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Survival Disparities from Soft-Tissue Sarcoma in Hispanic Subpopulations

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Abstract

Background: Although ethnic Hispanics originate from diverse, global communities, clinical investigations rarely explore the health of distinct subpopulations. Cancer is the leading cause of death for Hispanics worldwide. The impact of soft-tissue sarcomas (STS) in particular lack description, limiting prognostic insight at a clinical level. To our knowledge, this study is the first to analyze outcomes from STS among Hispanic subpopulations. Aims and Objectives: To conduct a multivariate survival analysis comparing all-cause and malignancy-related outcomes of STS patients based off: 1. Ethnicity, 2. Hispanic subpopulation of origin. Study Design: Retrospective Cohort Study. Setting: National cancer database analysis performed at UTMB Galveston. Materials and Methods: Adults diagnosed with primary STS between 1973-2015 reported within the Surveillance, Epidemiology and End Results database were studied. Demographic, tumor characteristic, treatment and survival data were extracted. Statistical Analysis: All-cause and malignancy-related survival were compared via multivariate cox regression. All models were adjusted for demographic, tumor characteristic and treatment variables and designated non-Hispanics as the reference group. Results: 98,469 patients with a mean follow-up of 73.33 months (SD, 90.78) were included. Multivariate analysis of ethnicity found that Hispanics had a significantly lower all-cause mortality risk (HR, .941; $p < .001$) and malignancy-related mortality risk (HR, .950; $p = .002$) compared to non-Hispanics. However, multivariate analysis of subpopulations found that 'Cuban' (HR, 1.256; $p = .008$) and 'other Spanish origin including Europe' (HR, 1.361; $p < .001$) groups had a significantly higher all-cause mortality risk compared to non-Hispanics. 'Cuban' (HR, 1.255; $p = .022$), 'Puerto Rican' (HR, 1.146; $p = .044$), and 'other Spanish origin including Europe' (HR, 1.377; $p < .001$) groups also had a significantly higher adjusted malignancy-related mortality risk. Conclusions: Outcomes from STS greatly differ between Hispanic communities. Research to better characterize the impact of this disease can improve identification of and care for communities experiencing a disparate disease burden.

Keywords: Soft-tissue Sarcoma, Hispanic, Survival, Ethnicity, SEER, Cancer, Oncology.

INTRODUCTION

Hispanics are a heterogenous ethnic group that are projected to represent 25% of the United States population by 2050.[1] They are a diverse group originating from several distinct communities across the globe. Despite this diversity, most clinical investigations examine ethnic Hispanic health as a whole, with minimal consideration of the subpopulation from which they originate.

Cancer is the leading cause of death for ethnic Hispanics worldwide.[2] More recently, findings from multiple cancer studies show that outcomes can vastly differ between Hispanic subpopulations. Soft-tissue sarcomas (STS) are a rare group of cancers that arise from musculoskeletal and connective tissue. The wide variability of clinical manifestations, genetic features and histologic characteristics create obstacles to treatment and prognostic assessment of patients with the disease.[3-4] The precise etiology of STS is poorly understood, with a short list of risk factors identified including family cancer syndromes, prior radiotherapy, and carcinogen exposure.[5,6]

Previous soft-tissue sarcoma research found that significant differences in incidence, survival and treatment exist based off patient race and ethnicity; these investigations led to the current notion that Hispanic STS patients have a lower disease-specific mortality risk compared to non-Hispanic patients.[7-9] Limited research has expanded upon these findings and no study to date has analyzed STS outcomes for distinct Hispanic subpopulations; this analysis is necessary to truly characterize the impact of these malignancies on

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Hispanic communities and unveil potential disparities that may exist.

We conducted a multivariate survival analysis to assess the role of ethnicity and subpopulation of origin in outcomes of STS patients within the Surveillance, Epidemiology, and End Results (SEER) database.

MATERIALS AND METHODS

Ethical Statement

The UTMB Institutional Review Board (IRB) Chairman or designee reviewed this project on December 6, 2018 and determined that this submission did not meet the definition of, "human subject research", as defined by the regulations at 45 CFR46.012 (d)(f) and at 21 CFR 56, Therefore, this study of publicly available data did not require IRB approval or oversight.

Study Cohort

Malignant STS cases between 1973-2015 were extracted from the National Cancer Institute's SEER database for retrospective analysis. 126,026 cases of malignant STS were identified using the site recode selection "5 Soft Tissue Sarcomas". Only primary tumors (107,463/126,017) were selected for the study. Amongst these cases, only those with sufficient survival data were analyzed (105,448/107,454). Cases with known survival months and a specified cause-specific death classification of "alive or dead of other cause" or "dead due to this diagnosis" were considered to have sufficient survival data. Individuals of all NAACCR Hispanic Identification Algorithm (NHIA) derived origins with the exception of "NHIA Surname Only" were included (103,694/105,448). This analysis included only patients age 18 years or over (98,469/105,448). The SEER registry used for data collection was titled Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973-2015 varying).[10]

Subpopulation Identification

NHIA origin classification data were used to group patients for subpopulation analysis as: 'Non-Hispanic', 'Mexican', 'Cuban', 'Puerto Rican', 'South/Central American', 'Dominican Republic', 'Other Spanish Origin including Europe' and 'Hispanic, Unspecified'.

The South/Central American group did not include Brazil. 'Hispanic, Unspecified' referred to Hispanic patients with no other specification of origin.

Covariate Data

Demographic, tumor descriptor and treatment data were extracted for all cases. Sociodemographic variables included were age, sex, race marital status and *county-attributed median family income. Tumor descriptive variables included tumor type, grade, summary stage, laterality and total number of in situ/malignant tumors. Treatment variables included use of surgery, use of radiation and use of chemotherapy.

*the SEER database does not report individual socioeconomic data for patients therefore county-level descriptors were used to gauge socioeconomic status.

Statistical Analysis

Descriptive statistical analysis of sociodemographic, tumor and treatment data were performed to determine subpopulation characteristics. Multivariate cox regression analysis was used to compare all-cause and malignancy-related mortality risk based off ethnicity (Hispanics vs non-Hispanics). Multivariate cox regression analysis was then used to compare all-cause and malignancy-related mortality risk based off subpopulation of origin. Non-Hispanics served as the reference group for all cox regression analyses performed. All multivariate analyses adjusted for the following covariates: age, sex, race, marital status, county-attributed median family income, tumor type, grade, summary stage, laterality, total number of in-situ/malignant tumors, use of surgery, use of radiation and use of chemotherapy.

RESULTS

Cohort Description

98,469 patients met the inclusion criteria. Mean follow-up time for the cohort was 73.33 months (SD, 90.781). 88.9% (87,582/98,469) of the cohort identified ethnically as non-Hispanic, while 11.1% (10,887/98,469) identified as Hispanic. Amongst Hispanics, 31.8% (3,460/10,887) identified as "Mexican", 1.7% (180/10,887) as "Cuban", 3.9% (422/10,887) as "Puerto Rican", 11.3% (1,226/10,887) as "South/Central American". 3.5% (382/10,887) as "other Spanish origin (including Europe)" and 47.5% (5,173/10,887) as "Hispanic, Unspecified". Sociodemographic, tumor and treatment characteristics of subpopulations are presented in tables 1-3, respectively.

Table 1: Sociodemographic Characteristics of Cohort Based off Subpopulation of Origin

		Subpopulation of Origin						
		NH	MX	CB	DR	PR	SCA	OSO
		N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)
Age	18-39 Years Old	21661 (25.0)	1319 (38.1)	38 (21.0)	14 (31.8)	143 (34.0)	435 (35.5)	114 (29.8)
	40-59 Years Old	30697 (35.0)	1336 (38.6)	71 (39.0)	20 (45.5)	166 (39.0)	496 (40.5)	121 (31.7)
	60+ Years Old	35224 (40.0)	805 (23.3)	71 (39.0)	10 (22.7)	113 (27.0)	295 (24.0)	147 (38.5)
Sex	Female	35786 (41.0)	1364 (39.4)	45 (25.0)	19 (43.2)	162 (38.0)	522 (42.6)	132 (34.6)
	Male	51796 (59.0)	2096 (60.6)	135 (75.0)	25 (56.8)	260 (62.0)	704 (57.4)	250 (65.4)
County-Attributed Median Family Income	$22,500-$64,820	29756 (34.0)	1960 (56.6)	92 (51.0)	11 (25.0)	70 (17.0)	659 (53.8)	237 (62.0)
	$64,821-$88,550	30943 (35.0)	922 (26.6)	34 (19.0)	19 (43.2)	195 (46.0)	222 (18.1)	91 (23.8)
	$88,551-$132,070	26842 (31.0)	578 (16.8)	54 (30.0)	14 (31.8)	157 (37.0)	345 (28.1)	52 (13.6)
	Unknown	41 (< 0.10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

Table 1 Footnotes: NH, non-Hispanic; MX, Mexican; CB, Cuban; DR, Dominican Republic; PR, Puerto Rico; SCA, South/Central American; OSO, Other Spanish Origin including Europe; N%, Valid Percent.

Table 2: Tumor Characteristics of Cohort Based off Subpopulation of Origin

		Subpopulation of Origin						
		NH	MX	CB	DR	PR	SCA	OSO
		N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)
Tumor Type	Fibromatous neoplasm	19933 (22.8)	480 (13.9)	25 (13.9)	6 (13.6)	55 (13.0)	165 (13.5)	59 (15.4)
	Rhabdomyosarcoma	1620 (1.8)	94 (2.7)	2 (1.1)	0 (0.0)	11 (2.6)	31 (2.5)	7 (1.8)
	Specified (excluding Kaposi)	36867 (42.1)	1497 (43.3)	57 (31.7)	26 (59.1)	156 (37.0)	512 (41.8)	147 (38.5)
	Kaposi sarcoma	18291 (20.9)	994 (28.7)	73 (40.6)	6 (13.6)	149 (35.3)	380 (31)	121 (31.7)
	Unknown	10871 (12.4)	395 (11.4)	23 (12.8)	6 (13.6)	51 (12.1)	138 (11.3)	48 (12.6)
Total # of in-situ/malignant tumors	1	78527 (89.7)	3191(92.2)	163 (90.6)	39 (88.6)	395 (93.6)	1094 (89.2)	346 (90.6)
	2+	9055 (10.3)	269(7.8)	17 (9.4)	5 (11.4)	27 (6.4)	132 (10.8)	36 (9.4)
Grade	Grade I	7476 (8.5)	265 (7.7)	11 (6.1)	11 (25.0)	26 (6.2)	90 (7.3)	29 (7.6)
	Grade II	7727 (8.8)	304(8.8)	6 (3.3)	1 (2.3)	24 (5.7)	97 (7.9)	35 (9.2)
	Grade III	8791 (10.0)	294 (8.5)	26 (14.4)	5 (11.4)	49 (11.6)	147 (12.0)	54 (14.1)
	Grade IV	12243(14.0)	639(18.5)	26 (14.4)	8 (18.2)	52 (12.3)	189 (15.4)	33 (8.6)
	Unknown	51345 (58.6)	1958(56.6)	111 (61.7)	19 (43.2)	271 (64.2)	703 (57.3)	231 (60.5)
Summary Stage	Local	22574 (25.8)	1057(30.5)	37 (20.6)	22 (50.0)	91 (21.6)	344 (28.1)	48 (12.6)
	Regional Extension	5668 (6.5)	304(8.8)	13 (7.2)	6 (13.6)	34 (8.1)	114 (9.3)	25 (6.5)
	Regional Node	838 (1.0)	62(1.8)	1 (0.6)	0 (0.0)	3 (0.7)	30 (2.4)	7 (1.8)
	Regional Extension + Regional Node	519 (0.6)	39(1.1)	0 (0.0)	1 (2.3)	4 (0.9)	17 (1.4)	1 (0.3)
	Regional (NOS)	26 (0.0)	1(0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Distant	5531 (6.3)	362(10.5)	18 (10.0)	5 (11.4)	40 (9.5)	106 (8.6)	20 (5.2)
	Unknown	52426 (59.9)	1635(47.3)	110 (61.1)	10 (22.7)	250 (59.2)	615 (50.2)	281 (73.6)

Table 2 Footnotes: NH, non-Hispanic; MX, Mexican; CB, Cuban; DR, Dominican Republic; PR, Puerto Rico; SCA, South/Central American; OSO, Other Spanish Origin including Europe; N%, Valid Percent; #, Number; NOS, not otherwise specified.

Table 3: Treatment Characteristics of Cohort Based off Subpopulation of Origin

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		Subpopulation of Origin						
		NH	MX	CB	DR	PR	SCA	OSO
		N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)	N (N %)
Surgery	Yes	59644 (68.1)	2071 (59.9)	86 (47.8)	33 (75.0)	242 (57.4)	754 (61.5)	219 (57.3)
	No	26671 (30.5)	1352 (39.1)	92 (51.1)	10 (22.7)	163 (38.6)	450 (36.7)	159 (41.6)
	Unknown	1267 (1.4)	37 (1.1)	2 (1.1)	1 (2.3)	17 (4.0)	22 (1.8)	4 (1.1)
Radiation	Yes	24752 (28.3)	1066 (30.8)	45 (25.0)	13 (29.5)	121 (28.7)	373 (30.4)	140 (36.6)
	No/Unknown	62830 (71.7)	2394 (69.2)	135 (75.0)	31 (70.5)	301 (71.3)	853 (69.6)	242 (63.4)
Chemotherapy	Yes	17951 (20.5)	1053 (30.4)	51 (28.3)	8 (18.2)	111 (26.3)	323 (26.3)	85 (22.3)
	No/Unknown	69631 (79.5)	2407 (69.6)	129 (71.7)	36 (81.8)	311 (73.7)	903 (73.7)	297 (77.7)

Table 3 Footnotes: NH, non-Hispanic; MX, Mexican; CB, Cuban; DR, Dominican Republic; PR, Puerto Rico; SCA, South/Central American; OSO, Other Spanish Origin including Europe; N%, Valid Percent.

Table 4: Multivariate Survival Analysis Based off Subpopulation of Origin

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		Overall Survival		Malignancy-Related Survival	
	Origin	HR (95% CI)	*p*	HR (95% CI)	*p*
Adjusted Mortality-Risk	NH	ref	ref	ref	ref
	MX	0.926 (.881,.972)	0.002	0.938 (.889,.991)	0.021
	CB	1.256 (1.060,1.487)	0.008	1.255 (1.034,1.523)	0.022
	DR	0.553 (.277,1.106)	0.094	0.417 (.173,1.002)	0.05
	PR	1.099 (.976,1.238)	0.119	1.146 (1.004-1.309)	0.044
	SCA	0.868 (.801,.941)	0.001	.904 (.827,.988)	0.026
	OSO	1.361 (1.214,1.527)	< .001	1.377 (1.207,1.571)	< .001
	HP (NOS)	0.911 (.874,.949)	< .001	0.908 (.866,.952)	< .001

Table 4 Footnotes: HR, hazard ratio; CI, confidence interval; NH, non-Hispanic; MX, Mexican; CB, Cuban; DR, Dominican Republic; PR, Puerto Rico; SCA, South/Central American; OSO, Other Spanish Origin including Europe; HP, Hispanic; NOS, not otherwise specified; p, p-value.

Multivariate Survival Analysis - Ethnicity

Upon multivariate analysis, both overall and malignancy-related survival significantly differed based off ethnicity. Hispanic STS patients had a significantly lower all-cause mortality risk (HR, .941; 95% CI .915, .969; p < .001) compared to non-Hispanics. Hispanics also had a significantly lower malignancy-related mortality risk (HR, .950; 95% CI .919, .981; p = .002) compared to non-Hispanics.

Multivariate Survival Analysis – Subpopulation of Origin

Upon multivariate analysis both all-cause mortality risk (p < .001) and malignancy-related mortality risk (p < .001) significantly differed based of subpopulation of origin. Adjusted all-cause and malignancy-related hazard ratios are displayed in table 4.

DISCUSSION

Our multivariate analysis comparing survival based off ethnicity found that all-cause (p < .001) malignancy-related (p = .002) mortality significantly differed between Hispanics and non-Hispanics. These results are consistent with those of prior research, which had found that Hispanics had a 15% lower risk of death compared to non-Hispanic Whites via multivariate analysis. The phenomena described as the Hispanic paradox may account for the observation of slightly better overall and cause-specific survival for Hispanics compared to non-Hispanics.[11] This phenomenon refers to patterns of comparable or better health outcomes among Hispanics compared to non-Hispanic Whites despite disparities in factors such as socioeconomic status. Without an analysis of subpopulations, it would be unclear whether the occurrence of this phenomena could be attributed to some subgroups rather than all subgroups. Interestingly, our multivariate analysis of subpopulations found that all-cause (p < .001) and malignancy-related (p < .001) mortality-risk also between subgroups of different origin. All-cause mortality risk was significantly lower in Mexican and South/Central Americans compared to non-Hispanics, suggesting that the Hispanic paradox applies to these communities only. Conversely, 'other Spanish origin including Europe' and Cubans both had a significantly higher all-cause mortality-risk compared non-Hispanics. Cuban, Puerto Rican and 'other Spanish origin including Europe' subgroups all had a significantly higher malignancy-related mortality risk compared to non-Hispanics, while Mexicans and South/Central Americans were found to have a significantly lower malignancy-related mortality risk. Results from previous subpopulation studies of different cancers found similar survival patterns as our analysis, with lower mortality rates in Mexicans, and higher mortality rates in Cubans and Puerto Ricans.[12-14] Another study examining cancer-related death in Hispanics similarly found that mortality rates were generally lower for Dominicans and South/Central Americans.[15]

The majority of health-related research study Hispanics as a single group; our results suggest that this approach leads to less effective characterizations as they may only apply to certain Hispanic communities.

There may be multiple explanations for why notable health differences exist between Hispanic communities. Homburger et al. found significant genetic variations among Latinos through a large study using genome-wide SNP data.[16] One study assessing genetic contributions to breast cancer development in Hispanic women found that the presence of protective variants differed by origin.[17] Soft-tissue malignancies are strongly linked to genetic cancer syndromes, therefore genetic variability amongst Hispanics may play a role in the differences observed. Sociocultural differences between communities may influence exposure to modifiable risk factors. One large retrospective study found that modifiable risk factors account for 45.1% of cancer deaths across all populations and tumor types; multiple studies have also shown that modifiable factors such as smoking, obesity and participation in cancer screening differ between Hispanic communities.[19-21] For instance, a national cancer report found that Cubans had higher smoking rates compared to other Hispanic groups whereas Puerto Ricans and Mexicans were least likely to smoke.[19] However, studies also found that heavy tobacco use and/or alcohol use behaviors are more common amongst Cubans and Puerto Ricans.[22,23] Such differences can lead to variability in overall health and subsequent outcomes from disease.

The present study had several limitations. Given that our analysis was conducted using a national database, we were confined to the variables provided by SEER, and therefore could not account for factors such as migration history or past medical history. Also, the retrospective nature of this study could have limited the identification other potential confounders that were not reported as variables within the database. However, our study provides value as an initial investigation of comparative outcomes from STS amongst Hispanic subpopulations in the United States. Future studies should explore such factors and their potential role as confounders to the survival differences observed. We also could not account for miscoding that may have occurred when data was recorded in the registry. Additionally, a significant number of Hispanic patients did not have any further specification of ethnic origin. To account for this, these individuals were grouped into one category when performing subpopulation survival analysis. Improved efforts to record complete demographic data for all individuals can allow better accounting for these individuals in future studies. Furthermore, individual data related to socioeconomic status was not available. For this reason, county-attributed median family income was included in our analysis as a general assessment of socioeconomic status. Data regarding tumor characteristic variables including grade and summary stage were missing for some members of the cohort and treatment variables such as use of radiation or chemotherapy were reported with limited specificity. The authors addressed these limitations by grouping missing data separately as "unknown" whenever possible, and subsequently adjusting for all variables upon multivariate survival analysis.

CONCLUSION

To our knowledge, this study is the first to assess comparative outcomes of STS in Hispanic subpopulations. Our findings suggest that although Hispanics as whole have better outcomes compared to non-Hispanics with STS, subpopulation analysis is absolutely crucial as outcomes from the disease drastically differ between specific communities. With respect to non-Hispanics, our subpopulation analysis generally showed that Mexicans and South/Central Americans with STS exhibit better survival, while Cubans, Puerto Ricans and those with European background exhibit poorer survival. Our findings are consistent with patterns in the current, although limited literature that compares outcomes from cancer between Hispanic subpopulations. As mentioned, ethnic Hispanics come from diverse communities across the globe. Despite their common ethnic identity significant genetic, environmental and sociocultural variations exist leading to distinct health risks, challenges and experiences from disease. Our investigations strongly encourage future clinical research to assess the influence of specific origin on findings and conclusions regarding the health of the Hispanic population. Specific analysis of subpopulations leads to better characterization of their unique disease burdens, improving identification of patients with a greater potential for aggressive disease. This insight can be applied by clinicians to more effectively assess the expected clinical course and prognosis of an individual patient, which in turn may influence the approach to treatment. Ultimately, better understanding the clinical and epidemiologic significance of soft-tissue sarcoma may lead to improved care for this, otherwise poorly understood, group of malignancies.

Current Knowledge

The U.S. Center for Disease Control and Prevention reports that although cancer incidence among Hispanics is roughly half that of non-Hispanics, the disease remains the leading cause of death for ethnic Hispanics worldwide. In more recent years, there has been a growing research interest to understand the health of diverse Hispanic subpopulations. The U.S. National Health Interview Survey 2010-2014 conducted by the CDC showed that health status varies widely between these subpopulations and noted the importance of considering Hispanic subgroups when examining Hispanic health. The survey reported that the Puerto Rican subgroup had a poorer health status overall, and that South/Central American subgroup had a similar to better health status when compared to non-Hispanics in the United States, consistent with findings from other studies. Soft-tissue sarcomas are a group of malignancies whose etiology is incompletely understood. However, a handful of soft-tissue sarcoma studies have shown differences in incidence, treatment and survival based off race and ethnicity, providing valuable clinical knowledge about these diseases. These studies have led to the current understanding that Hispanics with soft-tissue sarcoma have a lower malignancy-related mortality risk compared to non-Hispanics. Our analysis is a significant contribution to the current literature; to the authors' knowledge, our study of soft-tissue sarcomas is the first to elucidate major survival differences through a deeper analysis of Hispanic subpopulations.

Conflicts of Interest

Disclosures: The authors of this manuscript have no conflict of interest to declare.

Author Contribution

1. Talha Ayaz, BS – This author contributed to the original conception and design of the study and participated in data extraction, statistical analysis, interpretation of results and drafting of the manuscript. This author approved the final version of this manuscript for publication.

2. Shaunak Patel, BS – This author participated in literature review, interpretation of results and contributed significantly to drafting of the manuscript. This author approved the final version of this manuscript for publication.

3. Adil Shahzad Ahmed, MD - This author participated in development of the study methodology, clinical contextualization of results and revision of the manuscript critically for intellectual content. This author approved the final version of this manuscript for publication.

4. Asad Loya, BS - This author participated in development of the study methodology, assisted with data extraction and review of statistical methods. T This author approved the final version of this manuscript for publication.

5. Vinod Kumar Panchbhavi, MD, FACS - This author served as the senior author for this manuscript, providing guidance through all aspects including study conception, refinement of methodology, interpretation of data and drafting/revision of manuscript. This author approved the final version of this manuscript for publication.

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