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Disparities in utilization of treatment for clinical stage I-II pancreatic adenocarcinoma by area socioeconomic status and race/ethnicity

Douglas S. Swords, MD, MS[a,b,*], Sean J. Mulvihill, MD[a], Benjamin S. Brooke, MD, PhD[a], David E. Skarda, MD[a,b], Matthew A. Firpo, PhD[a], Courtney L. Scaife, MD[a]

[a] Department of Surgery, University of Utah, Salt Lake City
[b] Surgical Services Clinical Program, Intermountain Healthcare, Salt Lake City, UT

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ABSTRACT

Background: Utilization of multimodality therapy for clinical stage I-II pancreatic ductal adenocarcinoma is associated with meaningful prolongation of survival. Although the qualitative existence of disparities in treatment utilization by socioeconomic status and race/ethnicity is well documented, the absolute magnitudes of these disparities have not been previously quantified.

Methods: The exposures in this retrospective cohort study of the 2010–2015 National Cancer Database were a 7-value area-level socioeconomic status index and race/ethnicity. Main outcomes were surgery, chemotherapy, and multimodality therapy (surgery *and* chemotherapy). Adjusted rate differences were calculated after logistic regression. Models excluded intermediate variables. Overall survival was evaluated in unadjusted and adjusted analyses.

Results: Of 43,760 patients, 63.4% underwent surgery. Of 39,808 patients without chemotherapy contraindications, refusal, or missing data, 75.1% received chemotherapy and 51.4% received multimodality therapy. Adjusted rate differences for utilization of surgery, chemotherapy, and multimodality therapy in the lowest socioeconomic status patients were −10.0 (95% confidence interval [CI] −12.4 to −7.5), −12.7 (95% CI −16.3 to −9.1), and −15.4 (95% CI −18.8 to −12.0), respectively, versus the highest socioeconomic status patients. Adjusted rate differences for multimodality therapy utilization in non-Hispanic Black and Hispanic patients were −10.1 (95% CI −13.6 to −6.7) and −11.8 (95% CI −14.3 to −9.2), respectively, versus non-Hispanic White patients. Median overall survival increased in a graded fashion from 14.1 (95% CI 13.4–14.8) months in the lowest socioeconomic status patients to 20.2 months (95% CI 19.6–20.8) in the highest socioeconomic status patients. Survival differences were attenuated but not eliminated in multivariable Cox models.

Conclusion: Socioeconomic status and race/ethnicity are more powerful determinants of whether patients receive treatment for clinical stage I-II pancreatic ductal adenocarcinoma than previously appreciated. Nationwide quality improvement efforts aimed at addressing these inequities are warranted.

Introduction

Five-year survival rates for resectable pancreatic ductal adenocarcinoma (PDAC) exceeding 25% are achievable with surgery and chemotherapy (ie, multimodality therapy [MMT]).[1–3] Patients with potentially resectable or borderline resectable (BR) tumors deemed amenable to resection represent a subgroup of PDAC patients with a realistic opportunity for long-term survival. Chemotherapy is indicated regardless of stage in PDAC, and the addition of chemotherapy to surgery increases 5-year survival to 20%–30% from approximately 10% with surgery alone.[4–7] Despite this, rates of surgery and chemotherapy remain surprisingly low in the United States[8–18] and Europe.[18]

Accurate quantification of disparities in the utilization of appropriate health care interventions is a major goal of disparities research. The qualitative existence of disparities in the utilization of surgery and chemotherapy for PDAC by race/ethnicity and by components of socioeconomic status (SES) is well documented.[8,10–19] Nevertheless, the magnitudes of these disparities have not been accurately quantified because of three common methodologic pitfalls in previous studies. First, area income and education variables have been simultaneously included in multivariable models as proxies for SES.[8,13] Because income and education are strongly correlated, this practice causes each variable to "adjust away" much of the

* Corresponding author: Department of Surgery, University of Utah, 30 North 1900 East, Salt Lake City, UT 84132.
E-mail address: douglas.swords@hsc.utah.edu (D.S. Swords).

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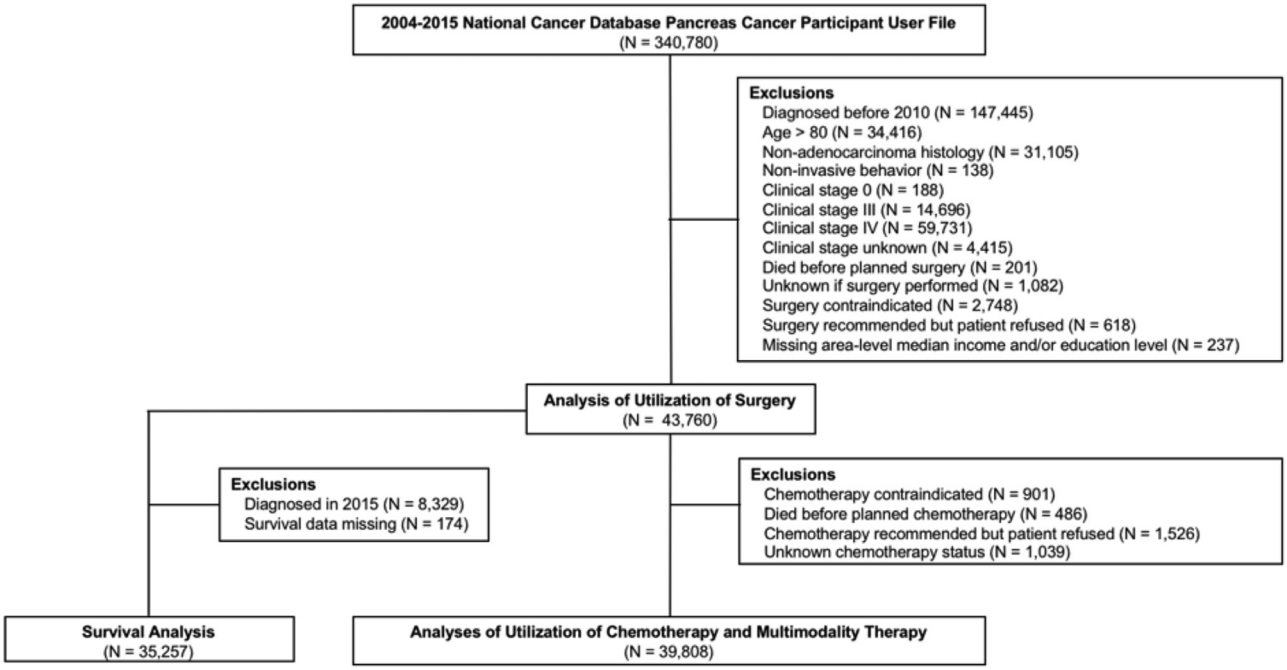

Fig. 1. Flowchart of exclusions and analytic cohorts.

effect of the other, making effect sizes uninterpretable.[20] Second, most studies report only odds ratios (ORs) despite recommendations to also report adjusted absolute rate differences (ARDs).[21,22] This can confuse readers about the absolute magnitude of disparities because of the dimensionless nature of the OR and its divergence from the risk ratio with common outcomes.[21,23,24] Finally, intermediates, or postexposure variables lying along the causal pathway between exposure and outcome, are frequently adjusted for in multivariable models.[25] This usually causes "overadjustment bias" toward the null.[25–27] Overadjustment bias is especially consequential in disparities research because it causes estimates of disparities to appear spuriously small, diverting attention from actual disparities.[28] An accurate assessment of the magnitude of disparities used in guideline-recommended treatment for clinical stage I-II PDAC by SES and race/ethnicity is therefore needed.

Our objective was to address this knowledge gap using the 2010–2015 National Cancer Database (NCDB). Area income and education variables were combined to form a novel SES index. Estimates of effect size are presented as adjusted rates, ARDs, *and* adjusted risk ratios to permit easy interpretation of the magnitude of disparities. Finally, we considered whether candidate covariates could plausibly be intermediate variables that lay along the causal pathway *between* the exposures of interest (SES and race/ethnicity) and treatment utilization rather than *before* the exposures of interest. Our overall hypothesis was that accounting for these common methodologic issues would reveal larger disparities based on SES and race/ethnicity in the utilization of guideline-recommended treatments than previously appreciated.

Methods

Data source and exclusion criteria

This study used the 2015 participant user file (PUF) of the NCDB, a nationwide hospital-level database that captures 70% of cancers in the United States.[29,30] The NCDB was used instead of the Surveillance, Epidemiology, and End Results (SEER) registry because it contains accurate chemotherapy data, granular area-level SES variables, and more patients.[31]

The study population comprised patients 19–80 years of age who had clinical stage I-II PDAC, with no treatment contraindications or refusal. Exclusions are presented in the Fig. 1. The clinical stage was recoded by pathologic stage for resected patients with undocumented clinical stage.[13] Patients with missing income or education levels were excluded because those variables formed the SES index. Survival analyses excluded patients diagnosed in 2015, whose survival data are unavailable. Missing indicators were used for chemotherapy status in survival analyses for those with contraindications, refusal, etc.

SES index

A SES index was created from area income and education variables, which are quartiles of continuous variables from the 2012 American Communities Survey defined at the ZIP Code Tabulation Area (ZCTA)-level.[32,33] The United Stats has 33,120 ZCTAs vs 3,220 counties.[34] SES-related variables in the standard SEER database are defined at the county level.[31] Values of "4" for these variables indicate ZCTAs with the highest incomes and graduation rates. The correlation between these variables was tested by calculating Spearman ρ. The SES index was calculated as (income + education) – 1 (Table 1). The index had 7 values; 7 indicated the highest SES.

Outcome measures

The three main outcomes were utilization of surgery, chemotherapy (neoadjuvant *and/or* adjuvant for resected patients), and MMT (surgery and chemotherapy). Overall survival (OS), the secondary outcome, was measured starting at diagnosis. Survival time was right censored at 5 years.

Covariate selection and intermediate variables

Covariates available at the time of treatment decisions were considered for inclusion in multivariable models.[25] Commission of Cancer (CoC) hospital type was not adjusted for because that would have required excluding 4,672 of 27,762 resected patients (16.8%) who had surgery at a nonreporting hospital. Because more

Table 1
Cross tabulation of area-level income and education variables, demonstrating how the socioeconomic status index was calculated*.

	Median ZCTA-level High School Non-Completion Rate			
Median ZCTA-level Income	≥ 21% (n = 7,340) *(1 point)*	13%-20.9% (n = 11,466) *(2 points)*	7%-12.9% (n = 14,300) *(3 points)*	< 7% (n = 10,654) *(4 points)*
< $38,000 (n = 7,687) (1 point)	n = 4,246 *(1 + 1) - 1 = 1*	n = 2,739 *(1 + 2) - 1 = 2*	n = 580 *(1 + 3) - 1 = 3*	n = 122 *(1 + 4) - 1 = 4*
$38,000-$47,999 (n = 10,340) (2 points)	n = 1,953 *(2 + 1) – 1 = 2*	n = 4,547 *(2 + 2) – 1 = 3*	n = 3,400 *(2 + 3) – 1 = 4*	n = 440 *(2 + 4) – 1 = 5*
$48,000-$62,999 (n = 11,612) (3 points)	n = 983 *(3 + 1) – 1 = 3*	n = 3,190 *(3 + 2) – 1 = 4*	n = 5,598 *(3 + 3) – 1 = 5*	n = 1,841 *(3 + 4) – 1 = 6*
≥ $63,000 (n= 14,121) (4 points)	n = 158 *(4 + 1) – 1 = 4*	n = 990 *(4 + 2) – 1 = 5*	n = 4,722 *(4 + 3) – 1 = 6*	n = 8,251 *(4+ 4) – 1 = 7*

* Cells with the same color of shading indicate cells with the same socioeconomic status index values.

of these patients were non-Hispanic white (NHW) (85.2% vs 80.3%), their exclusion could have introduced bias. Aside from variables handled as intermediates, covariate selection was nonparsimonious.

In models where the SES index was the exposure, insurance status and evaluation at multiple CoC-accredited hospitals ("PUF_MULT_SOURCE") were conceptually suspicious for being intermediates. Patients with higher SES might have access to better insurance and the opportunity to be evaluated at multiple CoC-accredited hospitals, which could both be associated with treatment utilization. These two variables were handled as intermediates after the validity of these assumptions was confirmed (Supplemental Methods and Supplemental Tables 1–3).

Non-Hispanic black (NHB) patients and some other minorities are more likely to live in low-SES areas because of the US history of segregationist housing policies.[35,36] After confirmation of this relationship in these data, SES was additionally handled as an intermediate in models where race/ethnicity was the exposure (Supplemental Methods and Supplemental Tables 1 and 4).

Statistical analysis

Univariate associations among covariates and binary outcomes were assessed with χ^2 tests. Missing data were coded with a missing indicator. Adjusted associations among covariates and binary outcomes were assessed with logistic regression models that accounted for clustering at the census division level. Average marginal effect estimation was used to obtain adjusted risk ratios, adjusted rates, and ARDs.[37–40] Only race/ethnicity and SES index were reported for MMT because it was a composite.

Treatment utilization by race/ethnicity *and* SES index was evaluated by adding an interaction term between race/ethnicity and SES index and calculating adjusted rates.[37,41] These results for Asian and other or unknown race/ethnicity patients were not reported because these groups were small. *P* values for interactions among NHB and Hispanic race/ethnicity and SES index were evaluated to assess whether the overall associations between race/ethnicity and treatment utilization varied across the SES gradient.

Unadjusted OS was examined by calculating median unadjusted OS and fitting unadjusted Cox proportional hazards models that clustered on census division. Multivariable Cox models controlling for confounders were fitted. For the analysis of OS by SES index, a final model that additionally controlled for utilization of surgery and chemotherapy was fitted. OS was not examined by race/ethnicity, given our focus on treatment utilization, because differences in tumor biology between race/ethnicity groups could contribute to survival differences.[42]

Sensitivity analyses

Sensitivity analyses were performed to understand how methodologic decisions affected the main results. First, income and education were handled as the exposures in models that included these components rather than the SES index to determine whether the index revealed larger disparities than would have been appreciated if each of its component were instead the exposure. Second, income *and* education were simultaneously included in models rather than the SES index to demonstrate how strong correlations between variables that measure two aspects of the same entity can obscure actual associations. Finally, models were repeated with the SES index as the exposure and intermediate variables included to determine the extent to which this widespread practice biased results toward the null.[26]

Results

Table 1 presents how the SES index was calculated. ZCTA-level income and education levels were strongly correlated (Spearman $\rho = 0.68$; $P < .001$). Patient characteristics by SES index are presented in Supplemental Table 1. Rates of NHB and Hispanic race/ethnicity increased in a graded fashion from 4.6% and 2.3%, respectively, in the highest SES areas to 30.1% and 11.1%, respectively, in the lowest SES areas. Rates of having a comorbidity decreased from 39.7% to 30.7% with increasing SES. For patients younger than 65 years of age, private insurance rates increased from 47.6% to 80.7% with increasing SES.

SES and surgery

Of 43,760 patients with clinical stage I-II PDAC, a total of 27,762 (63.4%) underwent surgery (Table 2). Adjusted surgery rates significantly increased in a graded fashion from 58.3% (95% confidence interval [CI] 55.3%–61.2%) in the lowest SES areas to 68.2% (95% CI 66.3%–70.2%) in the highest SES areas.

Table 2
Univariate and multivariable associations of covariates with utilization of surgery.

	Univariate analysis, number (%)*		Multivariable analysis		
	Surgery utilized ($n = 27,762$)	Surgery omitted ($n = 15,998$)	Adjusted rate of surgery, % (95% CI)	Adjusted rate difference, % (95% CI)†	Adjusted RR for omission of surgery (95% CI)†
SES index	$P < .001$				
1 (Lowest)	2,406 (8.7)	1,840 (11.5)	58.3 (55.3–61.2)	**−10.0 (−12.4 to −7.5)**	**1.31 (1.23–1.40)**
2	2,815 (10.1)	1,877 (11.7)	60.7 (57.7–63.7)	**−7.5 (−9.7 to −5.3)**	**1.24 (1.17–1.31)**
3	3,753 (13.5)	2,357 (14.7)	61.6 (58.9–64.2)	**−6.7 (−7.8 to −5.6)**	**1.21 (1.18–1.24)**
4	4,284 (15.4)	2,586 (16.2)	62.2 (59.6–64.8)	**−6.0 (−7.4 to −4.7)**	**1.19 (1.15–1.23)**
5	4,488 (16.2)	2,540 (15.9)	63.4 (61.7–65.2)	**−4.8 (−6.2 to −3.4)**	**1.15 (1.10–1.20)**
6	4,339 (15.6)	2,224 (13.9)	65.9 (63.6–68.2)	**−2.3 (−4.1 to −0.5)**	**1.07 (1.02–1.13)**
7 (Highest)	5,677 (20.5)	2,574 (16.1)	68.2 (66.3–70.2)	0 [Reference]	1 [Reference]
Race/ethnicity	$P < .001$				
NHW	22,521 (81.1)	12,208 (76.3)	64.7 (62.5–66.8)	0 [Reference]	1 [Reference]
NHB	2,824 (10.2)	2,199 (13.8)	57.2 (55.4–59.1)	**−7.4 (−8.9 to −5.9)**	**1.21 (1.16–1.26)**
Hispanic	1,287 (4.6)	884 (5.5)	60.5 (56.7–64.4)	**−4.1 (−7.0 to −1.3)**	**1.12 (1.04–1.20)**
Asian	722 (2.6)	399 (2.5)	63.9 (61.6–66.1)	−0.8 (−2.4 to 0.8)	1.02 (0.98–1.07)
Other/unknown	408 (1.5)	308 (1.9)	57.0 (52.4–61.6)	**−7.7 (−11.5 to −3.9)**	**1.22 (1.12–1.33)**
Age, years	$P < .001$				
19–49	1,669 (6.0)	690 (4.3)	71.9 (69.3–74.4)	0 [Reference]	1 [Reference]
50–59	5,688 (20.5)	2,865 (17.9)	67.3 (65.1–69.6)	**−4.5 (−6.0 to −3.1)**	**1.16 (1.10–1.22)**
60–69	10,534 (37.9)	5,451 (34.1)	65.9 (63.9–67.9)	**−6.0 (−7.3 to −4.6)**	**1.21 (1.15–1.28)**
≥ 70	9,871 (35.6)	6,992 (43.7)	57.9 (55.6–60.2)	**−14.0 (−16.1 to −11.8)**	**1.50 (1.39–1.61)**
Sex	$P = .18$				
Male	14,337 (51.6)	8,155 (51.0)	63.3 (61.1–65.6)	0 [Reference]	1 [Reference]
Female	13,425 (48.4)	7,843 (49.0)	63.6 (61.5–65.6)	0.2 (−0.6 to 1.1)	0.99 (0.9–1.02)
Charlson-Deyo	$P < .001$				
0	18,002 (64.8)	10,393 (65.0)	63.0 (60.8–65.3)	0 [Reference]	1 [Reference]
1	7,534 (27.1)	4,106 (25.7)	65.3 (63.2–67.4)	**2.3 (1.0–3.6)**	**0.94 (0.91–0.97)**
2	1,610 (5.8)	1,026 (6.4)	62.3 (59.1–65.6)	−0.7 (−3.3 to 1.9)	1.02 (0.95–1.09)
≥ 3	616 (2.2)	473 (3.0)	57.5 (53.1–62.0)	**−5.5 (−10.5 to −0.5)**	**1.15 (1.02–1.30)**
Cancer history	$P = .003$				
No	22,293 (80.3)	13,032 (81.5)	63.1 (61.0–65.2)	0 [Reference]	1 [Reference]
Yes	5,469 (19.7)	2,966 (18.5)	65.0 (62.7–67.2)	**1.9 (0.7–3.0)**	**0.95 (0.92–0.98)**
Tumor location	$P < .001$				
Head	20,224 (72.9)	11,306 (70.7)	64.3 (62.0–66.5)	0 [Reference]	1 [Reference]
Body	1,947 (7.0)	1,712 (10.7)	52.8 (49.8–55.8)	**−11.5 (−13.5 to 09.4)**	**1.32 (1.26–1.38)**
Tail	2,822 (10.2)	714 (4.5)	79.3 (77.2–81.4)	**15.0 (12.9–17.2)**	**0.58 (0.53–0.63)**
Other/NOS	2,769 (10.0)	2,266 (14.2)	55.1 (53.1–57.0)	**−9.2 (−11.0 to −7.4)**	**1.26 (1.20 to 1.32)**
Clinical stage	$P < .001$				
I	10,170 (36.6)	4,657 (29.1)	68.7 (65.5–71.8)	0 [Reference]	1 [Reference]
II	17,592 (63.4)	11,341 (70.9)	60.8 (58.8–62.7)	**−7.9 (−10.4 to −5.4)**	**1.25 (1.15–1.36)**
Urban/rural status	$P < .001$				
Metropolitan	22,535 (81.2)	12,807 (80.1)	63.5 (61.3–65.7)	0 [Reference]	1 [Reference]
Urban	4,053 (14.6)	2,551 (16.0)	62.7 (60.4–65.0)	−0.8 (−2.9 to 1.4)	1.02 (0.96–1.08)
Rural	487 (1.8)	322 (2.0)	61.7 (56.7–66.7)	−1.8 (−6.4 to 2.9)	1.05 (0.93–1.18)
Unknown	687 (2.5)	318 (2.0)	67.5 (64.2–70.8)	**4.0 (1.0–7.0)**	**0.89 (0.81–0.98)**
Year of diagnosis	$P < .001$				
2010	4,088 (14.7)	2,137 (13.4)	65.8 (63.2–68.5)	0 [Reference]	1 [Reference]
2011	4,219 (15.2)	2,366 (14.8)	64.0 (61.3–66.8)	−1.8 (−3.6 to 0.05)	1.05 (0.99–1.11)
2012	4,551 (16.4)	2,624 (16.4)	63.4 (60.9–65.9)	**−2.4 (−3.8 to −1.1)**	**1.07 (1.03–1.11)**
2013	4,697 (16.9)	2,745 (17.2)	63.1 (60.6–65.5)	**−2.8 (−4.7 to −0.8)**	**1.08 (1.02–1.14)**
2014	5,018 (18.1)	2,986 (18.7)	62.6 (60.1–65.1)	**−3.2 (−5.3 to −1.1)**	**1.09 (1.03–1.16)**
2015	5,189 (18.7)	3,140 (19.6)	62.4 (60.8–63.9)	**−3.5 (−5.7 to −1.2)**	**1.10 (1.03–1.18)**
Insurance status‡	$P < .001$				
Private	10,563 (38.1)	4,766 (29.8)	—	—	—
Medicare	14,251 (51.3)	9,068 (56.7)	—	—	—
Medicaid	1,464 (5.3)	1,068 (6.7)	—	—	—
Other government program	389 (1.4)	323 (2.0)	—	—	—
Uninsured	405 (1.5)	506 (3.2)	—	—	—
Unknown	690 (2.5)	267 (1.7)	—	—	—
Evaluated at > 1 CoC hospital‡	$P < .001$				
No	18,712 (67.4)	12,707 (79.4)	—	—	—
Yes	9,050 (32.6)	3,291 (20.6)	—	—	—

* Column percentages may not sum to 100% because of rounding.
† Bold values for adjusted risk differences and adjusted risk ratios from the multivariable model indicate significance at a P value of $< .05$.
‡ Insurance status and evaluation at > 1 CoC hospital were not included in this multivariable model because they were intermediate variables.
RR, risk ratio; *NOS*, not otherwise specified.

SES and chemotherapy

Among 39,808 patients in the chemotherapy utilization analysis, a total of 29,896 (75.1%) received chemotherapy (Table 3). Adjusted chemotherapy rates significantly increased in a graded fashion from 68.3% (95% CI 63.4%–73.1%) in the lowest SES areas to 80.0% (95% CI 76.4%–83.6%) in the highest SES areas.

SES and multimodality therapy

Among 39,808 patients in the MMT utilization analysis, a total of 20,463 (51.4%) received MMT (Table 4). Adjusted MMT rates significantly increased in a graded fashion from 42.6% (95% CI 38.3%–46.9%) in the lowest SES areas to 58.0% (95% CI 55.2%–60.9%) in the highest SES areas.

Table 3
Univariate and multivariable associations of covariates with utilization of chemotherapy.

	Univariate analysis, number (%)*		Multivariable analysis		
	Chemotherapy utilized ($n = 29,896$)	Chemotherapy omitted ($n = 9,912$)	Adjusted rate of chemotherapy, % (95% CI)	Adjusted risk difference, % (95% CI)†	Adjusted RR for omission of chemotherapy (95% CI)†
SES index	$P < .001$				
1 (Lowest)	2,575 (8.6)	1,214 (12.3)	68.3 (63.4–73.1)	**−11.8 (−15.4 to −8.2)**	**1.59 (1.39–1.82)**
2	2,907 (9.7)	1,309 (13.2)	69.0 (63.6–74.4)	**−11.0 (−14.1 to −8.0)**	**1.55 (1.41–1.71)**
3	4,000 (13.4)	1,497 (15.1)	72.7 (69.9–75.6)	**−7.3 (−9.2 to −5.4)**	**1.37 (1.23–1.52)**
4	4,718 (15.8)	1,492 (15.1)	75.7 (72.9–78.5)	**−4.3 (−6.7 to −1.9)**	**1.22 (1.08–1.37)**
5	4,947 (16.6)	1,486 (15.0)	76.7 (74.1–79.3)	**−3.4 (−5.4 to −1.4)**	**1.17 (1.05–1.30)**
6	4,655 (15.6)	1,377 (13.9)	77.2 (74.3–80.2)	**−2.8 (−4.8 to −0.8)**	**1.14 (1.03–1.26)**
7 (Highest)	6,094 (20.4)	1,537 (15.5)	80.0 (76.4–83.6)	0 [Reference]	1 [Reference]
Race/ethnicity	$P < .001$				
NHW	24,145 (80.8)	7,548 (76.2)	75.9 (72.7–79.2)	0 [Reference]	1 [Reference]
NHB	3,296 (11.0)	1,202 (12.1)	74.8 (71.0–78.7)	−1.1 (−3.7 to 1.5)	1.05 (0.94–1.16)
Hispanic	1,307 (4.4)	662 (6.7)	67.8 (62.7–72.9)	**−8.2 (−11.6 to −4.7)**	**1.39 (1.20–1.49)**
Asian	750 (2.5)	279 (2.8)	72.1 (69.5–74.6)	**−3.9 (−5.8 to −1.9)**	**1.16 (1.07–1.26)**
Other/unknown	398 (1.3)	221 (2.2)	63.6 (58.8–68.4)	**−12.3 (−16.2 to −8.4)**	**1.51 (1.34–1.71)**
Age, years	$P < .001$				
19–49	1,839 (6.2)	383 (3.9)	83.5 (80.5–86.4)	0 [Reference]	1 [Reference]
50–59	6,521 (21.8)	1,510 (15.2)	81.5 (78.3–84.6)	−2.0 (−4.7 to 0.7)	1.12 (0.96–1.31)
60–69	11,448 (38.3)	3,327 (33.6)	77.3 (73.9–80.7)	**−6.1 (−8.6 to −3.7)**	**1.37 (1.21–1.56)**
≥ 70	10,088 (33.7)	4,692 (47.3)	68.1 (64.8–71.4)	**−15.4 (−17.8 to −13.0)**	**1.93 (1.70–2.19)**
Sex	$P = .33$				
Male	15,350 (51.3)	5,145 (51.9)	74.5 (71.1–77.9)	0 [Reference]	1 [Reference]
Female	14,546 (48.7)	4,767 (48.1)	75.8 (72.8–78.7)	**1.3 (0.6–1.9)**	**0.95 (0.93–0.97)**
Charlson-Deyo	$P < .001$				
0	19,710 (65.9)	6,327 (63.8)	75.2 (72.0–78.5)	0 [Reference]	1 [Reference]
1	7,931 (26.5)	2,612 (26.4)	76.0 (72.7–79.4)	0.8 (−0.2 to 1.8)	0.97 (0.93–1.01)
2	1,654 (5.5)	669 (6.8)	72.5 (69.2–75.9)	**−2.7 (−4.2 to −1.1)**	**1.11 (1.04–1.18)**
≥ 3	601 (2.0)	304 (3.1)	67.7 (65.1–70.3)	**−7.6 (−9.9 to −5.2)**	**1.30 (1.19–1.43)**
Cancer history	$P = .82$				
No	24,172 (80.9)	8,004 (80.8)	74.8 (71.4–78.1)	0 [Reference]	1 [Reference]
Yes	5,724 (19.2)	1,908 (19.3)	76.5 (73.9–79.1)	**1.7 (0.4–3.0)**	**0.93 (0.89–0.98)**
Tumor location	$P < .001$				
Head	21,796 (72.9)	6,904 (69.7)	75.9 (72.8–79.0)	0 [Reference]	1 [Reference]
Body‡	2,487 (8.3)	847 (8.6)	74.7 (70.6–78.8)	−1.2 (−2.4 to 0.02)	**1.05 (1.01–1.10)**
Tail	2,347 (7.9)	887 (9.0)	73.0 (69.3–76.7)	**−2.9 (−4.5 to −1.3)**	**1.12 (1.05–1.19)**
Other/NOS	3,266 (10.9)	1,274 (12.9)	72.2 (68.9–75.5)	**−3.7 (−5.0 to −2.3)**	**1.15 (1.09–1.21)**
Clinical stage	$P < .001$				
I	9,476 (31.7)	3,933 (39.7)	71.0 (67.6–74.3)	0 [Reference]	1 [Reference]
II	20,420 (68.3)	5,979 (60.3)	77.2 (74.0–80.4)	**6.3 (4.9–7.7)**	**0.78 (0.74–0.83)**
Urban/rural status	$P = .003$				
Metropolitan	24,304 (81.3)	7,906 (79.8)	75.0 (71.9–78.2)	0 [Reference]	1 [Reference]
Urban	4,353 (14.6)	1,595 (16.1)	75.2 (71.8–78.6)	0.2 (−1.3 to 1.7)	0.99 (0.93–1.05)
Rural	529 (1.8)	181 (1.8)	77.1 (70.0–84.3)	2.1 (−3.3 to 7.5)	0.92 (0.72–1.16)
Unknown	710 (2.4)	230 (2.3)	74.5 (69.9–79.0)	−0.6 (−3.2 to 2.0)	1.02 (0.92–1.13)
Year of diagnosis	$P < .001$				
2010	4,045 (13.5)	1,695 (17.1)	70.3 (67.5–73.2)	0 [Reference])	1 [Reference]
2011	4,371 (14.6)	1,639 (16.5)	72.5 (69.6–75.3)	**2.1 (1.2–3.1)**	**0.93 (0.90–0.96)**
2012	4,845 (16.2)	1,698 (17.1)	74.0 (70.0–78.1)	**3.7 (1.6–5.8)**	**0.87 (0.80–0.95)**
2013	5,040 (16.9)	1,677 (16.9)	75.0 (71.7–78.4)	**4.7 (3.7–5.7)**	**0.84 (0.80–0.88)**
2014	5,619 (18.8)	1,677 (16.7)	77.2 (73.4–80.9)	**6.9 (4.9–8.8)**	**0.77 (0.70–0.85)**
2015	5,976 (20.0)	1,548 (15.6)	79.8 (76.8–82.8)	**9.5 (8.2–10.7)**	**0.68 (0.63–0.73)**
Insurance status§	$P < .001$				
Private	11,674 (39.1)	2,731 (27.6)	—	—	—
Medicare	14,932 (50.0)	5,874 (59.3)	—	—	—
Medicaid	1,737 (5.8)	549 (5.5)	—	—	—
Other government program	411 (1.4)	224 (2.3)	—	—	—
Uninsured	723 (2.4)	347 (3.5)	—	—	—
Unknown	419 (1.4)	187 (1.9)	—	—	—
Evaluated at > 1 CoC hospital§	$P < .001$				
No	19,943 (66.7)	8,125 (82.0)	—	—	—
Yes	9,953 (33.3)	1,787 (18.0)	—	—	—

* Column percentages may not sum to 100% because of rounding.
† Bold values for adjusted risk differences and adjusted risk ratios from the multivariable model indicate significance at a P value of $< .05$.
‡ Occasionally, the RR can be significant when the ARD is not.
§ Insurance status and evaluation at > 1 CoC hospital were not included in this multivariable model because they were intermediate variables.
RR, risk ratio; *NOS*, not otherwise specified.

Race/ethnicity and treatment utilization

Table 5 presents the associations between race/ethnicity and treatment utilization in models that handled the SES index as an intermediate. Disparities in the utilization of surgery and MMT among NHB and Hispanic patients were larger in these models. Furthermore, NHB race/ethnicity was significantly associated with chemotherapy omission, whereas it was not when the SES index was adjusted for (Table 3).

Table 4
Univariate and multivariable associations of covariates with utilization of multimodality therapy (ie surgery and chemotherapy).

	Univariate analysis, Number (%)*		Multivariable analysis		
	Multimodality therapy ($n = 20,463$)	Multimodality therapy omitted ($n = 19,345$)	Adjusted rate of multimodality therapy, % (95% CI)	Adjusted risk difference, % (95% CI)†	Adjusted RR for omission of multimodality therapy (95% CI)†
Race/ethnicity	$P < .001$				
NHW	16,837 (82.3)	14,856 (76.8)	52.8 (49.7–55.9)	0 [Reference]	1 [Reference]
NHB	2,004 (9.8)	2,494 (12.9)	46.4 (44.1–48.7)	**–6.4 (–8.9 to –3.9)**	**1.14 (1.08–1.20)**
Hispanic	841 (4.1)	1,128 (5.8)	44.4 (39.8–48.9)	**–8.4 (–11.3 to –5.5)**	**1.18 (1.12–1.24)**
Asian	517 (2.5)	512 (2.7)	49.3 (45.8–52.8)	**–3.5 (–5.7 to –1.3)**	**1.07 (1.03–1.12)**
Other/unknown	264 (1.3)	355 (1.8)	42.2 (38.3–46.1)	**–10.6 (–13.9 to –7.4)**	**1.23 (1.15–1.30)**
SES index	$P < .001$				
1 (Lowest)	1,565 (7.7)	2,224 (11.5)	42.6 (38.3–46.9)	**–15.4 (–18.8 to –12.0)**	**1.37 (1.28–1.46)**
2	1,908 (9.3)	2,308 (11.9)	46.0 (41.3–50.6)	**–12.1 (–14.6 to –9.5)**	**1.29 (1.24–1.34)**
3	2,666 (13.0)	2,831 (14.6)	48.6 (45.3–52.0)	**–9.4 (–11.0 to –7.8)**	**1.22 (1.18–1.27)**
4	3,182 (15.6)	3,028 (15.7)	51.0 (47.9–54.1)	**–7.1 (–9.0 to –5.2)**	**1.17 (1.12–1.22)**
5	3,378 (16.5)	3,055 (15.8)	52.0 (49.8–54.3)	**–6.0 (–8.6 to –3.4)**	**1.14 (1.08–1.21)**
6	3,305 (16.2)	2,727 (14.1)	54.7 (51.8–57.6)	**–3.4 (–5.1 to –1.6)**	**1.08 (1.04–1.12)**
7 (Highest)	4,459 (21.8)	3,172 (16.4)	58.0 (55.2–60.9)	0 [Reference]	1 [Reference]

* Column percentages may not sum to 100% because of rounding.
† Bold values for adjusted risk differences and adjusted risk ratios from the multivariable model indicate significance at a P value of $< .05$.
RR, risk ratio.

Table 5
Association of race/ethnicity with utilization of treatment in models that considered socioeconomic status index as an intermediate variable*.

Race/ethnicity	Adjusted rate of treatment, % (95% CI)	Adjusted risk difference, % (95% CI)†	Adjusted risk ratio for omission of treatment (95% CI)†
Outcome 1: Utilization of surgery			
NHW	65.0 (62.6–67.4)	0 [Reference]	1 [Reference]
NHB	55.3 (53.4–57.2)	**–9.7 (–11.5 to –8.0)**	**1.28 (1.22–1.34)**
Hispanic	58.8 (55.0–62.6)	**–6.2 (–9.3 to –3.2)**	**1.18 (1.09–1.27)**
Asian	64.4 (62.0–66.8)	–0.6 (–2.8 to 1.6)	1.02 (0.96–1.08)
Other/unknown	57.0 (52.3–61.8)	**–8.0 (–11.7 to –4.2)**	**1.23 (1.13–1.34)**
Outcome 2: Utilization of chemotherapy			
NHW	76.4 (72.3–80.1)	0 [Reference]	1 [Reference]
NHB	72.1 (67.3–76.9)	**–4.3 (–8.1 to –0.6)**	**1.18 (1.03–1.36)**
Hispanic	65.0 (59.4–70.6)	**–11.4 (–15.0 to –7.8)**	**1.48 (1.34–1.65)**
Asian	72.7 (70.3–75.1)	**–3.8 (–6.0 to –1.6)**	**1.16 (1.05–1.28)**
Other/unknown	63.7 (58.5–68.9)	**–12.7 (–16.9 to –8.5)**	**1.54 (1.34–1.76)**
Outcome 3: Utilization of multimodality treatment (ie, surgery and chemotherapy)			
NHW	53.4 (49.8–57.0)	0 [Reference]	1 [Reference]
NHB	43.3 (40.2–46.4)	**–10.1 (–13.6 to –6.7)**	**1.22 (1.13–1.31)**
Hispanic	41.6 (37.1–46.2)	**–11.8 (–14.3 to –9.2)**	**1.25 (1.20–1.31)**
Asian	50.1 (46.5–53.6)	**–3.3 (–6.2 to –0.5)**	**1.07 (1.01–1.14)**
Other/unknown	42.2 (37.9–46.6)	**–11.2 (–14.7 to –7.6)**	**1.24 (1.16–1.33)**

* Each model adjusted for age, sex, Charlson-Deyo score, cancer history, tumor location, clinical stage, urban/rural status, and year of diagnosis. Each model also included a clustered sandwich estimator with US census division of the reporting hospital as the cluster variable. These models *did not* adjust for socioeconomic status index because it was considered an intermediate variable when race/ethnicity was the exposure of interest.
† Bold values for adjusted risk differences and adjusted risk ratios from the multivariable model indicate significance at a P value of $< .05$.

Additive effect of race/ethnicity and SES

Supplemental Tables 5–7 present adjusted rates of treatments by race/ethnicity *and* the SES index. Adjusted treatment rates for the least and most advantaged patients were quite disparate. For example, adjusted rates of MMT for NHB and Hispanic patients living in the lowest SES areas were 38.7% (95% CI 35.7%–41.7%) and 34.6% (95% CI 27.7%–41.6%), respectively, compared with 59.8% (95% CI 56.6%–63.0%) for NHW patients living in the highest SES areas (Supplemental Table 6).

Interaction testing

We found no significant interactions between NHB or Hispanic race/ethnicity and the SES index for utilization of surgery or MMT or between Hispanic race/ethnicity and the SES for the utilization of chemotherapy (Supplemental Tables 5–7). This indicates that the overall associations between race/ethnicity and treatment utilization were fairly constant over the socioeconomic gradient for these outcomes. Conversely, there *was* a significant interaction between NHB race/ethnicity and the SES index for chemotherapy utilization (Supplemental Table 6). These significant interactions revealed that NHB patients with moderate–high SES had lower chemotherapy rates than NHW patients with comparably high SES, whereas lower SES NHB patients had a similar utilization of chemotherapy to lower SES NHW patients.

SES and overall survival

OS was longest for patients who received MMT, intermediate for those who received surgery without chemotherapy, and worst for unresected patients (Table 6). We found a graded relationship between higher SES and longer OS, such that unadjusted OS was 6 months longer for patients living in the highest SES areas versus those living in the lowest SES areas. Sequential adjustment for baseline factors and treatment utilization attenuated but did not erase this relationship.

Table 6
Unadjusted and adjusted overall survival by treatment utilized and socioeconomic status index.

Treatment utilized	Unadjusted OS*		Adjusted OS*	
	Median OS, months (95% CI)	HR (95% CI)	Model 1† HR (95% CI)	
No surgery	9.4 (9.1–9.5)	**3.04 (2.96–3.13)**	**2.93 (2.77–3.10)**	–
Surgery without chemotherapy	16.0 (15.3–16.6)	**1.53 (1.47–1.58)**	**1.44 (1.35–1.54)**	–
MMT	26.1 (25.6, 26.5)	1 [Reference]	1 [Reference]	–
SES index	Median OS, months (95% CI)	HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
1 (Lowest)	14.1 (13.4–14.8)	**1.39 (1.31–1.47)**	**1.32 (1.26–1.40)**	**1.23 (1.18–1.28)**
2	14.8 (14.2–15.6)	**1.31 (1.23–1.39)**	**1.27 (1.18–1.36)**	**1.17 (1.09–1.26)**
3	15.6 (14.9–16.2)	**1.30 (1.25–1.35)**	**1.27 (1.22–1.33)**	**1.21 (1.14–1.29)**
4	16.1 (15.5–16.5)	**1.26 (1.22–1.29)**	**1.23 (1.19–1.28)**	**1.19 (1.16–1.23)**
5	17.7 (17.1–18.4)	**1.14 (1.10–1.18)**	**1.13 (1.09–1.18)**	**1.10 (1.05–1.15)**
6	18.4 (17.6–19.1)	**1.09 (1.04–1.14)**	**1.09 (1.03–1.14)**	**1.07 (1.05–1.11)**
7 (Highest)	20.2 (19.6–20.8)	1 [Reference]	1 [Reference]	1 [Reference]

* Bold values for Cox models indicate significance at a P value of $< .05$.
† Model 1 adjusted for age, sex, SES index, race/ethnicity, Charlson-Deyo score, cancer history, tumor location, clinical stage, urban/rural status, year of diagnosis, insurance status, and evaluation at > 1 Commission on Cancer hospital.
‡ Model 2 adjusted for age, sex, race/ethnicity, Charlson-Deyo score, cancer history, tumor location, clinical stage, urban/rural status, year of diagnosis, insurance status, and evaluation at > 1 Commission on Cancer hospital.
§ Model 3 adjusted for the covariates included in Model 2 and utilization of surgery and chemotherapy.
HR, hazard ratio; *MMT*, multimodality therapy.

Sensitivity analyses

When the components of the SES index were the exposures rather than the SES index, the magnitudes of treatment utilization disparities were smaller (Supplement Tables 8 and 9). In models that included area income *and* education levels, associations among these exposures and treatment utilization were attenuated or absent because of the strong correlation between the two components of the SES index (Supplemental Table 10). Finally, in models that *included* intermediate variables, associations between the SES index and treatment utilization were biased toward the null, as expected (Supplemental Table 11).[26]

Discussion

In this contemporary study of 43,760 patients with clinical stage I-II PDAC, we observed a graded relationship between higher SES and increased utilization of surgery, chemotherapy, and the composite outcome of MMT. Living in the lowest SES areas was associated with lower adjusted rates of surgery and chemotherapy than all factors except age $\geq$ 70 years (and other or unknown race/ethnicity for chemotherapy). This SES index, which included both ZCTA-level income and education rates, revealed larger disparities in treatment utilization than were obtained when using the common practice of simultaneously adjusting for both components. Likewise, avoiding the overadjustment bias introduced by adjusting for intermediates resulted in larger estimates of disparity magnitudes. Finally, SES was associated with OS in a graded fashion, and adjustment for baseline covariates and treatment utilization only partially attenuated this relationship. These findings show that SES and race/ethnicity are more powerful determinants of whether patients receive guideline-recommended treatments for clinical stage I-II PDAC than previously understood.

Most studies of disparities in treatment utilization in PDAC have focused on the association of race/ethnicity with the utilization of surgery.[8,10–15,19] Studies also reported associations of area income and education levels with surgery utilization[8,13] and associations of race/ethnicity[16,17] and SES[17] with MMT utilization. Lutfi et al. recently combined the NCDB income and education variables to form a composite SES variable, which was associated with surgery utilization.[12] However, their SES variable had only three values and they presented ORs as the only effect measure. Our study is the first to quantify such a large, graded association between SES and receipt of surgery and chemotherapy.

The SES-based disparities in the utilization of surgery and chemotherapy were additive, such that disparities in the MMT utilization were larger than disparities in the utilization of its components. Although most earlier studies examined only utilization of surgery,[8,10–15] the utilization of MMT is probably a more important outcome. Adjuvant therapy trials in PDAC demonstrate 5-year survival of 10% with surgery alone versus approximately 20%–30% with MMT.[4–7] Our survival analysis likewise emphasizes that surgery is necessary but insufficient.

No previous studies have demonstrated a robust, graded relationship between area SES and OS (Table 6). Adjustment for baseline characteristics in Model 2 attenuated observed disparities by SES by a small degree, emphasizing that survival differences were largely not attributable to measured differences in baseline factors between SES groups (ie, the Charlson-Deyo score). Adjustment for utilization of surgery and chemotherapy in Model 3 attenuated disparities more but did not erase them. This suggests that residual disparities are attributable either to deleterious effects of the SES through mechanisms other than the treatment utilization or attributable to aspects of the treatment not captured by these two binary variables.

Limitations

The largest limitation of this study is that we used ZCTA-level measures of the SES. SES would ideally be measured at the individual level or at a smaller area level.[43] Although the NCDB is superior to standard SEER data in that it provides ZCTA-level data rather than county-level data, other databases include census block–level SES data.[44] Such indices might reveal even larger disparities, but using them would limit analyses to a smaller section of the country. Second, SES also includes employment status,[45] which we lacked data on. Third, this was a retrospective analysis, and we could not control for unmeasured confounders that contributed to treatment selection bias. Fourth, we did not analyze radiation utilization. Although radiation is commonly used, it is not essential for all patients.[4] Fifth, we ignored hospital-level variables to avoid introducing bias by excluding patients resected at nonreporting hospitals. Whether treatment at a high-quality hospital ameliorates the deleterious effects of the low SES and minority race/ethnicity remains unknown. Sixth, the NCDB does

not include information on performance status or social support. Absent data on these factors, we cannot know with certainty that surgery was actually appropriate in some unresected low SES and minority patients. Finally, we were unable to determine whether surgery and chemotherapy are underutilized in the most privileged patients (ie, highest SES and NHW). A University of Pittsburgh audit of its institutional NCDB file found that many patients with omitted surgery were treated with initial surgical intent or actually had BR or locally advanced tumors.[11] Of unresected patients included in our chemotherapy utilization analysis, 4,391 of 9,433 (68.2%) received chemotherapy. It is possible that many of these patients had resectable or BR tumors, began intended neoadjuvant therapy, and had progression or complications precluding resection. Defining the *optimal* rates of surgery and chemotherapy for patients in the NCDB with clinical stage I-II PDAC who do not have treatment contraindications or refusal remains a research priority. Until this is done, the true extent of underutilization of surgery will remain poorly understood.

Policy and future research implications

These results have implications for efforts to increase equity in the treatment utilization among patients with PDAC and to improve OS. Most significantly, the rates of surgery (70%), chemotherapy (81%), and MMT (60%) among the most privileged (ie, the highest SES and NHW) patients could be accepted as minimum benchmarks for all patients. The CoC administers accreditation programs for breast and rectal cancer.[46,47] Creation of a similar program for PDAC in an effort to increase treatment rates for all patients to these minimum benchmarks, among other goals, could be a strategy to drive improvements in survival. As stated earlier in this report, future studies need to answer two fundamental questions. First, are some of the 30% of most advantaged (ie, the highest SES and NHW) patients who do not currently receive surgery actually appropriate surgical candidates? Second, what are the underlying reasons that low SES and minority patients undergo treatment at lower rates? Is this because such patients are less likely to be seen at high-quality centers? Is it partially explained by lower performance status in such patients? Answering these questions will require studies using granular, multicenter data from sources other than the NCDB. Answering these questions would facilitate the rational design of quality improvement efforts.

Research methods implications

Part of the motivation for this study was to demonstrate simple methods to improve the quality of studies using the NCDB to examine treatment utilization disparities. We believe that such studies might be improved by using the SES index herein, presenting ARDs in addition to relative effect measures, and carefully considering whether candidate covariates are actually intermediate variables. Insurance status and evaluation at multiple CoC-accredited hospitals appear to be intermediates when the exposure is the SES, and the SES can be considered an intermediate when the exposure is race/ethnicity.

Conclusions

Utilization of surgery and chemotherapy for clinical stage I-II PDAC increases in a graded fashion with increasing ZCTA-level SES. Equally important, NHB and Hispanic patients have lower surgery utilization than NHW patients across the entire SES gradient. These clinical stage I-II patients are the subgroup of PDAC patients with the best chances of long-term survival. Increasing utilization of appropriate curative-intent treatment among lower SES NHW and minority patients may represent a realistic opportunity for improvements in population-level survival.

National Cancer Database Disclosure: The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.10.035.

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