male sex is a significant risk factor for poor HRS and RFS in HCC. Our prognostic models can predict HRS and RFS in patients with HCC.

2. Introduction

Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancer cases [1], and is the sixth most common cancer type and the fourth leading cause of cancer-related death [2]. Exposure to hepatitis B, hepatitis C and aflatoxin are the major risk factors for the development of HCC [3], a disease requiring treatment through the cooperation of multiple disciplines, such as surgical therapy, chemotherapy drug embolization therapy and targeted drug therapy [4].

A couple of meaningful epidemiologic features are noticed in patients with HCC, including distinct discrepancies among geographic regions, racial and ethnic groups, and gender [5]. A disparity in the incidence of HCC exists between men and women, and significantly higher incidence is observed in men [2,6,7]. Increased risk among men is partially explained by their higher viral hepatitis and alcoholic cirrhosis exposure. On the other hand, an animal experiment indicated that estrogen receptors may be involved in the suppression of

malignant transformation of preneoplastic liver cells [8]. In recent years, a variety of studies have also clearly established that androgens have unfavorable effects on hepatocarcinogenesis, whereas estrogen has a protective effect [9-11], particularly in HBV-related HCC [12]. To date, several studies have reported that women have better survival prognosis than men with HCC [13-15]. Yu, et al. [16] observed female patients have a better outcome than male patients, but only exist in BCLC stage 0-B, in which female sex was identified to be a favorable factor for overall survival (OS) (HR = 0.617, p = 0.011) and progression-free survival (PFS) (HR = 0.728, p = 0.019). And in multicenter study by Xu, et al. 17, late recurrence (more than 2 years) after HCC resection was significantly associated with male sex. However, a retrospective cohort study consisting of 1886 HCC patients suggested that women have no significant advantages in HCC survival outcomes than men. The main reason may lie to that woman in their study were significantly older than men and the older age of women may lead to less curative treatment options for the patients or the physician [18]. Despite extensive efforts by many researchers to investigate the prognostic effects of sex in HCC19, the controversy of whether men have poorer survival in HCC requires further exploration. In the present large cohort retrospective study, we explored the effect of sex on survival outcomes in HCC, ensuring that confounding factors were strictly controlled by the method of Propensity Score Matching (PSM). We determined the ability of sex to predict survival prognosis, and provided nomograms serving as convenient predictive tools for HCC.

3. Patients and Methods

3.1. Patients

Patients hospitalized in the First Affiliated Hospital of Guangxi Medical University between June 2012 and June 2018, who first received primary curative hepatectomy for a primary diagnosis of HCC, were eligible for our study. Patients who met the following exclusion criteria were excluded: no confirmation of HCC in pathological diagnosis, presence of other malignant tumors, missing clinical data and a follow-up of less than 2 years and not died of HCC (see flowchart in Figure 1). Ultimately, 1,024 patients (of 1,947 patients) were eligible to proceed to the next data analysis; the group comprised 161 women and 863 men.

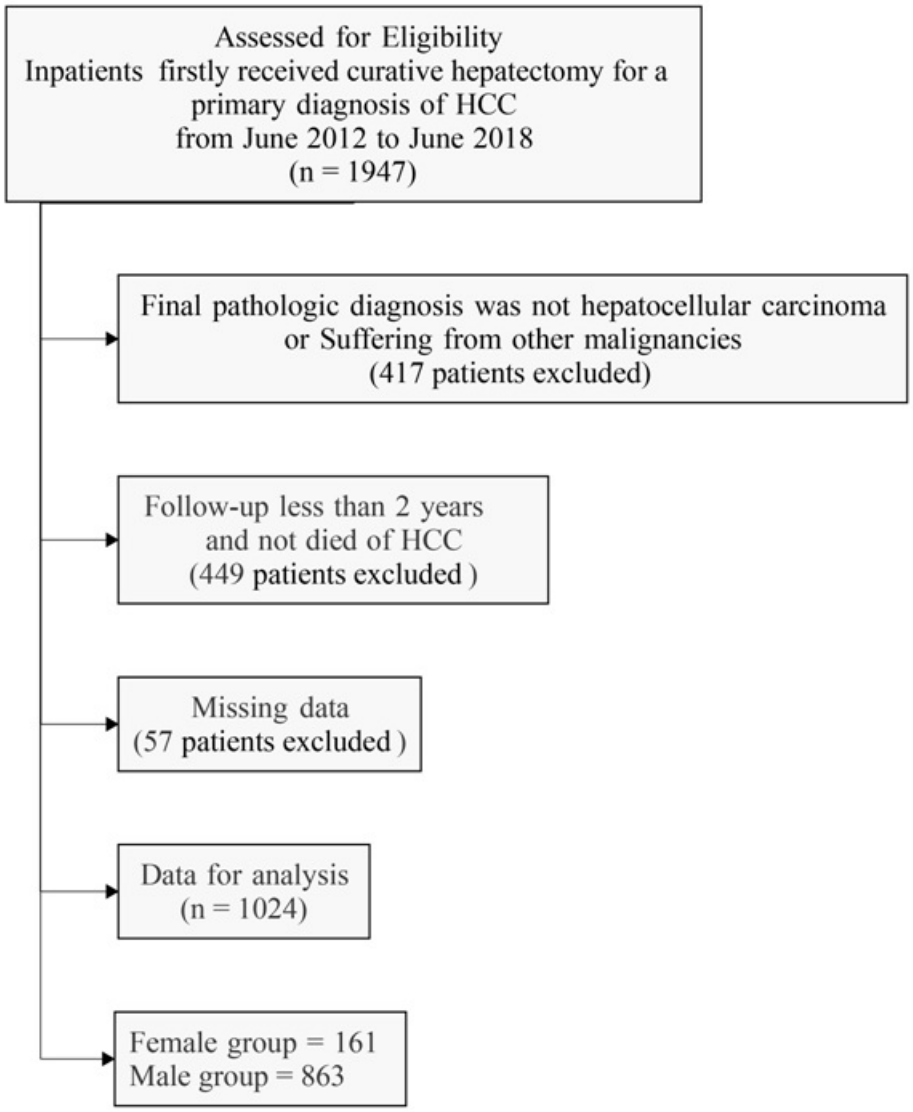

Figure 1: Flow chart

3.2. Diagnosis and Definitions

In our study, the diagnosis of HCC was based on the postoperative pathological diagnosis. According to the Guidelines for diagnosis and treatment of primary liver cancer in China (version 2017), we defined radical hepatectomy according to the following principles: tumor resection margin ≥1 cm; no apparent portal vein or hepatic vein carcinoma embolism during surgery; no peripheral organ invasion; no tumor contaminating the abdominal cavity before or during surgery (seen when tumors rupture and hemorrhage); and no recurrence within 2 months, on the basis of CT or MRI examination.

3.3. Hepatectomy and Follow-up

All patients underwent a complete preoperative evaluation and adequate preparation before hepatectomy, including good control of blood glucose levels, necessary nutritional supplementation, exclusion of contraindications, <15% ICG retention rate at 15 min and a residual liver volume greater than 40% of the standard liver volume. The scope of hepatectomy was planned and determined on the basis of preoperative imaging and intraoperative ultrasound. The operation process mainly included liver separation and vascular or bile duct ligation, hilar vascular occlusion and inferior vena cava occlusion. After the operation, the abdominal cavity was soaked in sterile water, and the abdominal drainage tube was placed. According to the surgeon's intraoperative judgment, 5-fluorouracil (5-FU) was administered on the cutting surface or omentum after hepatectomy. Regular follow-up was performed from the date of hepatectomy, every 3 months after the hepatectomy, subsequently every 6 months. The HCC-related survival (HRS) was calculated from the date of hepatectomy to the date of HCC-related death, loss to follow-up, or the date of follow-up termination (December 31, 2019), whichever came first. The endpoint event (HCC-related death) was 27.3% (280/1024). And the relapse free survival (RFS) was calculated from the date of hepatectomy to the date of tumor recurrence, or the date of last follow up. Recurrence was based on changes in postoperative alpha-fetoprotein (AFP) levels and imaging (CT, contrast-enhanced ultrasound and MRI) re-examination findings in the patients. During the follow-up, 31.4% (321/1024) of patients experienced tumor recurrence; artery embolization, radiofrequency ablation, and other treatments were performed when recurrence was found. The total rate of loss to follow-up was 6.7% (69/1024), primarily because long time periods had elapsed after the operation, and the patients could not be contacted again.

3.4. Statistical Analysis

Microsoft Excel 2016, Python 3.7.3 (https://www.python.org/) and R 3.6.2 (https://www.r-project.org/) were the statistical analysis tools used in our study. Continuous variables were recorded as the median value and quartile, and the Mann-Whitney U test was then used. Classification variables were processed as percentages and tested with Pearson's chi-squared test or Fisher's exact test. We used Propensity Score Matching (PSM), a method for decreasing selection bias in observational studies and eliminating the effects of measured confounding variables [20,21]. In the present study, variables that were associated with survival outcome and were distributed differently between the female group and the male group were used as indicators to score and match (method = nearest, ratio = 3, caliper = 0.05). These were age, body mass index (BMI), smoking habit, alcohol intake habit, hypertension, type 2 diabetes mellitus (T2DM), albumin, γ-glutamyl transpeptidase (GGT), total bilirubin, lymphocytes, cirrhosis, Child-Pugh grade, hepatitis background, alpha fetoprotein (AFP), tumor number, tumor size, PVTT stage, hepatic vein tumor thrombus, BCLC stage, CNLC stage, HKLC stage, blood loss, radical hepatectomy, local 5-FU, pathological grade and microvascular invasion. The HRS and RFS were calculated by the Kaplan-Meier method, and was compared using the log rank test. And the Cox regression model was used to analyze the survival data in univariate and multivariate analysis. The performants of the developed models were assessed by calculating the concordance index of the models. The discriminatory abilities of the models were compared by calculating areas under the receiver operating characteristic curve (AUC). P values were computed, and a difference was considered statistically significant at $P < 0.05$.

4. Results

4.1. Patient Characteristics

The clinical characteristics of the entire cohort are displayed in Table 1. Men had significantly higher scores for BMI, smoking habit proportion, alcohol intake habit proportion, T2DM proportion, Alt, GGT and lymphocytes value, whereas women were significantly older (all $P < 0.05$). The male group and female group had approximately the same scores for Child-Pugh grade, tumor size, tumor number, BCLC staging, CNLC staging and HKLC staging. And no significant differences were found after PSM (Table 1).

4.2. Survival Analysis

In HRS analysis, during the median period of 3.332 years follow-up, 247 patients (28.6%) in the male group died, and the follow-up time was 3.343 (0.189–7.307) years. In the female group, 33 patients (20.5%) died, and the follow-up time was 3.288 (0.211–7.342) years. Regarding RFS, 284 patients (32.9%) in the male group experienced tumor recurrence, whereas the female group had a lower recurrence, with 37 patients (23.0%). In pre-PSM analysis, the HRS and RFS were lower in the male group than the female group (HRS: log rank $P = 0.047$ Figure 2A; RFS: log rank $P = 0.014$ Figure 2C). Survival analysis with the Cox proportional hazards model suggested that the male group had a more adverse HRS and RFS than the female group (HRS: $P = 0.049$, HR = 1.442, 95%CI = 1.002–2.073; RFS: $P = 0.015$, HR = 1.531, 95%CI = 1.087–2.156; univariate analysis in Table 2). In multivariate analysis (Figure 2B, D), male sex was also observed to be a major contributor to poorer HRS and RFS. In post-PSM analysis, the HRS at 1, 3 and 5 years significantly differed between the male group (91.4%, 75.8% and 66.8%, respectively) and

female group (94.4%, 82.9% and 79.2%, respectively; log rank P = 0.035 Figure 3A). The RFS at 1, 3 and 5 years was again significant different between the male group (86.5%, 68.0% and 55.5%, respectively) and female group (88.8%, 78.0% and 66.1%, respectively; log rank P = 0.028 Figure 3B).

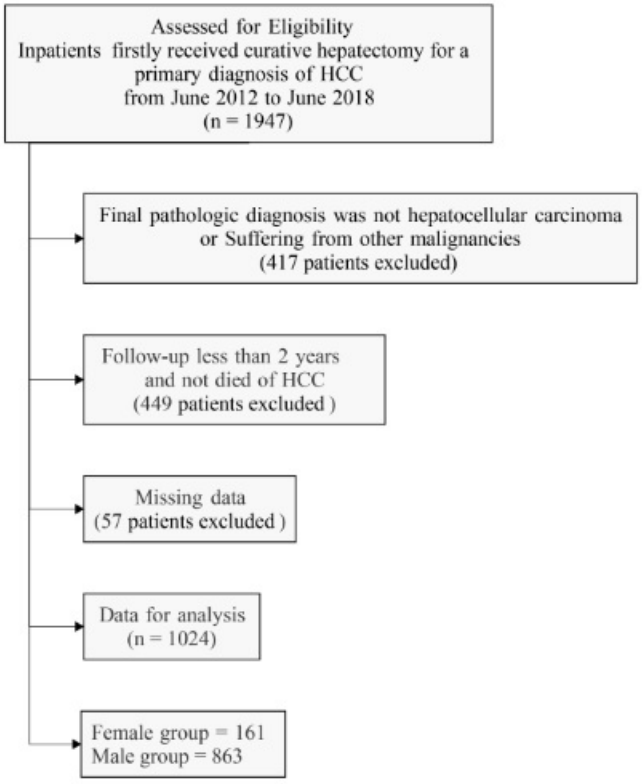

Figure 2: Survival curves between different sex and forest plots for multivariate analysis in pre-PSM cohort

Note: (A, C), Female group showed better HRS and RFS than male group; (B, D), male sex was reported to be an important risk factor for OS and RFS in multivariate analysis.

4.3. Survival Model

Sex was observed to be a significant risk factor for the survival prognosis of HCC. Therefore, to achieve good prediction of the HRS and RFS in patients with HCC, we used important risk factors to construct survival models for HRS and RFS. In the model for predicting HRS, we selected sex, lymphocytes, T2DM, cirrhosis, AFP, BCLC stage, radical hepatectomy and MVI as predictors to establish the prognostic model. The model had a moderate predictive accuracy, and the concordance index was 0.714 (95%CI= 0.683-0.745). Our prognostic model had a higher discriminatory ability than other models commonly used in clinical practice, such as BCLC stage, CNLC stage and HKLC stage (Figure 4A, B, C). Good agreement was also observed in the calibration curves (Figure 4D, E, F). Finally, a nomogram is provided for use as a convenient and effective prognostic tool (Figure 5). To predict RFS, we used sex, BCLC stage, cholecystectomy, radical hepatectomy and MVI as predictors to establish a prognostic model, with a 0.620 (95%CI= 0.588-0.652) concordance index. The prognostic model for RFS also showed a clear improvement in predictive ability compared with that of BCLC stage, and a similar or even better discriminatory ability than those of CNLC stage and HKLC stage (Figure 6A, B, C). The calibration curves (Figure 6D, E, F) demonstrating the model agreement and a nomogram for convenient clinical use were also provided (Figure 7).

5. Discussion

The findings of our study are mainly reflected in two aspects. First, the survival prognosis after hepatectomy for HCC significantly differed between the male group and female group, and the male group had poorer HRS and RFS. Second, we combined sex and other risk factors to establish prognostic models for HRS and RFS. Compared with BCLC stage, CNLC stage and HKLC stage, our models showed equal or better discriminatory ability. In previous studies, survival outcomes for various tumors in men and women have been found to differ significantly. Men were thought to have poorer prognosis than women in most cancers, and decreasing the influence of male sex on prognosis could significantly affect the global cancer burden [22-25]. Various factors may potentially drive the sex disparities in cancer prognosis, such as sex-related biologic factors, e.g., sex hormones, and sex-related environmental and behavioral factors, e.g., alcohol consumption [26]. For HCC, comparative studies have reported that women exhibit better survival outcomes than men [27-29]. Our study also demonstrated a better survival prognosis in women than men. The protective effect of estrogen may be a reasonable explanation for this finding [30,31]. BCLC staging, a well-known staging system

for HCC, is widely used because of its good discrimination ability [32,33]. However, BCLC stage also has disadvantages in classifying HBV-related HCC [34]. In contrast, HKLC stage may perform better than BCLC stage, particularly in HBV-related HCC in Asia [35]. On the basis of cumulative experience in the diagnosis and treatment of liver cancer in China, CNLC stage, updated in 2019, has played an important role in HCC stage and treatment guidance [36]. In terms of treatment guidance, BCLC stage recommends more conservative treatment options [37]. We have also observed recommendation of more aggressive treatments on the basis of CNLC stage and HKLC stage in the middle or advanced stage of BCLC stage. In our study, compared with CNLC stage and HKLC stage, BCLC stage clearly had a poorer predictive effect on prognosis, partly because 83.3% of our cohort had a background of hepatitis B infection. Despite this shortcoming, BCLC stage was an important indicator for patients with HCC and thus was qualified to serve as a predictor together with sex in the survival models in our study. Similarly, sex also played a decisive role in HCC-related prediction. Yang, et al [38]. Have introduced a nomogram to predict the probability of RFS for patients who have undergone radiofrequency ablation, in which sex is a heavily weighted score factor. In a study by Nam, et al. 39, a sex-based model has been established to predict the probability of hepatocarcinogenesis. The models for OS and RFS prediction in our present study, which were based on a combination of BCLC stage, sex and other risk factors, displayed good predictive ability. The newly established models showed a stronger predictive ability than BCLC stage, thus reinforcing the relatively weak predictive ability of BCLC stage. Moreover, the models had a prognostic ability equal to or better than those of CNLC stage or HKLC stage, thus suggesting our models' potential utility and clinical applicability. The nomograms for OS and RFS provided in our study are strongly recommended as convenient predictive tools for HCC. The advantages of our study are that (1) a relatively large cohort was examined, and (2) the prognostic models based on sex had a better predictive ability than BCLC stage, CNLC stage and HKLC stage, and may have strong potential for clinical applicability. However, the present study also has some its limitations. The PSM method was used in our study to eliminate the effects of measured confounding variables, but there still existed the effects from unmeasured confounding variables. And although our models were based on a large cohort, the participants came from a single center; consequently, external validation is needed. Therefore, we will focus on providing further validation in our future work.

6. Conclusion

In present study, we found that men have poorer prognosis in terms of HRS and RFS than women. The newly established models for predicting HRS and RFS in patients with HCC had good discriminatory ability, and the nomograms would serve as convenient predictive tools for HCC.

7. Funding

This work was supported in part by the National Natural Science Foundation of China (No. 81560535, 81802874 and 81072321), Natural Science Foundation of Guangxi Province of China (Grant No. 2018GXNSFBA138013); the Guangxi Key R and D Program (grant no. GKEAB18221019); Natural Science Foundation of Guangxi Province of China (Grant No. 2020GXNSFAA159127); Guangxi Natural Sciences Foundation (No. GuiKeGong 1104003A-7); and Guangxi Health Ministry Medicine Grant (Key-Scientific Research-Grant Z201018); Key laboratory of High-Incidence-Tumor Prevention & Treatment (Guangxi Medical University), Ministry of Education (GKE2018-01).

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