# The Impact of Socioeconomic Status on Staging, Prognosis in Hepatocellular Carcinoma

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**Research**

**Keywords:** socioeconomic status, TNM stage, Hepatocellular carcinoma SEER database

**Posted Date:** September 20th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-900439/v1

# Abstract

**Purpose**: We conducted this large population-based study to evaluate the impact of socioeconomic status (SES) factors on cancer-specific survival (CSS) of patients with hepatocellular carcinoma (HCC). We further assessed the predictive value of a novel TNM-SES staging system which incorporated these SES factors with TNM stage.

**Methods**: A total of 13791 patient diagnosed with HCC from 2012-2016 were retrieved from the large population database. Cox proportional hazards regression model and Harrell's concordance index (C-index) was used to identify the SES factors associated with CSS and analyze the prognostic value of TNM-SES stage. Kaplan–Meier curves and log-rank test were performed to evaluate CSS.

**Results**: Four SES factors (marital status, insurance status, education, household income) were identified as the prognostic predictor associated with CSS. The SES-2 (lower SES) stage was significantly correlated to unfavorable CSS of the patients with HCC, with a 32.0% increased risk (HR = 1.32, 95% CI (1.26 - 1.39), P<0.001), after adjusting for several confounders. The C-index of the TNM-SES stage was 0.735(95% CI (0.729 - 0.741)) which was higher than that of the TNM stage (0.718, 95%CI (0.712 - 0.724)), indicating a high accuracy of prognostic prediction.

**Conclusion**: Our comprehensive study revealed that SES was significantly associated with prognosis of patient with HCC after adjusting several confounders. The novel TNM-SES staging system which combined TNM stage and SES stage had more superior predictive value than traditional TNM stage. Disparity on SES should receive more attention for patients with HCC in clinical management.


# Introduction

Hepatocellular carcinoma (HCC) is the most common cancer and the third leading cause of cancer-related deaths worldwide[1]. Despite great advance had made in the treatment modality for HCC, the prognosis of HCC remains dismal with 1-year survival < 50%[2], because only several therapies such as hepatic surgery, ablation and transplantation offered the opportunity for cure for early-stage disease[3]. The survival outcome of patients with HCC is influenced by various variate,including biological factors and socioeconomic status (SES). The impact of biological factors on the prognosis of patient with HCC have been extensively investigated, such as sex, AFP level, portal vein invasion and so on[4–8]. Recently, the effects of SES on cancer survival has received considerable interests. SES contains household income, educational attainment, employment status, insurance status and marital status, and encompasses quality of life attributes as well as the opportunities and privileges afforded to people within society. Previous studies[9, 10] have indicated that patients with HCC with low SES status have more advanced stage at diagnosis and worse prognosis. However, as far as we know, the effect of SES on the tumor stage at diagnosis and the prognosis of patient with HCC has not yet been investigated together as an independent parameter.

The American Joint Committee on Cancer (AJCC) staging system has been widely used to stratify patients for treatment strategy and predictive prognosis in clinical management. Nevertheless, the TNM staging system only incorporates the size and extent of the tumor (T stage), the number of nearby positive lymph nodes (N stage) and whether to metastasis (M stage), without involvement of the SES of patients, which also plays a critical role in prognosis of patient with HCC. Hence, a novel staging system for patients with HCC, which combine traditional TNM stage and SES stage, is needed to accurately predict prognosis in clinical management. In this large population-based study, we firstly evaluated the effect of several SES factors, including insurance status, marital status, country percentage with bachelor degree, country-level median household income and country percentage with employed on cancer-specific survival (CSS) of patients with HCC using the data from the Surveillance, Epidemiology, and End Results (SEER) database. Accordingly, the SES stage was generated by sever SES factors associate with CSS. Ultimately, we constructed a novel TNM-SES stage system which incorporate the traditional TNM stage with SES stage, and further evaluated its prognostic value in clinical management.

## Materials And Methods

# Database and patient selection

We obtained the clinical information of patients with HCC from the Surveillance, Epidemiology, and End Results (SEER) program (1973–2016), which collects and publishes cancer incidence and survival data from population-based registries covering about 28% of the population of the United States. Patients who were diagnosed with primary HCC between January 1 2012 and December 31 2016 were retrieved for our study, with the primary site code (C22.0) and histological types codes (8170/3-8175/3). The SES information of the patients with HCC were analyzed in our study, including insurance status, marital status, country percentage with bachelor degree, country-level median household income and country percentage with employed. The classifications of insurance status and marital status were based on the data from the SEER program. The classifications of country percentage with bachelor degree and Country percentage with employed were according to the quadratic method of the number of patients in our study, while we divided the group of country-level median household income in line with the classification of household income in the United States. We only enriched the patients with aged 18–65 years at diagnosis, because patients aged ≥ 65 years were qualified for Medicare in US, which may make the research bias in our study. The patients without survival time > 1 month and adequate clinical information were excluded in our study.

# The Classification Of Ses Stage

Four SES factors associated with cancer-specific survival (CSS) were selected using Cox proportional hazards regression model, including insurance status, marital status, country percentage with bachelor degree and country-level median household income. As showed in Fig. 1, patients in our study were sorted out by the different status of four important SES factors. The corresponding hazard ratios (HRs)

values which were obtained by Cox proportional hazards regression model were assigned as the parameter values to indicate the status of patients with each four SES factors. The SES prognostic scores of patients were calculated by adding the parameter values of four significant SES factors. The SES prognostic scores ranged from 3.64 to 4.44 in our study, with a score of 3.64 indicating the optimal survival outcome and a score of 4.44 indicating the dismal survival outcome. Then, patients were divided into two groups on the basis of cutoff SES prognostic score (score of 3.93), which was the median SES prognostic scores. Patients with SES prognostic scores < 3.93 were allocated into SES-1stage group (higher SES), while patients in SES-2 stage group (lower SES) were with SES prognostic scores > 3.93. For example, the SES prognostic score of a patient who was Medicaid (1.19) and Divorced (1.11) and lived in the country where 31.24%-39.07% people with bachelor degree (0.89) and the country with 45.00- 59.99K of median household income (0.97), was 4.16, and then this patient was allocated into SES-2 stage group. Finally, a new staging system (TNM-SES stage) were achieved by combining TNM stage (I, II, IIIA, IIIB, IIIC, IVA, IVB) with SES-1stage or SES-2 stage.

# Statistical analysis

Categorical variables were presented as frequencies and evaluated using the chi-square test or Fisher's exact test. The endpoint was cancer-specific survival (CSS) defined as the time from the data of diagnosis until death from HCC. Univariate and multivariate survival analyses were performed using Cox proportional hazards regression model. The hazard ratios (HRs) with their 95% confidence intervals (95% CIs) were calculated. The survival analysis of different factors was evaluated by using the Kaplan–Meier curves and log-rank test. We further assessed the performance of two staging system (TNM stage and TNM-SES stage) using Harrell's concordance index (C-index), where a larger value indicates better prognosis. The statistical analysis was performed using R software (version 3.5.1) and GraphPad Prism software version 6.0 (GraphPad Software, Inc., La Jolla, CA). All tests were two-sided, and $p < 0.05$ was considered statistically significant.

## Results

# Overall characteristics of the HCC patients

By using the SEER program, a total of 13791 patients diagnosed as primary HCC between January 1 2012 and December 31 2016 were identified in our study. The clinical characteristics of the included patients were showed in Table 1. Overall, a majority of patients with HCC were male (82.7%), white (68.1%) and with age of 56–60 years (37.0%). More than half of the patients (54.8%) had localized-stage HCC at initial diagnosis and 16.5% patients had distant-stage HCC. The most common TNM stage in our study was stage I with 5482 patients (39.8%). In term of SES factors, most patients were insured (62.3%) and married (48.4%). Notably, only 8.6% patients and 6.5% patients had received hepatic surgery and liver transplant, respectively. Approximately half of patients (54.2%) had undertaken chemotherapy.

Table 1
The characteristics of patients with hepatocellular carcinoma

| Characteristic | | No.(%) |
|---|---|---|
| Age | ≤ 50 | 1719 (12.5) |
| | 51–55 | 2865 (20.8) |
| | 56–60 | 5100 (37.0) |
| | ≥ 65 | 4107 (29.8) |
| Sex | Female | 2391 (17.3) |
| | Male | 11400 (82.7) |
| Race | White | 9397 (68.1) |
| | Black | 2282 (16.5) |
| | Other* | 2112 (15.3) |
| Stage | Localized | 7563 (54.8) |
| | Regional | 3954 (28.7) |
| | Distant | 2274 (16.5) |
| TNM stage | I | 5482 (39.8) |
| | II | 2995 (21.7) |
| | IIIA | 1209 ( 8.8) |
| | IIIB | 1057 ( 7.7) |
| | IIIC | 233 ( 1.7) |
| | IVA | 616 ( 4.5) |
| | IVB | 2199 (15.9) |
| Insurance | Insured | 8587 (62.3) |
| | Medicaid | 4353 (31.6) |
| | Uninsured | 851 ( 6.2) |
| Marital status | Married | 6668 (48.4) |
| | Never married | 4220 (30.6) |

indicates American Indian/AK Native, Asian/Pacific Islander,and unknown

**shown in US dollars

| Characteristic | | No.(%) |
|---|---|---|
| | Divorced | 2433 (17.6) |
| | Widowed | 470 ( 3.4) |
| Country % with bachelor degree | 7.64–22.82% | 3663 (26.6) |
| | 22.83–31.23% | 3419 (24.8) |
| | 31.24%-39.07% | 3662 (26.6) |
| | 39.08–57.51% | 3047 (22.1) |
| Country-level median household income** | 19.26-44.99K | 1867 (13.5) |
| | 45.00- 59.99K | 3361 (24.4) |
| | 60.00-74.99K | 5180 (37.6) |
| | 74.99-110.97K | 3383 (24.5) |
| Country % with employed | 1.29–5.8% | 3682 (26.7) |
| | 5.81–7.06% | 3595 (26.1) |
| | 7.07–8.53% | 3166 (23.0) |
| | 8.54–17.16% | 3348 (24.3) |
| Surgery | no surgery | 11712 (84.9) |
| | surgery | 1188 ( 8.6) |
| | transplant | 891 ( 6.5) |
| Chemotherapy | No | 7475 (54.2) |
| | Yes | 6316 (45.8) |
| indicates American Indian/AK Native, Asian/Pacific Islander,and unknown | | |
| **shown in US dollars | | |

Four SES factors related to CSS of patients with HCC

During follow-up, 55.9% (N = 7713) of patients with HCC died. As shown in Table 2, univariate analysis indicated that age, sex, race, stage, TNM stage,insurance status, marital status, country percentage with bachelor degree, country percentage with employed, country-level median household income, surgery and chemotherapy were significantly associated with CSS. Then we added these factors into the multivariate analysis. The results showed these four SES factors (insurance status, marital status, country percentage with bachelor degree and country-level median household income) were related to CSS. Other important predictors also included age, sex, race, stage, TNM stage surgery and chemotherapy.

Table 2
Univariate and multivariate analysis of CSS of patients with HCC

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value |
| Age | | | | |
| ≤ 50 | 1(Reference) | 1 | 1(Reference) | 1 |
| 51–55 | 1.09(1.01–1.18) | 0.031* | 1.11(1.03–1.20) | 0.010* |
| 56–60 | 1.04(0.97–1.12) | 0.300 | 1.04(0.96–1.12) | 0.320 |
| ≥ 65 | 0.99(0.92–1.07) | 0.828 | 1.03(0.95–1.11) | 0.515 |
| Sex | | | | |
| Female | 1(Reference) | 1 | 1(Reference) | 1 |
| Male | 1.38(1.29–1.47) | < 0.001* | 1.20(1.13–1.28) | < 0.001* |
| Race | | | | |
| White | 1(Reference) | 1 | 1(Reference) | 1 |
| Black | 1.25(1.18–1.33) | < 0.001* | 1.07(1.01–1.04) | 0.032* |
| Other** | 0.88(0.82–0.94) | < 0.001* | 0.98(0.92–1.05) | 0.612 |
| Stage | | | | |
| Localized | 1(Reference) | 1 | 1(Reference) | 1 |
| Regional | 2.81(2.67–2.96) | < 0.001* | 1.40(1.29–1.51) | < 0.001* |
| Distant | 6.88(6.48–7.31) | < 0.001* | 1.44(1.08–1.93) | 0.014* |

Abbreviation: CSS: cancer-specific survival; HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval

* indicates significance of P <0.05.

**indicates American Indian/AK Native, Asian/Pacific Islander and unknown

***shown in US dollars

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value |
| TNM stage | | | | |
| I | 1(Reference) | 1 | 1(Reference) | 1 |
| II | 1.23(1.15–1.32) | < 0.001 | 1.20(1.12–1.30) | < 0.001 |
| IIIA | 3.51(3.25–3.80) | < 0.001 | 2.92(2.66–3.20) | < 0.001 |
| IIIB | 5.12(4.72–5.55) | < 0.001 | 3.53(3.16–3.94) | < 0.001 |
| IIIC | 5.04(4.34–5.85) | < 0.001 | 3.99(3.33–4.48) | < 0.001 |
| IVA | 4.63(4.20–5.11) | < 0.001 | 3.14(2.78–3.56) | < 0.001 |
| IVB | 7.86(7.37–8.40) | < 0.001 | 4.77(3.54–6.43) | < 0.001 |
| Insurance staus | | | | |
| Insured | 1(Reference) | 1 | 1(Reference) | 1 |
| Medicaid | 1.42(1.36–1.49) | < 0.001 | 1.19(1.13–1.25) | < 0.001 |
| Uninsured | 2.12(1.95–2.30) | < 0.001 | 1.33(1.22–1.45) | < 0.001 |
| Marital status | | | | |
| Married | 1(Reference) | 1 | 1(Reference) | 1 |
| Never married | 1.36(1.30–1.44) | < 0.001 | 1.08(1.02–1.14) | 0.006 |
| Divorced | 1.31(1.23–1.39) | < 0.001 | 1.11(1.08–1.19) | 0.001 |
| Abbreviation: CSS: cancer-specific survival; HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval | | | | |
| indicates significance of P <0.05. | | | | |
| indicates American Indian/AK Native, Asian/Pacific Islander and unknown | | | | |
| ***shown in US dollars | | | | |

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value |
| Widowed | 1.15(1.01–1.30) | 0.037 | 1.11(0.97–2.26) | 0.119 |
| Country % with bachelor degree | | | | |
| 7.64–22.82% | 1(Reference) | 1 | 1(Reference) | 1 |
| 22.83–31.23% | 0.89(0.83–0.94) | < 0.001 | 0.95(0.88–1.03) | 0.204 |
| 31.24%-39.07% | 0.83(0.78–0.88) | < 0.001 | 0.89(0.83–0.98) | 0.014 |
| 39.08–57.51% | 0.71(0.67–0.76) | < 0.001 | 0.86(0.78–0.95) | 0.004 |
| Country-level median household income*** | | | | |
| 19.26-44.99K | 1(Reference) | 1 | 1(Reference) | 1 |
| 45.00- 59.99K | 0.91(0.84–0.97) | 0.006 | 0.97(0.90–1.05) | 0.421 |
| 60.00-74.99K | 0.76(0.71–0.81) | < 0.001 | 0.83(0.76–0.91) | < 0.001 |
| 74.99-110.97K | 0.65(0.61–0.70) | < 0.001 | 0.78(0.69–0.87) | < 0.001 |
| Country % with employed | | | | |
| 1.29–5.8% | 1(Reference) | 1 | 1(Reference) | 1 |
| 5.81–7.06% | 1.14(1.07–1.21) | < 0.001 | 0.99(0.93–1.07) | 0.972 |
| 7.07–8.53% | 1.15(1.06–1.24) | < 0.001 | 0.93(0.86–1.01) | 0.126 |

Abbreviation: CSS: cancer-specific survival; HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval

 indicates significance of P <0.05.

indicates American Indian/AK Native, Asian/Pacific Islander and unknown

***shown in US dollars

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value |
| 8.54–17.16% | 1.24(1.17–1.33) | < 0.001 | 0.89(0.85–1.03) | 0.071 |
| Surgery | | | | |
| no surgery | 1(Reference) | 1 | 1(Reference) | 1 |
| surgery | 0.30(0.27–0.33) | < 0.001 | 0.32(0.29–0.36) | < 0.001 |
| transplant | 0.07(0.06–0.09) | < 0.001 | 0.10(0.08–0.12) | < 0.001 |
| Chemotherapy | | | | |
| No | 1(Reference) | 1 | 1(Reference) | 1 |
| Yes | 0.75(0.71–0.78) | < 0.001 | 0.10(0.55–0.61) | < 0.001 |
| Abbreviation: CSS: cancer-specific survival; HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval | | | | |
| indicates significance of P <0.05. | | | | |
| indicates American Indian/AK Native, Asian/Pacific Islander and unknown | | | | |
| ***shown in US dollars | | | | |

# Baseline Characteristics Of Patients With Hcc In Two Ses-stage

Based on the cutoff SES prognostic score, 6,860 included patients (49.7%) were allocated to SES-1(higher SES) stage group, and 6931(50.3%) patients were assigned to SES-2 (lower SES) stage group. As illustrated in table S1, there were significant differences in most parameters (except sex) between two SES stages. Patients age 61–65 years with higher SES had higher rate than those with lower SES (32.7% vs 26.9%, P < 0.001). Patients with lower SES were more likely Black than those with higher SES (20.4% vs 12.6%, P < 0.001). High rates of Localized-stage HCC and TNM I-II stage HCC were seen in patients with higher SES than those with lower SES (57.8% vs 51.9%, 41.7% vs 37.9%, 23.3% vs 20.2%, overall P < 0.001). As expected, patients with higher SES had lower rate of unemployment (P < 0.001). Patients with higher SES were more likely to receive liver resection or liver transplant than those patients with lower SES stage (10.9% vs 6.3%, 7.7% vs 5.2%, P < 0.001). The higher rate of chemotherapy was also observed in patients with higher SES (48.0% vs 43.6%, P < 0.001).

# Ses Stage Associated With Css Of Patients With Hcc

Multivariate cox regression analysis indicated that SES-2 stage was significantly correlated to CSS of the patients with HCC, with a 32.0% increased risk (HR = 1.32, 95%CI (1.26–1.39), P < 0.001), as shown in table S2. The Kaplan-Meier curves also showed that the patients with higher SES had the better prognosis with those with lower SES (P < 0.001), as shown in Fig. 2. We further analyzed the effect of SES stage on CSS of patients in each stage (localized, regional and distant), the survival curves also indicated the better outcome of CSS in patients with higher SES, compared with those with lower SES (P < 0.001, P < 0.001, P = 0.0062, respectively). Furthermore, the stratified analysis of CSS by age, sex and race showed the consistent results (all P < 0.001), as presented in Figure S1.

# Prognostic Value Of Tnm-ses Stage

The concordance index (C-index) of the TNM-SES stage was 0.735,(95% CI(0.729–0.741)) which was higher than that of the TNM stage(0.718, 95% CI(0.712–0.724)), indicating a high accuracy of prognostic prediction. AS presented in Fig. 3, the vast majority of patients with SES-1 stage (expect IIIC) showed better prognosis than who had SES-2 stage in the same TNM stage. Interestingly, some patients with SES-1 stage had an increased CSS, compared with patients with SES-2 stage and a lower TNM stage, such as II-S1 vs I-S2(p < 0.001).

The HRs of each TNM-SES stage were demonstrated by using the Cox proportional hazards regression model, as shown in Fig. 4. In line with the Kaplan–Meier curves, patients with SES-1 stage had the lower HR than those with SES-2 stage at same TNM stage. It is worth mentioning that a higher HR was observed in patients with SES-2 stage compared with patients who had SES-1 stage and more TNM sage. For instance, patients with II-S1 stage (HR = 1.26,95% CI(1.13–1.39)) had an increase CSS than patients with I-S2 stage (HR = 1.65, 95% CI(1.51–1.80)). Notably, except IVB stage, the patients with IIIB-S2 had the highest HR (7.72, 95% CI(6.89–8.66)) than patients who had IIIC or IVA stage. Almost the same HRs was seen in patients with IIIB, IIIC and IVA stage.

## Discussion

The impact of socioeconomic status (SES) on the prognosis and clinical management of cancer patients had received more attention. Several investigations[10–12] indicated SES disparities, such as marital status, insurance status and household income were associated with the cancer stage at diagnosis and survival outcome of patients with HCC. However, as far as we know, few studies had investigated more than three SES factors in one research and not involved into TNM sating system as an independent parameter. In this large-scale study, four SES factors (insurance status, marital status, country percentage with bachelor degree and country-level median household income) associated with CSS of patients with HCC were identified to construct a SES stage which divided the eligible patients into SES-1stage (higher

socioeconomic status) and SES-2 stage (lower socioeconomic status). Subsequently, a superior staging system was generated to predictive prognosis by combining the TNM stage and the SES stage.

One previous study[13] based on a large population of more one million cancer patients in the United States indicated that unmarried patients had higher risk of presentation with metastasis, under-utilization of definitive treatment and unfavorable survival outcome, compared with married patients. Several investigations[14–16] also demonstrated that marital status was significantly associated with prognosis in HCC and other cancers. In line with these studies, our results also showed that patients of never married, divorced and widowed had higher risk of mortality (all p values < 0.001). The favorable survival of married patients may be explained by the emotional support by spouse and the better financial situation, which may bring about better prognosis. It was reported[17–19]that unmarried patients experienced more stress and depression and worse survival, compared to married patients. Otherwise, one study[20] found that depression and anxiety were significantly associated with breast cancer recurrence. In the meantime, married patients had better obedience to the prescribed surveillance and treatment than unmarried patients, which may result into higher rate of recurrence and worse prognosis[21–23].

The insured status and higher household income reflected better financial status to cope with the increasing cost of health care. Several previous studies[12, 24, 25] demonstrated that patients with Medicaid and uninsured and lower household income had more advanced HCC tumor stage and unfavorable survival of patients with HCC. Patients with poor financial status experienced delays in access to regular HCC surveillance and were likely to received surgery and transplantation[26–28], which may explain the worse prognosis of these patients.

As we expected, the education disparities have an impact on lifestyle, health care and disease surveillance and treatment[29–31]. The higher education patients with HCC were younger than the less education patients due to more active health management. Several studies[9, 24] demonstrated that less education was significantly correlated with under-utilization of HCC surveillance and effective treatment, more advanced disease and unsatisfactory survival.

Recently, the correlation of socioeconomic status and the health of population had received more attention. Socioeconomic status is an important factor of the heath inequality, as a very robust positive association between socioeconomic status and health was confirmed[32]. And socioeconomic status was correlated with not only cancer disease but also chronic stress, heart disease, ulcers, type 2 diabetes[33]. We constructed SES stage to divide the eligible patients into SES-1stage (higher socioeconomic status) and SES-2(lower socioeconomic status) stage by using HRs of four SES factors associated with CSS. In our analysis, higher SES patients were likely to have early stage HCC and receive surgery, transplantation and chemotherapy. After adjusting for several confounders, such as age, race, sex and tumor stage, disparity of SES was significantly associated with CSS of patient with HCC. The explanation of this result is the combined influence of four aforementioned factors.

Traditional AJCC TNM staging system was widely used to stratify patients for treatment selection and prognosis prediction in clinical practice. However, this algorithm only focused the clinicopathological features of tumor and not concerned the socioeconomic status. As shown in our results, lower SES stage revealed a 32.0% increased risk of CSS, compared to higher SES stage, indicating that SES was a significant prognostic predictor of survival. The C-index of TNM-SES stage was higher than that of TNM stage (0.735 vs 0.718),indicating a superior predictive value. The vast majority of higher SES stage patients (expect IIIC) showed better prognosis in comparison with those who had lower SES stage in the same TNM stage. However, it was be noted that there was no statistical difference in IIIC stage patient in terms of SES p < 0.384). This result may be explained by the following reason. Firstly, relatively insufficient patients with IIIC stage may make statistical bias, which covered up the prognostic value of SES, compared with patients with other stages. Besides, IIIC HCC stage is characterized by Tumor with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum. As represented in our study, the HRs of IIIC stage was higher than that of IVA stage in same SES stage, indicating the worse prognosis of patient with IIIC stage. The aggressive biological factors of IIIC stage may impaired the effect of SES on survival. Interestingly, a higher HR was observed in patients with NBF1 stage compared with patients who had NBF0 stage and more TNM sage, which revealed the superior prognostic value of SES stage. It was worthy to mentioning that there was no significant difference of HRs among the IIIB, III and IV in corresponding SES stage, and even the higher HRs were observed in stage IIIB than stage IVA in both SES stage. This result demonstrated that direct invasion of adjacent organs and lymph node metastasis may not have meaningful effect on survival of patient on HCC. It was reported in several studies[34–36] that microvascular invasion was associated with unfavorable prognosis.

This large population-based information from the SEER database enhanced the generalizability and creditability of our investigation. However, it should be noted that there were several limitations in our study. Firstly, the SES only incorporated five factors (insurance status, marital status, country percentage with bachelor degree, country-level median household income and country percentage with employed) and attained four factors associate with CSS of patient with HCC in our study. Actually, SES also included other elements, such as religion, occupation and wealth, which were not registered in SEER database. Secondly, the TNM staging system registered in SEER database was not specific for HCC and not commonly used in clinical practice. The burden of tumor, hepatic function and microvascular invasion also played a critical role in survival outcome of HCC, which was lacked in SEER database. Finally, there was not information of transcatheter arterial chemoembolization (TACE) and systemic therapy in SEER database, which was an important treatment for unresectable HCC. Despite with these limitations, our large-scale comprehensive investigation revealed a significant effect of SES on staging, prognosis and clinical management for HCC.

# Conclusion

Our comprehensive study revealed that SES was significantly associated with prognosis of patient with HCC after adjusting several confounders. The novel TNM-SES staging system which combined TNM

stage and SES stage had more superior predictive value than traditional TNM stage. Disparity on SES should receive more attention for patients with HCC in clinical management.

# Declarations

### Ethics approval and consent to participate

We conducted this study in compliance with the ethical standards of the institutional and with the 1964 Helsinki declaration. The Ethics Committee and Institutional Review Board of Zhongshan Hospital of Fudan University approved our study. The SEER data-use agreement was attained to analysis the data from this data-set (ID:11452-Nov2019). As this study is based on the publicity available database without identifying patient information, written informed consent was not required.

### Consent for publication

Not applicable.

### Availability of data and materials

All data generated or analysed during this study are included in this published article.

### Competing interests

The authors declare that they have no conflict of interest.


### Funding

Not applicable


### Author's contribution

Z.Y and J.L contributed to study concepts and design. Y.Z and W.Z contributed to data acquisition, analysis and interpretation. J.M and Z.Z contributed to data analysis and statistical analysis. M.Y and Y.Z contributed to quality control of data and algorithms. Y.Z contributed to manuscript editing. Z.Y and J.L contributed to manuscript review.


### Acknowledgements

Not applicable


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# Figures

| Insurance status (points) | Marital status(points) | Country % with bachelor degree (points) | Country-level median household income (points) |
|---|---|---|---|
| Insured ( 1.00 ) | Married (1.00) | 7.64-22.82% (1.00) | 19.26-44.99K (1.00) |
| Medicaid ( 1.19 ) | Never married (1.08) | 22.83-31.23% (0.95) | 45.00- 59.99K (0.97) |
| | Divorced (1.11) | 31.24%-39.07% (0.89) | 60.00-74.99K (0.83) |
| Uninsured ( 1.33 ) | Widowed (1.11) | 39.08-57.51% (0.86) | 74.99-110.97K (0.78) |


**Figure 1**

The socioeconomic status (SES) prognostic scores of the patients with HCC

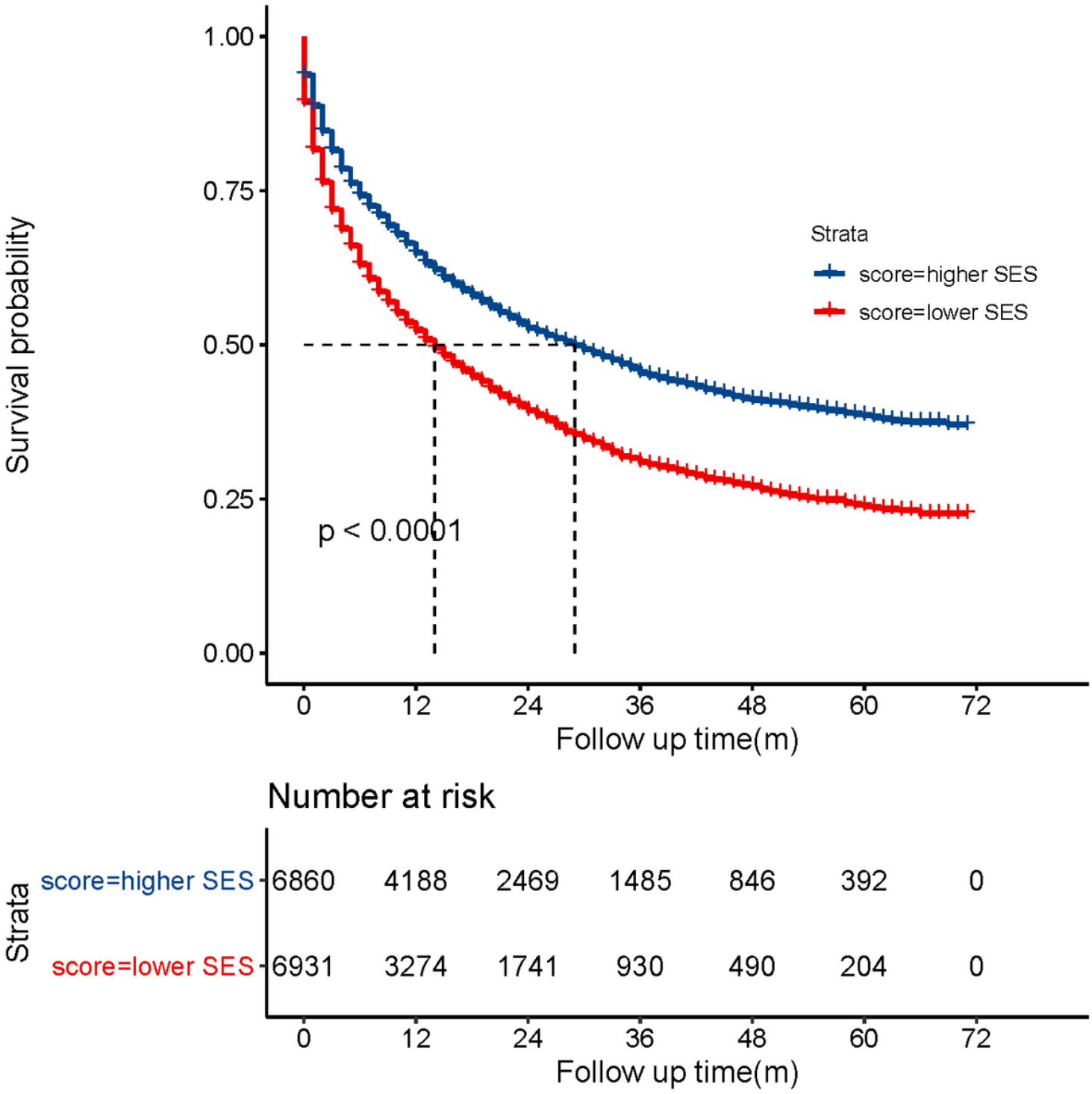
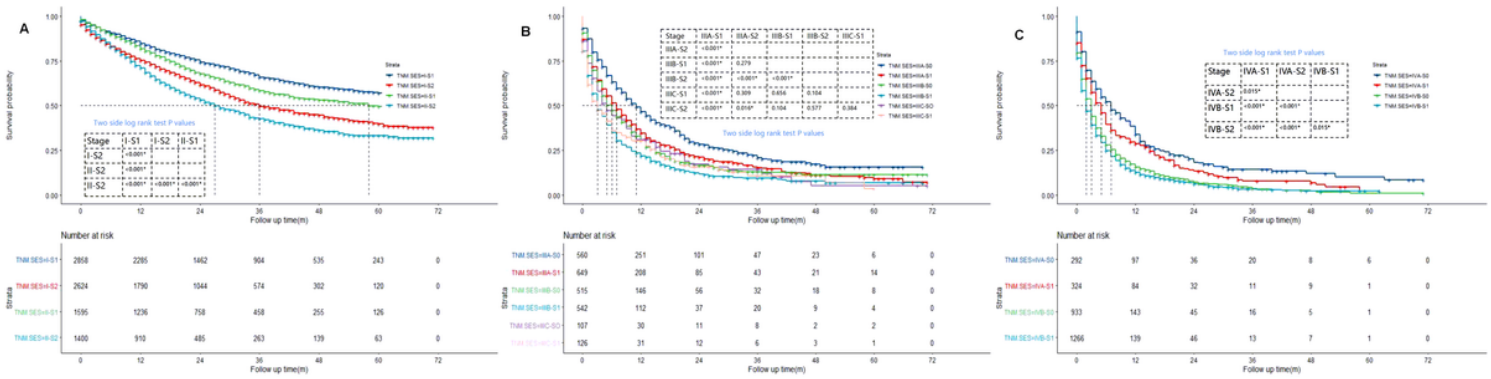



**Figure 2**

Kaplan-Meier curve shows the cancer-specific survival (CSS) of patient with HCC in two SES stage.




## Figure 3

Kaplan-Meier curve show the cancer-specific survival (CSS) of patient with HCC in each TNM (tumor node metastasis)-SES (socioeconomic status) stage.

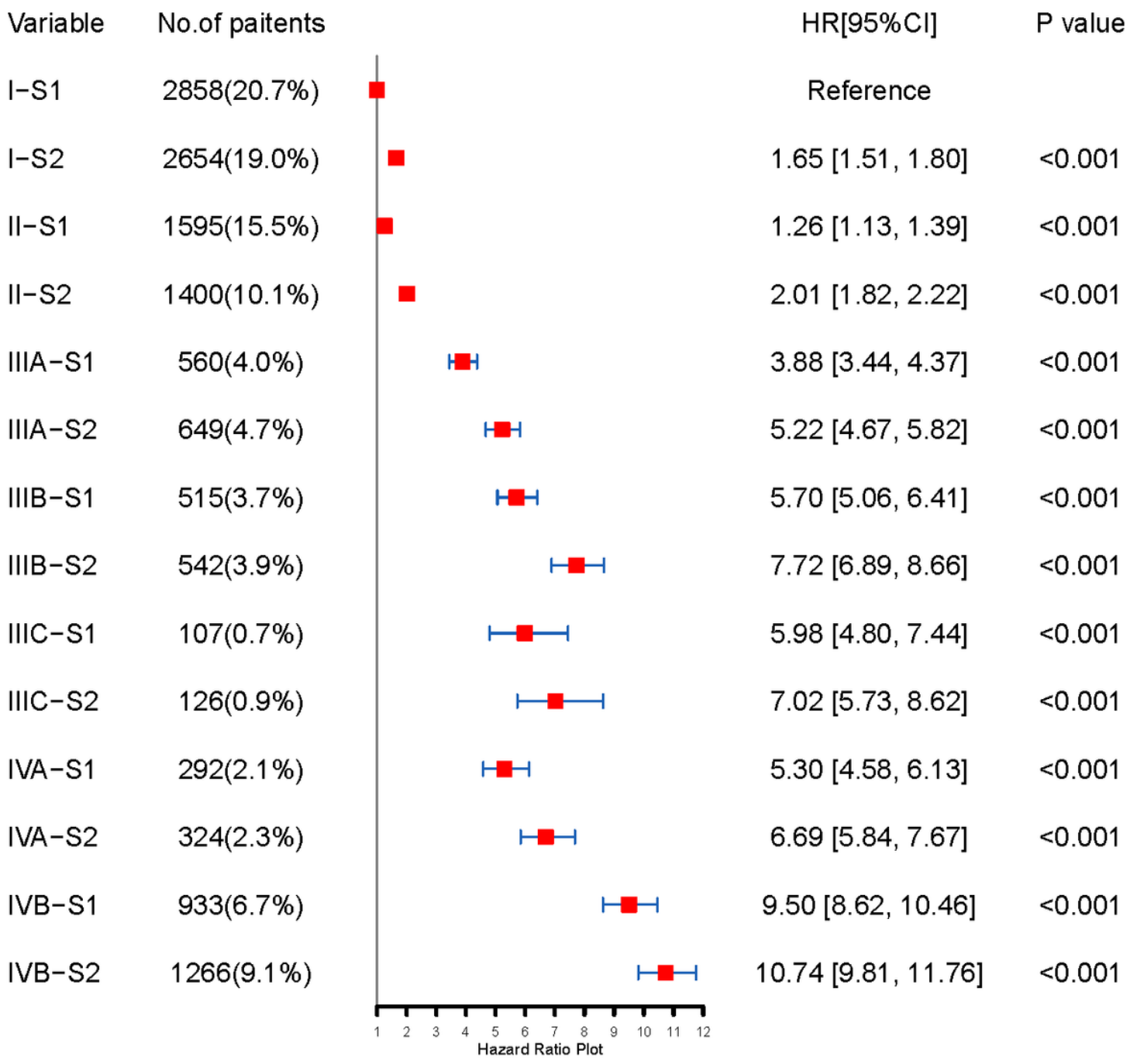



**Figure 4**

Prognostic value of TNM (tumor node metastasis)-SES (socioeconomic status) stage.

## Supplementary Files

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