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The Hispanic Paradox in Non-Small Cell Lung cancer

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ORIGINAL RESEARCH REPORT

The Hispanic Paradox in Non-Small Cell Lung Cancer

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Abstract

Objective/Background: **According to the U.S. Census Bureau, 18% of the total population in the United States identified themselves as Hispanic in 2016 making it the largest minority group. This study aimed to evaluate the effect of Hispanic ethnicity on the overall survival of patients with non-small cell lung cancer (NSCLC) using a large national cancer database.**

Methods: **We used the National Cancer Database to identify patients diagnosed with NSCLC between 2010 and 2015. The two comparative groups for this study were non-Hispanic Whites (NHWs) and Hispanics. The primary outcome was overall survival.**

Results: **Of the 555,475 patients included in the study, 96.9% and 3.1% were NHWs and Hispanics with a median follow up of 12.6 months (interquartile range 4.1−30.6) and 12.1 months (interquartile range 3.8−29.5), respectively. Hispanics were more likely to be uninsured, and live in areas with lower median household income or education level. In the age-, sex-, and comorbidities-adjusted Cox model, the overall survival was significantly better in Hispanics compared with NHWs (hazard ratio [HR] 0.92, 95% confidence interval 0.90−0.93, $p < .001$). In a demographic, socioeconomic, clinical, and facility characteristics adjusted Cox model, Hispanics had further improvement in survival (HR 0.79, 95% confidence interval 0.78−0.81, $p < .001$). The survival advantage was seen in all cancer stages: Stage I—HR 0.76 (0.71−0.80), Stage II—HR 0.85 (0.79−0.92), Stage III—HR 0.81 (0.77−0.85), and Stage IV—HR 0.79 (0.77−0.81).**

Conclusion: **Hispanic ethnicity was associated with better survival in NSCLC. This survival advantage is likely the result of complex interactions amongst several physical, social, cultural, genomic, and environmental factors.**

Keywords: Carcinoma, Non-small-cell lung, Ethnic groups, Hispanic Americans/statistics & numerical data, Registries, Survival rate

1. Introduction

According to the U.S. Census Bureau, 18% of the total population in the United States identified themselves as Hispanic in 2016 making it the largest minority group [1]. Hispanics are known to have lower average socioeconomic status and limited health care access compared with non-Hispanic Whites (NHWs) [2−4]. Even with the aforementioned inequalities, several studies have concluded that Hispanics have health outcomes comparable to or even better than NHWs for certain medical conditions [2,5]. This observation has been termed as the "Hispanic Paradox" [6]. Several social, genetic, and lifestyle factors have been proposed to explain the Hispanic Paradox [5,7,8].

The incidence and mortality of lung cancer in Hispanics are approximately 50% lower than in NHWs [9]. Nonetheless, lung cancer remains the leading cause of cancer-related deaths in both Hispanics and NHWs [9,10]. Studies on the relationship between Hispanic ethnicity and non-small cell lung (NSCLC) survival have had inconsistent conclusions [11−17]. This study aimed to evaluate the effect of Hispanic ethnicity on the overall survival of patients with NSCLC using a large national cancer database.

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This database collects extensive data variables for analyses that allowed us to explore the impact of various socioeconomic, demographic, and clinical characteristics on the overall survival [18].

2. Methods

2.1. Data source

We used the National Cancer Database (NCDB) to identify patients diagnosed with NSCLC between 2010 and 2015. The NCDB is a nationwide oncology database that prospectively collects from more than 1500 Commission on Cancer-accredited programs and includes ~70% of all new cancer diagnoses in the United States [18]. The database provides a wide array of de-identified information about patient demographics, tumor-specific details, facility, the first course of cancer treatment, and overall survival. The study was approved by the Institutional Review Board, University of Louisville, Kentucky.

2.2. Cohort selection and outcomes

The two comparative groups for this study were NHWs and Hispanics. The cohort selection criteria are shown in Fig. 1. Hispanic ethnicity was identified using the NCDB coding variable "SPANISH_HISPANIC_ORIGIN". This variable codes Hispanic ethnicity by origin (Mexican, Cuban, Puerto Rican, etc.). Of note, the majority of the patients (61%) were coded as Hispanic "not otherwise specified". The country of birth data is not collected by the NCDB. A sensitivity analysis was done to evaluate the impact of the missing Hispanic ethnicity status (Appendix Table A1).

The primary outcome was overall survival. The NCDB does not collect information on disease-specific survival. The impact of available socioeconomic (insurance type, income, and level of education) demographic, clinical, and facility characteristics on overall survival was also analyzed. Education and income variables in the NCDB are defined as the number of adults in the patient's zip code who did not graduate from high school and median household income for each patient's area of residence, and are estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from the American Community Survey data and adjusted for inflation, respectively. Both education and household income are categorized as quartiles based on equally proportioned ranges among all U.S. zip codes [18].

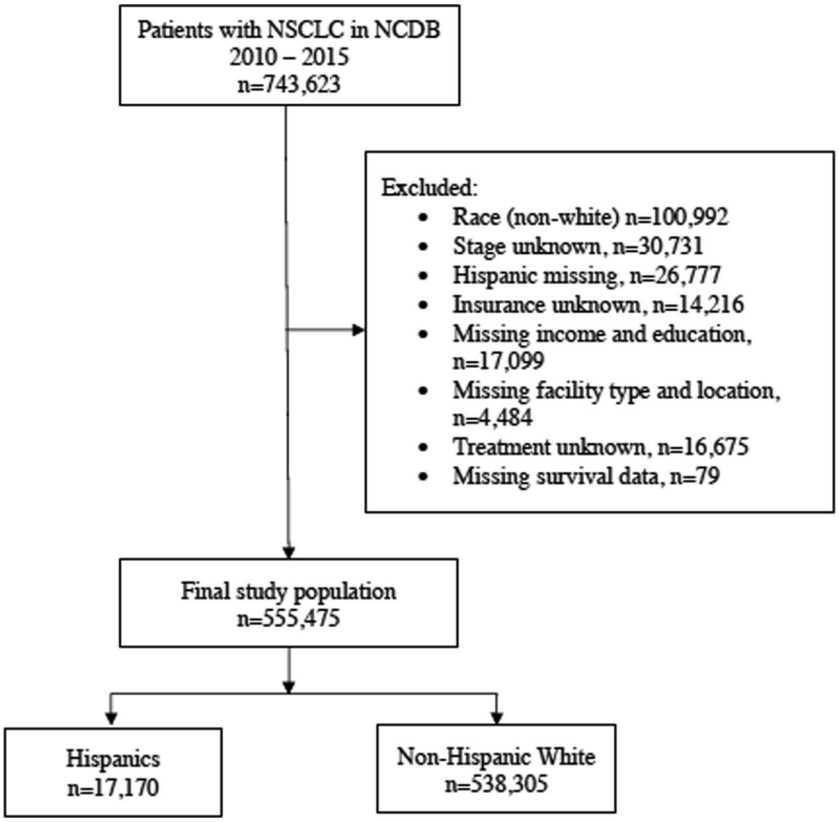

Fig. 1. Flow diagram of study population. NCDB = National Cancer Database; NSCLC = non-small cell lung cancer.

2.3. Statistical analysis

Baseline characteristics were compared between NHWs and Hispanics using the Fisher exact test for the categorical variables and the Wilcoxon rank-sum test for the continuous variables. The Kaplan–Meier method was used to estimate unadjusted survival times which were compared with the log-rank test. The multivariable Cox regression model was built by including all clinically relevant covariates that were significantly associated with the outcome of univariable analysis with a cutoff p value of 0.2 (Appendix Table A2). All clinically relevant interactions between the covariates were also included in the model. The proportional hazards assumption was tested using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. The model was stratified on the nonproportional covariates. Finally, we evaluated the fit of the final model by using the Cox–Snell residuals. To elucidate the effect of demographic, socioeconomic, clinical, and facility characteristics on overall survival in NSCLC, four separate multivariate survival models were built. Model 1 was adjusted for age, sex, and comorbidities. Model 2 included covariates in Model 1 plus socioeconomic factors (insurance, education, and income level). Model 3 included covariates in Model 2 plus facility type, location, and distance. Finally, Model 4 included covariates in Model 3 plus stage, histology, and treatment modalities. The covariates were introduced into the model using a staged approach to provide insight into which covariates had a relatively greater influence on the effect estimate. A two-sided p value < 0.05 was considered statistically significant. All the analyses were performed by STATA statistical software, version 16 (Stata Corporation, College Station, TX, USA).

3. Results

A total of 555,475 patients met the inclusion criteria for this study (Fig. 1). The NHWs and Hispanics comprised 96.9% and 3.1% of the study cohort with a median follow up of 12.6 months (interquartile range [IQR] 4.1–30.6) and 12.1 months (IQR 3.8–29.5), respectively. The demographics and clinical characteristics of the patients are shown in Table 1. Hispanics were younger and had a lower proportion of females compared with the NHWs cohort. Hispanics were more likely to be uninsured (7.1% vs. 2.6%, $p < .001$) and lived in areas with lower median household income (27.7% vs. 17.3%

Table 1. Demographics and clinical characteristics of the study population.

	Non-Hispanic Whites	Hispanics	p value
Sample size (n = 555,475)	538,305	17,170	
Age, y (%)			<0.001
• <60	18.9	22.6	
• 60–75	51.8	50	
• >75	29.3	27.4	
Female (%)	48.5	44.6	<0.001
Insurance (%)			<0.001
• None	2.6	7.1	
• Private	25.8	24.3	
• Government[a]	71.6	68.6	
Median household income, $ (%)			<0.001
• <40,227	17.3	27.7	
• 40,227–50,353	24.4	24.4	
• 50,354–63,332	25	24.1	
• >63,332	33.3	23.8	
Education[b] (%)			<0.001
• ≥17.6	17.7	53	
• 10.9–17.5	28.1	21.6	
• 6.3–10.8	30.6	16.1	
• <6.3	23.6	9.3	
Charlson-Deyo comorbidity score (%)			0.001
• <1	55.8	58.7	
• ≥1	44.2	41.3	
Stage (%)			<0.001
• I	29.2	24.2	
• II	10.3	9.3	
• III	20.1	19.4	
• IV	40.4	47.1	
Histology (%)			<0.001
• Adenocarcinoma	55.8	61	
• Squamous	29.6	23.8	
• Other	14.6	15.2	
Treatment modality (%)			
• Chemotherapy	45.1	46	0.017
• Surgery	30.9	28.6	<0.001
• Radiation	42.9	36.3	<0.001
• No treatment	11.8	16.5	<0.001
Facility type[c] (%)			<0.001
• CCP	10.3	8	
• CCCP	45.3	37.7	
• ARP	30.4	38.6	
• ICP	14	15.7	
Facility location[c] (%)			<0.001
• Northwest	21.6	19.4	
• West	12.8	30	
• Midwest	28	8.5	
• South	37.6	42.1	

Note. ARP = academic/research practice; CCCP = Comprehensive Community Cancer Program; CCP = community cancer practice; ICP = integrated cancer practice; y = year.

[a] Medicare, Medicaid and other government insurance.

[b] Education: This provides a measure of the percentage of adults in the patient's zip code who did not graduate from high-school and is categorized as equally proportioned quartiles among all US zip codes.

[c] Suppressed for age < 40 y.

with income <$40,227; $p < .001$), and lower education level (53% vs. 17.7% where ≥ 17.6% adults did not graduate from high school; $p < .001$). Hispanics had a higher likelihood of advanced disease stage at diagnosis, adenocarcinoma histology, and of receiving no cancer-directed treatment compared with NHWs. Initial treatment at an academic institution was received by 38.6% with median distance traveled for treatment being 6.7 miles (IQR 3.3–13.4) compared with that by 30.4% and 10.5 miles (IQR 4.5–24.7) in Hispanic and NHW groups, respectively ($p < .001$ for all comparisons).

In the age-, sex-, and comorbidities-adjusted survival model (Model 1), Hispanics had a statistically significant improvement in survival compared with NHWs (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.90–0.93, $p < .001$). In Model 4 (adjusted for all covariates) the Hispanics had further improvement in survival (HR 0.79, 95% CI 0.78–0.81, $p < .001$). The higher proportion of advanced cancer stage and no cancer-directed treatment in Hispanics were the most significant covariates that, when adjusted, explained the survival difference between Model 1 and Model 4. The HRs of all the models are shown in Table 2. The median overall survival was 17.9 months (95% CI 17.1–18.5) in Hispanics and 15.9 months (95% CI 15.8–16.0) in NHWs, $p < .001$ (Fig. 2). The median overall survival and 5-year overall survival rate stratified by stage are shown in Table 3. In Model 4 subgroup analysis, Hispanics had better survival in all cancer stages: stage I—HR 0.76 (95% CI 0.71–0.80), stage II—HR 0.85 (95% CI 0.79–0.92), stage III—HR 0.81 (95% CI 0.77–0.85), and stage IV—HR 0.79 (95% CI 0.77–0.81).

In subgroup analysis, Hispanic ethnicity was associated with better survival in all the age groups (27% in < 60 years, 19% in 60–75 years, and 19% in > 75 years), and both sexes (males—20% and females—21%). The improvement in survival in Hispanics was by 36% in the uninsured patients, 22% in the lowest income quartile, and 21% in lowest education quartile compared with NHWs in the same subgroups. Interestingly, the survival was comparatively even better in the lowest socioeconomic group (uninsured, lowest income, and education quartile), HR 0.55 (95% CI 0.47–0.64, $p < .001$) than the highest group (private insurance, highest income, and education quartile), HR 0.77 (95% CI 0.68–0.88, $p < .001$) (Figs. 3 and 4). An improvement in survival was also seen in all histologic subtypes (adenocarcinoma—23%, squamous—14%). Detailed subgroup analyses are available in Appendix Table A3.

Table 2. Cox proportional hazard models for mortality in non-hispanic whites and hispanics with non-small cell lung cancer.

	Non-Hispanic White	Hispanics HR [95%CI]	*p* value
Model 1[a]	Reference	0.92 (0.90–0.93)	<0.001
Model 2[b]	Reference	0.88 (0.87–0.90)	<0.001
Model 3[c]	Reference	0.91 (0.89–0.92)	<0.001
Model 4[d]	Reference	0.79 (0.78–0.81)	<0.001

[a] Model 1: adjusted for age, sex, and comorbidities.
[b] Model 2: Model 1 plus insurance status, education, and income level.
[c] Model 3: Model 2 plus facility type, location, and distance.
[d] Model 4: Model 3 plus stage, histology, and treatment.

4. Discussion

In our study, we used a large database to determine the effect of Hispanic ethnicity on the NSCLC overall survival in the United States. Previous studies have inconsistently reported similar or better NSCLC survival outcomes in Hispanics compared with other racial/ethnic groups [11,12,14,16]. We report an 8% better survival in Hispanics with NSCLC compared with NHWs in age, sex, and comorbidities adjusted model. When we adjusted for all the potential confounders (Model 4), the survival was further improved by 22% in Hispanics.

The Hispanic population is especially vulnerable to cancer care disparities due to disproportionately lower socioeconomic status compared with NHW population [2–4]. Consequently, Hispanic patients have a higher likelihood of having *de novo* advanced stage and receive no treatment [9]. There are several socioeconomic determinants of health like income, education, culture/linguistic barriers, insurance, and occupation that lead to underutilization of health care by the Hispanic community [19]. In our study, maybe the reason adjusting for available socioeconomic factors (Model 2) did not fully account for the higher proportion of advanced disease and recipient of no treatment (Model 4) in Hispanics is because we were able to include only three available socioeconomic factors—insurance, zip code level income, and education in the model. Although, some studies have reported a higher risk of advanced-stage cancer diagnosis in Hispanics even when socioeconomic status and health care access are similar [20,21].

Several factors have been suggested to explain the "Hispanic paradox" including the low prevalence of smoking, community support, genetics, dietary habits, and selective immigration patterns [5,7,8,14]. Due to the limitations of the database, we were unable to determine the effects of these factors. A

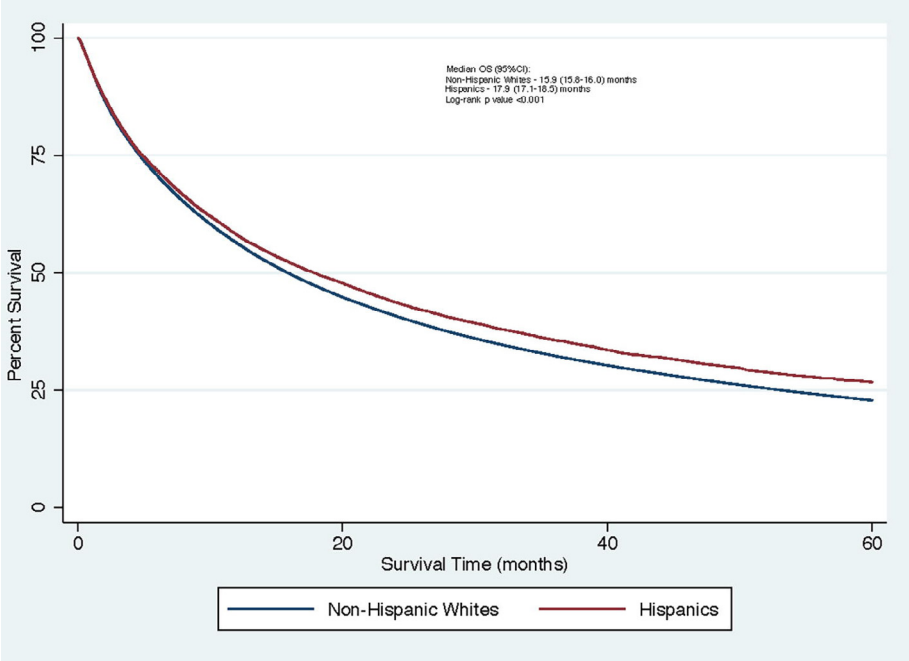

Fig. 2. Kaplan-Meier estimates of overall survival in Hispanics versus Non-Hispanic Whites.

study by Patel et al. [22] in women reported that decreased mortality risk in Hispanics was attenuated when adjusted for several sociodemographic factors including, but not limited to education, diet, and physical activity. Lower smoking prevalence has been reported in the U.S. Hispanic population than in NHWs (15.4% vs. 22.2% in 2009, respectively) [23]. This overall lower tobacco smoking prevalence and the trend towards less daily cigarette consumption in the Hispanic population may partly explain the lower risk of mortality in patients with NSCLC [24] and also the explanation for the higher proportion of adenocarcinoma NSCLC subtype [25]. Interestingly, a multiethnic cohort study showed that smoking-associated lung cancer risk was higher in NHWs compared with Hispanics, even after matching for cigarette consumption implicating genetic predisposition [26,27].

Studies have reported higher epidermal growth factor receptor (*EGFR*) (26–48%) and lower *KRAS* (14–16%) mutation frequencies in Hispanics [28–31]. The identification of driver mutations like *EGFR* has led to the development of targeted therapy in NSCLC that has significantly improved the survival of patients with metastatic disease [32]. Also, a higher response rate has been reported in Mexican–Hispanic patients with *EGFR*-mutated NSCLC treated with erlotinib, particularly those who had wood-smoke exposure [33]. Although currently there is no approved therapy directed against *KRAS*, mutated status has been associated with a worse prognosis [34]. In contrast, the frequencies of *EGFR* and *KRAS* mutation are approximately 20% and 27% in the NHWs, respectively [31,35,36].

Moreover, in our study Hispanics had better overall survival outcomes in early-stage lung cancers treated with curative intent. Studies with competing risk analysis have suggested that this may be due to an increased risk of mortality in

Table 3. Median Survival Time (mOS) and 5-y Overall Survival (OS) Rate of Non-Small Cell Lung Cancer in Non-Hispanic Whites and Hispanics Stratified by Stage.

	Non-Hispanic Whites		Hispanics		
Stage	mOS, mo (95% CI)	5-y OS (%)	mOS, mo (95% CI)	5 y OS (%)	*p* value
I	58.5 (57.9–59.0)	49.1	Not reached	58.6	<0.001
II	32.2 (31.6–32.8)	34.1	39.3 (35.5–46.3)	40.9	<0.001
III	15.8 (15.6–16.0)	16.6	19.5 (18.0–20.8)	23.1	<0.001
IV	5.4 (5.3–5.5)	4.1	7.1 (6.7–7.4)	8	<0.001
Overall	15.9 (15.8–16.0)	22.8	17.9 (17.1–18.5)	26.7	<0.001

Note. CI = confidence interval; mo, month; y = year.

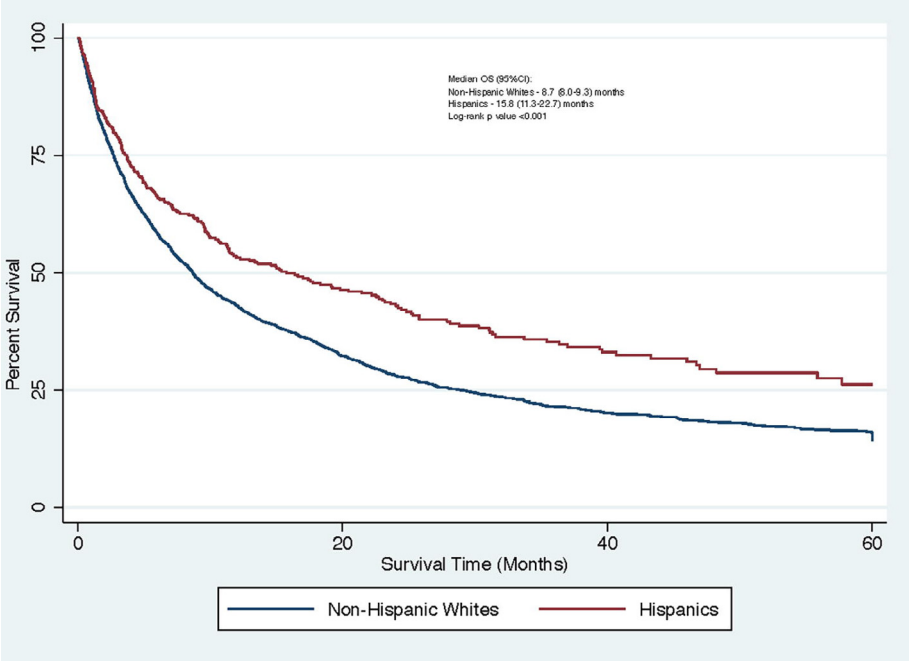

Fig. 3. Kaplan-Meier estimates of overall survival in Hispanics versus Non-Hispanic Whites in the lowest socioeconomic group (uninsured, lowest income, and education quartile). CI = confidence interval; mo = month; OS = overall survival.

NHWs from causes like a cardiovascular and pulmonary disease rather than lung cancer itself [37,38]. Other studies have pointed toward the genomic profile of Hispanics as a possible contributing factor [39,40].

The concept of healthy migration and "Salmon bias" postulates that there is a selective pressure on the healthier population to migrate to the United States and the sick patients tend to migrate back to their native countries, respectively [41]. The return

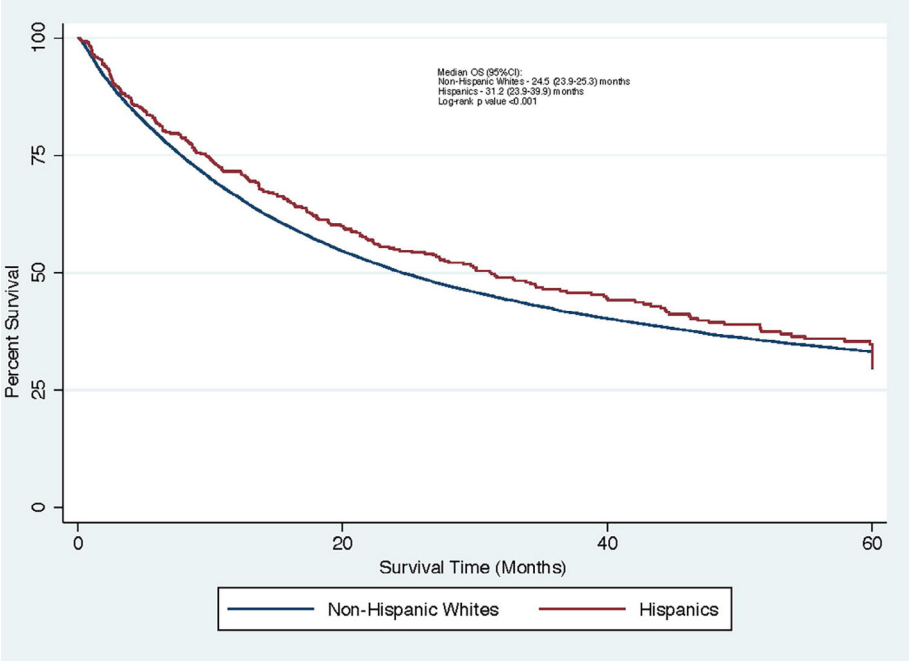

Fig. 4. Kaplan-Meier estimates of overall survival in Hispanics versus Non-Hispanic Whites in the highest socioeconomic group (private insurance, highest income, and education quartile).

of patients to their native country after diagnosis may lead to incomplete death ascertainment. One study using the California Cancer Registry has shown better NSCLC survival outcomes in the foreign compared with the U.S.-born Hispanic population [14]. Acculturation with the adaptation of high-risk habits like increase in smoking, obesity, alcohol consumption, dietary changes, and a decrease in physical activity in the U.S.-born Hispanics likely plays a role in this survival difference and further highlights the impact of these factors on health outcomes [42–44]. Although, this migration pattern may contribute to, but does not completely explain the better health outcomes of Hispanics in the United States [41].

Regarding dietary habits, of particular interest is the fact that there could be an up to five times higher yearly consumption of legumes among Hispanics. Legumes may decrease systemic inflammation that has been linked to susceptibility to chronic obstructive pulmonary disease and lung cancer [45].

Limitations of this study include the unavailability of variables like the country of birth, smoking status, driver mutations, detailed comorbidities, and performance status that may affect the NSCLC survival outcomes. Details about systemic therapy like the use of target and immuno therapies were also unavailable. Patient-level income and education along with other social determinants of health are not available. Also, the NCDB does not report recurrence-free or cancer-specific survival. The NCDB is not a population-based database and includes only patients treated at Commission on Cancer designated programs that tend to have more cancer care services and are in urban locations [46]. Of note, it is important to point out that Hispanics are a very heterogeneous population due to several different ethnic origins (e.g., Mexicans, Puerto Ricans, and Cubans, etc.) that were not accounted for in this study. There are significant health, social, and cultural differences amongst these nativities that may impact health outcomes [47].

The Hispanic population is one of the most rapidly growing in the United States and is projected to be 29%—more than one-quarter of the U.S. population by 2060 [1]. Although the Hispanic ethnicity appears to be associated with better NSCLC survival in the United States, there are significant health inequalities. The Hispanic survival advantage is likely the result of complex interactions amongst several physical, social, genomic, and environmental factors. Future studies must attempt to elucidate these factors to not only improve cancer survival in Hispanics, but also to integrate modifiable prognostic factors in the care of the general population. With precision medicine reshaping the field of oncology, focusing on the genomic profile of NSCLC in the minority populations that are underrepresented in clinical trials is essential to advance care in these populations.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hemonc.2021.02.004.

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