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Mediation analyses of socioeconomic factors determining racial differences in the treatment of diffuse large B-cell lymphoma in a cohort of older adults

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Abstract

Despite near universal health coverage under Medicare, racial disparities persist in the treatment of diffuse large B-cell lymphoma (DLBCL) among older patients in the United States. Studies evaluating DLBCL outcomes often treat socioeconomic status (SES) measures as confounders, potentially introducing biases when SES factors are mediators of disparities in cancer treatment.

To examine differences in DLBCL treatment, we performed causal mediation analyses of SES measures, including: metropolitan statistical area (MSA) of residence; census-tract poverty level; and private Medicare supplementation using the Surveillance, Epidemiology and End Results-Medicare linked database between 2001 and 2011. In this retrospective cohort study of DLBCL patients ages 66+ years, we conducted a series of multivariable logistic regression analyses estimating odds ratios (OR) and 95% confidence intervals (CI) relating chemo- and/or immuno-therapy treatment and each SES measure, comparing non-Hispanic (NH)-black, Hispanic/Latino, and Asian/Pacific Islander (API) to NH-white patients.

Compared to NH-white patients, racial/ethnic minority patients had lower odds of receiving chemo- and/or immuno-therapy treatment (NH-black: OR 0.84, 95% CI 0.65, 1.08; API: OR 0.80, 95% CI 0.64, 1.01; Hispanic/Latino: OR 0.78, 95% CI 0.64, 0.96) and higher odds of lacking private Medicare supplementation and residence within an urban MSA and poor census tracts. Adjustment for SES measures as confounders nullified observed racial differences. In causal mediation analyses, between 31% and 38% of race/ethnicity differences were mediated by having private Medicare supplementation.

Providing equitable access to Medicare supplementation may reduce disparities in receipt of chemo- and/or immuno-therapy treatment in older DLBCL patients.

Abbreviations: API = Asian/Pacific Islander, CI = confidence intervals, DLBCL = diffuse large B-cell lymphoma, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, MSA = metropolitan statistical area, NDE = natural direct effects, NH = non-Hispanic, NIE = natural indirect effects, OR = odds ratios, PM = proportion mediated, R-CHOP = Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, SEER = Surveillance, Epidemiology and End Results, SEM = structural equation modeling, SES = socioeconomic status, TE = total effects, U.S. = United States.

Keywords: chemotherapy, diffuse large B-cell lymphoma, immunotherapy, mediation analysis, racial disparities

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype among adults and the incidence rate of DLBCL is over 40 per 100,000 individuals in adults ages 70 years and older.[1–3] The introduction of rituximab to chemotherapy treatment regimens (e.g., R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has resulted in considerably improved survival in patients with DLBCL.[4–6] Despite the availability of highly effective regimens, racial differences persist in the treatment of DLBCL.[7–9] In the United States (U.S.), NH-black DLBCL patients typically present at younger ages, with more advanced stages of disease, and more frequently with B symptoms (e.g., fever night sweats and weight loss) compared to non-Hispanic (NH) white patients.[1,7] Hispanic/Latino patients present at later stages of follicular non-Hodgkin lymphoma when compared to NH-white and NH-black patients.[10] Although NH-black patients have a lower overall incidence of DLBCL, they are less likely to receive treatment and have worse survival compared to NH-white patients.[7]

Among the factors that contribute to the under treatment of DLBCL, insurance has a critical role given its direct relation to cost of treatment. Insurance status (uninsured and Medicaid vs privately insured) is associated with survival in DLBCL patients 18 to 64 years of age.[11] Less is known about whether and how insurance supplementation is associated with receipt of DLBCL treatment in the Medicare-aged U.S. population. Even though all adults over the age of 65 years have health coverage through Medicare, a greater proportion of NH-white Medicare beneficiaries have private supplementation plans and a lower proportion are dual Medicare-Medicaid eligible.[12] Patients without private Medicare supplementation incur higher out-of-pocket costs relative to their total income when they receive care,[13,14] representing a greater financial burden that is associated with poorer adherence to cancer treatment.[15,16]

Lower individual and community socioeconomic status (SES) are also associated with poorer health outcomes and increased risk of mortality among cancer patients.[17–19] Most epidemiologic studies account for SES by modeling it as a confounder or an effect modifier when examining the relationship between racial disparities and cancer treatment or mortality.[18,19] A confounder is defined as a characteristic *associated* with both the exposure and the outcome, though not in the causal pathway.[20] We hypothesize, as depicted in our *a priori* causal diagram (Supplemental Figure 1, http://links.lww.com/MD/D377), that race and ethnicity may determine or predict SES measures and we therefore consider SES measures to be potential mediators in a causal pathway between race/ethnicity and treatment of DLBCL in older patients. With the development of mediation analysis, it is possible to better understand how incorporating a mediator as a confounder in statistical modeling can bias effect estimates; misspecifying or possibly over adjusting the model could explain the conflicting findings and interpretations in observational studies of health disparities.[21]

No known study has conducted a mediation analysis evaluating the relationship between race and ethnicity and differences in the treatment of older patients with DLBCL using the Surveillance Epidemiology and End Results (SEER) Medicare-linked database.[22] Our objective was to conduct causal mediation analyses examining associations between race and ethnicity and receipt of chemo- and/or immuno-therapy (vs no chemo- and/or immuno-therapy) with potential mediation by patient- and community-level SES variables:

(i) having Medicare private supplementation;
(ii) metropolitan statistical area (MSA) of residence; and
(iii) census-tract poverty level.

2. Methods

2.1. Data and participants

These analyses were conducted among patients ages 66 years and older diagnosed with DLBCL using the SEER-Medicare linked database between 2001 and 2011. Patients with DLBCL were identified using World Health Organization International Classification of Diseases for Oncology, third edition histology codes for 'DLBCL, NOS [not otherwise specified]' (codes: 9680, 9688, 9737, 9738, 9684, and 9735) available within the SEER dataset.[23] Data from this period coincides with the greater evidence and increasing use of rituximab in addition to standard multiple chemotherapy regimens to improve outcomes in older adults with DLBCL.[4] This database links population-based cancer registries in the U.S. with Medicare administrative claims data (medical claims from Parts A and B, and prescription claims from Part D).[22,24,25] Medicare is the primary payer for over 93% of the U.S. population ≥65 years of age,[26] making it possible to conduct epidemiologic studies to examine treatment and health outcomes in older adult cancer patients.[22,24,25]

Medicare beneficiaries ages 66 years and older with a diagnosis of histologically confirmed first primary DLBCL between 2001 and 2011 were eligible for inclusion in this study. Patients with first primary DLBCL include those with (1) DLBCL as their first and only cancer diagnosis or (2) DLBCL as the first of multiple cancer diagnoses. Patients were required to be continuously enrolled in Medicare Parts A and B for at least one year prior to and following diagnosis (unless died) with Medicare as their primary payer. If individuals died in <12 months following diagnosis, then they were required to have continuous coverage of Medicare Parts A and B prior to death. We did not condition enrollment on survival, which would have induced bias. Individuals with Medicare administered through a managed care organization were excluded because our data may not comprehensively capture administrative claims determining their treatment. Individuals with non-age-related eligibility for Medicare were also excluded from the analysis. Patients with missing data on race/ethnicity and our potential SES mediators of interest were also excluded from the sample. Our final analytic cohort included 9484 patients ages 66 years and older with DLBCL (Supplemental Figure 2, http://links.lww.com/MD/D378).

The SEER-Medicare linked database is available to investigators only under a limited data use agreement. While we cannot directly share these data files, the programming code used for these analyses are available upon request. The institutional review board of the University of Illinois at Chicago approved this study and determined using de-identified data to be exempt from human subjects research requiring informed consent.

2.2. Covariates

Receipt of infused, systemic therapies (or oral equivalents) was determined using administrative claims with current procedure

terminology and ICD-9-CM codes by providers.[27] Similar to other studies utilizing the SEER-Medicare linked database,[7–9] patients who received rituximab plus chemotherapy, rituximab monotherapy or other systemic chemotherapy in the year following diagnosis are here forward referred to as having received "any chemo- and/or immuno-therapy." Patients with no documentation of these treatments in the year following diagnosis are classified here forward as receiving "no chemo- and/or immuno-therapy".

Information on the exposure and other important covariates including race/ethnicity (NH-white, NH-black, Asian/Pacific Islander (API), Hispanic/Latino), age, sex, year of diagnosis, Ann Arbor stage, and presence of B symptoms at diagnosis were collected from SEER registry-reported data at cohort entry. The modified Charlson Comorbidity Score was determined using administrative medical claims data and was calculated from 12 months prior to diagnosis.[28] Finally, we also used these data to collect information on the 3 measures of SES mediators (i.e., private Medicare supplement status [yes vs no], MSA [urban vs nonurban], and ≥10% census-tract poverty level [yes vs no]), categorized as binary variables in these analyses. Beneficiaries were considered to have "Medicare without private supplement" if they lacked any supplement or had Medicaid (dual-eligible); all other beneficiaries had some form of private Medicare supplementation documented. Our definition of private Medicare supplementation did not include Medigap. These classifications were documented from the enrollment information at the time of DLBCL diagnosis. Urban MSAs were those with a population of at least 1,000,000; all others were considered non-urban MSAs.

2.3. Statistical analyses

Descriptive analyses described the difference in distribution of covariates overall and by receipt of any chemo- and/or immuno-therapy. Statistical significance was tested using t-test or Pearson's chi-squared for continuous and categorical variables, respectively. Mediation analyses follow the product method approach described by VanderWeele et al.[21,29] This method estimates the presence of mediation, direct effects, and indirect effects through a series of regression analyses. First, we conducted univariate (Eq. (1)) and multivariable (Eq. (2)) analyses regressing the outcome (i.e., any chemo- and/or immuno-therapy) on the exposure (i.e., race/ethnicity) and a priori measured confounders (Supplemental Figure 1, http://links.lww.com/MD/D377). In our models below, a represents the level of the exposure, m represents fixing the mediator (M) at a constant level, and c are the measured confounders adjusted for in the model.

$$E[Y_{aM_{a*}} - Y_{a*M_{a*}}] = \sum_m E[Y|a,m] - E[Y|a*,m] \quad (1)$$

$$NDE = E[Y_{aM_{a*}} - Y_{a*M_{a*}}|c]$$
$$= \sum_{c,m} E[y|a,m,c] - E[Y|a*,m,c]P(m/a*,c)P(c) \quad (2)$$

We then conducted univariate (Eq. (3)) and multivariate (Eq. (4)) analyses separately regressing mediators (i.e., the potential SES mediators of interest) on race/ethnicity and a priori measured confounders. Using these estimates, we calculated the natural direct effects (NDE) (Eq. (2)), natural indirect effects (NIE) (Eq. (4)), and total effects (TE) (Eq. (5)).[30] The direct effect describes

the exposure-outcome relationship that does not include the mediator (θ); and the indirect effect describes the part of the exposure-outcome relationship that incorporates the mediator (1 − θ). While our approach accounted for the possibility of interaction among these SES measures and race/ethnicity, we did not find evidence of significant interaction with these mediators of interest and thus, interaction terms were not included in the final models.

$$E[Y_{aMa} - Y_{aMa*}] = \sum_m E[Y|a,m]P(m|a) - P(m|a*) \quad (3)$$

$$NIE = E[Y_{aMa} - Y_{aMa*}]$$
$$= \sum_{c,m} E[Y|a,m,c]P(m|a,c) - P(m\ a*,c)P(c)] \quad (4)$$

$$TE(a,a*) = NDE + NIE$$
$$= E[Y_{aMa*} - Y_{a*Ma*}] + E[Y_{aMa} - Y_{a*M*}] \quad (5)$$

To estimate the extent to which the exposure-outcome relationship is affected by the mediator, we conducted a proportion-mediated calculation (Eq. (6)) using the PARAMED module in Stata. We used the calculated coefficients from the logistic regression and linear regression models to characterize the outcome and mediator variables respectively. All analyses were [30] conducted using Stata Release 14 (College Station, TX).[31]

$$PM = \frac{NDE*(NIE - 1)}{NDE*NIE - 1} \quad (6)$$

3. Results

We report descriptive characteristics of Medicare beneficiaries diagnosed with DLBCL who received any chemo- and/or immuno-therapy and those who did not receive such therapy in Table 1. Those receiving any chemo- and/or immuno-therapy were younger (median 76 vs 80 years) and had slightly fewer female patients (54% vs 56%). Compared to patients that received any chemo- and/or immuno-therapy, a lower proportion of Medicare recipients that received no chemo- and/or immuno-therapy had private Medicare supplementation (61% vs 67%), and a greater proportion lived in an urban MSA (59% vs 56%) and in census-tracts with poverty levels of ≥10% (45% vs 41%). In Table 2, we describe characteristics of Medicare beneficiaries with DLBCL by race/ethnicity. A slightly greater proportion of NH-white Medicare beneficiaries (61%) received treatment with any chemo- and/or immuno-therapy compared to NH-black (58%), API (55%), and Hispanic/Latino beneficiaries (55%). Regardless of racial/ethnic group, the majority (>90%) of patients treated with any chemo- and/or immuno-therapy received R-CHOP regimens. A lower proportion of NH-black (45%), API (37%), and Hispanic/Latino patients (36%) had private Medicare supplementation compared to NH-white patients (70%); and more racial/ethnic minority patients lived in an urban MSA (64%, 74%, and 64% respectively) compared to their NH-white counterparts (55%). Furthermore, more NH-black (75%) and Hispanic/Latino patients (63%) lived in census-tracts with poverty levels of ≥10% compared to NH-white (40%) and API patients (39%).

In Table 3, we report results from logistic regression models for the association between race/ethnicity and odds of treatment with

Table 1

Descriptive characteristics of Medicare recipients with diffuse large B-cell lymphoma in the Surveillance, Epidemiology and End Results Program registries by treatment status, 2001–2011.

n (%)	All N = 9484 (100%)	Any chemo- and/or immuno-therapy[*] n = 5680 (59.9%)	No chemo- and/or immuno-therapy[*] n = 3804 (40.1%)	P
Age, years				
Median (interquartile range)	78 (11.0)	76 (10.0)	80 (11.0)	
66–69	1293 (13.6)	931 (16.4)	362 (9.5)	<.001
70–74	2015 (21.3)	1396 (24.6)	619 (16.3)	
75–79	2253 (23.8)	1495 (26.3)	758 (19.9)	
80–84	2128 (22.4)	1152 (20.3)	976 (25.7)	
85+	1795 (18.9)	706 (12.4)	1089 (28.6)	
Sex				
Male	4271 (45.0)	2607 (45.9)	1664 (43.7)	.039
Female	5213 (55.0)	3073 (54.1)	2140 (56.3)	
Race				
NH-white	8000 (84.4)	4850 (85.4)	3150 (82.8)	.007
NH-black	340 (3.6)	197 (3.5)	143 (3.8)	
Asian/Pacific Islander	534 (5.6)	296 (5.2)	238 (6.3)	
Hispanic/Latino	610 (6.4)	337 (5.9)	273 (7.2)	
Year of diagnosis				
2001–2004	2241 (23.6)	1328 (23.4)	913 (24.0)	.258
2005–2008	3608 (38.0)	2199 (38.7)	1409 (37.0)	
2009–2011	3635 (38.3)	2153 (37.9)	1482 (39.0)	
Ann Arbor stage				
I	2601 (27.4)	1532 (27.0)	1069 (28.1)	<.001
II	1777 (18.7)	1172 (20.6)	605 (15.9)	
III	1499 (15.8)	967 (17.0)	532 (14.0)	
IV	3091 (32.6)	1742 (30.7)	1349 (35.5)	
Unknown	516 (5.4)	267 (4.7)	249 (6.6)	
NCI Charlson comorbidity score				
0	2610 (27.5)	1844 (32.5)	766 (20.1)	<.001
1	2280 (24.0)	1552 (27.3)	728 (19.1)	
2+	4143 (43.7)	2235 (39.4)	1908 (50.2)	
Unknown	451 (4.8)	49 (0.9)	402 (10.6)	
Selected SES variables				
Medicare payer type				
Medicare with no private supplementation[†]	3353 (35.4)	1865 (32.8)	1488 (39.1)	<.001
Medicare with private supplementation	6131 (64.7)	3815 (67.2)	2316 (60.9)	
Metropolitan statistical area				
Urban MSA[‡]	5382 (56.8)	3152 (55.5)	2230 (58.6)	.003
Non-urban MSA	4102 (43.3)	2528 (44.5)	1574 (41.4)	
Census-tract poverty				
0% to <10%	5440 (57.4)	3334 (58.7)	2106 (55.4)	.001
10–100%	4044 (42.6)	2346 (41.3)	1698 (44.6)	

MSA = metropolitan statistical area, NH = non-Hispanic.

[*] Includes rituximab and chemotherapy (RCHOP), rituximab monotherapy, other chemotherapy, or other monotherapy. Patients who received radiation treatment alone were considered to have no chemo-immunotherapy.

[†] Medicare without private supplementation includes dual eligible Medicaid-Medicare patients and without any Medicare supplementation.

[‡] Urban MSAs were those with a population of at least 1,000,000.

any chemo- and/or immuno-therapy. In multivariable models adjusting for measured confounders (C_1), NH-black (OR 0.89, 95% CI 0.72, 1.11), API (OR 0.81, 95% CI 0.68, 0.96) and Hispanic/Latino patients (OR 0.80, 95% CI 0.68, 0.95) had lower odds of receiving treatment compared to NH-white patients. When adjusting for Medicare with private supplement as a confounder, the observed associations between race/ethnicity and treatment were attenuated toward the null or remained non-statistically significant (black: OR 0.89, 95% CI 0.69, 1.14; API: OR 0.86, 95% CI 0.68, 1.08; Hispanic/Latino: OR 0.84, 95% CI 0.69, 1.04). Adjustment for the other possible mediators as confounders in these models resulted in a smaller magnitude of attenuation in effect estimates.

In Table 4, we report results from logistic regression models for the associations between race/ethnicity and the SES mediators of interest. NH-black and Hispanic/Latino patients had higher odds of having Medicare without private supplementation, residence in an urban MSA and in a census-tract with ≥10% poverty in both crude and multivariable adjusted logistic regressions among racial/ethnic minorities compared to NH-white patients. API patients also had higher odds of having Medicare without private supplementation and residence in an urban MSA but were similar to NH-white patients in respect to census-tract poverty levels.

Based on the regression coefficients estimated in these multivariable analyses, Table 5 reports the calculated causal natural direct effect, natural indirect effect, total effect and the

Table 2

Descriptive characteristics of Medicare recipients with diffuse large B-cell lymphoma in the Surveillance, Epidemiology and End Results Program registries by race/ethnicity, 2001–2011.

n (%)	NH-white n = 8000 (84.4%)	NH-black n = 340 (3.6%)	Asian/Pacific Islander n = 534 (5.6%)	Hispanic/Latino n = 610 (6.4%)	P
Age, years					
Median (interquartile range)	78 (11)	75 (10)	78 (10)	76 (11)	
66-69	1047 (13.1%)	69 (20.3%)	56 (10.5%)	121 (19.8%)	<.001
70-74	1665 (20.8%)	89 (26.2%)	115 (21.5%)	146 (23.9%)	
75-79	1894 (23.7%)	75 (22.1%)	149 (27.9%)	135 (22.1%)	
80-84	1836 (22.9%)	57 (16.8%)	121 (22.7%)	114 (18.7%)	
85+	1558 (19.5%)	50 (14.7%)	93 (17.4%)	94 (15.4%)	
Sex					
Male	3631 (45.4%)	124 (36.5%)	257 (48.1%)	259 (42.5%)	.003
Female	4369 (54.6%)	216 (63.5%)	277 (51.9%)	351 (57.5%)	
Treatment type					
None	3150 (39.4%)	143 (42.1%)	238 (44.6%)	273 (44.8%)	.007
Any chemo- and/or immuno-therapy[*]	4850 (60.6%)	197 (57.9%)	296 (55.4%)	337 (55.2%)	
Rituximab + Chemotherapy	4542 (56.8%)	178 (52.4%)	282 (52.8%)	316 (51.8%)	
Year of diagnosis					
2001–2004	1974 (24.7%)	91 (26.8%)	74 (13.9%)	102 (16.7%)	<.001
2005–2008	3056 (38.2%)	116 (34.1%)	211 (39.5%)	225 (36.9%)	
2009–2011	2970 (37.1%)	133 (39.1%)	249 (46.6%)	283 (46.4%)	
Ann Arbor stage					
I	2232 (27.9%)	85 (25.0%)	134 (25.1%)	150 (24.6%)	.210
II	1482 (18.5%)	61 (17.9%)	115 (21.5%)	119 (19.5%)	
III	1256 (15.7%)	65 (19.1%)	72 (13.5%)	106 (17.4%)	
IV	2614 (32.7%)	111 (32.6%)	165 (30.9%)	201 (33.0%)	
NCI Charlson comorbidity score					
0	2255 (28.2%)	77 (22.6%)	135 (25.3%)	143 (23.4%)	.014
1	1940 (24.3%)	83 (24.4%)	132 (24.7%)	125 (20.5%)	
2+	3455 (43.2%)	160 (47.1%)	234 (43.8%)	294 (48.2%)	
Selected SES variables					
Medicare payer type					
Medicare with no private supplementation	2438 (30.5%)	186 (54.7%)	336 (62.9%)	393 (64.4%)	<.001
Medicare with private supplementation[†]	5562 (69.5%)	154 (45.3%)	198 (37.1%)	217 (35.6%)	
Metropolitan statistical area					
Urban[‡]	4377 (54.7%)	219 (64.4%)	396 (74.2%)	390 (63.9%)	<.001
Non-urban	3623 (45.3%)	121 (35.6%)	138 (25.8%)	220 (36.1%)	
Census-tract poverty					
0% to <10%	4801 (60.0%)	86 (25.3%)	324 (60.7%)	229 (37.5%)	<.001
10–100%	3199 (40.0%)	254 (74.7%)	210 (39.3%)	381 (62.5%)	

MSA = metropolitan statistical area, NH = non-Hispanic.

[*] Includes rituximab and chemotherapy (RCHOP), rituximab monotherapy, other chemotherapy, or other monotherapy. Patients who received radiation treatment alone were considered to have no chemo-immunotherapy.

[†] Medicare without private supplementation includes dual eligible Medicaid-Medicare patients and without any Medicare supplementation.

[‡] Urban MSAs were those with a population of at least 1,000,000.

Table 3

Logistic regression models for the receipt of any chemo- and/or immuno-therapy[*] among black, Asian/PI and Hispanic compared to non-Hispanic white Medicare recipients with diffuse large B-cell lymphoma in the Surveillance, Epidemiology and End Results, 2001–2011.

	Crude model	Multivariable-adjusted model[†]	Mediator-adjusted models[‡]		
			Private Medicare supplementation	Urban MSA	Census-tract poverty ≥10%
Receipt of treatment			OR (95% CI)		
NH-white	Reference	Reference	Reference	Reference	Reference
NH-black	0.89 (0.72, 1.11)	0.84 (0.65, 1.08)	0.89 (0.69, 1.14)	0.84 (0.65, 1.08)	0.89 (0.69, 1.15)
Asian/Pacific Islander	0.81 (0.68, 0.96)[*]	0.80 (0.64, 1.01)	0.86 (0.68, 1.08)	0.81 (0.65, 1.02)	0.81 (0.65, 1.02)
Hispanic/Latino	0.80 (0.68, 0.95)[**]	0.78 (0.64, 0.96)[*]	0.84 (0.69, 1.04)	0.78 (0.64, 0.96)[*]	0.82 (0.67, 1.01)

MSA = metropolitan statistical area, NH = non-Hispanic.

[*] Includes rituximab and chemotherapy (RCHOP), rituximab monotherapy, other chemotherapy, or other monotherapy. Patients who received radiation treatment alone were considered to have no chemo-immunotherapy.

[†] Multivariable model adjusted for age, sex, Ann Arbor stage, NCI Charlson comorbidity score at diagnosis, year of diagnosis, SEER-registry, and radiation.

[‡] Multivariable models adjusted for age, sex, Ann Arbor stage, NCI Charlson comorbidity score at diagnosis, year of diagnosis, SEER-registry, and radiation; Mediators adjusted in separate models for private Medicare supplementation (private supplementation/no private supplementation), census-tract poverty (<10%, ≥10%), and MSA (urban, non-urban).

[*] $P \leq .05$.

[**] $P < .001$.

Logistic regression models for lacking private Medicare supplementation, living in a big metro area, and living in a census-tract with <10% poverty among black, Asian/PI and Hispanic compared to non-Hispanic white Medicare recipients with diffuse large B-cell lymphoma in the Surveillance, Epidemiology and End Results, 2001–2011.

	No private Medicare supplementation		Urban MSA		Census-tract poverty ≥10%	
	Crude[*]	Adjusted[†]	Crude[*]	Adjusted[†]	Crude[*]	Adjusted[†]
	OR (95% CI)					
NH-white	Reference	Reference	Reference	Reference	Reference	Reference
NH-black	2.76 (2.21, 3.43)[**]	2.61 (2.04, 3.33)[**]	1.50 (1.19, 1.88)[**]	1.25 (0.89, 1.75)	4.43 (3.46, 5.68)[**]	5.32 (3.98, 7.11)[**]
Asian/Pacific Islander	3.87 (3.23, 4.64)[**]	2.87 (2.29, 3.60)[**]	2.38 (1.95, 2.90)[**]	2.18 (1.55, 3.05)[**]	0.97 (0.81, 1.16)	1.42 (1.13, 1.79)[*]
Hispanic/Latino	4.13 (3.48, 4.91)[**]	3.22 (2.64, 3.94)[**]	1.47 (1.24, 1.74)[**]	0.98 (0.76, 1.27)	2.50 (2.11, 2.96)[**]	3.21 (2.61, 3.94)[**]

MSA = metropolitan statistical area, NH = non-Hispanic.
[*] Mediator model for race/ethnicity.
[†] Multivariable mediator models adjusted for age, gender, Ann Arbor stage, NCI Charlson comorbidity score at diagnosis, year of diagnosis, SEER-registry, and radiation.
[*] $P \le .05$.
[**] $P < .001$.

proportion mediated by the three SES mediators of interest in our casual pathway. The total effects from the mediation analyses were similar to the total effects found in the regression modeling that treats SES mediators as confounders (Table 3). For the observed differences in likelihood of treatment of patients ≥66 years of age with DLBCL with any chemo- and/or immuno-therapy, private Medicare supplementation accounted for the greatest proportion mediated for NH-black (38%), API (34%) and Hispanic/Latino patients (31%); as mediators, MSA and census-tract poverty levels of ≥10% accounted for only a modest amount of the observed differences in treatment by racial/ethnic group (between 5–10% and 6–11%, respectively) (Table 5).

4. Discussion

To our knowledge, this is the first study to investigate SES as a mediator for the association between race/ethnicity and the receipt of chemo- and/or immuno-therapy in patients 66 years of age and older with DLBCL. Past epidemiologic studies modeling SES as a confounder or effect modifier when evaluating receipt of cancer treatment and mortality have conflicting results.[9,11,19,32] While SES was demonstrated to attenuate any differences in cancer-specific and all-cause survival by race/ethnicity when

adjusted as a confounder,[19] we contend that it is possibly more appropriate to consider SES measures as mediators to avoid introducing bias and minimize the possibility of spurious findings.[33] Mediation analyses that determine a proportion effect mediated provide an estimate of how much of the observed effect of race/ethnicity on treatment receipt would be reduced if we could fix the value of SES for the entire population,[29] an important interpretation for health policy decisions. These findings support the role of health policies, SES, and race/ethnicity on disparities in DLBCL survival.[18,34]

In previous studies, lack of insurance or having coverage with Medicaid only was associated with lower survival in younger lymphoma patients ages 18 to 64 years.[35] When comparing racial/ethnic minorities to NH-white DLBCL patients 66+ years of age in our analysis using SEER Medicare linked database, a large proportion (31–38%) of the effect of race/ethnicity on receiving any chemo- and/or immuno-therapy treatment was mediated by having private Medicare supplementation. Our findings are consistent with the available, although limited, literature describing differences in DLBCL treatment by racial/ethnic group and lower treatment rates among those with less comprehensive insurance coverage.[9,11,19] Given that the highest incidence of DLBCL occurs in the older adults covered by

Mediated association between race/ethnicity and receipt of any chemo- and/or immuno-therapy[*] by socioeconomic status (single mediation analyses).

	Private Medicare supplementation		Urban MSA		Census-tract poverty ≥10%	
NH-white (reference)						
NH-black	NDE	0.951	NDE	0.934	NDE	0.931
	NIE	0.969	NIE	0.997	NIE	0.991
	TE	0.922	TE	0.931	TE	0.923
	PM:	37.7%	PM:	4.6%	PM:	11.1%
Asian/Pacific Islander	NDE	0.905	NDE	0.873	NDE	0.868
	NIE	0.945	NIE	0.989	NIE	0.986
	TE	0.856	TE	0.863	TE	0.856
	PM:	34.2%	PM:	7.2%	PM:	8.4%
Hispanic/Latino	NDE	0.861	NDE	0.816	NDE	0.809
	NIE	0.929	NIE	0.976	NIE	0.985
	TE	0.800	TE	0.797	TE	0.797
	PM:	30.6%	PM:	9.5%	PM:	5.8%

MSA = metropolitan statistical area, NDE = natural direct effect, NH = non-Hispanic, NIE = natural indirect effect, PM = proportion mediated $PM = \frac{NDE*(NIE-1)}{NDE*NIE-1}$, TE = total effect.
[*] Includes rituximab and chemotherapy (RCHOP), rituximab monotherapy, other chemotherapy, or other monotherapy. Patients who received radiation treatment alone were considered to have no chemo-immunotherapy.

Medicare,[36] understanding substantial mediators to treatment access is critically important. This knowledge creates an opportunity for medical providers to optimize treatment outcomes and policymakers to provide equitable public health gains from highly effective breakthrough treatments such as rituximab-based therapy.

Despite the improvements in cancer care, racial disparities persist in treatment and survival in DLBCL and non-Hodgkin lymphoma in general. Access to medical treatments is characterized in the health services literature in multiple ways including affordability, availability, accessibility, accommodation, and acceptability.[37] This suggests that minority patients continue to experience barriers to effective treatments for DLBCL owed in a considerable extent to SES-related factors like private Medicare supplementation.[8,9,17] Treatment of non-Hodgkin lymphoma, and DLBCL specifically, with R-CHOP regimens is highly efficacious and improves survival regardless of race/ethnicity.[8,19] Beyond cancer treatment, racial disparities may also persist due to differences in cancer prevention, screening, and outreach.[17]

Among our mediators, private Medicare supplementation affected whether patients with DLBCL were treated with chemo- and/or immuno-therapy; however, population-level SES proxy measures (i.e., MSA and census-tract poverty level) accounted for only minimal mediated effects. In other studies, low neighborhood-level SES is associated with higher odds of not receiving cancer treatment when compared to patients from higher SES areas.[17,32,38] Therefore, further research using more detailed geographic data is warranted to determine the role of these factors in relation to racial/ethnic disparities in the treatment of DLBCL.

4.1. Policy implications

DLBCL five-year mortality has declined for the past two decades, in large part due to the introduction of rituximab-based treatment.[6] However, groups have benefited unequally from this advancement—racial minorities and individuals with no insurance or public insurance have higher rates of not receiving treatment and mortality.[9,11,19] According to Phelan and Link's theory of fundamental causes, disparities persist because individuals with higher SES have more resources and this leads to greater and more immediate access to new medical treatments and technologies.[39] This is a major cause for concern because as the field of oncology continues to progress toward more precision medicine and targeted therapy, the potential for worsening disparities among under resourced populations is daunting. Our findings suggest that improving access to private Medicare supplementation may reduce racial disparities in the receipt of treatment and may in turn have implications on cancer-specific mortality among Medicare recipients with DLBCL. This would be possible through policies that provide a subsidy for private supplementation for low-income Medicare beneficiaries. Medicare part D, for example, improved access to prescription medications among low-income adults by subsidizing the cost of the private supplement (i.e. Low Income Subsidy).[40] Expansion of Medicaid to a greater number of older adults is another option for policymakers. However, considering that dual-eligible Medicare beneficiaries have lower receipt of cancer treatments compared to beneficiaries with private insurance,[41] expanded Medicaid coverage would need to be comparable to that of private supplementation.

Rising costs of cancer treatment and out-of-pocket expenses represent a significant burden on cancer patients and barriers to care.[12,16] Out-of-pocket expenses for Medicare beneficiaries with cancer vary by supplemental insurance—beneficiaries with Medicaid have the lowest average expenditure and beneficiaries with no supplemental insurance have the highest expenditure,[13] although our study did not evaluate the role of out-of-pocket expenses on DLBCL outcomes. Together with our findings, these studies suggest that improving access to cancer treatments may lead to a reduction cancer disparities among racial/ethnic minorities.[42]

4.2. Limitations

There were limitations to our approach in this study. Analytically, applying the product method assumes that there are no unmeasured confounders in the exposure–outcome, mediator–outcome, and exposure–mediator relationships.[29] In this study using cancer registry and linked administrative claims data, residual confounding by unmeasured covariates is always possible given its observational nature and the use of mediator proxy measures. While SEER-Medicare captures many sociodemographic variables that are typically missing from other large administrative claims data, it was not possible to collect information on other important determinants for receipt of cancer treatments, such as: individual-level SES, ability to pay/cost-sharing, transportation, caregiver status, and important clinical considerations in treatment decision making (e.g., functional or performance status). Also, private Medicare supplementation plans are heterogeneous and vary in extent of additional coverage for beneficiaries. While we measured continuous Medicare enrollment and supplementation status at the time of DLBCL diagnosis, we were unable to distinguish whether supplementation (Part C) lapsed but patients remained enrolled on Parts A and B. An unmeasured confounder that is correlated with our mediators and may have contributed to the observed proportion mediated. However, we do not believe this could account entirely for the observed magnitude of the proportion mediated.

Given the dichotomous structure of our variables, we were unable to conduct a sensitivity analysis that estimated the proportion mediated using a different analytic method such as structural equation modeling (SEM), which requires the use of continuous variables.[43] Generalized SEM is a new method that accommodates dichotomous/categorical variables, but is unable to estimate indirect effects for comparison to our main approach.[44]

Our findings have limited generalizability due to sampling from SEER reporting regions (instead of the entire U.S.), exclusion of patients who did not have Medicare as the primary payer, and other inclusion/exclusion criteria. Other studies have reported lower rates (23%) of non-treatment of older DLBCL patients in the SEER-Medicare linked database,[45] while we identified that 40% of our cohort did not receive treatment. This difference in observed treatment (or absence thereof) may be explained by our exclusion of patients with a history of lymphoma diagnosis, non-age related Medicare eligibility, and requirements on continuous enrollment. Prior studies also classified patients as treated if they had only one chemo- and/or immuno-therapy diagnostic or procedural claim following DLBCL diagnosis.[45] We required two or more claims for a specific chemotherapeutic agent within 3 months of each other,

not including a single date of service with the ICD-9-CM code indicating an encounter for antineoplastic chemotherapy (V58.11). Determining treatment from a sole claim for a single chemotherapeutic agent could represent intolerance (e.g., hypersensitivity) or the decision to not continue treatment (e.g., high cost or patient burden). Similarly, the use of a single ICD-9-CM code indicating the occurrence of an antineoplastic administration is not necessarily for a chemotherapeutic agent (e.g., Mesna administration post-cyclophosphamide). Indeed, the authors of the previous study of DLBCL treatment concluded that suboptimal duration of treatment was associated with poor outcomes, similar to that of having not received any treatment.[45]

Lastly, the age of onset of DLBCL among NH-black patients is lower compared to other racial/ethnic groups. Therefore, racial disparities in younger patients with respect to SES mediators such as having robust insurance were beyond the scope of this analysis.

5. Conclusion

Understanding health insurance-related disparities in lymphoma treatment and outcomes remains an important concern for oncologists and health policy makers. We found that between 31% and 38% of the observed differences in DLBCL treatment between racial/ethnic minority patients (i.e., NH-black, API, and Hispanic/Latino patients) and NH-white patients were mediated by having private Medicare supplementation. Census-tract-level SES factors (i.e., MSA and census-tract poverty level) yielded only modest mediation effects. Further research examining the role of other SES characteristics at the person and community level as possible mediators of differences in receipt of treatment by race/ethnicity is needed to confirm our findings. Still, understanding of mediation by socioeconomic measures such as Medicare supplementation provides important evidence for policymakers to consider actions to reduce cancer health disparities in the treatment of DLBCL.

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