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Original Article

The impact of socioeconomic status on the survival of men with early-onset prostate cancer

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Abstract: Prostate cancer (PCa) is generally considered a disease of older men; however, about 10% of new diagnoses in the US occur in men ≤ 55 years old. Socioeconomic status (SES) has been shown to influence survival in patients with PCa; however, the impact of SES on men with early-onset PCa remains undescribed. Using the National Cancer Database, we identified adult men ≤ 55 years of age with a diagnosis of prostatic adenocarcinoma between 2004-2018. Descriptive statistics were used to characterize differences among different SES groups. Kaplan-Meier (KM) and Cox regression analyses were used to assess the effect of SES on overall survival (OS). A total of 112,563 young patients with PCa with a median follow-up of 79.0 months were identified. Compared to high SES patients, low SES patients were more likely to be African American (42.4% vs. 8.6%; P<0.001), Hispanic (9.5% vs. 2.7%; P<0.001), and uninsured (5.2% vs. 1.1%; P<0.001); they were also more likely to live in a rural area (3.2% vs. 0.1%; P<0.001) and have stage IV disease (5.5% vs. 3.1%; P<0.001). KM analysis showed that a decreasing SES was directly associated with lower rates of OS (log-rank test P<0.001). On multivariable analysis, SES was found to have a negative effect on OS (low SES vs. high SES; hazard ratio [HR] 1.54; 95% confidence interval [CI] 1.41-1.68; P<0.001). In patients with early-onset PCa, SES was associated with lower OS. SES may be considered when implementing programs to improve the management of patients with early-onset PCa.

Keywords: Prostate cancer, social determinants of health, outcomes

Introduction

Despite being considered a disease of older men, 10% of new PCa diagnoses occur in men ≤ 55 years old (defined as early-onset PCa) [1]. During the last few decades, men ≤ 55 years old have experienced the greatest increase in PCa incidence [2]. In addition, men diagnosed with early-onset PCa have been shown to have worse 5- and 10-year survival rates compared to men 56-80 years old [1]. This is expected as patients with early-onset PCa tend to present with high-risk and advanced-stage disease [3].

Important biological differences may exist in early-onset PCa compared to late-onset PCa. Early-onset PCa has shown to have a more significant genetic component supporting the idea that a clinical subtype may exist in men with early-onset PCa. Rare genetic variants with low penetrance are potential candidates and are poorly identified in published studies. Men with early-onset PCa are more likely to have higher cause-specific mortality than others and are at higher risk for disease progression due to their extended life expectancy [31].

In early-onset PCa, patients with fast growing tumors may be entirely missed by screening as the timeframe from onset to developing symptoms is short. Additionally, the effect of length bias is specifically pronounced in early-onset PCa with its shortened latency period. Therefore, rapidly growing tumors in young men with brief window for detection would be associated with worst prognosis and advanced disease. Shortened sojourn time for PCa in young patients suggest that the most aggressive tumors will occur more commonly in early-onset PCa [32].

Although biology is most likely the culprit for differences in clinicopathologic features among early-onset PCa patients, sociodemographic factors may also play a role. In the US, young

uninsured adults are more likely to be men, belong to a racial or ethnic minority, and have lower family income [4]. Despite the expanded access to health insurance coverage provided by the Patient Protection and Affordable Care Act (ACA), select young adults may forego buying health care coverage due to higher premiums, highlighting the fact that household income is closely linked to insurance status [5, 6]. Thus, it is critically important to explore the relationship between sociodemographic factors and outcomes in patients with early-onset PCa.

To optimize cancer screening, the impact of not only biological factors but also socioeconomic characteristics must be considered. There is various evidence in the literature showing that lower socioeconomic status (SES) is associated with poor health and increased mortality. Men with low SES may have reduced health literacy and awareness decreasing the need to seek medical attention. However, men with high SES have an increased incidence in PCa that may be attributed to different behavior towards their health and screening. In addition, the role of poor nutrition and environmental risk factor exposure in disease progression and mortality among men with low SES increases the probability of developing early-onset PCa. Therefore, men with low SES could be a high-priority group for PCa screening at a younger age compared to the standard of care.

It is well established that sociodemographic factors, such as income, education, and social support, influence both the incidence and survival rates of PCa [7]. However, the degree of impact that SES has on disease features and outcomes among patients with early-onset PCa has not been well defined. Herein, we used the National Cancer Database (NCDB) to evaluate the association between SES and early-onset PCa outcomes.

Patients and methods

Data acquisition

Data from the 2004 to 2018 NCDB was obtained after Institutional Review Board approval as an exempt study. The NCDB is a national cancer registry database sponsored by the American College of Surgeons and the American Cancer Society. Data is captured from more than 1500 hospitals in the US, accounting for almost 34 million records, and representing approximately 70% of all new cancer cases in the US. The Participant User Files (PUF) contain de-identified data compliant with the Health Insurance Portability and Accountability Act (HIPAA) [8].

Study population

From 1,742,973 PCa patients captured in the NCDB during 2004-2018, we included those aged 18-55 years with the diagnosis of prostatic adenocarcinoma (*International Classification of Diseases for Oncology, Third Edition [ICD-O-3]* code 8140). We excluded patients with unknown race, ethnicity, insurance status, income quartile, education level, facility type, distance to hospital, follow-up information, NCDB analytic stage, and area of residence. Patients with missing pathologic confirmation of PCa or those with a secondary malignancy were also excluded. A summary of the inclusion and exclusion criteria can be found in **Figure 1**.

Study variables

We evaluated the following variables: age, race, ethnicity, insurance type, pathologic TNM stage, American Joint Committee on Cancer (AJCC) stage group, Charlson-Deyo comorbidity index (CDCI), population density of the patient's county of residence (metropolitan [>20,000 population in the metro area], urban [>2500 to >20,000 population adjacent to the metro area], or rural [<2500 population]), distance to facility, and facility type (community [>100 to ≤ 500 newly diagnosed cancer cases per year], comprehensive community [>500 newly diagnosed cancer cases per year], academic [>500 newly diagnosed cancer cases per year in addition to providing postgraduate medical education], or integrated network cancer program [a joint venture with multiple facilities, at least 1 hospital, no minimum for newly diagnosed cancer cases per year]).

To establish the impact of SES, the quartile assignments of median income and education level were combined to create a composite SES measure. Income and education level, as specified by the NCDB, were determined by matching each patient's ZIP code at the time of diagnosis with data derived from the 2016 *American*

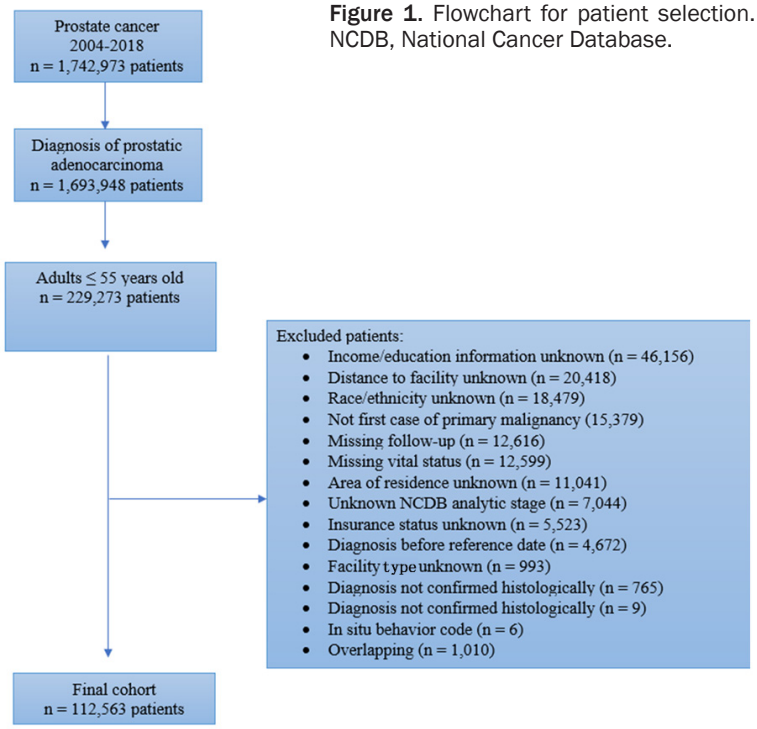

Figure 1. Flowchart for patient selection. NCDB, National Cancer Database.

Community Survey on median household income and the percentage of people aged ≥ 25 years old who had not earned a high school diploma, respectively. Income quartiles were defined as: <$40,227 (Q1), $40,227 - $50,353 (Q2), $50,354 - $63,332 (Q3), and ≥ $63,333 (Q4). Likewise, education quartiles were defined as proportion of men without high school diploma: ≥ 17.6% (Q1), 10.9% - 17.5% (Q2), 6.3% - 10.8% (Q3), and <6.3% (Q4) [9]. The quartile assignments (Q1, Q2, Q3, Q4) of the income and education measures were added together to form four composite SES categories: 2-3= Low SES; 4-5= Mid-Low SES; 6-7= Mid-High SES; and 8= High SES.

Outcome

The primary outcome from our analysis was overall survival (OS), which was defined as the number of months from the date of PCa diagnosis to the date of death or last reported follow-up. The NCDB does not collect data on cancer-specific survival or recurrence.

Statistical analysis

Continuous variables are presented as the median and interquartile range (IQR) with SES group differences evaluated using the Kruskal-Wallis test. Categorical variables are reported as frequency and percentage, evaluated using the chi-square test. Unadjusted differences in OS between SES groups were evaluated using the Kaplan-Meier method with the log-rank test. A multivariable Cox regression model was used to study SES group differences in OS after adjusting for clinical, patient, and facility covariates. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Corp, Armonk, NY, USA) and R version 4.1.0, with significance defined as two-tailed P<0.05 for all tests. For R, we used the Rcommander package and EZR PlugIn [10].

Results

The study cohort was compromised of 112,563 patients with early-onset PCa (**Figure 1**). Median follow-up for the cohort was 79.0 months. Compared to high SES patients, low SES patients were more likely to be African American (42.4% vs. 8.6%; P<0.001), Hispanic (9.5% vs. 2.7%; P<0.001), and uninsured (5.2% vs. 1.1%; P<0.001); they were also more likely to live in a rural area (3.2% vs. 0.1%; P<0.001) and have stage IV disease (5.5% vs. 3.1%; P<0.001). In addition, low SES patients were less likely to receive care at integrated network cancer programs, and less likely to undergo radical prostatectomy (RP) (**Table 1**). On KM analysis, a decreasing SES was directly associated with lower rates of OS (log-rank test P<0.001) (**Figure 2**).

After adjusting for age, race, ethnicity, travel distance, comorbidity burden (as per the CDCI), area of residence, facility type, insurance status, stage group, and surgical treatment on multivariable Cox regression, SES was found to have a negative effect on OS (low SES vs. high SES; hazard ratio [HR] 1.54; 95% confidence interval [CI] 1.41-1.68; P<0.001). Other predictors of mortality included: age (HR per year increase 1.02; 95% CI 1.01-1.03; P<0.001),

Table 1. Patient and tumor characteristics by socioeconomic status groups

Characteristic	Total	Low SES	Mid-low SES	Mid-high SES	High SES	*P*-value
n (%)	112563	21343 (19.0%)	27260 (24.2%)	34989 (31.1%)	28971 (25.7%)	
Age (median [interquartile range])	52.00 [50.00, 54.00]	52.00 [50.00, 54.00]	52.00 [50.00, 54.00]	52.00 [50.00, 54.00]	52.00 [50.00, 54.00]	0.684
Race (%)						
Caucasian	86756 (77.1)	11771 (55.2)	20742 (76.1)	28558 (81.6)	25685 (88.7)	<0.001
African American	22881 (20.3)	9049 (42.4)	5872 (21.5)	5468 (15.6)	2492 (8.6)	
Other	2926 (2.6)	523 (2.5)	646 (2.4)	963 (2.8)	794 (2.7)	
Hispanic ethnicity (%)						
Yes	5910 (5.3)	2020 (9.5)	1650 (6.1)	1472 (4.2)	768 (2.7)	<0.001
No	106653 (94.7)	19323 (90.5)	25610 (93.9)	33517 (95.8)	28203 (97.3)	
Insurance status (%)						
Not Insured	2756 (2.4)	1113 (5.2)	728 (2.7)	584 (1.7)	331 (1.1)	<0.001
Medicaid	4451 (4.0)	2000 (9.4)	1199 (4.4)	896 (2.6)	356 (1.2)	
Medicare	4873 (4.3)	1895 (8.9)	1343 (4.9)	1119 (3.2)	516 (1.8)	
Other Government	2396 (2.1)	487 (2.3)	707 (2.6)	786 (2.2)	416 (1.4)	
Private Insurance/Managed Care	98087 (87.1)	15848 (74.3)	23283 (85.4)	31604 (90.3)	27352 (94.4)	
Facility type (%)						
Academic/Research Program	48658 (43.2)	9190 (43.1)	10551 (38.7)	14864 (42.5)	14053 (48.5)	<0.001
Comprehensive Community Cancer Program	37786 (33.6)	7650 (35.8)	10101 (37.1)	11920 (34.1)	8115 (28.0)	
Integrated Network Cancer Program	21349 (19.0)	3501 (16.4)	5068 (18.6)	6716 (19.2)	6064 (20.9)	
Community Cancer Program	4770 (4.2)	1002 (4.7)	1540 (5.6)	1489 (4.3)	739 (2.6)	
Distance to hospital (miles)	12.9 [6, 30]	11.20 [4.40, 38.60]	14.80 [6.00, 37.30]	13.40 [6.40, 27.90]	12.00 [6.80, 22.40]	<0.001
Area of residence (%)						
Rural	1570 (1.4)	686 (3.2)	514 (1.9)	329 (0.9)	41 (0.1)	<0.001
Urban	46665 (41.5)	11143 (52.2)	14849 (54.5)	13912 (39.8)	6761 (23.3)	
Metro	64328 (57.1)	9514 (44.6)	11897 (43.6)	20748 (59.3)	22169 (76.5)	
Charlson-Deyo Comorbidity Index (%)						
0	98720 (87.7)	17850 (83.6)	23701 (86.9)	30917 (88.4)	26252 (90.6)	<0.001
1	11829 (10.5)	2860 (13.4)	3022 (11.1)	3521 (10.1)	2426 (8.4)	
≥ 2	2014 (1.8)	633 (3.0)	537 (2.0)	551 (1.6)	293 (1.0)	
Surgical treatment (%)						
Radical prostatectomy	92746 (82.4)	16477 (77.2)	22103 (81.1)	29316 (83.8)	24850 (85.8)	<0.001
No surgery	17142 (15.2)	4175 (19.6)	4441 (16.3)	4937 (14.1)	3589 (12.4)	
Other treatment	2522 (2.2)	667 (3.1)	671 (2.5)	687 (2.0)	497 (1.7)	
Unknown	153 (0.1)	24 (0.1)	45 (0.2)	49 (0.1)	35 (0.1)	

Analytic stage group (%)						
Stage I	18328 (16.3)	3465 (16.2)	4542 (16.7)	5572 (15.9)	4749 (16.4)	<0.001
Stage II	73399 (65.2)	13613 (63.8)	17475 (64.1)	23036 (65.8)	19275 (66.5)	
Stage III	16213 (14.4)	3091 (14.5)	4038 (14.8)	5043 (14.4)	4041 (13.9)	
Stage IV	4623 (4.1)	1174 (5.5)	1205 (4.4)	1338 (3.8)	906 (3.1)	
pT (%)						
0	86 (0.1)	16 (0.1)	22 (0.1)	25 (0.1)	23 (0.1)	<0.001
1	686 (0.6)	185 (0.9)	168 (0.6)	197 (0.6)	136 (0.5)	
2	69872 (62.1)	12330 (57.8)	16519 (60.6)	22111 (63.2)	18912 (65.3)	
3	17832 (15.8)	3490 (16.4)	4422 (16.2)	5508 (15.7)	4412 (15.2)	
4	442 (0.4)	103 (0.5)	116 (0.4)	139 (0.4)	84 (0.3)	
X	11935 (10.6)	2371 (11.1)	2930 (10.7)	3687 (10.5)	2947 (10.2)	
Missing	11710 (10.4)	2848 (13.3)	3083 (11.3)	3322 (9.5)	2457 (8.5)	
pN (%)						
0	70169 (62.3)	12826 (60.1)	16556 (60.7)	22087 (63.1)	18700 (64.5)	<0.001
1	2628 (2.3)	561 (2.6)	654 (2.4)	790 (2.3)	623 (2.2)	
X	26072 (23.2)	4766 (22.3)	6490 (23.8)	8135 (23.3)	6681 (23.1)	
Missing	13694 (12.2)	3190 (14.9)	3560 (13.1)	3977 (11.4)	2967 (10.2)	
pM (%)						
0	30123 (26.8)	5332 (25.0)	7152 (26.2)	9424 (26.9)	8215 (28.4)	<0.001
1	997 (0.9)	271 (1.3)	285 (1.0)	290 (0.8)	151 (0.5)	
X	19077 (16.9)	3437 (16.1)	4666 (17.1)	6102 (17.4)	4872 (16.8)	
Missing	62366 (55.4)	12303 (57.6)	15157 (55.6)	19173 (54.8)	15733 (54.3)	
Lymphovascular invasion (%)						
Present/Identified	3837 (5.4)	779 (5.5)	885 (5.1)	1204 (5.5)	969 (5.3)	<0.001
Absent/Not identified	50696 (70.9)	9544 (67.7)	12205 (70.3)	15675 (71.5)	13272 (73.0)	
Unknown	17012 (23.8)	3771 (26.8)	4263 (24.6)	5048 (23.0)	3930 (21.6)	
Surgical margins (%)						
Residual tumor	20411 (18.1)	3945 (18.5)	5134 (18.8)	6375 (18.2)	4957 (17.1)	<0.001
No residual tumor	73169 (65.0)	12770 (59.8)	17218 (63.2)	23137 (66.1)	20044 (69.2)	
No primary site surgery	17142 (15.2)	4175 (19.6)	4441 (16.3)	4937 (14.1)	3589 (12.4)	
Margins not evaluable	912 (0.8)	249 (1.2)	243 (0.9)	252 (0.7)	168 (0.6)	
Unknown or not applicable	929 (0.8)	204 (1.0)	224 (0.8)	288 (0.8)	213 S0.7)	

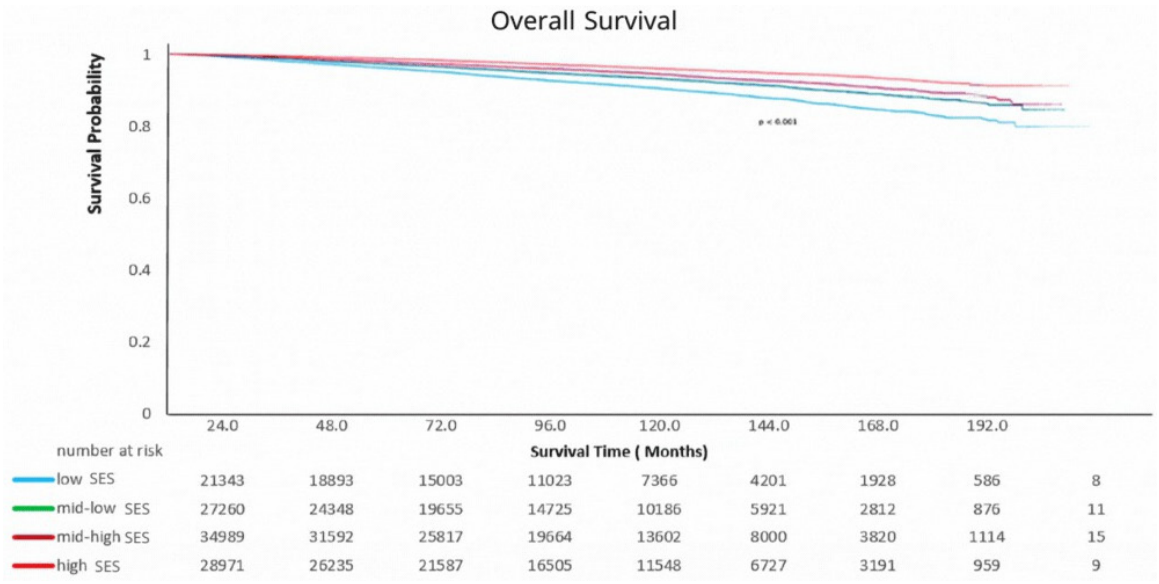

Figure 2. Kaplan-Meier curve for overall survival stratified by socioeconomic status (SES).

stage group (stage IV vs. stage I; HR 17.65; 95% CI 15.84-19.65; P<0.001), comorbidity burden (CDCI ≥ 2 vs. CDCI=0; HR 1.89; 95% CI 1.66-2.15; P<0.001), area of residence (rural vs. metropolitan; HR 1.24; 95% CI 1.03-1.50; P=0.026), and insurance status (no insurance vs. private insurance; HR 2.10 95% CI 1.88-2.33; P<0.001) (**Table 2**).

Discussion

PCa mortality among men ≤ 55 years old is low but has been increasing during the past few decades [1, 2]. This could be in part explained by the recommendations of the European and North American urological associations regarding PSA screening in men aged over 55 years. Because screening for PCa is variable and unclear in men less than 55 years age, early onset PCa in younger men may remain undetected until later disease stage. In addition, men with early-onset PCa are more likely to be symptomatic at the time of the diagnosis which could predict worse disease compared to the standard of care PCa patients identified merely based on PSA screening-prompted prostate needle biopsy according to current clinical guidelines and protocols [11-14].

In general, cancer patients with low SES have poor survival outcomes compared to those with high SES [15]. Factors affecting social differences in cancer diagnosis, treatment, and prognosis remain incompletely understood, but have been linked to disease characteristics, patient's factors, and health care access and quality [16]. Advanced cancer stage and pathologic features at the time of the diagnosis are associated with poor outcomes, and are often hypothesized as being related to health disparities affecting survival outcomes [17].

In our study, low SES was assessed by income and education level. A study by Watson et al., including 2194 men with PCa, showed that men living in low SES neighborhoods as defined by lower income and lower educational levels were less likely to receive definitive treatment [18]. Tomic et al. found that men with lower income were less likely to receive definitive treatment for intermediate, high risk, and very high-risk PCa, and more likely to have positive surgical margins at prostatectomy. Moreover, low SES patients with very low-risk PCa are less likely to be offered active surveillance for their disease compared with men at higher SES levels [19]. This is concordant with our data, which showed that younger men with low SES are more likely to present with advanced-stage disease at the time of diagnosis and less likely to receive definitive treatment in the form of RP.

Men with a low SES also tend to have a higher comorbidity burden. These men usually have poor general health and lifestyle risk factors including physical inactivity and smoking, along with a higher incidence of obesity and metabolic syndrome which limit the options for defin-

Table 2. Multivariable Cox proportional hazard model for overall mortality

Parameter	Hazard ratio	Lower 95% CI	Upper 95% CI	*P*-value
Socioeconomic status				
High	Reference			
Mid-high	1.23	1.14	1.33	<0.001
Mid-low	1.36	1.25	1.48	<0.001
Low	1.54	1.41	1.68	<0.001
Age (per year increase)	1.02	1.01	1.03	<0.001
Race				
Caucasian	Reference			
Black	0.94	0.88	1.00	0.050
Other	0.81	0.68	0.97	0.024
Hispanic ethnicity				
No	Reference			
Yes	0.61	0.54	0.70	<0.001
Insurance status				
Private	Reference			
Not insured	2.10	1.88	2.33	<0.001
Medicaid	2.25	2.05	2.47	<0.001
Medicare	2.38	2.18	2.60	<0.001
Other government	1.20	0.99	1.45	0.066
Facility type				
Academic/Research	Reference			
Comprehensive community	1.17	1.10	1.25	<0.001
Integrated cancer network	1.07	1.00	1.16	0.053
Community	1.23	1.10	1.38	<0.001
Distance to hospital (per mile increase)	1.00	1.00	1.00	0.009
Area of residence				
Metropolitan	Reference			
Urban	1.05	0.99	1.11	0.1
Rural	1.24	1.03	1.50	0.026
Charlson-Deyo Comorbidity Index				
0	Reference			
1	1.55	1.44	1.67	<0.001
≥ 2	1.89	1.66	2.15	<0.001
Surgical treatment				
No surgery	Reference			
Radical prostatectomy	0.28	0.26	0.30	<0.001
Other treatment	0.88	0.78	1.00	0.055
Unknown	1.03	0.46	2.30	0.9
Analytic stage group				
I	Reference			
II	1.82	1.64	2.03	<0.001
III	4.62	4.10	5.21	<0.001
IV	17.65	15.84	19.65	<0.001

itive treatment. In the current study, we showed that patients with low SES are more likely to have a higher comorbidity burden, and a higher comorbidity burden was associated with worse OS.

It has been postulated that African American men carry a higher incidence and mortality rate for PCa compared to other racial or ethnic groups [20-22]. Compared to Caucasian Americans, African American men tend to be younger, have a more advanced disease stage at the time of diagnosis, and are more likely to have metastatic disease with a lower OS when treated for PCa [21, 23-27]. In our cohort, when adjusted for available potential confounders, African American race was not associated with worse OS. A recent study by Wen et al. concluded that African Americans diagnosed with localized high-grade PCa who underwent RP have a 51% higher overall mortality rate compared to Caucasian American patients, however adjusting for education level, income, and insurance status, the disparities in mortality rates dropped to 30%. Adjusting for comorbid conditions and nonclinical parameters the overall mortality disparity decreased to 19% [28].

Quality of cancer care is another key factor influencing outcomes in cancer patients. In our cohort, we showed that the mortality rate among patients with early-onset PCa was higher among those not insured,

those treated at community cancer centers, and those who lived in rural areas. All these factors potentially impede young men diagnosed with PCa with from receiving prompt curative treatment at high-quality centers compared with men in higher SES [19, 29, 30].

Although our study addresses the mortality rate in a large population of young men diagnosed with PCa, the current study is not without limitations. The retrospective nature of our cohort may lead to indication and selection biases. In the current study, we defined low SES based on educational level and income; however, the use of those factors as indicators of SES does not cover all aspects of SES concerning health. We were unable to assess the effect of other factors such as lifestyle habits, health awareness, health beliefs, and health behavior. Also, we were only able to assess the OS among young men with PCa; however, we are not able to assess PCa-specific survival or recurrence due to the absence of such information in the NCDB.

Conclusions

Socioeconomic inequities among men diagnosed with early-onset PCa affect OS. SES in men with early-onset prostate cancer could be considered in prognostic algorithms and implemented in management programs to improve overall outcomes among these men.

Disclosure of conflict of interest

None.

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