Impact of Socioeconomic Factors on Prognosis and Clinical Management in Patients with Hepatocellular Carcinoma

Bing-Bing Su, Bao-Huan Zhou*, Dou-Sheng Bai, Jian-Jun Qian, Chi Zhang, Sheng-Jie Jin, Guo-Qing Jiang*

Department of Hepatobiliary Surgery, Clinical Medical College, Yangzhou University, Yangzhou, China

Cite this article as: Su B, Zhou B, Bai D, *et al*. Impact of socioeconomic factors on prognosis and clinical management in patients with hepatocellular carcinoma. *Turk J Gastroenterol.* 2021; 32(8): 667-677.

ABSTRACT

Background: *The prognosis for patient survival using the tumor–node–metastasis (TNM) staging system may be imperfect, as it based only on biological factors and does not include the socioeconomic factors (SEFs). We integrated the SEFs into the TNM system (TNM-SEF), and evaluated whether the novel TNM-SEF staging system showed better prediction capacity and improved clinical guidance in hepatocellular carcinoma (HCC).*

Methods: *We selected data of 12 514 cases with HCC between 2010 and 2015 from the SEER database. The Kaplan–Meier survival curves and Cox proportional hazards regression were used to analyze cancer-specific survival (CSS) among the TNM-SEF stages.*

Results: *Multivariate Cox analyses showed that insurance status, marital status, year of diagnosis, and income were prominent prognostic SEFs (all P < .05). When compared with the SEF0 stage, the SEF1 stage was significantly associated with a 36.1% increased risk of cancer-specific mortality in HCC overall, a 22.2% increased risk of metastatic HCC, and a 41.8% increased risk of non-metastatic HCC (all P < .001). The concordance index of the TNM-SEF stage (0.768) was better than that of the TNM stage (0.764). Furthermore, patients with SEF0 stage showed higher 5-year CSS than those with SEF1 stage (I: 48.7% vs. 28.1%; II: 41.0% vs. 25.1%; IIIA: 12.8% vs. 5.0%; IIIB: 7.8% vs. 6.0%; IIIC: 6.4% vs. 6.7%; IVA: 8.4% vs. 2.5%; IVB: 2.1% vs. 0.8%; all P < .05).*

Conclusion: *We have proved that the SEF stage is an independent predictor for HCC. The combined SEF stage with TNM staging warrants more clinical attention, for improved prognostic prediction and clinical guidance.*

Keywords: *Socioeconomic factors, hepatocellular carcinoma, TNM staging system, SEER, prognostication*

INTRODUCTION

Hepatocellular carcinoma (HCC), the sixth most common malignant tumor, is the fourth leading cause of cancer mortality worldwide.[1] Disease factors and patient factors, such as the biological factors and socioeconomic factors (SEFs) affect the prognosis of HCC. The influence of different biological factors on survival in HCC patients has been investigated, including the factors like tumor–node–metastasis (TNM) staging and tumor size.[2-4] Some studies have shown that SEFs, including marital status, socioeconomic status, insurance, employment, and education are associated with the survival of HCC patients.[5-9] However, as far as we know, SEFs have not yet been researched in the prognostic prediction of HCC. Besides, prognostication using the TNM staging system is only based on the extent of invasion of the primary tumor, status of lymph node metastasis, and distant spread. The TNM system is not optimal for clinical prognostic prediction and treatment,[10] therefore, a more accurate prognostic prediction system with a combination of the TNM staging system or other prognostic factors is necessary. However, the knowledge regarding the combination of the TNM stage and SEFs for prediction in HCC remains extremely limited.

We conducted a population-based study to explore the impact of different SEFs, such as income, level of education, year of diagnosis, employment status, insurance status, and marital status, on survival in HCC. We then chose those factors that were independent prognostic factors for further study. The purpose of our study was to propose and evaluate the novel combination of TNM stage and SEF stage (TNM-SEF stage) in terms of the clinical prognostication and management of HCC.

MATERIALS AND METHODS

Data Source and Patients

The Surveillance, Epidemiology, and End Results (SEER) database is an almost universally accepted source of information about cancer in the United States. Moreover,

**These authors contributed equally to this work*

Corresponding author: ***Guoqing Jiang****, e-mail:* ***jgqing2003@hotmail.com***

Received: ***July 31, 2020*** *Accepted:* ***January 13, 2021*** *Available Online Date:* ***September 8, 2021***

DOI: 10.5152/tjg.2021.20617

it is a general database, including almost all newly diagnosed cancers occurring where individuals reside in SEER-participating areas, representing about 28% of the United States population. All data of demographic and tumor variables were extracted from the SEER database. In a previous study, researchers have discussed the characteristics and representativeness of this population-based database.[11]

We extracted the following data: gender, race, age, year of diagnosis, pathological grade, TNM stage, tumor size, insurance status, marital status, county percentage with a bachelor's degree, county percentage unemployed, county-level median household income, surgical status, SEER cause-specific death classification, SEER other-cause-of-death classification, survival months, and vital statistics.

The data of patients in our study, diagnosed with HCC between January 1, 2010 and December 31, 2015, were selected using SEER-Stat software (SEER*Stat 8.3.5, https://seer.cancer.gov/seerstat/software/). Those patients with a diagnosis of HCC (Histology codes 8170 to 8175) and only 1 primary tumor were selected for this study. We excluded patients with unknown race, diagnosis confirmation, insurance status, income, tumor size, marital status, and TNM stage. We also excluded patients in whom it was unknown whether surgery was performed. We also excluded patients who were 65 years or older, because these patients are generally enrolled in or qualify for medical insurance benefits. Additionally, we excluded patients younger than 19 years, as most people in that age group are unmarried (Figure 1).

MAIN POINTS

- *The socioeconomic factors (SEF) were independent predictors for HCC.*
- *At each TNM stage, all of the HRs of each tumor-node-metastasis-socioeconomic factors (TNM-SEF) stage showed that patients with TNM-SEF0 stage had lower HRs than those with TNM-SEF1 stage.*
- *Some HRs of patients with TNM-SEF1 stage even exceeded the HRs of those with TNM-SEF0 stage who had higher TNM stages.*
- *The C-index of the TNM-SEF stage was larger than that of the only TNM stage.*
- *The novel TNM-SEF staging system could make the precision of prognostic prediction and clinical guidance more accurate in HCC.*

SEF Stage and Statistical Analysis

We performed multivariate Cox regression analysis for all prognostic predictors with a value of $P < .05$ in the univariate analysis of SEF (marital status, insurance status, median household income, and year of diagnosis). Hazard ratios (HRs) were used with 95% CI. The analysis results showed that insurance status, median household income, marital status, and year of diagnosis were significant prognostic SEFs of HCC cause-specific survival (HCSS).

We stratified patients based on the prognostic score incorporating the 4 SEFs, as shown in Figure 2. Firstly, the point in each group of SEF equivalents was regarded as the HR value. We then calculated the summation of the points (HRs) in the 4 SEFs as the total prognostic score for each patient. For instance, in a married and uninsured patient with HCC whose income and year of diagnosis were $43.83-$53.16 K, and 2010, respectively, the point is calculated as the summation of 1.000, 1.406, 1.041, and 1.223, which equals 4.670. The total scores ranged from 3.919 to 4.885, with a full-scale prognostic score based on the 4 SEFs, which was 3.919 for the best prognosis; patients with a score of 4.885 had the worst prognosis. Then we divided the prognostic score into 2 groups, and the median value of the prognostic score was regarded as the cutoff point. Lower scores were assigned to the SEF0 stage and higher scores were assigned to the SEF1 stage.

Statistical Analysis

We used the chi-square test to compare baseline patient demographics and tumor characteristics. We used multivariate Cox analysis to determine the prognosis of the SEF stage as well as the combined TNM stage and SEF stage (TNM-SEF stage). The primary endpoint of this study was HCSS, a specified time from the date of diagnosis to the date of death owing to HCC. We used Kaplan–Meier survival curves to assess the prognostic prediction of each TNM-SEF stage. Additionally, we used the concordance index (C-index) to evaluate the discriminative abilities of the TNM-SEF staging system. A value of $P < .05$ was considered to indicate a significant difference. All statistical analyses were conducted using the IBM SPSS Version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Using the selection criteria, we identified 12 514 patients with HCC diagnosed between January 1, 2010 and December 31, 2015. The baseline characteristics of patients with HCC included in our study are shown in

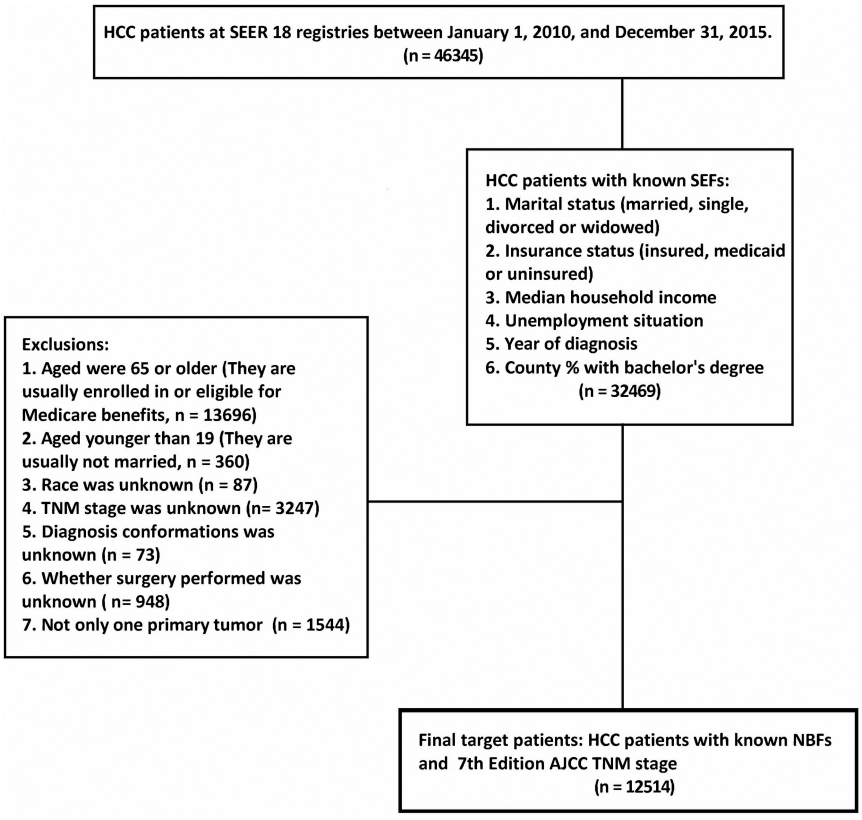

Figure 1. Flow diagram of patient population selected from the Surveillance, Epidemiology, and End Results (SEER) database.

Table 1. Compared with the general population, patients with HCC were more likely to be male (82.6%). Most patients (86.6%) were aged from 51 to 64 years, White (68.0%), and insured (57.4%).

Association of SEFs With HCSS

The univariate analysis showed that race, sex, tumor size, surgery, grade, TNM stage, insurance status, marital status, county percentage with bachelor's degree, household

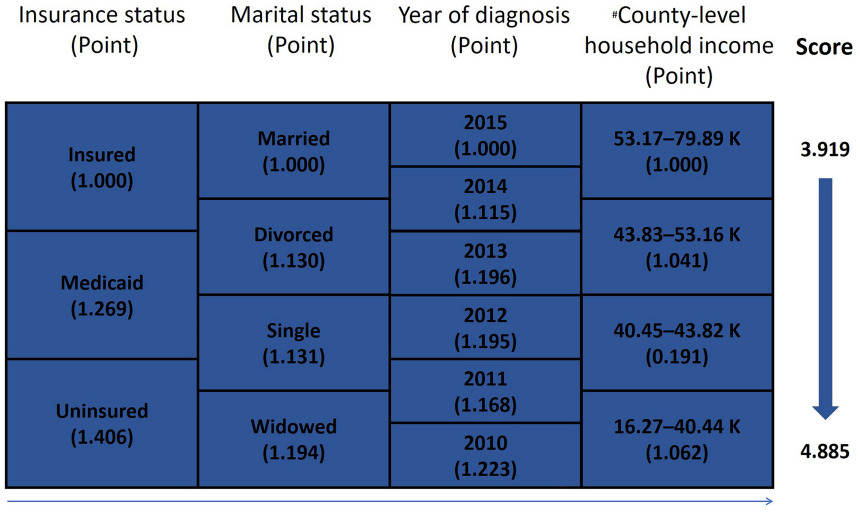

Figure 2. Patient prognostic score in hepatocellular carcinoma (HCC): risk-stratifications.

Table 1. Baseline Characteristics of Patients With Hepatocellular Carcinoma Included in Our Study

Variable	*n*%
Race	
White	8507 (68.0%)
Black	1985 (15.9%)
Other*	2022 (16.1%)
Sex	
Male	10340 (82.6%)
Female	2174 (17.4%)
Tumor grade	
Well differentiated	1176 (9.4%)
Moderately differentiated	1849 (14.8%)
Poorly differentiated	929 (7.4%)
Undifferentiated	67 (0.5%)
Unknown	8493 (67.9%)
TNM stage	
I	4880 (39.0%)
II	2693 (21.5%)
IIIA	1130 (9.0%)
IIIB	941 (7.5%)
IIIC	229 (1.8%)
IVA	566 (4.5%)
IVB	2075 (16.6%)
Surgery	
Performed	3459 (27.6%)
Not performed	9055 (72.4%)
County % with bachelor degree	
5.43-17.55%	3181 (25.4%)
17.56-24.86%	3538 (28.3%)
24.87-30.81%	2911 (23.3%)
30.82-51.31%	2884 (23.0%)
County-level median household income#	
16.27-40.44 K	3129 (25.0%)
40.45-43.82 K	3203 (25.6%)
43.83-53.16 K	3125 (25.0%)
53.17-79.89 K	3057 (24.4%)
County % who were unemployed	
1.83-4.76%	3128 (25.0%)
4.77-5.93%	3152 (25.2%)
5.94-8.23%	3721 (29.7%)
8.24-17.17%	2513 (20.1%)
Year of diagnosis	
2010	1893 (15.1%)
2011	2028 (16.2%)
2012	2125 (17.0%)
2013	2088 (16.7%)
2014	2187 (17.5%)
2015	2193 (17.5%)
Tumor size	
<3 cm	3800 (30.4%)
3-5 cm	3047 (24.3%)
>5 cm	4403 (35.2%)
Unknown	1264 (10.1%)
Age at diagnosis (years)	
19-50	1676 (13.4%)
51-55	2739 (21.9%)
56-60	4555 (36.4%)
61-64	3544 (28.3%)
Insurance status	
Insured	7187 (57.4%)
Medicaid	4428 (35.4%)
Uninsured	899 (7.2%)
Marital status	
Married	6255 (50.0%)
Single	3914 (31.3%)
Divorced	1890 (15.1%)
Widowed	455 (3.6%)

*Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown.
#County-level median household incomeshown in US dollars.
TNM, tumor, node, metastasis.

income, and percentage of unemployed were all independently associated with HCSS (all $P < .05$). We analyzed these factors in the multivariate Cox analysis. The results demonstrated that SEFs including insurance status, year of diagnosis, household income, and marital status, were all independent predictors for survival (Table 2).

Table 2. Univariate Survival Analysis for Evaluating the Influence on HCSS Using Data from the SEER Database

			Univariate Analysis			Multivariate Analysis		
Variable	Reference	Characteristic	HR (95% CI)	*SE*	*P*	HR (95% CI)	*SE*	*P*
Race	Black	White	0.814 (0.796-0.862)	0.029	<.001	0.974 (0.918-1.033)	0.030	.376
		Other*	0.687(0.637-0.742)	0.039	<.001	0.868 (0.802-0.940)	0.041	<.001
Age	19-50	51-55	1.105 (1.026-1.191)	0.038	.009	1.163 (1.079-1.254)	0.038	<.001
		56-60	1.062 (0.991-1.139)	0.035	.088	1.144 (1.066-1.228)	0.036	<.001
		61-64	1.033 (0.961-1.111)	0.037	.378	1.160 (1.077-1.249)	0.038	<.001
Sex	Male	Female	0.768 (0.724-0.815)	0.030	<.001	0.881 (0.829-0.936)	0.031	<.001
County% with bachelor degree	30.82–51.31%	24.87–30.81%	1.143 (1.072-1.218)	0.052	<.001	1.011 (0.934-1.096)	0.041	.780
		17.56–24.86%	1.202 (1.131-1.278)	0.047	<.001	1.041 (0.950-1.414)	0.047	.388
		5.43-17.55%	1.321 (1.241-1.405)	0.048	<.001	1.089 (0.987-1.210)	0.050	.088
County % who were unemployed	1.83–4.76%	4.77-5.93%	1.079 (1.015-1.147)	0.031	.015	1.011 (0.945-1.082)	0.034	.749
		5.94-8.23%	1.135 (1.070-1.203)	0.030	<.001	1.078 (0.997-1.166)	0.040	.059
		8.24-17.17%	1.282 (1.203-1.366)	0.032	<.001	1.035 (0.954-1.124)	0.042	.408
Grade	Well differentiated	Moderately differentiated	1.103 (0.996-1.221)	0.052	.059	1.218 (1.099-1.349)	0.052	<.001
		Poorly differentiated	2.142 (1.920-2.390)	0.056	<.001	1.794 (1.605-2.004)	0.057	<.001
		Undifferentiated	3.349 (2.573-4.360)	0.135	<.001	2.299 (1.764-2.997)	0.135	<.001
		Unknown	1.928 (1.772-2.097)	0.043	<.001	1.356 (1.244-1.477)	0.044	<.001
Tumor size	<3 cm	3-5 cm	1.640 (1.537-1.751)	0.033	<.001	1.384 (1.296-1.479)	0.034	<.001
		>5 cm	3.328 (3.141-3.526)	0.030	<.001	1.990 (1.857-2.133)	0.035	<.001
		Unknown	5.654 (5.241-6.100)	0.039	<.001	2.513 (2.308-2.737)	0.043	<.001
Surgery	Performed	Not performed	4.158 (3.910-4.421)	0.031	<.001	2.765 (2.581-2.961)	0.035	<.001
TNM stage	I	II	1.150 (1.079-1.226)	0.033	<.001	1.189 (1.114-1.269)	0.033	<.001
		IIIA	2.729 (2.530-2.943)	0.039	<.001	1.529 (1.403-1.666)	0.044	<.001
		IIIB	3.940 (3.639-4.266)	0.041	<.001	2.305 (2.161-2.555)	0.043	<.001
		IIIC	4.068 (3.526-4.694)	0.073	<.001	2.656 (2.295-3.073)	0.074	<.001
		IVA	3.756 (4.411-4.137)	0.049	<.001	2.215 (2.004-2.447)	0.051	<.001
		IVB	5.898 (5.542-6.276)	0.032	<.001	2.986 (2.786-3.199)	0.035	<.001
Insurance status	Insured	Medicaid	1.503 (1.437-1.573)	0.023	<.001	1.269 (1.210-1.332)	0.025	<.001
		Uninsured	2.105 (1.946-2.277)	0.040	<.001	1.406 (1.296-1.527)	0.042	<.001
County-level household median income#	53.17-79.89 K	43.83-53.16 K	1.104 (1.038-1.174)	0.032	.002	1.041 (0.967-1.121)	0.038	.288
		40.45-43.82 K	1.141 (1.073-1.214)	0.031	<.001	0.919 (0.833-1.014)	0.050	.091
		16.27-40.44 K	1.355 (1.275-1.439)	0.031	<.001	1.062 (0.968-1.165)	0.072	.205

Table 2. Univariate Survival Analysis for Evaluating the Influence on HCSS Using Data from the SEER Database (*Continued*)

Variable	Reference	Characteristic	Univariate Analysis			Multivariate Analysis		
			HR (95% CI)	*SE*	*P*	HR (95% CI)	*SE*	*P*
Year of diagnosis	2015	2014	1.068 (0.985-1.158)	0.041	.112	1.115 (1.028-1.209)	0.041	.009
		2013	1.161 (1.072-1.257)	0.041	<.001	1.196 (1.103-1.296)	0.041	<.001
		2012	1.172 (1.083-1.268)	0.040	<.001	1.195 (1.104-1.294)	0.040	<.001
		2011	1.122 (1.036-1.216)	0.041	<.001	1.168 (1.078-1.265)	0.041	<.001
		2010	1.230 (1.135-1.332)	0.041	<.001	1.223 (1.128-1.326)	0.041	<.001
Marital status	Married	Single	1.411 (1.345-1.481)	0.025	<.001	1.131 (1.073-1.191)	0.027	<.001
		Divorced	1.305 (1.227-1.388)	0.031	<.001	1.130 (1.016-1.204)	0.032	<.001
		Widowed	1.200 (1.069-1.346)	0.059	.002	1.194 (1.062-1.343)	0.060	.003

*Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown.
#Shown in US dollars.
TNM, tumor, node, metastasis; HR, hazard ratio; CI, confidence interval; SE, standard error; HCSS, hepatocellular carcinoma cancer-specific survival; SEER, Surveillance, Epidemiology, and End Results.

Association of SEF Stage With HCSS

The SEF0 stage was attributed to 6300 patients (50.3%) and SEF1 stage was attributed to 6214 patients (49.7%). The multivariate analysis suggested that the SEF stage was an independent predictor of survival. When compared with the SEF0 stage, the SEF1 stage was independently associated with a 36.1% increased risk of cancer-specific mortality (HR: 1.361, 95% CI: 1.303-1.422, $P < .001$; Table 3). We also performed multivariable Cox analysis in patients with non-metastatic (TNM stage I-III) HCC ($n = 9873$) and metastatic (TNM stage IV) HCC ($n = 2641$). The 2 outcomes proved that the SEF stage was independently associated with cancer-specific mortality. In patients with metastatic HCC, we observed a 22.2% increased risk of cancer-specific mortality in the SEF1 stage as compared with the SEF0 stage (HR: 1.222, 95% CI: 1.126-1.326, $P < .001$; see Supplementary Table 1). However, in non-metastatic HCC, a 41.8% increased risk of cancer-specific mortality was observed in the SEF1 stage as compared with the SEF0 stage (HR: 1.418, 95% CI: 1.345-1.494, $P < .001$; see Supplementary Table 2); this result was slightly higher than that in the overall cohort, suggesting that the efficacy of the prognostic prediction of SEF stage was improved in the TNM stage I-III HCC patients.

Prognostic Prediction of TNM-SEF Stage

The C-index of the TNM-SEF stage (0.768, 95% CI: 0.774-0.762) was larger than that of the TNM stage (0.764, 95% CI: 0.770-0.758). We used the Kaplan–Meier survival analysis of SEF-TNM stages (the TNM staging system including I, IIA, IIB, IIC, IIIA, IIIB, IIIC, IVA, and IVB, combined with SEF0 stage or SEF1 stage) to assess the prognostic prediction ability of the SEF-TNM stages, as seen in Figure 3. The figure also shows an increased HCSS in patients with stage SEF0-TNM as compared with those who had stage SEF1-TNM, at each TNM stage. For instance, we found an increased HCSS in IIA-SEF0 stage as compared with IIA-SEF1 stage (5-year HCSS: 41.0% vs. 25.1%, $\chi^2 = 92.24$; $P < .001$; Figure 4). Notably, we also found a decreased HCSS in I-SEF1 stage as compared with IIA-SEF0 stage (5-year HCSS: 28.1% vs. 41.0%, $\chi^2 = 63.94$; $P < .001$; Figure 4) and in IIIC-SEF1 stage as compared with IVA-SEF0 stage (5-year HCSS: 1.7% vs. 8.4%, $\chi^2 = 12.51$; $P < .001$; Figure 4).

Multivariate Cox analysis to compare the HRs of each TNM-SEF stage showed that patients with TNM-SEF0 stage had lower HRs than those with TNM-SEF1 stage, at each TNM stage (Figure 4). Interestingly, some HRs of patients with TNM-SEF1 stage even exceeded the HRs

Table 3. Multivariable Cox Regression Analyses of Independent Prognostic Factors in Hepatocellular Carcinoma

			Cancer-Specific Survival		
Variable	Reference	Characteristic	HR (95% CI)	*SE*	*P*
Race	Black	White	0.958 (0.903-1.015)	0.030	.147
		Other*	0.837 (0.774-0.905)	0.040	<.001
Age	19-50	51-55	1.161 (1.077-1.252)	0.038	<.001
		56-60	1.130 (1.053-1.212)	0.036	.001
		61-64	1.134 (1.054-1.220)	0.037	.001
Sex	Male	Female	0.876 (0.825-0.930)	0.030	<.001
County % with bachelor degree	30.82-51.31%	24.87-30.81%	1.035 (0.964-1.111)	0.036	.341
		17.56-24.86%	1.039 (0.962-1.122)	0.039	.329
		5.43-17.55%	1.096 (1.013-1.185)	0.040	.022
County % who were unemployed	1.83-4.76%	4.77–5.93%	1.020 (0.954-1.090)	0.034	.569
		5.94–8.23%	1.064 (0.990-1.145)	0.037	.094
		8.24–17.17%	1.034 (0.955-1.119)	0.040	.407
Grade	Well	Moderately	1.231 (1.111-1.364)	0.052	<.001
		Poorly	1.806 (1.616-2.017)	0.056	<.001
		Undifferentiated	2.204 (1.691-2.872)	0.135	<.001
		Unknown	1.367 (1.254-1.489)	0.044	<.001
Tumor size	< 3 cm	3-5 cm	1.391 (1.303-1.486)	0.034	<.001
		> 5 cm	2.000 (1.866-2.144)	0.035	<.001
		Unknown	2.521 (2.316-2.745)	0.043	<.001
Surgery	Performed	Not performed	2.763 (2.580-2.959)	0.035	<.001
TNM stage	I	II	1.192 (1.116-1.272)	0.033	<.001
		III A	1.533 (1.407-1.670)	0.044	<.001
		III B	2.357 (2.168-2.563)	0.043	<.001
		III C	2.655 (2.296-3.072)	0.074	<.001
		IV A	2.223 (2.012-2.456)	0.051	<.001
		IV B	3.007 (2.807-3.222)	0.035	<.001
SEF stage	Stage 0	Stage 1	1.361 (1.303-1.422)	0.022	<.001

*Other includes American Indian/Alaska Native, Asian/Pacific Islander, and unknown.
TNM, tumor, node, metastasis; HR, hazard ratio; CI, confidence interval; SE, standard error; SEF, socioeconomic factor.

of those with TNM-SEF0 stage who had higher TNM stages. For example, as shown in Figure 4, when taking stage I-SEF0 as a reference, the HR was higher in patients with I-SEF1 stage (HR: 1.741, 95% CI: 1.607-1.886) than in those with II-SEF0 stage (HR: 1.206, 95% CI: 1.095-1.328); in patients with IIIA-SEF1 stage (HR: 4.470, 95% CI: 4.018-4.973) or IIIB-SEF1 stage (HR: 5.941, 95% CI: 5.309-6.649), as compared with patients who had IIIC-SEF0 stage (HR: 4.368, 95% CI: 3.505-5.444); and in patients with IIIB-SEF1 stage (HR: 5.941, 95% CI: 5.309-6.649) or IIIC-SEF1 stage (HR: 6.547, 95% CI: 5.412-7.919) as compared with patients who had IVA-SEF0 stage (HR: 4.480, 95% CI: 3.904-5.141).

DISCUSSION

Great progress has been made in the research on HCC at the levels of cellular and molecular biology.[12,13] However, only some studies have focused on prognostic SEFs such as marital status, socioeconomic status, insurance, employment, and education.[5-9] Furthermore, no research has studied more than 3 SEFs together in 1 study, and no studies have incorporated SEFs into the TNM staging

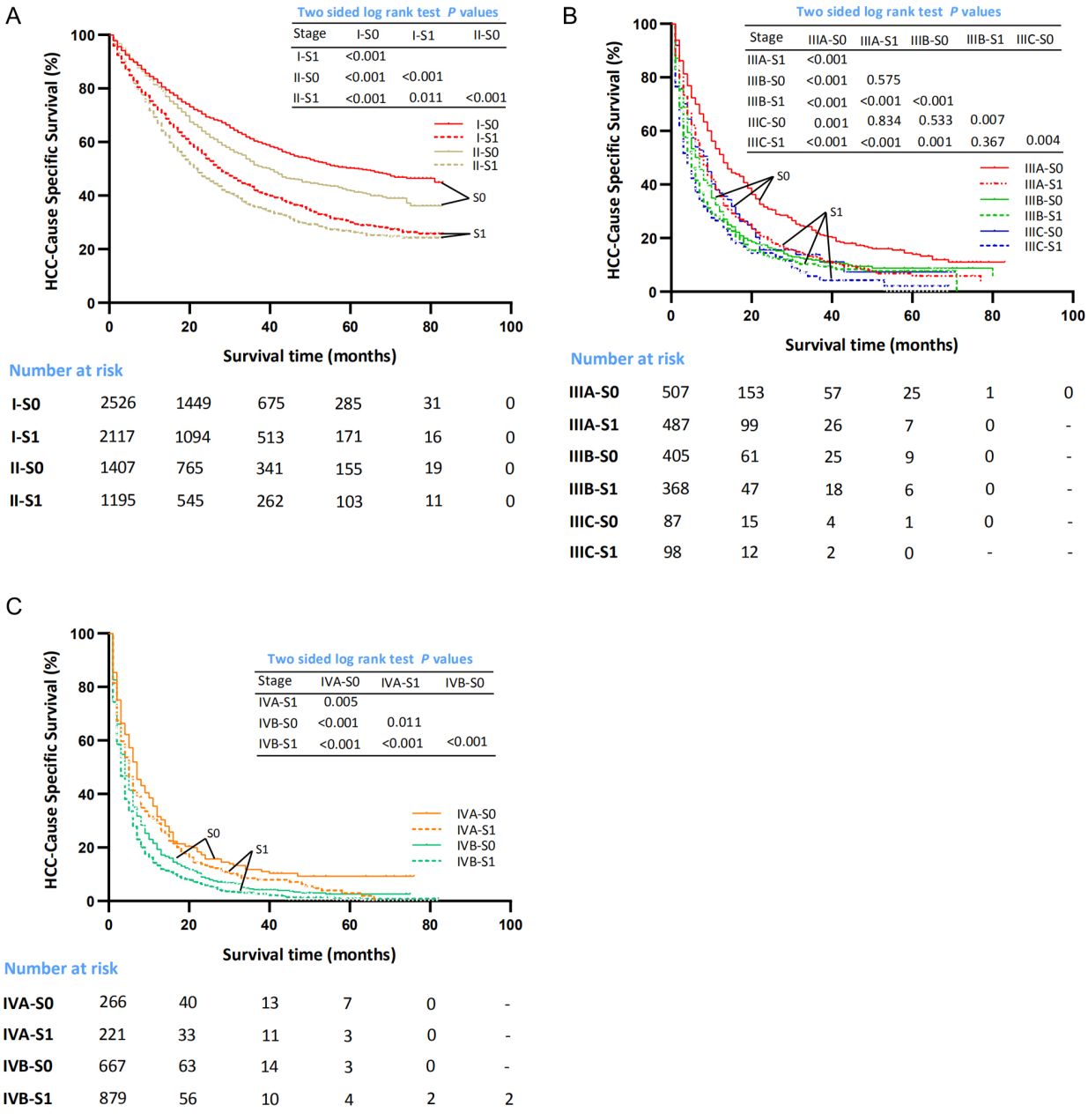

Figure 3. Kaplan–Meier survival curves of the tumor-node-metastasis-socioeconomic factor (TNM-SEF) staging system. (A) Cancer-specific survival (CSS) of the I-S0 stage, I-S1 stage, II-S0 stage, and II-S1 stage. (B) CSS of the IIIA-S0 stage, IIIA-S1 stage, IIIB-S0 stage, and IIIB-S1 stage, IIIC-S0 stage, and IIIC-S1 stage. (C) CSS of IVA-S0 stage, IVA-S1 stage, IVB-S0 stage, and IVB-S1 stage.

system to improve the prognostic prediction and clinical guidelines in HCC.

In 2016, a population-based study demonstrated that married patients had higher survival rates than unmarried patients.[5] A similar conclusion has been reached for nearly all cancers including pancreatic, gastric, colon, and rectal cancers,[14-17] among others. Some underlying reasons may be that marriage could improve cardiovascular, endocrine, and immune functions[18] and married patients are more likely to accept effective treatment, leading to longer survival.

Variable	No. of Patients	Univariate analysis			Multivariate analysis	
		5-year HCSS	Log rank χ2	*P*	HR (95% CI)	*P*
I-SEF0	2606	48.7%	Reference		Reference	<0.001
I-SEF1	2274	28.1%	194.94	<0.001	1.741 (1.607-1.886)	<0.001
II-SEF0	1436	41.0%	Reference		1.206 (1.095-1.328)	<0.001
II-SEF1	1257	25.1%	92.24	<0.001	1.932 (1.765-2.116)	<0.001
IIIA-SEF0	550	12.8%	Reference		2.963 (2.648-3.315)	<0.001
IIIA-SEF1	580	5.0%	41.86	<0.001	4.470 (4.018-4.973)	<0.001
IIIB-SEF0	457	7.8%	Reference		4.646 (4.138-5.216)	<0.001
IIIB-SEF1	484	6.0%	13.78	<0.001	5.941 (5.309-6.649)	<0.001
IIIC-SEF0	100	6.4%	Reference		4.368 (3.505-5.444)	<0.001
IIIC-SEF1	129	1.7%	8.46	0.004	6.547 (5.412-7.919)	<0.001
IVA-SEF0	296	8.4%	Reference		4.480 (3.904-5.141)	<0.001
IVA-SEF1	270	2.5%	7.98	0.005	5.651 (4.923-6.487)	<0.001
IVB-SEF0	855	2.1%	Reference		6.922 (6.304-7.602)	<0.001
IVB-SEF1	1220	0.8%	25.37	<0.001	8.687 (7.970-9.467)	<0.001

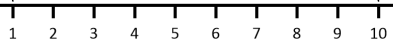

Figure 4. Prognosis of tumor-node-metastasis-socioeconomic factor (TNM-SEF) stage in hepatocellular carcinoma (HCC).

In other studies, Medicaid status or not having insurance is related with adverse survival compared with having insurance.[19,20] We considered that the poor prognosis of Medicaid status and lack of insurance might result in patients having a more advanced tumor stage at diagnosis and late or inadequate treatment after diagnosis .[9]

The diagnosis and treatment of diseases in medical institutions can be expected to gradually and substantially improve with time. This was proven in a previous study showing the year of diagnosis as an independent predictor in HCC.[7] Similar results were obtained in the present research.

We also found that a higher household income among patients was associated with relatively longer survival. The possible reasons may include early patient diagnosis and adequate treatment. Our results are consistent with prior research.[21]

Although the TNM staging system is widely used clinically in countries worldwide, it only considers certain biological factors, such as the extent of invasion of the primary tumor, the number of lymph nodes, and distant spread.[22] Although the TNM system has been modified many times, it is not yet optimal for prognostic prediction. TNM staging neither takes into account the SEF, nor the other biological factors that affect the prognosis of HCC. Hence, the need for a more comprehensive staging system that includes other biological factors or SEFs is a concern.

SEFs have not yet been systematically studied in the prognosis of HCC. Our study is the first to combine SEFs with the TNM staging system. In this research, the novel SEF stage (based on the combination of marital status, insurance status, year of diagnosis, and household income) was indicated to be an independent prognostic factor, and patients with SEF0 stage showed significantly increased HCSS as compared with those who had SEF1 stage at each TNM stage, especially TNM stage I-III. Additionally, our studies indicated that the SEF1 stage showed a 36.1% decreased risk of cancer-specific mortality in HCC overall when compared with the SEF0 stage, a 41.8% decreased risk in non-metastatic HCC, and a 22.2% decreased risk in metastatic HCC. This phenomenon indicated that the SEF stage plays a relatively important role in survival among patients with early-stage cancer; patients with SEF0 stage could receive a greater survival benefit in TNM stages I-III than in TNM stage IV.

Besides, the improved C-index of TNM-SEF also proved that the TNM-SEF staging system offers greater advantages concerning prognostic ability than the TNM staging system alone. Based on the above findings, the TNM-SEF staging system is more helpful in the accurate prognosis of survival in HCC and in more comprehensive clinical treatment and management in HCC patients.

Commonly, the more advanced the TNM staging of HCC at diagnosis, the worse the prognosis, that is, the poorer the prognosis expected in TNM stage II than stage I, in TNM stage III than stage II, and in TNM stage IV than stage III.[23] However, the present analysis manifested that the cancer-specific mortality of patients with HCC in several TNM-SEF1 stages exceeded that of patients with TNM-SEF0 stage who had higher TNM stages. For instance, the cancer-specific mortality was lower in patients with IIA-SEF0 stage than in those with stage I-SEF1, in patients with IIIC-SEF0 stage than in those with IIIB-SEF1 stage, and in patients with IVA-SEF0 stage than in those with IIIC-SEF1 stage. The phenomenon of these 3 subgroups indicates that the TNM-SEF stage may better reflect survival than the TNM stage, and SEF0 stage is associated with a better survival benefit than SEF1 stage.

Several potential limitations exist in our research. First, the overall cohort comprised 12 514 patients from the SEER database, but samples from some subgroups (e.g., IIIC-SEF0, IIIC-SEF1, IVA-SEF0, IVA-SEF1) were relatively small. Second, the applicability of our result is limited to America; the results may differ in other areas with different health care systems. Finally, because our data were retrospectively reviewed, future prospective studies are needed to validate our findings.

CONCLUSION

We proved that marital status, insurance status, household income, and year of diagnosis were all independent prognostic factors in HCC. Importantly, the SEF stage was a strongly independent prognostic factor, which warrants greater attention among healthcare professionals and institutions taking care of HCC patients. Greater attention is especially needed in patients with poor SEFs who may benefit from additional resources and support during therapy for HCC. The new staging system could therefore improve the accuracy of prognostic prediction and the clinical guidance in HCC, strongly supporting the combination of the SEF stage with the TNM staging system.

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human participants or animals performed by any of the authors. It has been permitted to obtain the data from SEER database (Reference Number 10778-Nov2018).

Informed Consent: As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.B.S., B.H.Z.,G.Q.J.; Design - B.B.S., D.S.B., J.J.Q.; Supervision - B.H.Z., C.Z., S.J.J; Resource - B.B.S,D.S.B, G.Q.J; Materials - B.B.S., B.H.Z., C.Z.; Data Collection and/or Processing - D.S.B., J.J.Q., S.J.J.; Analysis and/or Interpretation - D.S.B., C.Z., B.B.S.; Literature Search - B.B.S., G.Q.J., D.S.B.; Writing - B.B.S., B.H.Z., G.Q.J.; Critical Reviews -B.B.S., G.Q.J., D.S.B.

Acknowledgements: We would be grateful to the SEER database for its open access. And we thank Analisa Avila. ELS, of Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Conflict of Interest: The authors have no conflict of interests to declare.

Financial Disclosure: This work was supported by the Project of Invigorating Health Care through Science, Technology and Education: Jiangsu Provincial Medical Youth Talent (QNRC2016331).

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. [CrossRef]

2. Zhao J, Mao J, Li W. Association of tumor grade With long-term survival in patients With hepatocellular carcinoma After liver transplantation. Transplant Proc. 2019;51(3):813-819. [CrossRef]

3. Liu H, Cen D, Yu Y, et al. Does fibrosis have an impact on survival of patients with hepatocellular carcinoma: evidence from the SEER database? BMC Cancer. 2018;18(1):1125. [CrossRef]

4. Yang A, Xiao W, Chen D, et al. The power of tumor sizes in predicting the survival of solitary hepatocellular carcinoma patients. Cancer Med. 2018;7(12):6040-6050. [CrossRef]

5. Wu C, Chen P, Qian JJ, et al. Effect of marital status on the survival of patients with hepatocellular carcinoma treated with surgical resection: an analysis of 13,408 patients in the surveillance, epidemiology, and end results (SEER) database. Oncotarget. 2016;7(48):79442-79452. [CrossRef]

6. Shebl FM, Capo-Ramos DE, Graubard BI, McGlynn KA, Altekruse SF. Socioeconomic status and hepatocellular carcinoma in the United States. Cancer Epidemiol Biomarkers Prev. 2012;21(8):1330-1335. [CrossRef]

7. Kokabi N, Xing M, Duszak R, Jr, et al. Sociodemographic impact on survival in unresectable hepatocellular carcinoma: a survival

epidemiology and end results study. Future Oncol. 2016;12(2):183-198. [CrossRef]
8. Artinyan A, Mailey B, Sanchez-Luege N, et al. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. Cancer. 2010;116(5):1367-1377. [CrossRef]
9. Wang J, Ha J, Lopez A, et al. Medicaid and uninsured hepatocellular carcinoma patients have more advanced tumor stage and are less likely to receive treatment. J Clin Gastroenterol. 2018;52(5):437-443. [CrossRef]
10. Kamarajah SK, Frankel TL, Sonnenday C, et al. Critical evaluation of the American joint commission on cancer (ajcc). 8th ed staging system for patients with hepatocellular carcinoma (hcc): a surveillance, epidemiology, end results (seer) analysis. J Surg Oncol. 2018;117:644-650. [CrossRef]
11. Nathan H, Pawlik TM. Limitations of claims and registry data in surgical oncology research. Ann Surg Oncol. 2008;15(2):415-423. [CrossRef]
12. Zhang L, Niu H, Ma J, et al. The molecular mechanism of LncRNA34a-mediated regulation of bone metastasis in hepatocellular carcinoma. Mol Cancer. 2019;18(1):120. [CrossRef]
13. Nault JC, Galle PR, Marquardt JU. The role of molecular enrichment on future therapies in hepatocellular carcinoma. J Hepatol. 2018;69(1):237-247. [CrossRef]
14. Wang XD, Qian JJ, Bai DS, et al. Marital status independently predicts pancreatic cancer survival in patients treated with surgical resection: an analysis of the SEER database. Oncotarget. 2016;7(17):24880-24887. [CrossRef]
15. Shi RL, Chen Q, Yang Z, et al. Marital status independently predicts gastric cancer survival after surgical resection--an analysis of the SEER database. Oncotarget. 2016;7(11):13228-13235. [CrossRef]
16. Yang CC, Cheng LC, Lin YW, et al. The impact of marital status on survival in patients with surgically treated colon cancer. Med (Baltim). 2019;98(11):e14856. [CrossRef]
17. Li Z, Wang K, Zhang X, Wen J. Marital status and survival in patients with rectal cancer: A population-based STROBE cohort study. Med (Baltim). 2018;97(18):e0637. [CrossRef]
18. Gallo LC, Troxel WM, Matthews KA, Kuller LH. Marital status and quality in middle-aged women: associations with levels and trajectories of cardiovascular risk factors. Health Psychol. 2003;22(5):453-463. [CrossRef]
19. Du XL, Lin CC, Johnson NJ, Altekruse S. Effects of individual-level socioeconomic factors on racial disparities in cancer treatment and survival: findings from the National Longitudinal Mortality Study, 1979-2003. Cancer. 2011;117(14):3242-3251. [CrossRef]
20. Koroukian SM, Bakaki PM, Raghavan D. Survival disparities by Medicaid status: an analysis of 8 cancers. Cancer. 2012;118(17):4271-4279. [CrossRef]
21. Shen Y, Guo H, Wu T, et al. Lower education and household income contribute to advanced disease, less treatment received and poorer prognosis in patients with hepatocellular carcinoma. J Cancer. 2017;8(15):3070-3077. [CrossRef]
22. Yarbro JW, Page DL, Fielding LP, Partridge EE, Murphy GP. American Joint Committee on Cancer Prognostic Factors Consensus. American Joint Committee on Cancer prognostic factors consensus conference. Cancer Conference. 1999;86(11):2436-2446. [CrossRef]
23. Chun YH, Kim SU, Park JY, et al. Prognostic value of the 7th edition of the AJCC staging system as a clinical staging system in patients with hepatocellular carcinoma. Eur J Cancer. 2011;47(17):2568-2575. [CrossRef]