The Impact of Socioeconomic Status on Mortality in Patients with Hepatocellular Carcinoma: A Korean National Cohort Study

Woo Jin Yang¹, Danbee Kang², Myung Gyu Song¹, Tae-Seok Seo¹, and Ji Hoon Kim³

¹Department of Radiology, Korea University Guro Hospital, Korea University College of Medicine, ²Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, and ³Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

Background/Aims: We studied the impact of socioeconomic status (SES) on mortality in hepatocellular carcinoma patients and analyzed the effect of SES on initial treatment allocation.

Methods: A cohort study was conducted using data from the National Health Insurance Service-National Sample Cohort of Korea. A total of 3,032 hepatocellular carcinoma patients who were newly diagnosed between January 2003 and December 2013 were included. Income level was categorized as Medical Aid and ≤30th, 31st–70th, or >70th percentile as an SES indicator.

Results: The proportion of Medical Aid was 4.3%. The highest risks of all-cause mortality associated with Medical Aid were evident in the transcatheter arterial chemoembolization group (fully adjusted hazard ratio [HR], 2.40; 95% confidence interval [CI], 1.25 to 4.58), the other treatments group (fully adjusted HR, 2.86; 95% CI, 1.85 to 4.41), and the no treatment group (fully adjusted HR, 2.69; 95% CI, 1.79 to 4.04) but not in the curative treatment group. An association between the lower-income percentile and higher liver cancer-specific mortality was also observed, except in the curative treatment group. The association between income percentile and all-cause mortality was nonlinear, with a stronger association in the lower-income percentiles than in the higher income percentiles (p-value for nonlinear spline terms <0.05).

Conclusions: Patients in the lower SES group, especially patients not eligible for curative treatment, had an increased risk of mortality. In addition, the association between SES and the risk for mortality was stronger in the lower-income percentile than in the moderate to higher income percentiles. (Gut Liver 2022;16:976-984)

Key Words: Carcinoma, hepatocellular; Mortality; Social class; Socioeconomic status

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. The incidence of HCC is increasing worldwide, with significant morbidity and associated costs.¹-³ Despite the improvement in various treatment modalities for HCC, the long-term prognosis is still disappointing and the 5-year survival rate remains less than 15%.⁴ Accordingly, studies on various prognostic factors as well as treatment methods have been actively carried out. Among the prognostic factors, socioeconomic status (SES) has been found in many studies to have significant effects on the mortality of HCC patients.¹⁵-¹¹ However, it is still unclear whether this difference in mortality is a result of the independent effect of SES or a secondary consequence of the impact of other factors, especially treatment allocation.

In the existing literature, there have been conflicting results, with some studies showing no difference in treatment allocation according to the SES, while others reporting a significant impact of SES on treatment choice.⁹-¹³ Furthermore, the results of existing studies did not reveal which treatment allocation groups were particularly affected by SES. Therefore, the purpose of the present study was to reassess the impact of SES on the mortality of HCC patients and to analyze how the effect of SES varies with the initial
treatment allocation. We also aimed to determine if the lower the SES, the greater the impact on mortality.

### MATERIALS AND METHODS

1. **Study population and design**

   Specifically for this study, we used data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) of Korea. The NHIS-NSC is a population-based retrospective cohort comprised of a 2.2% representative sample of Korean citizens. Korea has a single-payer national health system, and the NHIS maintains national records of all covered inpatient and outpatient visits, procedures, and prescriptions. We used person-level longitudinal NHIS-NSC registration and claims data collected between January 1, 2002 and December 31, 2013. From this cohort, we identified 3,032 patients who were 40 years of age or older, who had a new diagnosis of HCC between April 1, 2003 and December 31, 2013, and who had at least 1 year records in insurance eligibility database before the HCC diagnosis (2,258 men and 774 women). The Institutional Review Board of Korea University Guro Hospital reviewed the protocol and exempted this study from full board review as we used only de-identified data (approval number: 2020GR0235). And the requirement for informed consent was waived.

2. **Data sources**

   The NHIS-NSC cohort consists of three databases on insurance eligibility, medical treatments, and medical care institutions. The insurance eligibility database contains information on age, sex, residential area, type of health insurance, income level, and disability. The medical treatment database contains information from treatment bills, including details of diseases and prescriptions. The medical care institution database contains information regarding the type of institution, establishment, location, number of beds, facilities, and physicians.

   NHIS claims for inpatient and outpatient visits, procedures, and prescriptions were coded using the International Classification of Diseases, 10th Revision and the Korean Drug and Anatomical Therapeutic Chemical Codes. The NHIS routinely audits the claims, and the data are considered reliable and have been used in numerous peer-reviewed publications.

3. **Study variables**

   HCC was defined as three or more outpatient clinic visits with an associated C22 code within a year, or one inpatient hospitalization with the same C code. In Korea, once a person receives a cancer diagnosis, he/she is registered in the National Cancer Registry with a specific code (called a C-code) that indicates to the system that the person has been diagnosed. C codes are carefully reviewed as they allow for additional insurance benefits for patients. C codes are carried forward in medical records and claims created for the patient. Therefore, HCC and other cancer diagnoses based on claims are considered reliable, and a 1-year look-back window excludes patients with a prior diagnosis at any time, not just patients who had a diagnosis of cancer in the previous year.

   The NHIS-NSC cohort data included mortality data which was provided by the Ministry of the Interior. The study outcomes were all-cause mortality and liver cancer-specific (C22) death. Information on the underlying disease and comorbidities, demographics, income level, residential area, and initial treatment was based on claim codes. Income level was categorized as Medical Aid and ≤30th, 31st-70th, and >70th percentile. Residential area was classified as metropolitan or rural. Metropolitan areas were defined as cities that have a population ≥500,000.

   Initial treatments after HCC diagnosis were classified as: radiofrequency ablation, surgical resection, liver transplantation, transarterial chemoembolization (TACE), and target drugs; other treatments including radiation therapy; and no treatment.

   Comorbidities during the year prior to the cancer diagnosis were identified from inpatient and outpatient claims and summarized using the Charlson comorbidity index. Among the comorbidities, decompensated cirrhosis was defined as the presence of disease code for ascites, hepatorenal syndrome, varix bleeding, and hepatic encephalopathy.

4. **Statistical analysis**

   The outcome of the study was all-cause mortality. Person-time was calculated from the date of HCC diagnosis to the date of death or the end of the study period (December 31, 2013). Survival curves were generated by the Kaplan-Meier product-limit method and were compared by log-rank tests. Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) for all-cause mortality and liver cancer-specific mortality using the Cox proportional hazard regression models. Outcomes were adjusted for potential confounding factors at the time of HCC diagnosis, including sex, age group, initial treatment, Charlson comorbidity index and decompensated cirrhosis. The pro-
portional hazards assumption was assessed using plots of the log (-log) survival function and Schoenfeld residuals.

In addition, subgroup analysis was performed to evaluate the association of income with all-cause mortality by initial treatment. Furthermore, for categorical analysis, we modeled the income percentiles as continuous variables using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the sample distribution to provide a flexible estimate of the dose-response relationship between income percentile and mortality. A p-value of <0.05 was considered as statistically significant. All analyses were performed using STATA version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

1. General characteristics

The mean (standard deviation) age at diagnosis of the study participants was 62.0 (11.4) years and 74.5% of the participants were men. Among the 3,032 patients who developed HCC during the study period, 131 patients (4.3%) were in the Medical Aid group, 650 (21.4%) in the ≤30th percentile income group, 1,049 (34.6%) in the 31st–70th percentile income group, and 1,202 (39.6%) in the >70th percentile income group. Among the four groups, the Medical Aid group patients were the oldest and most likely to be female, and least likely to have received curative therapies for HCC (8.4% vs 11.4% vs 11.7% vs 14.4% in Medical Aid, ≤30th percentile, 31st–70th percentile, and >70th percentile, respectively) (Table 1).

2. SES and all-cause mortality

During 13,727 person-years of follow-up (median follow-up, 4.0 years; interquartile range, 0.9 to 7.9 years), 1,005 patients died (71, 239, 334, and 361 in the Medical Aid, ≤30th, 31st–70th, and >70th percentile income groups, respectively). Mortality rates were higher in the Medical Aid (28 deaths per 100 person-years), 30th (eight deaths per 100 person-years) and 31st–70th percentile income group (seven per 100 person-years) than in the >70th percentile income group (six per 100 person-year) (Table 2, Fig. 1). In the multivariable model, initial treatment, Charlson comorbidity index and income percentile were independent predictors of all-cause mortality (Supplementary Table 1). The adjusted HRs (95% CIs) for all-cause mortality comparing the Medical Aid, ≤30th, and 31st–70th percentile income groups to the >70th percentile income group were 2.64 (2.03 to 3.42), 1.33 (1.12 to 1.56), and 1.09 (0.94 to 1.27), respectively (Table 2). When the association of income percentile with mortality was evaluated by initial treatment (Table 2, Fig. 1), the highest risk of

| Table 1. Characteristics of the Study Population at the Time of Liver Cancer Diagnosis |
|----------------------------------------------------------|
| Characteristics | Medical Aid | ≤30th percentile | 31st–70th percentile | >70th percentile | p-value |
| No. of patients | 131 | 650 | 1,049 | 1,202 | <0.001 |
| Sex | | | | | |
| Male | 81 (61.8) | 478 (73.5) | 821 (78.3) | 878 (73.0) | <0.001 |
| Female | 50 (38.2) | 172 (26.5) | 228 (21.7) | 324 (27.0) | |
| Age, yr | 65.5±12.2 | 62.2±11.4 | 60.3±10.7 | 63.0±11.6 | <0.001 |
| Residential area | | | | | <0.001 |
| Metropolitan | 75 (57.3) | 358 (55.1) | 604 (57.6) | 773 (64.3) | |
| Rural | 56 (42.7) | 292 (44.9) | 445 (42.4) | 429 (35.7) | |
| Initial treatment | | | | | <0.001 |
| Liver transplantation | 0 | 1 (0.2) | 1 (0.1) | 0 | |
| Resection | 5 (3.8) | 45 (6.9) | 91 (8.7) | 135 (11.2) | |
| RFA | 6 (4.6) | 28 (4.3) | 30 (2.9) | 39 (3.2) | |
| TACE | 21 (16.0) | 180 (27.7) | 363 (34.6) | 376 (31.3) | |
| Other treatments | 37 (28.2) | 226 (34.8) | 328 (31.3) | 363 (30.2) | |
| No treatment | 62 (47.3) | 170 (26.2) | 236 (22.5) | 289 (24.0) | |
| Decompensated cirrhosis | 12 (9.2) | 51 (7.9) | 88 (8.4) | 80 (6.7) | 0.40 |
| Charlson comorbidity index | 3.4±2.3 | 3.1±2.2 | 3.3±2.3 | 3.5±2.3 | 0.01 |

Data are presented as number (%) or mean±SD.
RFA, radiofrequency ablation; TACE, transarterial chemoembolization.
*Income percentile is based on household income.
3. SES and liver cancer-specific mortality

Liver cancer-specific mortality rates were also higher in the Medical Aid (25 deaths per 100 person-years), ≤30th (seven deaths per 100 person-years), and 31st–70th percentile income group (six per 100 person-years) than in the >70th percentile income group (five per 100 person-year) (Table 3, Fig. 2). Adjusted HRs (95% CIs) for liver cancer-specific mortality comparing the Medical Aid, ≤30th, and 31st–70th percentile income groups to the >70th percentile income group were 2.84 (2.14 to 3.75), 1.36 (1.14 to 1.63), and 1.08 (0.92 to 1.28), respectively (Table 3). When the association of income percentile with liver cancer-specific mortality was evaluated by initial treatment (Table 3, Fig. 2), the highest risk of liver cancer-specific mortality associated with Medical Aid was evident in patients with TACE, other treatments (chemotherapy, radiation, or target therapy), or no treatment, but not in patients with curative treatment (fully adjusted HR, 1.68; 95% CI, 0.39 to 7.13).

4. Spline regression model

In the spline regression model, the association between income percentile and the HR for all-cause mortality was nonlinear, with a stronger association at lower levels of income than at higher levels (p-value for nonlinear spline terms <0.05) (Fig. 3).

**DISCUSSION**

This large, nationwide cohort study demonstrated that SES was an independent risk factor for mortality in HCC patients. In particular, the association between lower SES and higher mortality was stronger in patients with non-curative treatment than in patients with curative treatment.
In spline regression models, the association between SES and mortality was nonlinear, with a stronger association at the lower levels of SES than at the median to high levels.

These results were similar to previous studies which indicated the impact of SES on overall HCC mortality. Abdel-Rahman reported that lower SES was associated with worse liver cancer-specific survival. In addition, Wang et al. found that the group with the least poverty (the highest SES group) was related with higher survival rates. Those authors highlighted that the SES disparity between Whites and Blacks may contribute to the parallel changes of incidence and survival between them. Joshi et al. demonstrated that SES is an independent predictor of liver cancer mortality.

There might be some possible explanations for these results. First of all, as previously reported, lower SES can result in delayed access of cancer patients to medical attention. As this study demonstrates, this might lead to a higher probability of presentation at an incurable disease stage. In previous literature, it has been noted that HCC patients with Medical Aid or no insurance were more likely to present with late-stage cancer, compared to patients with private insurance. In addition, individual-level risk factors could affect mortality in patients with HCC. The risk factors of poor individuals include low nutritional status, hazardous living and working conditions, inability to access medical care, and limited health literacy. Therefore, addressing these disparities is crucial to improve outcomes for all patients.
to afford to adequately treat illnesses, and others. These could be associated with the relatively poor conditions of the lowest SES groups and result in worse prognoses. Furthermore, HCC usually occurs as a complication of liver cirrhosis. The presence of a chronic disease and of reduced liver function restricts therapeutic approaches and exacerbates the costs of the disease. It is likely that the relatively higher costs in the continuing phase of care include costs associated with late treatment after the diagnosis as well as care for recurrences.

We also conducted subgroup analysis by type of treatment. When comparing subgroups according to the initial treatment allocation, the highest mortality rates associated with the Medical Aid group was evident in the TACE group (fully adjusted HR, 2.40; 95% CI, 1.25 to 4.58), the other treatments group (fully adjusted HR, 2.86; 95% CI, 1.85 to 4.41), and the no treatment group (fully adjusted HR, 2.69; 95% CI, 1.79 to 4.04), but not in patients in the curative treatment group (fully adjusted HR, 1.68; 95% CI, 0.39 to 7.13). In a previous study, the authors suggested that while patients with lower SES or less desirable insurance may present with more advanced liver disease or cancer, if they receive the appropriate treatment for their HCC stage and underlying liver disease, their insurance and perhaps even SES may not affect survival. However, in the current study, the lower SES groups showed a more severe impact on the mortality in patients with non-curative treatments.

When compared to the patients with curative treatments, the patients with TACE or palliative care can be expected to receive more repetitive treatments during their clinical course. These may lead to a further erosion of income as extra costs may be required to meet their medical needs. As a consequence, it is more difficult for the lower SES group to manage their health, and this could be associated with a worse prognosis.

Although the Korean government covers the direct cost for medical services for the lower SES group by Medical Aid Program or national cancer support program, the lower SES group might be burdened by out-of-pocket costs, which are related to the time taken to access medical services, including travel time or reduced earnings due to frequent absence from daily work. Therefore, the health profession should pay attention to patients’ ability to participate in continuing multiple phases of care after the initial treatment in patients with advanced HCC.

In spline regression models, the association between SES and mortality was nonlinear, with a stronger association between SES and mortality in patients with advanced HCC.

### Table 3. Liver Cancer-Specific Mortality According to Income Percentile at the Time of Liver Cancer Diagnosis

| Variable | No. of deaths | Incidence rate (per 100 person-years) | Adjusted HR [95% CI] |
|----------|---------------|--------------------------------------|----------------------|
| Overall  |               |                                      |                      |
| Medical Aid | 63            | 25                                   | 2.84 [2.14–3.75]     |
| ≤30th percentile | 206           | 7                                    | 1.36 [1.14–1.63]     |
| 31st–70th percentile | 280           | 6                                    | 1.08 [0.92–1.28]     |
| >70th percentile | 299           | 5                                    | Reference            |

Curative treatment (n=381)

| Variable | No. of deaths | Incidence rate (per 100 person-years) | Adjusted HR [95% CI] |
|----------|---------------|--------------------------------------|----------------------|
| Medical Aid | 2            | 11                                   | 1.87 [0.43–8.00]     |
| ≤30th percentile | 7            | 3                                    | 0.88 [0.37–2.09]     |
| 31st–70th percentile | 18           | 4                                    | 1.34 [0.71–2.53]     |
| >70th percentile | 20           | 3                                    | Reference            |

TACE (n=940)

| Variable | No. of deaths | Incidence rate (per 100 person-years) | Adjusted HR [95% CI] |
|----------|---------------|--------------------------------------|----------------------|
| Medical Aid | 9            | 28                                   | 2.49 [1.25–4.92]     |
| ≤30th percentile | 58           | 7                                    | 1.27 [0.92–1.75]     |
| 31st–70th percentile | 108          | 6                                    | 1.16 [0.88–1.52]     |
| >70th percentile | 118          | 5                                    | Reference            |

Other treatments (n=954)

| Variable | No. of deaths | Incidence rate (per 100 person-years) | Adjusted HR [95% CI] |
|----------|---------------|--------------------------------------|----------------------|
| Medical Aid | 22           | 48                                   | 3.06 [1.92–4.88]     |
| ≤30th percentile | 100          | 12                                   | 1.51 [1.16–1.97]     |
| 31st–70th percentile | 106          | 7                                    | 1.02 [0.78–1.33]     |
| >70th percentile | 118          | 8                                    | Reference            |

No treatment (n=757)

| Variable | No. of deaths | Incidence rate (per 100 person-years) | Adjusted HR [95% CI] |
|----------|---------------|--------------------------------------|----------------------|
| Medical Aid | 30           | 19                                   | 2.87 [1.85–4.45]     |
| ≤30th percentile | 41           | 4                                    | 1.31 [0.88–1.94]     |
| 31st–70th percentile | 48           | 4                                    | 1.02 [0.70–1.49]     |
| >70th percentile | 61           | 4                                    | Reference            |

HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization.

*Adjusted for age, sex, initial treatment, Charlson comorbidity index and decompensated cirrhosis.
tion at low levels of SES than at median to high levels. In light of their potential use in policy decision models, our findings highlight the important implications for identifying cutoff levels of the proper costs in HCC treatment. Further investigation is needed to determine the extra costs that affect mortality in the SES groups, and to make a supportive care system available to improve the survival rate in the lower SES group.

In this study, several limitations need to be considered. First, HCC stage was not adjusted for the outcome because the NHIS-NSC database does not contain information about stage. Instead, we performed subgroup analysis based on initial treatment allocation. Since the HCC stage is an essential factor for initial treatment allocation, the initial treatment modality might be a surrogate variable for HCC stage. Second, we did not have information on differences in lifestyle and we had only limited information on history of comorbidity and disease management based on claims. Third, we stratified SES according to the insurance fee. Funds for the Korean National Health Insurance are raised mainly from mandatory contributions, such as insurance fees paid by all residents. The contributions are determined by income and wealth of each individual or household. Thus, these contributions can be considered an appropriate surrogate marker for the SES but they cannot accurately represent the social characteristics. Fourth, we

Fig. 2. Liver cancer-specific mortality. Kaplan-Meier survival curves of patients with liver cancer according to income percentile and initial treatment. (A) Overall. (B) Curative treatment. (C) Transarterial chemoembolization. (D) Other treatment. (E) No treatment.
did not consider the etiology of HCC, depending on which the prognosis may vary.\textsuperscript{27,28} If there is a difference in etiology among the SES groups, such information can be also helpful in making health care policies, but we did not analyze this aspect. Finally, our study was conducted in Korea, a country with a single-payer health insurance system, and our findings may not be generalizable to other countries with different healthcare structures.

Although there were a few limitations, this study has several strengths. The sample used in this study was a national sample and this nationwide setting is difficult to be studied in other countries. This is because few countries have established database that represent the whole country rather than a specific patient group or population group. Our study has sufficient numbers of patients to ensure the adequate reliability of our mortality estimates. We also had previous records prior to admission to define comorbidities, which increases the prevalence of these conditions and results in better risk adjustment. Furthermore, the present study was a cohort study conducted in a setting where the entire nation receives similar benefits from the NHIS, with a relatively low individual financial burden.\textsuperscript{29} Even within this universal insurance coverage setting, different prognoses in mortality were observed across the SES spectrum. This suggests that more detailed socioeconomic intervention is needed for the lower SES group.

In conclusion, the lower SES group exhibited and increased risk of mortality, especially in intermediate and advanced HCC patients not eligible for curative treatment. In addition, the association between SES and the risk for mortality was stronger in the lower-income percentile than in the moderate to higher income percentiles. Policy makers need to focus more on the lowest income group to reduce socioeconomic and prognostic disparities.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: W.J.Y., M.G.S. Methodology: W.J.Y., D.K. Validation: J.H.K. Formal analysis: D.K. Writing-original draft preparation: W.J.Y., D.K. Writing-review & editing: M.G.S. Supervision: T.S.S. All the authors read and approved the final manuscript.

ORCID

Woo Jin Yang https://orcid.org/0000-0003-2392-2174
Danbee Kang https://orcid.org/0000-0003-0244-7714
Myung Gyung Song https://orcid.org/0000-0002-9861-2886
Tae-Seok Seo https://orcid.org/0000-0002-4427-0198
Ji Hoon Kim https://orcid.org/0000-0003-3924-0434

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl210567.

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