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Clinical-Bladder cancer

Socioeconomic and insurance status are independent prognostic indicators of higher disease stage and worse prognosis in bladder cancer

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Abstract

Objectives: Bladder cancer is the fourth most common cancer among males and poses a significant financial burden, yet there are no large-scale studies focused on the correlation between socioeconomic (SES) and insurance status and bladder cancer outcomes. The objective of this study was to determine the effect of SES and insurance type on outcomes in bladder cancer.

Materials and methods: A population-based search was performed using the National Cancer Institute's Surveillance, Epidemiology, and End Results 18 database. Patients aged 18 or older and diagnosed with bladder cancer between 2011 and 2015 were identified. Data on patient demographics, SES features, insurance status, tumor characteristics, and survival were collected. A county-level SES measure was created in a method consistent with prior literature. Primary outcomes were overall survival (OS) and disease-specific survival (DSS).

Results: A total of 91,308 patients were identified. Factors predictive of having muscle invasive disease included having Medicaid insurance, having no insurance, and being in the lowest SES quartile (all $P < 0.001$). Having Medicaid or no insurance was predictive of having node positive or metastatic disease ($P < 0.001$). Independent of T stage, patients in the lowest and second lowest SES quartiles had worse OS ($P = 0.004$ and $P = 0.022$, respectively) and DSS ($P < 0.001$ for both). Patients with Medicaid or no insurance had worse OS and DSS ($P < 0.001$ for all).

Conclusions: Lower SES status, Medicaid insurance, and having no insurance were all predictive of having higher tumor stage. Independent of tumor stage, being of lower SES, having Medicaid insurance, and having no insurance predicted worse OS and DSS. © 2019 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Socioeconomic; Insurance; Outcomes; Epidemiology

1. Introduction

Bladder cancer is the fourth most common cancer among males and accounts for 5% of new cancer diagnoses in the United States [1]. In 2018, there were an estimated 81,190 new diagnoses and 17,240 deaths due to bladder cancer, and incidence is expected to increase by 2020 [2,3]. With over 70% of new diagnoses occurring in patients aged 65 and older and an average lifetime cost of $65,158, bladder cancer poses a significant public health problem and financial burden [4].

In many studies of various cancer types, a link between lower socioeconomic status (SES) and both overall survival (OS) and disease-specific survival (DSS) has been observed [5−7]. A common finding among these studies is that individuals of lower SES present with more adverse tumor characteristics, including high grade and advanced stage [8]. Specific studies on SES in bladder cancer patients have assessed the impact of SES on delays in care, type of urinary diversion after radical cystectomy, hospital readmission rates after cystectomy, and perioperative complications after cystectomy [1,4,9,10]. Prior studies on the effect

of insurance status on oncologic outcomes have been published, but to our knowledge, no large-scale studies have focused on the correlation between insurance status and bladder cancer outcomes in the United States [11].

We use the SEER registry to analyze a contemporary cohort of patients to determine the impact of SES, with a focus on direct sociologic measures of poverty and education, and insurance status on disease presentation and oncologic outcomes.

2. Materials and methods

A population-based search for patients diagnosed with bladder cancer was performed using the National Cancer Institute's SEER 18 database [www.seer.cancer.gov]. The SEER registry provides county-level socioeconomic metrics derived from the US Census, which have been validated to accurately approximate individual SES in large databases [12]. The 18 registries represent 28% of the US population, and catchment areas are highly representative of the US population [8]. No Internal Review Board approval was required for this publicly available database that provides information with no personal identifiers.

Patients diagnosed with bladder cancer between 2011 and 2015 aged 18 or older were reviewed. This time period was chosen to adequately represent a contemporary cohort. Site-specific codes were used to identify primary tumors that originated in the urinary bladder (International Classification of Disease for Oncology, third Edition site codes C67.0-C67.9). The following primary data were extracted for analysis: patient age, sex, year of diagnosis, marital status (married or unmarried), race (white, black, Hispanic, Asian Pacific Islander, Native American, or unknown), socioeconomic measures, insurance status (private insurance, Medicaid, or uninsured), tumor grade, tumor stage, tumor size, treatment with surgery, cause of death, and survival months. Tumor grade was reclassified in a method consistent with prior literature, as either low grade for well or moderately differentiated histology, or high grade for poorly differentiated or undifferentiated histology [13,14]. Tumor stage was based on American Joint Committee on Cancer seventh edition TNM classification, and all T0 cases were excluded from analysis.

A county-level SES measure was created in a manner consistent with prior literature, based on the percentage of residents without a high-school diploma, percentage of persons below the poverty line, percentage of persons unemployed, and median household income [8,15]. These data were generated from the Census American Community Survey 5-year files from 2011 to 2015. Based on prior literature, each measure was normalized and weighted equally to create a composite SES score, which was then divided into quartiles [8,15]. Survival analysis was performed on patients for whom information on insurance and SES was known.

Primary outcome was defined as time in months from diagnosis to death from any cause for OS, and time from diagnosis to death specific to the cancer-related diagnosis for DSS. Descriptive epidemiological and survival statistics were calculated for all variables. Kaplan-Meier analysis was used to generate OS and DSS curves stratified by quartiles of SES and insurance status. Differences in survival were analyzed using log-rank tests. Multivariate Cox proportional-hazards regression, using hazards ratios (HR) with corresponding 95% confidence intervals (CI), was used to identify factors associated with worse OS and DSS. The multivariate model was adjusted for age, sex, race, marital status, tumor grade, tumor stage, and treatment with surgery. In the regression analysis predicting T classification as an outcome, a cutoff of ≥T2 was chosen as clinically relevant, since this stage cutoff represents the presence of muscle invasive disease and need for cystectomy. Statistical significance was set at the $P < 0.05$ threshold. Statistical analyses were performed using SPSS 21 software (IBM Corp., Armonk, NY).

3. RESULTS

The search identified 91,308 patients with carcinoma of the bladder from 2011 to 2015. Baseline demographic and clinical features of the cohort are reported in Table 1. Descriptive statistics for individual components of the SES score are presented in Table 2.

Lower SES was a significant predictor of worse OS and DSS ($P < 0.001$ and $P < 0.001$, respectively; Fig. 1). Patients in the lowest and second lowest SES quartiles had worse OS (HR 1.10, 95% CI 1.03−1.17, $P = 0.004$ and HR 1.08, 95% CI 1.01−1.16, $P = 0.022$, respectively) and DSS (HR 1.21, 95% CI 1.09−1.34, $P < 0.001$ and HR 1.18, 95% CI 1.06−1.31, $P = 0.002$, respectively; Table 3). OS and DSS were significantly different for patients based on insurance type ($P < 0.001$ and $P < 0.001$, respectively; Fig. 2). Patients with Medicaid had worse OS and DSS (HR 1.39, 95% CI 1.29−1.50, $P < 0.001$ and HR 1.32, 95% CI 1.18−1.47, $P < 0.001$, respectively). Similarly, uninsured patients had significantly worse OS and DSS (HR 1.56, 95% CI 1.33−1.84, $P < 0.001$ and HR 1.65, 95% CI 1.35−2.03, $P < 0.001$, respectively).

Demographic features predictive of worse OS included increased age and black race, while being of Asian Pacific Islander race or married was predictive of improved OS. Factors predictive of worse DSS included increased age and being female, while being married and receiving treatment with surgery were predictive of improved DSS (Table 3). High grade, high T stage, nodal involvement, and metastatic disease were all predictive of worse OS and DSS (Table 3).

Factors predictive of tumor stage classification ≥T2 included increased age, female sex, black race, Native American race, having Medicaid insurance, having no insurance, and being in the lowest SES quartile (all $P <$

Table 1
Overall cohort characteristics

Variable	91,308 (%)
Continuous measures	
Age, years, mean (SD)	71.9 ± 12.0
Tumor size, cm, mean (SD)	3.6 + 2.3
Categorical measures	
Sex	
Male	69,506 (76.1)
Female	21,802 (23.9)
Diagnosis year	
2011	17,760 (19.5)
2012	18,384 (20.1)
2013	18,166 (19.9)
2014	18,531 (20.3)
2015	18,467 (20.2)
Marital status	
Married	51,624 (56.5)
Not married	31,139 (34.1)
Unknown	8,545 (9.4)
Race	
White	74,734 (81.8)
Black	5,330 (5.8)
Hispanic	5,834 (6.4)
Asian Pacific Islander	3,787 (4.1)
Native American	312 (0.3)
Unknown	1,311 (1.4)
Insurance status	
Insured	76,899 (84.2)
Medicaid	6,822 (7.5)
Uninsured	1,414 (1.6)
Unknown	6,171 (6.8)
Grade	
Low	26,276 (28.8)
High	42,349 (46.4)
Unknown	22,683 (24.8)
T classification	
Ta/Tis	45,614 (50%)
T1	21,807 (23.9)
T2	12,996 (14.2)
T3	3,484 (3.8)
T4	3,022 (3.3)
Unknown	4,385 (4.8)
Node status	
No nodal involvement	83,203 (91.1)
Nodal involvement	3,901 (4.3)
Unknown	4,204 (4.6)
Metastatic disease	
No metastatic disease	87,606 (95.9)
Metastatic disease	3,499 (3.8)
Unknown	203 (0.2)
Intervention	
Surgery	82,588 (90.4)
No surgery	7,546 (8.3)
Unknown	1,174 (1.3)

cm = centimeters; SD = standard deviation.

Table 2
Components of socioeconomic score

Components of SES score	Mean	SD	Median
% of persons in patient's county with < high school degree	14.11%	5.92%	12.97%
% of persons in patient's county below the poverty level	15.05%	5.51%	14.47%
% unemployed in person's county	9.05%	2.49%	8.70%
Median household income in person's county	$60,691	$15,377	$57,640

SD = standard deviation; SES = socioeconomic.

disease included female sex, black race, Hispanic race, Asian Pacific Islander race, having Medicaid insurance, and having no insurance (all $P \leq 0.004$; Table 4). Lower SES was not a significant predictor of presenting with metastatic disease. Being married portended a decreased risk of presenting with ≥T2 disease, nodal involvement, and metastatic disease (all $P < 0.001$).

4. Discussion

Considering the high incidence and cost associated with bladder cancer, the association between SES, insurance status, and survival is of utmost importance. This study of a large, contemporary database is the first to assess the impact of SES, by direct measures of poverty and education, and insurance type on bladder cancer survival. We determined that socioeconomic and insurance status are independently predictive of worse survival. Specifically, patients in the lowest and second lowest SES quartiles, patients with Medicaid, and uninsured patients had significantly poorer OS and DSS compared to patients in higher SES quartiles and insured patients.

Prior literature has identified that increased T classification is linked to poorer SES, and is a predictor of worse prognosis in bladder and other cancers [5,8]. In a study on the link between SES and stage at diagnosis, patients with cancers of the colon, lung and bronchus, breast, cervix, uterus, and prostate were found to have more local stage disease in the highest SES group compared to the lowest SES group [16]. Similar to these findings, we identified that being in the lowest SES quartile was predictive of having stage T2 or higher disease, but was not predictive of nodal involvement or metastatic disease. Thus, it may be that while patients of lower SES have higher T stages when they visit their physicians, they will still see their physician for work-up and treatment prior to systemic spread.

Another study on the association between T stage and insurance status found that patients with Medicaid or no insurance had a higher risk of being diagnosed with advanced stage disease within various cancer types, but did not assess the impact on bladder cancer specifically [17]. A similar trend was observed in our study, where we identified that having Medicaid or no insurance was predictive of

0.001; Table 4). Factors predictive of node positive disease included female sex, black race, Native American race, having Medicaid insurance, and having no insurance, whereas presenting at increased age conferred a decreased risk (all $P \leq 0.001$; Table 4). SES did not predict the presence of nodal involvement. Factors predictive of metastatic
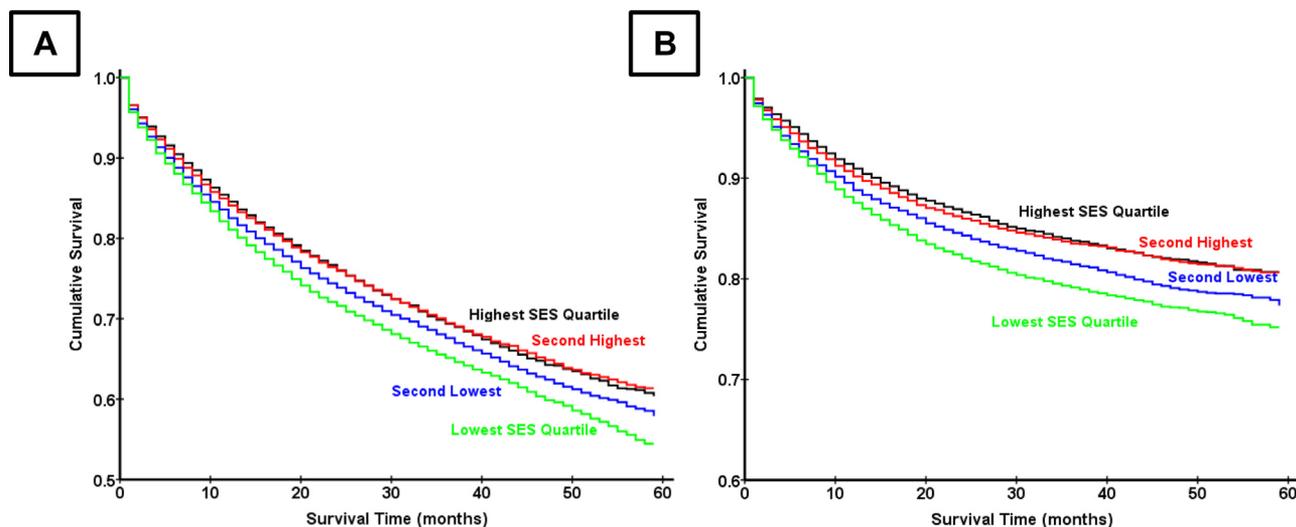
Fig. 1. Survival analysis of bladder cancer patients within different socioeconomic (SES) quartiles. Kaplan-Meier analysis of (A) overall survival and (B) disease-specific survival are shown for all patients.

having stage T2 or higher disease. Having Medicaid or being uninsured was also predictive of having node positive and metastatic disease. Our findings are congruent with current literature, which has acknowledged that being uninsured substantially increases healthcare costs and may prevent patients from pursuing treatment [2]. Delays to seeking treatment is not uncommon in cancer patients, as women with breast cancer who were uninsured or had public insurance were shown to have treatment delay times over 6 weeks compared to privately insured patients [18]. As such, patients with Medicaid or no insurance may delay seeking care until they experience systemic symptoms, but further study is needed to confirm.

Interestingly, we showed that independent of tumor stage, being in lower SES quartiles was predictive of worse survival outcomes. These results are in congruence with prior publications on the relationship between SES and cancer outcomes in general. In a study by Syriopulou et al. looking at a population of 2.5 million patients with various cancers, including bladder cancer, in England, the most affluent individuals lost less years of life due to their malignancy [19]. Another study found that patients with metastatic bladder cancer from the lowest SES quintile were half as likely to have chemotherapy as those from the highest quintile, and that not receiving chemotherapy was associated with greater mortality from bladder cancer [2]. In contrast, a study by Golombos et al. on bladder cancer patients who received cystectomy found that low SES was a significant predictor of perioperative complications, but did not have a significant impact on OS or DSS [1]. This study was performed at a tertiary referral center and analyzed 383 patients who underwent definitive radical cystectomy. Our large-scale study that utilizes a national database to analyze all bladder cancer patients, not just those receiving cystectomies, may more accurately represent the true

relationship between SES and oncologic outcomes in this population. Further study on why survival outcomes are inferior in patients of lower SES, whether it be due to delays in seeking care or lack of access to treatment, are warranted to better understand and address this issue.

This study also found that, independent of tumor stage, having Medicaid or no insurance portended worse survival outcomes. An analogous trend has been reported in the literature within different cancer types. For example, survival was worse for colorectal cancer patients who were uninsured or had Medicaid coverage compared to those who were privately insured [20]. Similarly, Medicaid patients with prostate cancer had higher DSS than patients with private insurance [21]. Another study assessing trends amongst various cancers in patients in New Jersey found that for most cancers, Medicaid and uninsured patients had significantly higher risk of death than insured patients, while for bladder cancers the higher risk was only significant in uninsured patients [11]. While our results deviate slightly from these bladder cancer outcomes, showing inferior survival in both uninsured and Medicaid patients, our results are based on a larger sample size from a national patient cohort, as opposed to a single state, and correlate with the national trend seen among various cancers.

We reported that uninsured patients had a higher risk of death compared to Medicaid patients using a multivariable Cox regression model that accounts for numerous demographic and clinical factors. The Kaplan-Meier survival analyses were unadjusted curves and demonstrated survival independent of other important factors including age, SES, and tumor grade and stage. Thus, the difference in survival outcomes seen in the Kaplan-Meier curves may be secondary to the fact that uninsured patients were of lower age, had lower tumor grade, and had fewer people in the lowest SES quartile than patients with Medicaid. Additionally, our

Table 3
Cox regression identifying factors associated with reduced overall and cancer-specific survival

Characteristic	Overall survival		Disease-specific survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.05 (1.04−1.06)	<0.001	1.04 (1.03−1.05)	<0.001
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	1.01 (0.96−1.06)	0.610	1.22 (1.14−1.32)	<0.001
Race				
White	Ref.	Ref.	Ref.	Ref.
Black	1.21 (1.11−1.32)	<0.001	1.12 (0.99−1.27)	0.063
Hispanic	0.94 (0.85−1.03)	0.227	0.97 (0.84−1.10)	0.656
Asian Pacific Islander	0.84 (0.75−0.95)	0.006	0.87 (0.73−1.03)	0.107
Native American	0.92 (0.64−1.31)	0.654	1.37 (0.84−2.25)	0.203
Marital status				
Unmarried	Ref.	Ref.	Ref.	Ref.
Married	0.79 (0.76−0.83)	<0.001	0.79 (0.74−0.85)	<0.001
Insurance status				
Insured	Ref.	Ref.	Ref.	Ref.
Medicaid	1.39 (1.29−1.50)	<0.001	1.32 (1.18−1.47)	<0.001
Uninsured	1.56 (1.33−1.84)	<0.001	1.65 (1.35−2.03)	<0.001
SES Composite quartile				
Highest	Ref.	Ref.	Ref.	Ref.
Second highest	0.98 (0.92−1.05)	0.695	1.03 (0.93−1.15)	0.493
Second lowest	1.08 (1.01−1.16)	0.022	1.18 (1.06−1.31)	0.002
Lowest	1.10 (1.03−1.17)	0.004	1.21 (1.09−1.34)	<0.001
Grade				
Low	Ref.	Ref.	Ref.	Ref.
High	1.36 (1.27−1.45)	<0.001	2.50 (2.21−2.83)	<0.001
Size (continuous)	1.07 (1.06−1.08)	<0.001	1.08 (1.07−1.09)	<0.001
T stage				
Ta/Tis	Ref.	Ref.	Ref.	Ref.
T1	1.74 (1.61−1.88)	<0.001	3.41 (2.89−4.02)	<0.001
T2	3.84 (3.54−4.15)	<0.001	10.06 (8.58−11.80)	<0.001
T3	4.20 (3.83−4.60)	<0.001	11.90 (10.05−14.08)	<0.001
T4	5.68 (5.13−6.29)	<0.001	15.97 (13.35−19.12)	<0.001
Node status				
Node negative disease	Ref.	Ref.	Ref.	Ref.
Node positive disease	1.37 (1.28−1.47)	<0.001	1.38 (1.26−1.52)	<0.001
Metastasis present				
No metastatic disease	Ref.	Ref.	Ref.	Ref.
Metastatic disease	3.27 (3.02−3.55)	<0.001	4.09 (3.70−4.52)	<0.001
Surgery status				
No surgery performed	Ref.	Ref.	Ref.	Ref.
Surgery performed	0.57 (0.49−0.65)	<0.001	0.58 (0.48−0.71)	<0.001

CI = confidence interval; HR = hazards ratio; Ref. = reference.

multivariable hazards regression analysis also controlled for marital status, as married men have better survival at every disease stage compared to unmarried men [11,22]. Another possibility may be that Medicaid patients have less access to care and may be shuffled around within the system, while uninsured patients can go to a safety net hospital and receive the needed care. Further study is warranted to understand the disparity in survival based on insurance status.

There are several limitations to address in this study, including an inherent risk of selection bias with a retrospective observational study [23]. Specifically, relying on the SEER database presents its own set of limitations, including a lack of information on patient comorbidities and health behaviors such as smoking status. Additionally, the socioeconomic data presented are at the county level and not the individual level. While the use of such data has been validated in multiple studies, it is not ideal [8]. Furthermore, while we adjusted our survival analysis to control for surgical intervention, information on treatment with chemotherapy, a common treatment in patients with bladder cancer, or other salvage systemic therapies is not available. As such, the effect of these interventions on survival could not be controlled. Nevertheless, this is the first large-scale study on the effect of socioeconomic and insurance status on bladder cancer survival, identifying key factors associated with worse disease presentation and survival.
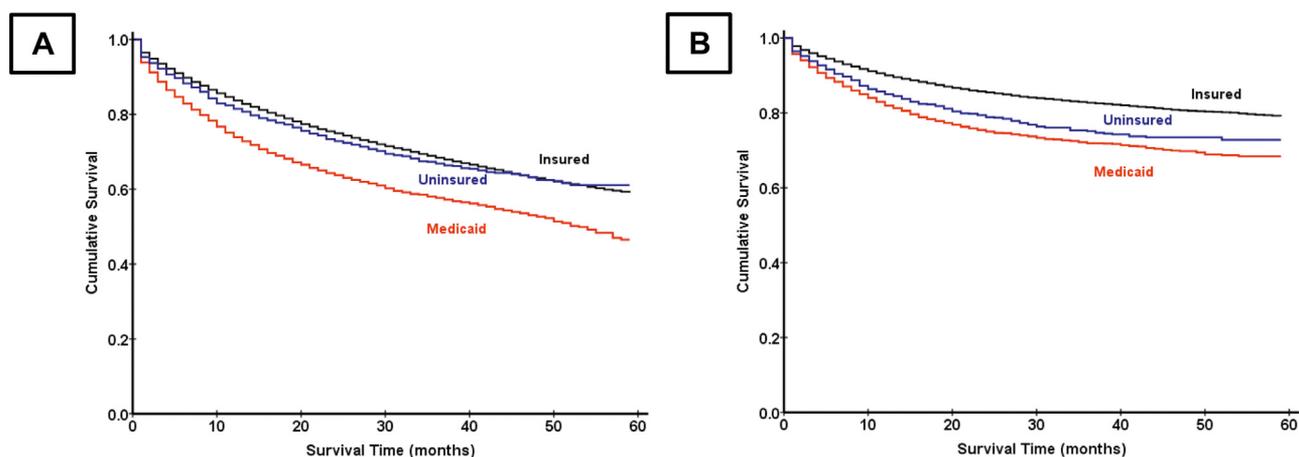
Fig. 2. Survival analysis of bladder cancer patients stratified by insurance type. Kaplan-Meier analysis of (A) overall survival and (B) disease-specific survival are shown for all patients.

Table 4
Separate multivariate logistic regression analyses for predictors of late disease presentation (T classification ≥T2, node positive disease, and metastatic disease)

Cofactor	Predictors of T classification ≥T2			Predictors of node positive disease			Predictors of metastatic disease		
	Hazards ratio	95% confidence interval	P value	Hazards ratio	95% confidence interval	P value	Hazards ratio	95% confidence interval	P value
Age (continuous)	1.01	1.00−1.01	<0.001	0.98	0.97−0.983	<0.001	1.00	0.99−1.00	0.898
Sex									
Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female	1.15	1.10−1.19	<0.001	1.13	1.05−1.22	0.001	1.13	1.05−1.23	0.002
Race									
White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Black	1.39	1.30−1.49	<0.001	1.42	1.26−1.61	<0.001	1.63	1.44−1.84	<0.001
Hispanic	1.07	1.00−1.15	0.036	1.19	1.05−1.35	0.005	1.32	1.16−1.51	<0.001
API	1.01	0.93−1.10	0.670	0.95	0.80−1.13	0.608	1.04	0.87−1.24	0.611
Native American	1.97	1.52−2.56	<0.001	2.22	1.48−3.31	<0.001	1.92	1.22−3.02	0.004
Marital status									
Unmarried	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Married	0.77	0.74−0.79	<0.001	0.76	0.71−0.82	<0.001	0.68	0.63−0.73	<0.001
Insurance status									
Insured	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medicaid	1.39	1.31−1.47	<0.001	1.45	1.30−1.61	<0.001	1.73	1.55−1.92	<0.001
Uninsured	1.51	1.33−1.71	<0.001	1.78	1.47−2.15	<0.001	2.04	1.66−2.51	<0.001
SES composite quartile									
Highest	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Second highest	1.00	0.95−1.05	0.925	1.05	0.95−1.16	0.319	0.93	0.84−1.04	0.219
Second lowest	1.04	0.99−1.10	0.073	1.04	0.94−1.15	0.444	1.00	0.90−1.12	0.907
Lowest	1.09	1.04−1.15	<0.001	1.02	0.92−1.13	0.618	0.98	0.88−1.09	0.775

API = Asian or Pacific Islander; Ref. = reference; SES = socioeconomic.

5. Conclusions

Lower SES, Medicaid insurance, and having no insurance are all predictive of having higher tumor stage. Independent of tumor stage, being of lower SES, having Medicaid insurance, and having no insurance predict worse OS and DSS. Further investigation is warranted to determine the underlying cause of these effects.

Conflict of interest

The authors have no conflict of interest to disclose.

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