ORIGINAL CONTRIBUTION

Mediating Factors Between Race and Time to Treatment in Colorectal Cancer

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BACKGROUND: Previous disparities research has demonstrated that underrepresented racial minority patients have worse colorectal cancer outcomes and that they experience unnecessary delays in time to treatment. These delays may explain worse colorectal cancer outcomes for minority patients and serve as a marker of inequalities in our healthcare system.

OBJECTIVE: This study aims to quantify the mechanisms that contribute to this disparity in treatment delay.

DESIGN: This is a retrospective analysis of colorectal cancer patients who underwent elective resection from 2004 to 2017. A causal inference mediation analysis using the counterfactual framework was utilized to estimate the extent to which racial disparities among patient factors explain the racial disparities in time to treatment. Mediators included income, education, comorbidities, insurance, and hospital type.

SETTINGS: This study was conducted at hospitals participating in the National Cancer Database.

PATIENTS: Stage I–III colorectal cancer patients, ≥18 years old, who underwent elective resection from 2004 through 2017 were included.

MAIN OUTCOMES MEASURES: The primary measures were indirect effects of mediators between race and delayed time to treatment.

RESULTS: Of the 504,405 patients (370,051 colon and 134,354 rectal), 10%, 5%, and 4% were black, Hispanic, and other. In multivariable models, compared to white patients, these patients had 25%, 27%, and 17% greater odds of delayed treatment. Mediation analyses suggested that 43%, 20%, and 31% of the treatment delay among them could be removed if an intervention equalized income, education, comorbidities, insurance, and hospital type to that of white patients. Treatment at an academic hospital explained 15% to 32% of the racial disparity and was the most potent mediator.

LIMITATIONS: This study was limited by its retrospective design and failure to capture all meaningful mediators.

CONCLUSIONS: Black, Hispanic, and other colorectal cancer patients experience treatment delays when compared to white patients. Equalization of the mediators used in this study could reduce treatment delays by 20% to 43% depending on the racial/ethnic group. Future research should identify other causes of racial disparities in treatment delay and intervene accordingly. See **Video Abstract** at http://links.lww.com/DCR/B871.

FACTORES MEDIADORES ENTRE LA RAZA Y EL TIEMPO HASTA EL TRATAMIENTO EN EL CÁNCER COLORECTAL

ANTECEDENTES: Investigaciones anteriores sobre disparidades han demostrado que los pacientes de minorías raciales subrepresentados tienen peores resultados de cáncer colorrectal y que experimentan retrasos innecesarios en el tiempo de tratamiento. Estos retrasos pueden explicar los peores resultados del cáncer

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colorrectal para los pacientes de minorías y servir como un marcador de desigualdades en nuestro sistema de salud.

OBJETIVO: Este estudio tiene como objetivo cuantificar los mecanismos que contribuyen a esta disparidad en el retraso del tratamiento.

DISEÑO: Este es un análisis retrospectivo de pacientes con cáncer colorrectal que se sometieron a resección electiva entre 2004 y 2017. Se utilizó un análisis de mediación de inferencia causal utilizando el marco contra factual para estimar hasta qué punto las disparidades raciales entre los factores del paciente explican las disparidades raciales en el tiempo hasta el tratamiento. Los mediadores incluyeron ingresos económicos, educación, comorbilidades, seguro médico y tipo de hospital.

AJUSTES: Este estudio se realizó en hospitales que participan en la Base de datos nacional del cáncer.

PACIENTES: Se incluyeron pacientes con cáncer colorrectal en estadio I–III, ≥18 años, que se sometieron a resección electiva entre 2004 y 2017.

PRINCIPALES RESULTADOS MEDIDAS: Las principales mediciones fueron el efecto indirecto de los mediadores entre la raza y el retraso en el tratamiento.

RESULTADOS: De los 504,405 pacientes (370,051 de colon, 134,354 rectal), 10%, 5%, 4% eran negros, hispanos, y otros, respectivamente. En modelos multivariables, en comparación con los pacientes blancos, estos pacientes tenían un 25%, 27%, y 17% más de probabilidades de retrasar el tratamiento. Los análisis de medición sugirieron que el 43%, 20%, 31% del retraso del tratamiento entre, respectivamente, podría eliminarse si una intervención igualara los ingresos económicos, la educación, las comorbilidades, el seguro médico y el tipo de hospital a los de los pacientes blancos. El tratamiento en un hospital académico demostró entre el 15% y el 32% de la disparidad racial y fue el mediador más potente.

LIMITACIONES: Este estudio estuvo limitado por su diseño retrospectivo; falla en capturar a todos los mediadores significativos.

CONCLUSIONES: Los pacientes negros, hispanos y otros con cáncer colorrectal experimentan retrasos en el tratamiento en comparación con los pacientes blancos. La igualación de los mediadores utilizados en este estudio podría reducir los retrasos en el tratamiento en un 20-43%, según el grupo racial / étnico. Las investigaciones futuras deberían identificar otras causas de disparidades raciales en el retraso del tratamiento e intervenir sobre ellas. Consulte **Video Resumen** en http://links.lww.com/DCR/B871.
(Traducción—Dr. Yolanda Colorado)

KEY WORDS: Colorectal cancer; Disparity; Mediation; Outcomes; Socioeconomics; Race.

There has been increased attention in the colorectal cancer (CRC) literature to identify factors associated with poor outcomes, particularly within the subset of marginalized patient populations. Knowledge of these factors could inform implementation of interventions to improve outcomes. Quality treatment of CRC demands prompt intervention once the diagnosis has been made. Many prior studies conducted on both colon and rectal cancer suggest that delays to initial treatment are associated with worse downstream outcomes.[1–7] Racial disparities within the medical system represent an unjust allocation of resources. The reason for these disparities is multifactorial, but almost certainly includes policy at the federal, state, community, hospital, and individual levels.[8–10]

A recent database analysis has demonstrated that delays greater than 40 days between diagnosis and surgery are associated with decreased overall survival in patients with stage I–III colon cancer.[11] In the current healthcare environment of finite resources, decisions are made at the physician, hospital, and system levels regarding optimal allocation and scheduling of treatment for CRC patients. Previous research into healthcare disparities has demonstrated that black and Hispanic patients were much more likely to experience treatment delays of >30 days for colon and rectal cancer when compared to white patients.[2]

No studies have evaluated the mechanisms explaining the relationship between race and time delays in CRC treatment, undeniably missing an opportunity to implement interventions that may reduce racial disparities in CRC treatment and outcomes.[12] This study aimed to address this important gap in the literature. The objective was to quantify the contribution of individual mediators that explain racial disparities in delays to initial treatment following CRC diagnosis. We hypothesized that mediators between race and delayed treatment could be identified and are likely to account for significant portions of this disparity.

METHODS

Data Source and Study Population

Following formal IRB exemption, the National Cancer Database (NCDB) participant user file was interrogated for all CRC cases from participating hospitals in patients ≥18 years old from 2004 to 2017 (the most current year within the NCDB). Stages I–III cancers were included, and stage IV was excluded; 504,405 CRC cases (370,051 colon and 134,354 rectal) were identified. Stratified analysis of colon and rectal cancers was also conducted (findings were consistent with the combined group and are presented in the supplemental content at http://links.lww.com/DCR/B872). Cases were analyzed for demographic information, pathologic findings, and treatment modality with a focus on time to treatment.

Exposure and Outcome

The exposure of interest was race; patients were categorized as white, black, Hispanic/Latino, and other. The other

group consisted of patients from the remaining racial/ethnic categories assessed by the NCDB after white, black, and Hispanic/Latino patients had been accounted for. The outcome variable was delayed treatment. The NCDB collects time to initial treatment, defined as the number of days between initial diagnosis (not recurrence of CRC) and initiation of treatment (chemotherapy, radiation, other therapy, or surgery). This was dichotomized at 30 days, as done in previously published literature.[2]

Mediators and Confounders

The 5 mediators evaluated were: income, education, comorbidity burden, academic facility status, and insurance status. All mediating variables were dichotomized for analysis. Income was split at $48,000, the median cutoff in the NCDB data dictionary. Education was evaluated at the zip code level with "high education" status defined as a zip code with <13% of the population failing to attain a high school degree (<13% marks the top two quartiles of US zip codes per the NCDB data dictionary). Comorbidities were split into ≥1 and 0 on the Charleson-Deyo score. Academic treatment was dichotomized to those treated at an academic facility or not. Insurance status was dichotomized as public (Medicaid, Medicare, other government) versus private. Patients who were labeled as uninsured (6% of total sample) were removed to allow for more effective dichotomization of this variable. The following confounders were included: age, sex, American Joint Committee on Cancer stage at diagnosis, facility location, and rural residence. Facility location was grouped by geographic regions of the US as defined by the NCDB data. Rural residence is based on county-level data obtained from the US Department of Agriculture, in which rural was defined as a county with a population less than 2500 individuals. The framework developed by VanderWeele and Robinson was used to differentiate between confounders and mediators.[12] The main tenet is that differences in outcomes between races is not caused by race directly, but rather by disparities in mediators.

Statistical Analysis

A causal inference mediation analysis using the counterfactual framework was utilized to understand the relationship between race and delayed time to treatment in CRC. This analysis focused on the mediating factors of income, education level, comorbidities, public insurance status, and treatment at an academic facility (Fig. 1). The outcome variable was delayed treatment. Before conducting the primary mediation analyses, we first verified the 3 assumptions of mediation analysis and confirmed that the 5 mediators of interest met criteria for mediation (Fig. 1).[12,13] First, the exposure (race) must be associated with the outcome, independent of confounders. This was assessed by fitting a multivariable logistic regression model with delayed treatment as the outcome and with race and confounders as independent variables.

Second, the exposure (race) must be associated with the mediator(s), independent of confounders. For this, 5 separate multivariable logistic regression models were fit (for each of the 5 mediator variables) with the mediator of interests designated as the outcome. Within these regression models, patient race, confounders, and the other mediators were designated as independent variables.

The last assumption of mediation analysis is that the mediator(s) are associated with the outcome, independent of both the exposure and the confounders. This model used delayed treatment (as previously defined) as the outcome and race, mediators, and confounders as independent variables.

After verifying that these assumptions were met, the primary mediation analysis was performed. Mediation investigates potential mechanisms that underlie the association between race and delayed treatment by examining how racial disparities in mediators lead to racial disparities in the delayed treatment. This analysis deconstructs the total effect of race on delayed treatment into indirect and direct effects. The indirect effect represents the proportion of the overall racial disparity in delayed treatment that would be reduced if the distribution of mediators were equalized across all races. The direct effect represents the proportion of the overall racial disparity that would remain after implementation of the aforementioned intervention. These effects were estimated, as well as the percent mediated using mediation SAS macros developed by Valeri and VanderWeele.[14] SAS

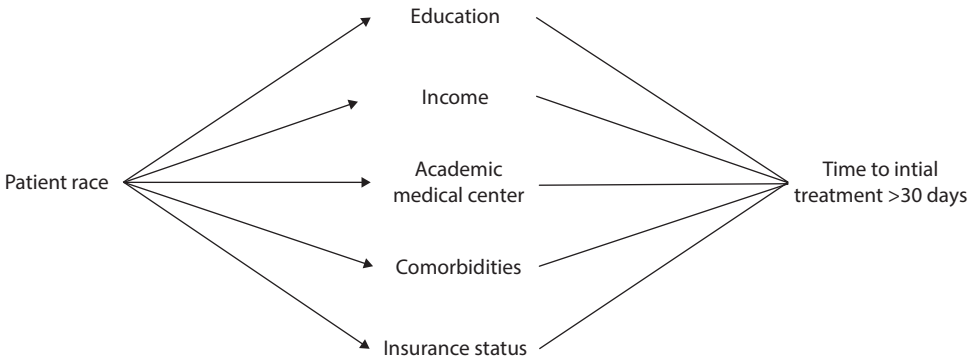

FIGURE 1. Direct acyclic graph of proposed causal pathway between patient race and time to initial treatment.

statistical software (Version 9.2; SAS Institute Inc, Cary, NC, USA) and GraphPad Prism (Version 9.0.0; GraphPad Software Inc, San Diego, CA, USA) were used for database management and statistical analyses.

RESULTS

The database identified 504,405 CRC patients (370,051 colon and 134,354 rectal) of whom 10%, 5%, and 4% were black, Hispanic, and other. Overall, 49% of the study population was female, 64.5% had private insurance, and 1.82% came from rural counties. The South Atlantic region contributed the greatest number of patients to this study (21%); 59% of patients had a high level of household income, and the majority came from counties with higher levels of education (complete demographic data available in Table 1).

In the entire cohort of patients, 179,734 (35.63%) had delay in treatment initiation >30 days. Among the 4 groups studied, the percent with treatment delay varied from 35% to 41%. χ^2 analysis detected a difference in the distribution of those with treatment delay between races ($p < 0.0001$).

Assumption 1: Exposure Association with Outcome

In adjusted models, all 3 comparator races demonstrated increased odds of delayed treatment independent of confounders (Table 2). Black (OR 1.25, 95% CI 1.20–1.34),

TABLE 1. Patient demographics

Demographic	*All patients*	*White*	*Black*	*Hispanic*	*Other*	*p*[a]
Total	504,405 (100)	412,959 (81.87)	49,689 (9.85)	23,352 (4.63)	18,405 (3.65)	
Sex						< 0.0001
Male	256,915 (50.93)	211,450 (51.20)	23,400 (47.09)	12,637 (54.12)	9428 (51.23)	
Female	247,490 (49.07)	201,509 (48.80)	26,289 (52.91)	10,715 (45.88)	8977 (48.77)	
Age at diagnosis, y, mean (SD)		69.61 (12.32)	65.57 (11.87)	65.58 (12.41)	65.49 (12.32)	< 0.0001
Diagnosis to treatment						< 0.0001
>30 days	179,734 (35.63)	142,980 (34.62)	19,703 (39.65)	9590 (41.07)	7461 (40.54)	
≤30 days	324,671 (64.37)	269,979 (65.38)	29,986 (60.35)	13,762 (58.93)	10,944 (59.46)	
Insurance						< 0.0001
Private	325,325 (64.50)	269,844 (65.34)	31,048 (62.48)	14165 (60.66)	10268 (55.79)	
Public	179,080 (35.50)	143,115 (34.66)	18,641 (37.52)	9187 (39.34)	8137 (44.21)	
Urban/rural zip code						< 0.0001
Urban/metro	495,210 (98.18)	404,535 (97.96)	49,170 (98.96)	23,286 (99.72)	18,219 (98.99)	
Rural	9195 (1.82)	8,424 (2.04)	519 (1.04)	66 (0.28)	186 (1.01)	
Medical facility region						< 0.0001
New England	31,375 (6.22)	28,399 (6.88)	1375 (2.77)	910 (3.90)	691 (3.75)	
Middle Atlantic	77,676 (15.40)	63,532 (15.38)	7281 (14.65)	3714 (15.90)	3149 (17.11)	
South Atlantic	106,758 (21.17)	82,691 (20.02)	17,110 (34.43)	4716 (20.20)	2241 (12.81)	
East North Central	95,180 (18.87)	82,944 (20.09)	8988 (18.09)	1667 (7.14)	1581 (8.59)	
East South Central	35,235 (6.99)	29,768 (7.21)	5068 (10.20)	127 (0.54)	272 (1.48)	
West North Central	43,305 (8.59)	40,297 (9.76)	1902 (3.83)	339 (1.45)	767 (4.17)	
West South Central	39,935 (7.92)	28,511 (6.90)	5418 (10.90)	4725 (20.23)	1281 (6.96)	
Mountain	19,463 (3.86)	18,727 (4.05)	452 (0.91)	1466 (6.28)	818 (4.44)	
Pacific	55,478 (11.00)	40,090 (9.71)	2095 (4.22)	5688 (24.36)	7605 (41.32)	
Stage at diagnosis						< 0.0001
Stage I	163,079 (32.33)	135,853 (32.90)	14,883 (29.95)	6800 (29.12)	5543 (30.12)	
Stage II	179,361 (35.56)	147,968 (35.83)	17,228 (34.67)	8061 (34.52)	6104 (33.16)	
Stage III	161,965 (32.11)	129,138 (31.27)	17,578 (35.38)	8491 (36.36)	6758 (36.72)	
Charleson-Deyo						< 0.0001
≥1	169,034 (33.51)	138,410 (33.52)	17,837 (35.90)	7670 (32.85)	5117 (27.80)	
0	335,371 (66.49)	274,549 (66.48)	31,852 964.10)	15,682 (67.15)	13,288 (72.20)	
Average zip code household income						< 0.0001
>48,000	298,076 (59.09)	255,681 (61.91)	17,072 (34.36)	11,717 (50.18)	13,606 (73.93)	
≤48,000	206,329 (40.91)	157,278 (38.09)	32,617 (65.64)	11,635 (49.82)	4799 (26.07)	
Zip code rate w/o high school degree attainment						< 0.0001
<13%	289,436 (57.38)	257,729 (62.41)	14,591 (29.36)	6705 (28.71)	10,411 (56.57)	
≥13%	214,969 (42.62)	155,230 (37.59)	35,098 (70.64)	16,647 (71.29)	7994 (43.43)	
Academic center treatment						< 0.0001
Yes	138,794 (27.52)	105,937 (25.65)	18,561 (37.35)	7363 (31.53)	6933 (37.67)	
No	365,611 (72.48)	307,022 (74.35)	31,128 (62.65)	15,989 (68.47)	11,472 (62.33)	

Data are presented as n (%) unless otherwise indicated. ANOVA = analysis of variance.
[a]All *p* values represent a χ^2 test except for the age variable which represents ANOVA.

TABLE 2. Total effect of race on treatment delay using white patients as a comparator group

Race	OR of delayed treatment (>30 days)	95% CI
Black vs white	1.25	1.20 to 1.34
Hispanic vs white	1.27	1.23 to 1.30
Other vs white	1.17	1.13 to 1.21

Hispanic (OR 1.27, 95% CI 1.23–1.30), and Other (OR 1.17, 95% CI 1.13–1.21) patients had 25%, 27%, and 15% increased odds of having a treatment delay relative to white patients. This confirms the overall racial disparity with the largest disparity seen in the Hispanic population.

Assumption 2: Exposure Association With Mediators

All comparator races were more likely to be treated in an academic medical center, have public insurance, and have lower education levels. Additionally, black and Hispanic patients were more likely to have a higher degree of baseline morbidity (OR 1.19, 95% CI 1.16–1.21 and OR 1.12, 95% CI 1.08–1.25). Black patients were the only comparator group noted to have a significantly lower income than the white reference group (OR 0.56, 95% CI 0.55–0.58) (Table 3).

Assumption 3: Mediator Association With Outcome

All five proposed mediators were found to be independently associated with treatment delay, independent of race and confounders (Table 4). Higher income (OR 0.95, 95% CI 0.94–0.97) and education (OR 0.95, 95% CI 0.94–0.97) were associated with lower odds of delayed treatment.

TABLE 3. Results of mediation analysis between race and treatment delay of >30 days after diagnosis

Mediators stratified by race	Association between race and mediator, OR (95% CI)	% of total effect attributable to mediator
Black vs white		
Income	0.56 (0.55–0.58)	6%
Education	0.40 (0.39–0.41)	1%
Comorbidities	1.19 (1.16–1.21)	2%
Public insurance status	1.31 (1.28–1.35)	2%
Academic treatment	1.74 (1.70–1.78)	32%
Hispanic vs white		
Income	0.97 (0.92–1.05)	0%
Education	0.25 (0.24–0.26)	1%
Comorbidities	1.12 (1.08–1.25)	2%
Public insurance status	1.40 (1.35–1.40)	2%
Academic treatment	1.40 (1.36–1.45)	15%
Other vs white		
Income	1.08 (0.97–1.24)	0%
Education	0.59 (0.57–0.61)	2%
Comorbidities	1.02 (0.92–1.21)	0%
Public insurance status	1.07 (1.05–1.08)	1%
Academic treatment	1.88 (1.82–1.94)	28%

TABLE 4. Effect of mediator on outcome variable (delay in treatment initiation >30 days)

Mediator	Association between mediator and outcome, OR (95% CI)
Income	0.95 (0.94–0.97)
Education	0.95 (0.94–0.97)
Comorbidities	1.04 (1.03–1.06)
Public insurance status	1.08 (1.07–1.10)
Academic treatment	1.73 (1.71–1.75)

Academic medical facility (OR 1.73, 95% CI 1.71–1.75), higher comorbidity burden (OR 1.04, 95% CI 1.03–1.06), and public insurance status (OR 1.09, 95% CI 1.07–1.10) were associated with higher odds of delayed treatment.

Mediation analyses suggested that 43%, 20%, and 31% of the treatment delay among black, Hispanic, and other patients could be removed if an intervention equalized their income, education, comorbidities, insurance, and hospital type to that of white patients. The largest mediating factor was treatment at an academic hospital which explained 32%, 15%, and 28% of the racial disparity in delayed time to treatment among black, Hispanic and Other patients. Stratified results of colon and rectal cancers were consistent with the combined results (see supplemental content at http://links.lww.com/DCR/B872).

DISCUSSION

This study demonstrates inequalities in the primary outcome of delayed treatment between black, Hispanic and Other patients when compared with white patients. This study adds to the literature by utilizing a causal inference mediation analysis to identify intermediary sources that explain this racial disparity. Much of the previous research assessing disparities adopt conventional regression models (not within the context of mediation) and treat race as a factor associated with a disparate outcome without understanding why it is associated with the outcome.[12,15] Regression models without mediation analyses do not consider that race is not a mutable factor amenable to intervention. Furthermore, as noted by Vanderweele and Robinson, the temporal ordering of variables is critical to understanding causation. Mediation aids in the assessment of factors, frequently more amenable to intervention, between patient race and any given outcome, thus identifying racial disparities in mediators as the causes of racial disparities in outcomes.[12]

Our causal inference mediation analysis assessed factors including income, education, comorbidities, insurance status and hospital type as potential mediators of delayed treatment for underrepresented racial minority patients. In total, our mediators were able to account for 43%, 20%, and 31% of the increase in treatment delay among black,

Hispanic, and other patients. This understanding is valuable for developing policy and targeted interventions that would likely reduce treatment delay inequalities. However, 57% to 80% of the racial disparity in time to treatment would remain and be caused by racial disparities in mediators not available in the database.

The most potent mediator in this study across the three comparator races was treatment at an academic medical center. This warrants further exploration into why academic centers are treating a disproportionate volume of black, Hispanic, and other patients. Furthermore, additional information describing the association between academic center treatment and delayed time to treatment will need to be elucidated if effective interventions are to be developed. One potential reason why academic centers may have longer treatment delays is the complexity inherent in referral patterns that may exist for patients diagnosed at other centers.

Disparities in outcomes such as mortality and quality-adjusted life years lost are likely driven by many smaller, compounded outcome disparities such as time to treatment, screening rate, and stage at presentation. It is likely that many of these aforementioned outcomes share mediators that account for racial disparity. Future research should continue to identify mediators with the goal of creating policies and interventions that produce equitable CRC care and outcomes.

The limitations to this study are those inherent to retrospective study design and the use of large databases. Retrospective studies may include selection bias and confounding. While the NCDB collects 70% of all cancer patients, there are still limitations, including possible selection bias coding errors, incomplete data, and missing variables that may be relevant to mediation analysis. Specific to our analysis, we suspect that rural patients and patients from minority races are underrepresented in the sample (when compared to the national population). For example, educational attainment was only available at the zip code level and only reflected high school degree attainment rate and, as such, measurement error may lead to biased results. Strengths of the study include the study design to assess mediating factors and the number of patients included in the analysis.

CONCLUSIONS

Racial disparity exists in the time to CRC treatment for black, Hispanic, and other patients when compared to white patients. Individual disparities may not have immediate and obvious clinical impact. However, the compounding effect over large populations and the effects from related disparities likely contribute to worse outcomes for underrepresented racial minorities. In this study, treatment at an academic medical center, insurance status, comorbidities, education, and income were all identified as mediators in CRC treatment delay disparity. This knowledge will allow health systems, policy makers, and physicians to implement interventions that reduce racial inequalities in CRC treatment.

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