Original Article

Impact of marital status on the prognosis of liver cancer patients without surgery and the critical window

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Background: Liver cancer (LC) is the second leading cause of cancer-associated mortality. However, the critical time window during the marital status may influence the prognosis of LC is still unknown.

Methods: Information on a total of 4,933 patients diagnosed with primary LC who had not undergone surgery was collected from the Surveillance, Epidemiology, and End Results (SEER) database to analyze the impact of marital status on the risk of cancer-specific mortality (CSM). All confirmed patients were monitored from January 1, 2010 until December 31, 2015 for the occurrence of death. We performed 1:1 propensity score matching among the married and non-married groups to eliminate dissimilarities in age, sex, race and clinical characteristics. Cox proportional hazards regression model was adopted to investigate the associations between marital status and the risk of CSM.

Results: Married patients were significantly negatively associated with the risk of CSM among patients compared to non-married status, with a hazard ratio (HR) [95% confidence interval (CI)] of 1.15 (1.07–1.23). The strongest associations were observed for patients with Grade II, American Joint Committee on Cancer (AJCC) I and III. Furthermore, the protective effect of marriage on the prognosis of LC was independent of sex, age, race, grade, AJCC and SEER stage. Unmarried or separated patients may have a worse prognosis.

Conclusions: Marriage was strongly associated with a positive prognosis among patients with LC, especially in the critical window of Grade II, AJCC I and III. This study highlights the important impact of marriage on cancer prognosis.

Keywords: Liver cancer (LC); marriage; prognosis; social support; survival analysis

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Introduction

Liver cancer (LC) has posed a serious threat to human health because of its rapid growth, and strong invasiveness (1). According to cancer statistics, LC is the second leading cause of cancer-associated mortality and ranks as the fifth most common malignancy globally. It is estimated that approximately 850,000 new LC cases are diagnosed each year worldwide, and this number is still rising (2-4). In the United States, with approximately 41,000 new cases and 29,000 deaths from LC each year, LC

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is highly lethal, with mortality rising faster than any other cancer, and only about one-fifth of patients can survive for 5 years after diagnosis (5). High morbidity and mortality impose a severe disease burden on the nation (6). Therefore, exploring the prognostic factors affecting patients with liver cancer is important for effective reduction and early prevention of the development of LC.

Many studies have confirmed the prognostic factors of LC mainly regarding clinical characteristics, such as surgery, tumor size, pathological grade and American Joint Committee on Cancer (AJCC) stage (7). Although some studies have developed various prognostic evaluation models for patients with LC based on clinical information, the C index for evaluating the accuracy of these models can only explain approximately 80% (8,9). This suggests that other potential factors affecting the prognosis of LC patients have not received attention. Social determinants, despite being little addressed, play a role in the development of LC that cannot be overlooked. Recently, increasing evidence has indicated that social support can greatly affect the prognosis of many cancers, such as pancreatic neuroendocrine cancer (10), colorectal cancer (11) and breast cancer (12). Thus, it is necessary to investigate the effect of social support on LC.

Social support, referring to various forms of external support, has been reported to have beneficial effects on overall well-being (13). Family support, which can affect patients' choice of treatment and improve patients' compliance with treatment, is one of the most important social supports that closely related to the prognosis. Support from spouses is the most important family support for adults, and marital status has been considered an independent social factor that determines the prognosis of cancer patients. In the United States, only 50% of Americans are married (14), the rest being single, separated, unmarried, divorced and widowed. Most studies have mainly focused on the prognosis of married and unmarried patients, while those who are separated, divorced, and widowed have been ignored (15,16). Some studies suggested that marriage as a prognostic factor showed both protective (17) and adverse (18) effects on the survival of cancer (19,20), while others found no association between marriage and tumor prognosis (21). However, some studies addressed cancer patients who had undergone surgery, which makes it difficult to compare the role of marriage and surgery on the prognosis of LC. Given that some patients cannot undergo surgery, effective interventions via social support may be more meaningful for these patients to improve their prognosis in addition to limited treatments. Due to the inconclusive epidemiological findings, the role of marriage on the prognosis of LC patients without surgery warrants further investigation. In addition, the survival time of cancer patients in each clinical stage is distinctive, and the sensitivity of marital status on prognosis in each clinical stage is also different. Hence, the susceptible windows, being interpreted as a stronger association between marital status and risk of death, urgently need to be identified.

In this study, we conclude that marriage plays a role in the prognosis of LC for patients who have not undergone surgery. To test this hypothesis, we conducted the present study by using data from the Surveillance, Epidemiology, and End Results (SEER) to explore the relationship between marital status and outcomes of LC patients without surgery, and to further identify the relative importance of the susceptible window during the stages of cancer development.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1885).

Methods

Patients characteristics

The SEER program collects cancer morbidity, treatment, and survival data from population-based cancer registry organizations. The program involves approximately 97% of incident cancers, and the cancer registry organizations cover approximately 26% of the United States population, which has a high degree of recognition in the world (22). We searched the SEER database to identify 46,000 patients diagnosed between 2010 and 2015. The year 2010 was selected as the first year of the study given that the AJCC 7th edition was introduced in SEER in 2010. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All the data are obtained from the public database, and there is no ethical approval.

The patient's elimination process is shown in Figure S1. We first excluded subjects with a diagnosed age <18 years and missing data with marital status and race. We then excluded subjects with missing data on the degree of tumor differentiation, tumor AJCC stage, and surgical status.

The variables in this study included demographic valuables (sex, age, race and marital status) and other valuables (pathological grade, AJCC and SEER stage). The endpoint of this study was liver cancer-specific mortality

(CSM). Patients who survived the last follow-up were defaulted to censor. The survival time calculation started from the time of diagnosis, and the total survival time was defied as the period from diagnosis to death. All confirmed patients were monitored for the occurrence of death from January 1, 2010 until December 31, 2015.

Based on the incidence characteristics and sample distribution of LC, we then divided the patients into three groups of different ages: ≤60, 60–75, and ≥75 years. The race included white, black, and other races.

The patients were subdivided into two groups: married and non-married (single, widowed, divorced, separated and unmarried). To exclude the heterogeneity of marital status and differences in baseline data, we performed 1:1 propensity score matching between the married and non-married groups.

Statistical analysis

Propensity score matching regarded marital status as a dependent variable, and each covariate (age, sex, race, grade, SEER stage and AJCC) was an independent variable. The propensity score value is estimated by logistic regression, and the 1:1 nearest neighbor matching method is used for matching. This process guarantees the matching result by defining the caliper value (caliper value =0.02), and then comparing the changes in the standard difference of covariates between groups before and after matching. When the absolute value of the standard difference is less than 0.1 (10%), the balance of variables between groups is better.

First, we used the Chi-square test to compare the demographic and clinical characteristics of patients with different marital statuses. Second, we adopted the Kaplan-Meier curve analysis and the log-rank test to analyze the prognosis among patients with different marital statuses. Third, multivariate Cox regression model was utilized to estimate the effect of demographic and clinical factors on the hazard risk of prognosis for patients with LC. All statistical analyses were performed by the statistical software package SPSS for Windows, version 22 (IBM Corp., Armonk, NJ, USA). The associations in the regression analysis were estimated as hazard ratios (HRs) with 95% confidence intervals (95% CIs). A P value <0.05 indicated statistical significance.

Results

We identified a total of 4,933 LC patients who had not undergone surgery between 2010 and 2015 from the SEER database. According to *Table 1*, 2,555 (51.7%) patients were married, and 1,897 (50.0%) patients were classified in various non-married states after matching. We observed that all demographics including sex, age and race were significantly associated with two different marital statuses (P<0.001). For the clinical characteristics, only significant differences in the AJCC stage were observed between different marital statuses. During the follow-up period, 2,060 patients died of LC in the non-married group. For the matched data set, the covariates were adequately balanced in the distribution of different marital statuses (P>0.05).

As displayed in *Figure 1*, the Kaplan-Meier survival analysis showed that the cancer-specific survival (CSS) rate of married patients was always higher than non-married group and the other marital status groups (P<0.05). When considering the matched data set, we found that the survival rate of the three groups was still different, and the median survival time of the married group was still longer than that of the single group after the log-rank test (P<0.05).

All of the above demographic and clinical variables were included in the Cox regression model. Marital status was associated with the CSM risk of LC patients. They were independent prognostic factors for LC patients without surgery, as shown in *Table 2*. Marital status had a significantly negative association with CSM risk. The non-married group had 9.3% (HR, 1.09; 95% CI, 1.03 to 1.16) risk increase in model I and 14% (adjusted HR, 1.14; 95% CI, 1.07 to 1.22) risk increase in CSM compared to the married group after performing a multivariable adjustment. In the matched data set, marriage also reduced the patient's risk of CSM to a greater degree (adjusted HR, 1.15; 95% CI, 1.07 to 1.23).

As shown in *Table 3*, we used a multivariate Cox regression model to assess the impact of marital status on CSM among different clinical characteristic subgroups. The strongest protective effect was observed in the AJCC stage III (adjusted HR, 1.26; 95% CI, 1.10 to 1.45). We found that marital status was a significant factor affecting the prognosis of patients who were grade II and AJCC stage I. In AJCC stage I, the CSM risk was 1.16 (adjusted HR, 1.16; 95% CI, 1.02 to 1.32) times that of the non-married group. The results failed to reach significant differences in the risk of death among different marital statuses in other AJCC stages and pathological grades between the two marital status groups.

Table 1 The distribution of marital status, in relation to baseline variables between the original and matched data sets

Variables	Original data set				Matched data set			
	Married, n (%)	Non-married, n (%)	Sdiff	P*	Married, n (%)	Non-married, n (%)	Sdiff	P†
Sample size, no.	2,555	2,378			1,897	1,897		
Age, years			–0.15	0.00			0.001	0.26
18–60	824 (32.3)	955 (40.2)			717 (37.8)	730 (38.5)		
60–75	1,172 (32.3)	983 (41.3)			853 (44.9)	826 (43.5)		
≥75	559 (21.9)	440 (18.5)			328 (17.3)	342 (18.0)		
Sex			–0.23	0.00			0.013	0.50
Female	403 (15.8)	612 (25.7)			378 (19.9)	367 (19.3)		
Male	2,152 (84.2)	1,766 (74.3)			1,520 (80.1)	1,531 (80.7)		
Race			–0.38	0.00			–0.012	0.26
Black	266 (10.4)	534 (22.5)			266 (14.0)	298 (15.7)		
White	1,798 (70.4)	1,606 (67.5)			1,420 (74.8)	1,369 (72.1)		
Other	491 (19.2)	238 (10.0)			212 (11.2)	231 (12.2)		
Grade			0.005	0.53			0.003	0.31
I	866 (31.5)	765 (32.2)			612 (32.2)	610 (32.1)		
II	1,071 (41.9)	969 (40.7)			757 (39.9)	767 (40.4)		
III	631 (24.7)	589 (24.8)			490 (25.8)	472 (24.9)		
IV	47 (1.8)	55 (2.3)			39 (2.1)	49 (2.6)		
SEER stage			–0.05	0.14			–0.008	0.26
Localized	1,023 (40)	1,018 (42.8)			786 (41.4)	806 (42.5)		
Regional	931 (36.4)	819 (34.4)			672 (35.4)	644 (33.9)		
Distant	601 (23.5)	541 (22.8)			440 (23.2)	448 (23.6)		
AJCC			–0.07	0.007			0.002	0.31
I	777 (30.4)	776 (32.6)			603 (31.8)	597 (31.5)		
II	307 (12.0)	342 (14.4)			244 (12.9)	260 (13.7)		
III	674 (26.4)	571 (24.0)			477 (25.1)	458 (24.1)		
IV	797 (31.2)	689 (29.0)			574 (30.2)	583 (30.7)		
Death	2,151	2,060			1,607	1,650		
Survival month	12.58±15.82	11.30±14.26			12.82±16.13	11.08±14.24		

Non-married include single, separated, unmarried, divorced and widowed. The matching factors included age, sex, race, pathological grade, AJCC and SEER stage. *, P value for χ^2 test. †, P value for McNemar's or McNemar-Bowker test. SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

Furthermore, to exclude the confounding caused by differences in patient baseline data and the heterogeneity of marital status, we redefined the single, separated/unmarried, divorced/widowed group. As displayed in *Figure 2*, the Kaplan-Meier survival analysis showed that the CSS rate of married patients was higher than that of the other groups (P<0.05). After matching, the married group was still longer than that of the non-married group (P<0.05).

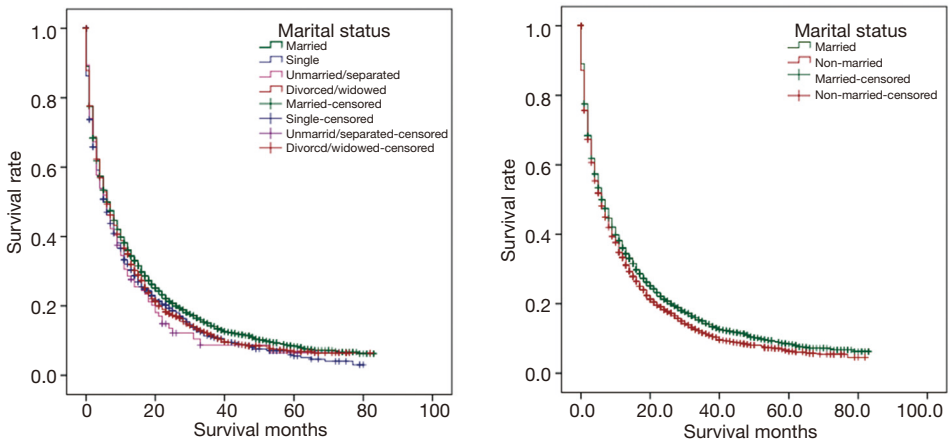

Figure 1 Kaplan-Meier survival curves demonstrating CSS rates of all patients according to marital status before matching. (A) CSS curves in LC patients without surgery among married and other groups (n=4,933), Chi^2=10.41, P=0.015; (B) CSS curves in LC patients without surgery among married and non-married groups (n=4,933), Chi^2=8.98, P=0.003. CSS, cancer-specific survival; LC, liver cancer.

Table 2 The association between marital status and prognosis in original and matched data sets

Variables	HR	95% CI	P
Model I			
Married	1.00		
Non-married	1.09	(1.03, 1.16)	0.004
Model II			
Married	1.00		
Non-married	1.14	(1.07, 1.22)	0.000
Model III			
Married	1.00		
Non-married	1.12	(1.05, 1.20)	0.001
Model IV			
Married	1.00		
Non-married	1.15	(1.07, 1.23)	0.000

Non-married include single, separated, unmarried, divorced and widowed. Model I did not adjust other variables before matching; Model II adjusted the variables include age, sex, race, grade, AJCC and SEER stage before matching; Model III did not adjust other variables after matching; Model IV adjusted the variables include age, sex, race, grade, AJCC and SEER stage after matching. HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

Discussion

To our knowledge, this study is one of the few studies to systematically investigate the impact of marriage on the risk of cancer death among LC patients who have not undergone surgery, and to further identify the critical window of the effect. Strikingly, we found that marriage had a significant protective effect on the risk of death among LC patients without surgery. We further observed that the AJCC III had relative importance of the impact in marriage in patients with LC. Moreover, we detected that marriage could decrease death risk of LC patients during Grade II and AJCC I stages. The survival rate of LC patients rapidly declined as the survival time increased, and the

Table 3 Stratified analysis of marital status impact on prognosis among clinical characteristics after matching

Variables	HR	95% CI	P	$P_{interaction}$
Model a				0.000
Grade I				
Married	1.00			
Non-married	1.10	(0.97, 1.25)	0.142	
Grade II				
Married	1.00			
Non-married	1.21	(1.08, 1.35)	0.001	
Grade III				
Married	1.00			
Non-married	1.10	(0.97, 1.26)	0.145	
Grade IV				
Married	1.00			
Non-married	1.00	(0.63, 1.60)	0.995	
Model b				0.000
AJCC I				
Married	1.00			
Non-married	1.16	(1.02, 1.32)	0.024	
AJCC II				
Married	1.00			
Non-married	1.04	(0.85, 1.28)	0.68	
AJCC III				
Married	1.00			
Non-married	1.26	(1.10, 1.45)	0.001	
AJCC IV				
Married	1.00			
Non-married	1.06	(0.94, 1.19)	0.327	

Model a adjusted the variables include age, sex, race, AJCC and SEER stage after matching; Model b adjusted the variables include age, sex, race, grade and SEER stage after matching. HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

decreasing rate remained steady 40 months after diagnosis. Our findings have significant implications for the effective control and early prevention of LC development.

The present study has several strengths. First, this is one of the few studies to systematically examine the impact of marital status on the prognosis of LC patients without surgery. Second, we collected a relatively large sample size of patients with LC, which can, to a large extent, ensure the accuracy and reliability of our results. Third, our findings may provide an effective strategy for public health and cancer control especially in sensitive populations.

We found a protective effect of marriage on the death risk of LC among patients without surgery. Subsequently, we compared the benefits of various treatments on the prognosis of LC through a literature review in Table S1 with marriage in this study. The benefit of patients

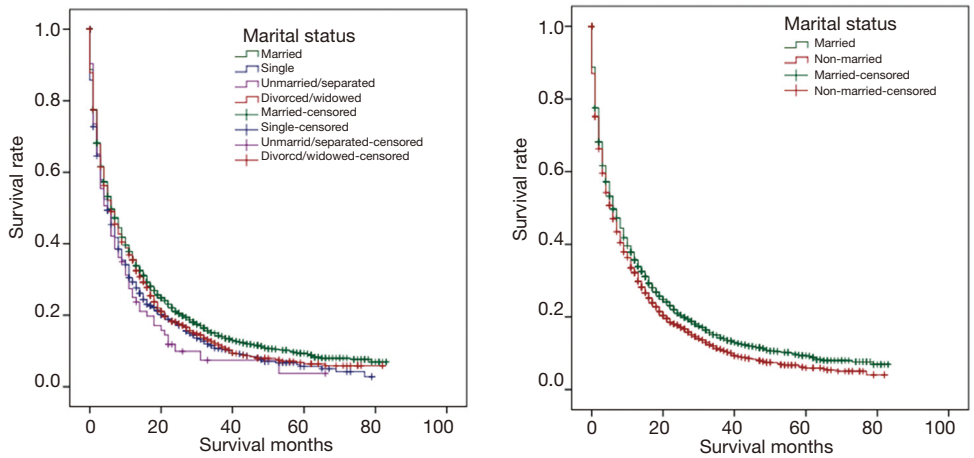

Figure 2 Kaplan-Meier survival curves demonstrating CSS rates of all patients according to marital status after matching. (A) CSS curves in LC patients without surgery among married and other groups (n=3,794), Chi^2=15.78, P=0.001; (B) CSS curves in LC patients without surgery among married and non-married groups (n=3,794), Chi^2=11.34, P=0.001. CSS, cancer-specific survival; LC, liver cancer.

receiving single-drug chemotherapy was very low compared to the benefits of marriage, and marital patients possessed a "nontherapeutic" benefit. This study was also a vigorous manifestation of the "biological-psychological-social" medical model, suggesting that we must pay attention to both physiological and psychosocial factors in the prevention and treatment of cancer (23,24). Social support is considered to be the individual's support from the outside world through various means, including material and spiritual guarantees, and directly promotes the physical and mental health of the individual (25). Previous studies have shown that lower social support is associated with a poorer prognosis for cancer patients (12). We found that marriage, one of the most important social supports, was associated with the positive prognosis of LC patients. How did marriage exert its role on the prognosis of cancer patients? Some studies revealed that the better prognosis of married cancer patients could partly be attributed to earlier diagnosis (26). Our results also showed that married patients in AJCC I were the highest proportion compared with the other two groups, indicating that married patients might tend to receive a diagnosis at an earlier stage. An additional explanation might be related to the spouse's recommendation to go for a health checkup once the problem was discovered (27). Therefore, patients went to the hospital earlier and received treatment in the earlier stage of the disease. Moreover, spouses could also prompt patients to follow health-related behaviors, directly or indirectly. Reblin *et al.* suggested that a shared social environment created in marriage could be important to motivate cancer patients to engage in healthy behaviors (28). Another reason might be to that patients could receive high-quality care from their spouse at home. Galbraith *et al.* found that more than 50% of prostate cancer patients' health-related outcome scores were related to spouses, which would be beneficial for the health of patients if their spouses participated in nursing (29).

We identified that the protective effect of marriage on the prognosis of LC was significantly stronger in critical time windows during pathological grades and AJCC stage. The CSM risk significantly decreased in married patients compared with other groups, which indicated that AJCC III may act as a critical time window for the strongest protective effect of marriage. We also found that married LC patients had a lower risk of death in Grade II and AJCC I stages than those non-married patients. Very few works have examined the protective effect of marriage in specific pathological grades or AJCC stages. Li *et al.* demonstrated that marriage has protective effects on patients with colorectal cancer in the AJCC (II, III and IV) based on all populations (30). Another study on hepatocellular carcinoma found that married patients had the lowest risk of death when the tumor was in the localized or regional (tumor has no metastasis) stage (31). Although the patient origins of these studies were different, the conclusions were consistent with our results. We drew the above conclusions by performing 1:1 propensity score matching between the marriage group and the non-marriage group

to eliminate the heterogeneity of various marital statuses and the differences in baseline data. The conclusions were consistent with previous results. It has become clear that marriage was negatively associated with the risk of LC death in the regional stage or moderately differentiated grade, suggesting that some genetic biomarkers are involved in the process of susceptibility (32). The association between marriage and survival in a specific period indicated an underlying biologically plausible explanation. Marriage was an important part of people's lives. It provided a haven to alleviate the mental and physical damage of individuals in response to stressful events. Hepatocellular carcinoma cells in Grade II were moderately differentiated and their malignancy was between Grade I and III. Adequate mental support could activate the immune system to eliminate malignant cancer cells and induce tumors to transform into lower grades (33). However, the biological mechanism by which marriage reduced the risk of death for patients in this period is still unknown and deserves further study.

Our study has several limitations worth noting. First, the SEER database did not include changes in the patient's marital status. The marital status of the study was recorded at the time of diagnosis. Only the marital status at the baseline level of each patient was analyzed. The relationship between marital status transition and disease prognosis was not studied. Second, married patients also have many different characteristics, such as the length of marriage and the happiness of the marriage. An unhappy marriage may have an adverse influence (34). Economic status is another recognized independent prognostic factor of LC (35). Third, the database did not provide relevant data. Additionally, the SEER database only provided surgical information and did not provide information on patients with radiotherapy, chemotherapy, palliative care, and immunotherapy. Other potential factors that could affect the prognosis of LC were not included in the multivariate analysis of this study.

Our study found a significant association between marital status and the overall mortality and CSM of LC patients without surgery. We further identified that this protective effect had relative importance during the AJCC III staging system. Marriage also exerted an important role in the decreased death risk of patients who live cancer in AJCC I and Grade II. Strikingly, marriage could greatly increase the survival rate of patients with LC. According to our analysis, we suggest that some effective strategies such as social support should be taken into account for cancer populations for early control and prevention. For single cancer patients, it is better to benefit from marriage to improve their prognosis in addition to clinical treatments.

Conclusions

Marriage is an independent factor that could significantly decrease the risk of death attributed to LC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1885

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1885). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All the data are obtained from the public database, and there is no ethical approval.

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Supplementary

Table S1 Comparison of HR for different endpoint associated with treatment reported in the literature with marriage in LC patients

Author, year	Study type	Reference	Treatment	Study population	Adjusted HR (95% CI)
Llovet *et al.*, 2002 (36)	Randomized controlled trial	Conservative treatment	Chemoembolisation (gelatin sponge, doxorubicin)	Child-Pugh class A or B, n=112	Overall mortality: 0.47 (0.25–0.91)
Bai *et al.*, 2013 (37)	Prospective non- randomized controlled trial	TACE	Sorafenib plus TACE	Unresectable intermediate or advanced HCC, n=304	Time-to-progression: 0.60 (0.42–0.85); median survival time: 0.61 (0.42–0.88)
Bruix *et al.*, 2017 (38)	Randomised, double-blind, parallel-group, phase 3 trial	Placebo	Regorafenib	Advanced HCC, n=843	Overall survival: 0.63 (0.50–0.79)
Cheng *et al.*, 2009 (39)	Multinational phase III, randomised, double-blind, placebo-controlled trial	Placebo	Sorafenib	Unresectable or metastatic hepatocellular carcinoma, n=304	Median survival time: 0.68 (0.50–0.93); median time to progression: 0.57 (0.42–0.79)
Kudo *et al.*, 2018 (40)	Open-label, randomised, phase 3 trial	Sorafenib	Sorafenib plus hepatic arterial infusion chemotherapy	Advanced and not suitable for resection, local ablation, or transarterial chemoembolization, n=205	Median survival time: 1.01 (0.74–1.37)
Pinter *et al.*, 2015 (41)	Randomized controlled trial, double-blind	TACE plus placebo	TACE plus doxorubicin	Early or intermediate HCC, n=40	Median survival time: 1.70 (0.80–3.60)
–	This study	Married	Non-married	AJCC III HCC, n=3,794	CSM: 1.26 (1.10–1.45)

HR, hazard ratio; LC, liver cancer; CI, confidence interval; TACE, transcatheter arterial chemoembolization; BCLC, Barcelona clinic liver cancer; CSM, cancer-specific mortality.

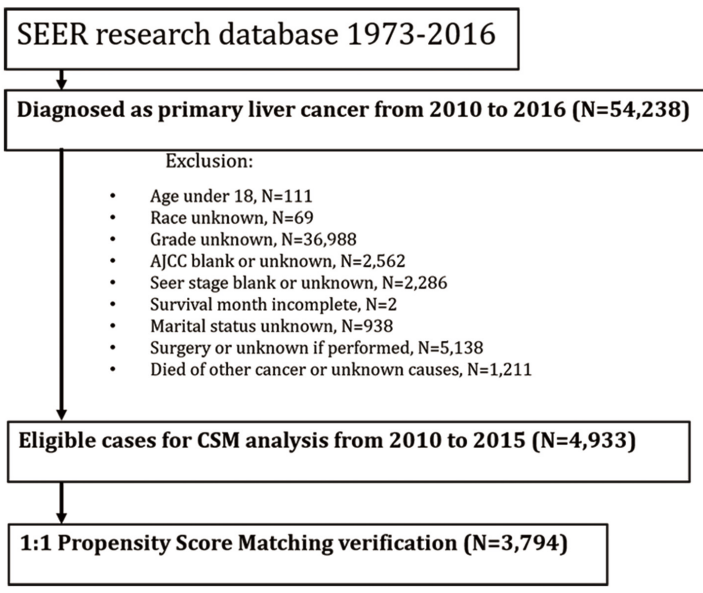

Figure S1 Flowchart of the enrolled patients in the study. SEER, Surveillance, Epidemiology, and End Results; CSM, cancer-specific mortality.

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