Title: Socioeconomic disparities in survival after high-risk neuroblastoma treatment with modern therapy

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Abbreviations Key:

Abbreviation	**Full Term**
OS	Overall survival
SES	Socioeconomic status
HR	Hazard ratio
ASCT	Autologous stem cell transplant
SEER	Surveillance, Epidemiology, and End Results
ACS	American Community Survey
FPL	Federal poverty level
Cox-PH	Cox proportional hazards

Abstract:

Background: Modern therapeutic advances in high-risk neuroblastoma have improved overall survival (OS), but it is unclear whether these survival gains have been equitable. This study examined the relationship between socioeconomic status (SES) and OS in children with high-risk neuroblastoma, and whether SES-associated disparities have changed over time.

Procedure: In this population-based cohort study, children <18 years diagnosed with high-risk neuroblastoma (diagnosis at age ≥12 months with metastatic disease) from 1991-2015 were identified through the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Associations of county-level SES variables and OS were tested with univariate Cox proportional hazards regression. For a sub-cohort diagnosed after 2007, insurance status was examined as an individual-level SES variable. Multivariable regression analyses with treatment era and interaction terms were performed when SES variables reached near-significance (p≤0.1) in univariate and bivariate modeling with treatment era.

Results: Among 1,217 children, 2-year OS improved from 53.0±3.4% in 1991-1998 to 76.9±2.9% in 2011-2015 (p<0.001). In univariate analyses, children in high-poverty counties (hazard ratio [HR]=1.74, 95% confidence interval [CI]=1.17-2.60, *p*=0.007), and those with Medicaid (HR=1.40, 95% CI=1.05-1.86, *p*=0.02) experienced an increased hazard of death. No interactions between treatment era and SES variables were statistically significant in multivariable analyses, indicating that differences in the OS between SES groups did not change over time.

Conclusions: Survival disparities among children with high-risk neuroblastoma have not widened over time, suggesting equitable access to and benefit from therapeutic advances. However, children of low SES experience persistently inferior survival. Interventions to narrow this disparity are paramount.

Introduction

Neuroblastoma is the most common solid extracranial tumor in childhood, with over 600 cases diagnosed per year in the United States.[1] High-risk neuroblastoma is associated with significant risk of relapse and death. However, advances in treatment for children with high-risk disease have led to impressive increases in survival over recent decades. Patients who receive the full complement of standard of care therapy (chemotherapy, radiation, surgery, autologous stem cell transplant (ASCT), and cytokine/immunotherapy) now experience a two-year overall survival (OS) as high as 86%, a striking survival gain over two decades.[2-5]

While these therapeutic advances hold incredible potential for improved patient outcomes, they require complex and highly-intensive treatment, which may not be equally accessible to all patients. Specifically, modern high-risk neuroblastoma treatment is typically delivered at large referral centers that have the capacity to provide ASCT, cytokine/immunotherapy, and advanced supportive care measures. This treatment lasts for around 18-months and includes multiple inpatient admissions. The adoption of centralized, intensive, and prolonged treatment as a modern standard of care may exacerbate existing disparities based on geographic distance from referral centers, differential or biased clinical trial enrollment, and/or family ability to adhere to treatment demands; all of which

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may cumulatively result in unequal survival gains benefitting children of higher socioeconomic status.[6-8]

A recent analysis of a heterogeneous population of patients with childhood cancer identified through the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database demonstrated that SES significantly mediated racial and ethnic survival disparities for a number of cancer diagnoses including neuroblastoma.[9] This high-level analysis identified the applicability of SES to survival outcome disparities in pediatric cancer but did not examine disease-specific risk groups to differentiate outcome disparities due to stage versus SES-related access disparities. Other specific analyses of neuroblastoma cohorts have identified poverty as an independent risk factor for relapse and death and have found that minority patients have higher prevalence of high-risk disease.[10,11] However, these analyses were restricted to patients enrolled on clinical trials. This poses limitations, given the possibility that families of lower SES and without private insurance may have more difficulty accessing and participating in trials and experimental therapies. The SEER database, as a national population-based registry, mitigates this limitation. Our specific aims for this study were to: (1) describe differences in OS among patients with high-risk neuroblastoma by individual- and county-level SES characteristics; and (2) investigate whether changes in OS over time in patients with high-risk neuroblastoma differ by these characteristics.

Methods:

Selection of Study Population

The analytic cohort was selected using individual- and population-based cancer registry data from the National Cancer Institute's SEER database using SEER*STAT 8.3.4 (Washington, D.C.). Pediatric patients (age <18 years) diagnosed with neuroblastoma from January 1, 1991 through December 31, 2015 were selected to allow for a minimum of 2-year follow-up at the time of SEER 8.3.4 release.[12] To approximate characteristics of high-risk (stage M) neuroblastoma according to the International Neuroblastoma Risk Group staging system used in most neuroblastoma clinical trials,[13] we restricted the analyses to patients with distant metastases and age ≥12 months at time of diagnosis. Based on data availability, for patients diagnosed from 1991-1992, we used the SEER-9 Registries; for patients diagnosed from 1992-2000, we used the SEER-13 Registries; for patients diagnosed from 2000 onwards, we used the SEER-18 Registries.[14] Geographic distribution varies depending on era, with the most recent/expansive registries (SEER-18) covering approximately 28% of the U.S. population and including 18 geographic registries (Native Alaska; Connecticut; Detroit, Michigan; Atlanta, Georgia; rural Georgia; greater Georgia excluding the two previous regions; San Francisco-Oakland, California; San Jose-Monterey, California; Los Angeles, California; California excluding the previous metropolitan areas; Hawaii; Iowa; Kentucky; Louisiana; New Mexico; New Jersey; Seattle-Puget Sound, Washington; Utah). Representative of the demographics of the entire U.S. population, this broad coverage allows SEER to account for diverse populations throughout the U.S., including 66.5% of Native Hawaiian/Pacific Islanders, 50.4% of Asians, 38.4% of Hispanics, 30.6% of American Indian/Alaska Natives, 24.9% of whites, and 25.6% of Black residents.[15] The study was deemed exempt from review by the Dana-Farber Cancer Institute's Institutional Review Board (DFCI protocol 18-409).

Measures of Socioeconomic Status

We examined measures of SES at the county level for the entire cohort, and at the individual level for a sub-cohort of patients. SEER includes county-level variables from the American Community Survey (ACS) County Attributes data.[16] County-level variables were determined based on the patient's residency county code at diagnosis. SEER utilizes ACS data based on the cancer case/year of diagnosis. County-level measures of SES were chosen a priori based on previous SEER analyses and disparities literature.[17-19] We included county-based poverty (proportion of households living below the federal poverty level (FPL)), educational attainment (proportion of individuals in county >25 years of age with less than high school education), unemployment (proportion of individuals in county >16 years of age unemployed), language isolation (proportion of households in county with no household member age ≥14 years who speaks English), and urban-rural status (population >1 million vs. population of 250,000 to 1 million vs. population <250,000). These variables were defined per SEER and ACS.[20] To maximally highlight disparities should they exist, we dichotomized each county-level variable at the 90th percentile cut-point (language isolation, education, unemployment) to define low-SES and high-SES cohorts. High-poverty counties were defined as those with greater than or equal to 20% of households living below 100% FPL.[21] As a sensitivity analysis, we also analyzed county-based poverty using a cut-point at the 90th percentile.

We examined individual-level insurance data for the sub-cohort of patients for whom it was available (diagnosed from 2007 onward) in addition to county-level. Insurance status was dichotomized as any public insurance coverage (i.e. Medicaid) versus non-Medicaid insurance (those

with Medicaid as a second insurer were coded as Medicaid, per SEER database convention). Given its rarity in pediatrics, patients without documented insurance (N=14) were excluded. Patients with Medicaid insurance were a priori considered low-SES. **Supplementary Table 1** details exact SEER variable names and descriptions.

Outcome

The primary outcome was OS, derived from SEER's "Survival Months" attribute, defined as months from date of cancer diagnosis to date of death from any cause, censored at date of last contact. We used OS rather than cancer survival given its lack of ambiguity and frequency of use in oncology clinical trials,[22] and the rarity of death from non-cancer causes among children with cancer. We reported 2-year OS based on available follow-up data for our cohort at the time of analysis. Three-year OS, given its consistency with recent publications,[3,23] was included as a sensitivity analysis (**Supplementary Table 2**) for those patients with sufficient follow-up time.

Covariates

Covariates included sex, race (white, black, or other), ethnicity (Spanish/Hispanic/Latino vs. non-Spanish/non-Hispanic/non-Latino) and diagnostic treatment era. We examined race and ethnicity as distinct constructs, given prior reports of differential health outcomes according to race and/or ethnicity.[24] Treatment eras were defined based on major advances in the standard-of-care for children with high-risk neuroblastoma: 1991-1998 (early treatment era) vs. 1999-2004 (multimodal treatment including ASCT)[5] vs. 2005-2010 (improved supportive care) vs. 2011-2015

(immunotherapy)[2] to allow for exploration of the potential interaction between treatment era and SES.

Statistical analysis

Descriptive statistics were used to summarize baseline cohort characteristics. Kaplan-Meier curves of OS were generated for the overall cohort and stratified by county- and individual-level variables, as well as insurance for the post-2007 sub-cohort. OS was compared between groups using the log-rank test. Univariate Cox proportional hazards (Cox-PH) regression was used to test the association of each SES variable with OS. The proportional hazards assumption was tested by visually examining log-log plots and by testing the interaction of selected covariates with time. Our results indicated no violation of the proportional hazards assumption.

We a priori defined a stepwise procedure to evaluate the relationship between SES variables and treatment era. First, for SES variables with $p \leq 0.1$ in univariate analyses, bivariable Cox-PH regressions were performed to test the effect of each SES variable and (continuous) treatment era on OS. Second, the variables with $p \leq 0.1$ in these bivariable analyses were then included in separate multivariable models for each SES variable. Lastly, the multivariable Cox-PH regressions tested each SES variable, treatment era, and the interaction of treatment era with the SES variable. If the interaction term was statistically significant, this would provide evidence that there was a significant difference in the change in OS over time between examined SES groups.

Subjects with missing data (<2% in all measured variables) were excluded from analysis. Notably, insurance status was only available in SEER for those diagnosed after 2007. Thus, analyses of insurance were performed solely in the sub-cohort of patients diagnosed after 2007.

We performed additional multivariable regression analyses with county-level poverty, race, ethnicity, and treatment era to explore the relative contributions of these variables to survival. For the sub-cohort of patients with insurance data, we built a second multivariable model including insurance.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p-values ≤ 0.05 were considered statistically significant. The data that support the findings of this study are publicly available through SEER.[25]

Results:

Study population

The analytic cohort included 1,217 patients (**Figure 1**). 550 patients were diagnosed after 2007 and formed the sub-cohort available for analyses of insurance status. Twenty-six percent of patients were non-White race and 20% were of Spanish/Hispanic/Latino ethnicity (**Table 1**). In the post-2007

sub-cohort (those for whom insurance data were available), 61% (338/550) were insured by Medicaid.

Univariate analysis of SES factors and treatment era with OS

Median follow-up was 6.08 years [range=0-24.92 years]. OS improved by treatment era (p<0.001) with 2-year OS (±standard error) increasing from 53.0±3.4% to 76.9±2.9% between 1991-1998 and 2011-2015 (**Figure 2**). In univariate analysis of OS (**Table 2**), increased hazard of death was seen in patients in high-poverty counties (≥20% of households below 100% FPL) compared to those in low-poverty counties (hazard ratio [HR]=1.74, 95% confidence interval [CI]=1.17-2.60, p=0.007). No other county-level SES factors were found to be statistically significant. In the post-2007 sub-cohort, individuals with any Medicaid experienced increased hazard of death compared to those with other insurance (HR=1.40, 95% CI=1.05-1.86, p=0.02).

Multivariable analysis of change in OS by SES factors over time

In multivariable analysis, we included the SES variables that were near significant in bivariable analysis (p≤0.1), treatment era, and the specific SES*treatment era interaction to assess whether SES-associated hazard ratio for OS changed over time. A separate model was created for each SES variable. As displayed in **Figure 3**, the SES*treatment era interaction is not statistically significant for either Spanish/Hispanic/Latino ethnicity (interaction p=0.800) or higher county-based poverty (interaction p=0.923), indicating that the SES-associated survival hazard did not change significantly over time.

166

167 *Sensitivity analyses*

168 A sensitivity analysis using the 90th percentile as a cut-point to define a high-poverty county, while
169 not statistically significant, did not differ greatly from the primary analysis (HR=1.15, 95% CI=0.89-
170 1.49, p=0.27). In multivariable modeling, the interaction between treatment era and county-level
171 poverty using this cut-point was similarly not statistically significant (p = 0.45). Additional sensitivity
172 analyses considering 3-year OS for the patients with sufficient follow-up time (N=1156) are included
173 in **Supplementary Table 2** and demonstrate similar findings to our primary analyses.

174

175 *Multivariable analyses including race and ethnicity in the model*

176 In a multivariable regression model for the entire cohort considering county-based poverty, race,
177 ethnicity, and treatment era, there was an increased hazard of death associated with higher county-
178 based poverty (HR=2.08, p<0.001, **Table 3**) and a lower hazard of death associated with later
179 treatment era (HR=0.78, p<0.001). Race and ethnicity were not significantly associated with survival.

180

181 In the post-2007 sub-cohort, higher county-based poverty (HR=2.38, p=0.001) and any Medicaid
182 insurance (HR=1.38, p=0.04) were statistically significantly associated with increased hazard of
183 death. Race, ethnicity, and treatment era were not statistically significant. Treatment era was
184 included in this second model for consistency although this sub-cohort notably only includes
185 patients diagnosed after 2007, limiting power of this analysis.

Discussion:

In a representative population of U.S. children with high-risk neuroblastoma, children living in high-poverty counties experienced a 74% increased hazard of death compared to those living in low-poverty counties. In a sub-cohort of children with available insurance data, those with any Medicaid insurance experienced a 40% increased hazard of death compared to those with other insurance. As reported elsewhere[4], OS for the entire cohort improved steadily over time (from 53% to 77%). Notably, while SES-related survival disparities persisted over time, they did not widen, despite a shift to a modern standard of care which includes highly-centralized and intensive therapy.

Our data build on prior work identifying SES-associated survival disparities in children with high-risk neuroblastoma treated on clinical trials[11] by investigating whether outcome disparities have increased with advances in care. This question is highly pertinent in the current era when the dual potential of precision medicine to improve outcomes while simultaneously worsening health disparities if these advances are not delivered equitably must be considered.[26-28] Our data demonstrate that despite a shift to a standard of care requiring resource-intense and highly centralized treatment, existing SES-associated disparities have not worsened. Although analyses of this cohort are limited by absence of patient-level treatment data in the SEER database, the equitable survival gains across all groups over time are encouraging and stand in contrast to widening disparities observed in other populations (e.g. asthma, adult cancers).[29,30] These data

suggest that access to treatment advances with known survival benefits has been generally equitable among children with high-risk neuroblastoma, perhaps due to the high reliance on clinical trial enrollment and delivery of protocolized care in pediatric oncology.

We did, however, observe persistent and clinically meaningful survival disparities associated with SES. That U.S. children of lower SES with high-risk neuroblastoma continue to die at higher rates than their higher SES counterparts must also be highlighted.[11] Despite focused policy statements and advocacy efforts identifying poverty as a major determinant and predictor of adverse health outcomes in children, these data demonstrate no improvements in this area over time. Recent studies in other cancer populations have similarly found insurance and neighborhood (i.e. county-based) poverty to be predictors of inferior outcomes.[31,32]

Of note, children with high-risk neuroblastoma receive intensive (largely inpatient) treatment for 18-months at specialized, tertiary care centers. Therefore, this population is in many ways optimally positioned to minimize disparities in care. Our finding that survival disparities persist even in this population suggests that there may be other fundamental mechanisms driving SES-related gaps, warranting exploration of mechanisms beyond access to care. Non-adherence to chemotherapy is a mechanism leading to disparate outcomes that has been well-described in pediatric acute lymphoblastic leukemia (ALL).[33,34] Future work could investigate if there are similar findings in high-risk neuroblastoma with outpatient GM-CSF/IL-2 and oral cis-retinoic acid. However, it is important to note that ALL treatment (which includes two years of outpatient-based therapy) contrasts sharply with the predominantly inpatient treatment of high-risk neuroblastoma. The intensity of high-risk

neuroblastoma treatment including multiple prolonged admissions may place excess and disproportionate burden on lower SES families who may have fewer resources for childcare, missed work/compensation, and household material needs. Whether access to relapse therapies, which are similarly intensive, is inferior in families of lower SES, leading to earlier death following relapse, should be investigated. Promising SES-focused interventions are being developed across various healthcare settings to address potential mechanisms underlying observed disparities. Examples include systematic provision of grocery and transportation services, clinic-based screening and referrals for community-based resources for a range of basic material needs, and free clinic-embedded tax services to assist families in obtaining earned income tax credits.[35-37] Future evaluation of such interventions to improve health equity in pediatric oncology is paramount.

Our study benefits from a robust, population-based sample across more than two decades of high-risk neuroblastoma treatment, allowing for analysis of changes in survival over time. The SEER database is uniquely positioned as a population-based registry to provide disparities data as it is intentionally biased to oversample minority populations and those that have traditionally been underrepresented in clinical trials.[38] Interestingly, we did not identify racial and ethnic disparities observed in other neuroblastoma cohorts.[9,10] Importantly, our cohort differs from these previous studies in that we restricted analyses to those with high-risk disease, which is more prevalent in minority populations. As such, our data may thus reflect prior findings that inferior survival observed for Black patients compared to their white counterparts was attributable to their higher prevalence of high-risk disease at diagnosis.[10] Our data build on recent publications demonstrating that SES mediates racial and ethnic survival disparities across pediatric cancer,[9] and that low-SES is associated

with inferior survival in the context of modern-era clinical trials.[11] These disparities disproportionately impact children of racial and ethnic minority status who disproportionately live in low-SES households due to structural disadvantages and biases. We importantly find that these disparities are not, however, worsening in the modern era of complex treatment delivery. Future attention to characterizing the relationships between SES and outcomes is essential to begin to narrow the survival gap.

There are important limitations to our data. Inherent to any large registry, SEER data are limited by missing data/unrecorded variables, coding reliability, and selection bias.[39] We utilized a proxy for high-risk (stage M) neuroblastoma in the absence of histological, genetic, and staging variables in SEER. While this proxy definition approximates elements of modern staging criteria, we may have misclassified children with lower risk disease. We similarly lacked access to patient-level treatment data, though our findings are consistent with SES-associated disparities in the clinical trial setting. Finally, we had access to individual-level (insurance) SES data for only the sub-cohort of patients diagnosed after 2007, limiting our ability to consider the impact of insurance across all treatment eras. Given the magnitude of the effect of insurance status on survival, however, similar findings would be expected prior to 2007. SEER also codes patients with Medicaid-only (e.g. based on income eligibility) and Medicaid as a second-insurer identically. Consequently, some patients with Medicaid as a second insurer may have been misclassified as low-SES, an error which would bias toward the null, lending additional weight to our finding of survival disparities according to insurance status.

Our findings are important for two reasons. First, our data demonstrate that a steady shift toward highly-centralized and intensive therapy has not resulted in worsened survival disparities for children of lower-SES despite the very reasonable concern that these children may have inferior access to modern therapeutic advances. These findings suggest that the highly-centralized and structured care delivery model of pediatric oncology allows for equitable integration of novel therapies into the standard of care. They suggest a model of care that could be applied to other patient populations—in oncology and more generally—for whom such therapies and other resource-intensive treatment modalities are entering the clinical space. Second, our data demonstrate that in the 21st century, children of low-SES continue to die at higher rates than their higher-SES counterparts. In other words, disparities have not worsened, but they have certainly not improved. These data should be a call to action in an era purportedly focused on issues of equity. Future research, while continuing to aim to improve survival and decrease toxicity for all children with cancer, must also work to elucidate mechanisms underlying SES-related disparities and incorporate interventions to address social determinants of health to ensure that these gains are experienced equitably.

Conflict of Interest Disclosures: Dr. Marron receives payment for participation on the Ethics Advisory Board of Partner Therapeutics for work unrelated to this research study. The remaining authors have no relevant conflicts of interest to disclose.

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Table 1. Individual- and County-level Patient Characteristics at Diagnosis (N = 1,217)

Individual-level variables	**No. / N (%)**
Sex	
Female	505/1217 (41)
Male	712/1217 (59)
Race[1]	
White	899/1211 (74)
Black	189/1211 (16)
Other minorities[2]	123/1211 (10)
Ethnicity	
Non-Spanish/Hispanic/Latino	977/1217 (80)
Spanish/Hispanic/Latino	240/1217 (20)
Treatment era	
1991 – 1998	215/1217 (18)
1999 – 2004	310/1217 (25)
2005 – 2010	391/1217 (32)
2011 – 2015	301/1217 (25)
County-level SES variables	**Median (Range) or No. / N (%)**
% of households in county below 100% FPL	9.17 (1.42-29.17)
% of individuals in county over the age of 25 years with a less than high school degree	16.57 (3.27-50.32)
% of households linguistically isolated	5.06 (0.00-19.17)

[1] Race unavailable for 6 individuals in cohort

[2] Other minorities include Asian or Pacific Islanders (N= 114) and American Indian/Alaska Natives (N=9)

% of unemployment	7.37 (1.54-17.38)
Urban/rural status[3]	
>1 million population	795/1204 (66)
250,000-1 million population	226/1204 (19)
<250,000 population	183/1204 (15)
Post-2007 sub-cohort	**No. / N (%)**
Insurance status	
Other	212/550 (39)
Medicaid	338/550 (61)

Table 2. Univariate Analysis for Individual- and County-level Factors on Overall Survival (OS)

Prognostic Factors	**No.**	**2-Year OS ± SE (%)**	**HR (95% CI)**	***P* value**
Sex				
Female	505	68.6 ± 2.1	Reference	.66
Male	712	69.1 ± 1.8	1.04 (0.88, 1.22)	
Race				
White	899	69.3 ± 1.6	Reference	.46
Black	189	70.6 ± 3.4	0.94 (0.75, 1.18)	
Other minorities	123	62.7 ± 4.6	1.15 (0.88, 1.49)	
Ethnicity				
Non-Spanish/Hispanic/Latino	977	69.0 ± 1.5	Reference	.10
Spanish/Hispanic/Latino	240	68.4 ± 3.2	1.18 (0.97, 1.43)	

[3] Urban/rural status unavailable for 13 individuals in cohort

Treatment Era (trend)[4]				
1991 – 1998	215	53.0 ± 3.4	0.79 (0.73, 0.86)	<.001
1999 – 2004	310	69.0 ± 2.6		
2005 – 2010	391	72.9 ± 2.3		
2011 – 2015	301	76.9 ± 2.9		
% of households in county below 100% FPL				
Low poverty (<20%)	1181	69.3 ± 1.4	Reference	.007
High poverty (≥20%)	36	55.4 ± 8.6	1.74 (1.17, 2.60)	
% of individuals in county over the age of 25 years with a less than high school degree				
<90th percentile (30%)				
≥90th percentile	1115	69.0 ± 1.4	Reference	.48
	102	68.6 ± 4.6	1.10 (0.85, 1.42)	
% of households linguistically isolated				
<90th percentile (13%)	1103	68.5 ± 1.5	Reference	.85
≥90th percentile	114	73.4 ± 4.4	0.97 (0.74, 1.29)	
% of unemployment				
<90th percentile (12%)	1102	68.3 ± 1.5	Reference	.54
≥90th percentile	115	74.9 ± 4.4	0.91 (0.68, 1.22)	
Urban/rural status by population				
>1 million	795	69.5 ± 1.7	Reference	.37

[4] Continuous treatment year was used in univariate analyses. HR indicates survival gain over time. For example, there is a 21% lower hazard of survival for patients diagnosed in 1999-2004 compared to those diagnosed in 1991-1998.

250,000-1 million	226	73.2 ± 3.1	0.94 (0.76, 1.16)	
<250,000 population	183	63.6 ± 3.7	1.14 (0.91, 1.41)	
Post-2007 sub-cohort				
Insurance status				
Other	338	79.6 ± 2.3	Reference	.02
Medicaid	212	69.9 ± 3.5	1.40 (1.05, 1.86)	

Table 3. Post-hoc Multivariable Models Including Race, Ethnicity, and Treatment Era

Individual and county level variables	**Hazard Ratio**	**Adjusted *P*-value**
Entire cohort (N = 1211)[5]		
County poverty dichotomized at ≥20% of households below poverty	2.08	<0.001
Race	*Global p: 0.430*	
White	Reference	Reference
Black	0.98	0.85
Other	1.18	0.22
Spanish/Hispanic/Latino ethnicity	1.22	0.05
Treatment era	0.78	<.001
Post-2007 sub-cohort (N = 548)[6]		
County poverty dichotomized at ≥20% of households below poverty	2.38	0.001
Race	*Global p: 0.542*	
White	Reference	Reference

[5] Race unavailable for 6 individuals in cohort

[6] Race unavailable for 2 individuals in sub-cohort

Black	0.81	0.30
Other	1.07	0.81
Spanish/Hispanic/Latino ethnicity	1.07	0.72
Medicaid insurance	1.38	0.04
Treatment era	0.99	0.95

Figure Legends

Figure 1. Study Cohort

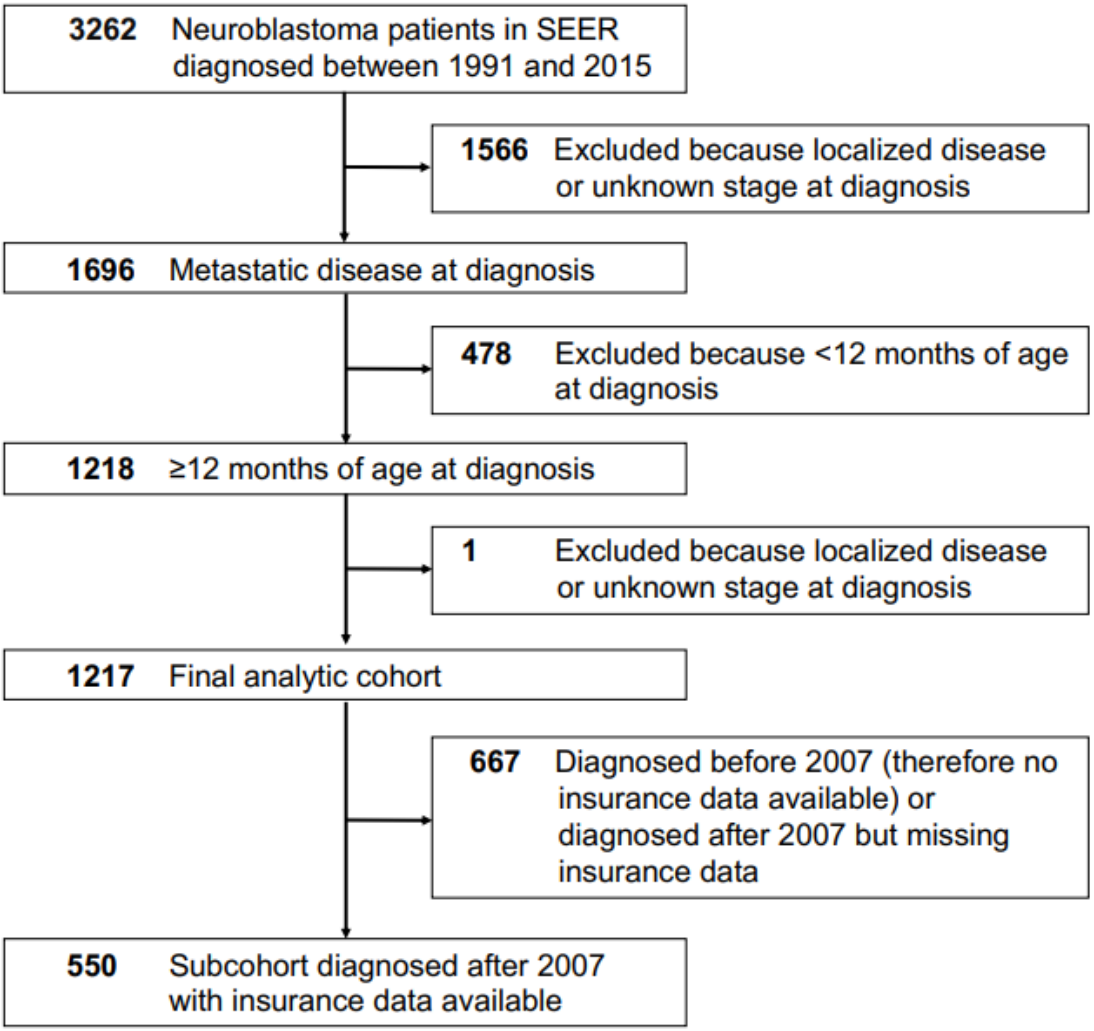


Figure 2. Kaplan Meier curves of Overall Survival (A. Overall Cohort (N=1217); B. Stratified by High- and Low-Poverty County (N=1217); C. Stratified by Insurance (post-2007 Sub-Cohort, N=550); D. Stratified by treatment era)

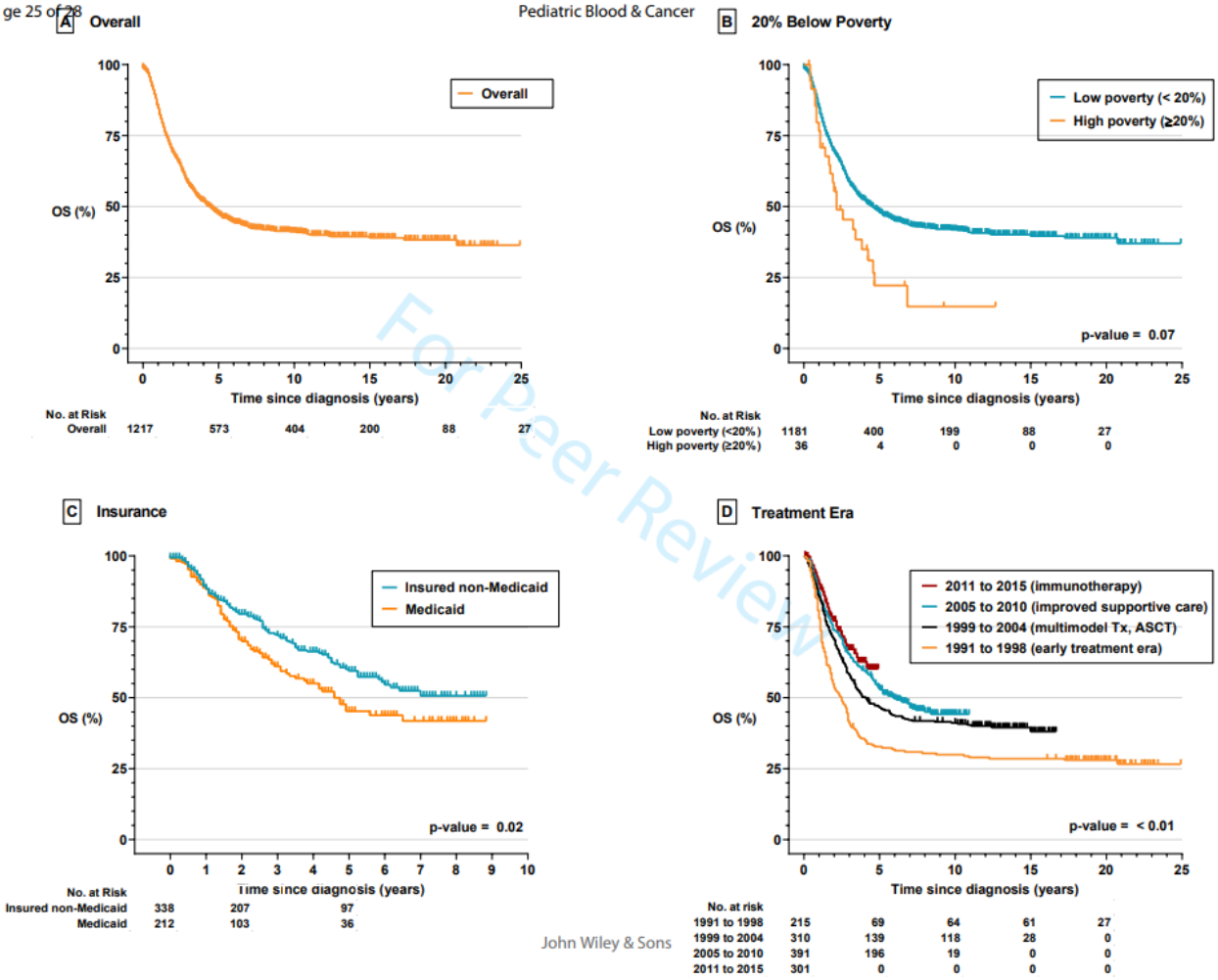
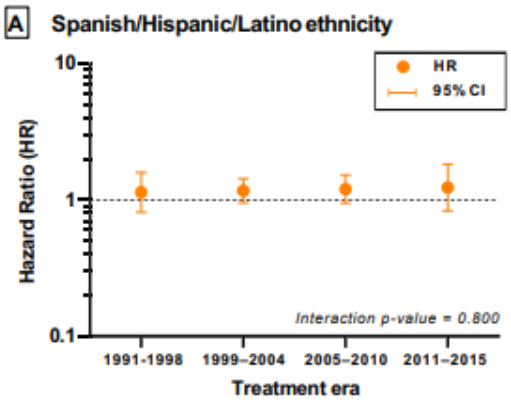
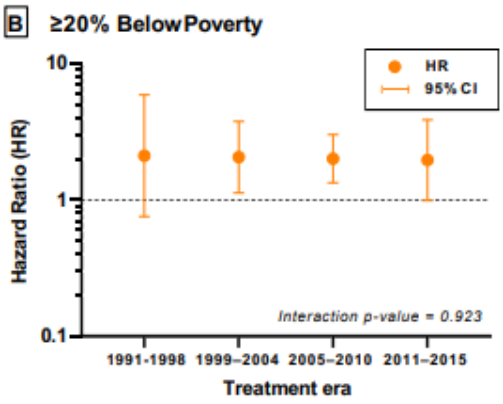


Figure 3. Hazard ratio plot with 95% CI of (A) Spanish/Hispanic/Latino ethnicity and (B) High-poverty county in multivariate analyses controlling for treatment era and SES*treatment era interaction on overall survival. Interaction p-value demonstrates the interaction effect of SES*treatment era. CI, confidence interval.



Treatment era	HR	95% CI
1991-1998	1.140	0.814-1.596
1999-2004	1.171	0.953-1.438
2005-2010	1.203	0.948-1.526
2011-2015	1.235	0.832-1.834



Treatment era	HR	95% CI
1991-1998	2.118	0.756-5.932
1999-2004	2.067	1.130-3.780
2005-2010	2.016	1.342-3.029
2011-2015	1.967	0.996-3.886