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 sought to examine the relationship between socioeconomic status (SES) and OS in children with high-risk neuroblastoma, and to investigate 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 ($p \leq 0.1$) 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 with Medicaid (hazard ratio [HR]=1.40, 95% confidence interval [CI]=1.05-1.86, p=0.02) and those in high-poverty counties (HR=1.74, CI=1.17-2.60, p=0.007) experienced an increased hazard of death. No interactions between treatment era and SES variables were statistically significant in multivariable analyses, indicating that changes in OS over time did not differ between groups.

Conclusions: Low SES is associated with inferior survival in children with high-risk neuroblastoma. Survival disparities have not widened over time, suggesting equitable access to and benefit from therapeutic advances. Interventions to narrow existing disparities 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 as high as 86%, a striking survival gain over two decades.[2-5]

While these therapeutic advances hold incredible potential for improving patient outcomes, there are critical questions of equity that must be examined given the risk of further widening disparities if these advances are disparately accessible to and/or disproportionately benefit those of higher socioeconomic status (SES). Specifically, high-risk neuroblastoma treatment typically is limited to large referral centers that have the capacity to deliver ASCT, cytokine/immunotherapy, and advanced supportive care measures. Such a shift may exacerbate disparities in access for underserved patients across the care continuum including delays in diagnosis, geographic distance from referral centers, and differential or biased clinical trial enrollment on clinical trials that may cumulatively result in unequal survival gains.[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. Our specific aims for this study were to: (1) describe differences in overall survival (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.[10] To approximate characteristics of high-risk (stage M) neuroblastoma according to the International Neuroblastoma Risk Group staging system used in most neuroblastoma clinical trials,[11] we restricted 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.[12] 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.[13] The study was deemed exempt from review by the Dana-Farber Cancer Institute's Institutional Review Board (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.[14] 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.[15-17] 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.[18] 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.[19] As a sensitivity analysis, we also analyzed county-based poverty using a cut-point at the 90th percentile.

69 We examined individual-level insurance data for the sub-cohort of patients for whom it was
70 available (diagnosed from 2007 onward) in addition to county-level. Insurance status was
71 dichotomized as any public insurance coverage (i.e. Medicaid) versus non-Medicaid insurance
72 (those with Medicaid as a second insurer were coded as Medicaid, per SEER database
73 convention). Given its rarity in pediatrics, patients without documented insurance were excluded.
74 Patients with Medicaid insurance were a priori considered low-SES. **Supplementary Table 1**
75 details exact SEER variable names and descriptions.
76
77 *Outcome*
78 The primary outcome was overall survival (OS), derived from SEER's "Survival Months"
79 attribute, defined as months from date of cancer diagnosis to date of death from any cause,
80 censored at date of last contact. We used OS rather than cancer survival given its lack of
81 ambiguity and frequency of use in oncology clinical trials,[20] and the rarity of death from non-
82 cancer causes among children with cancer. We reported 2-year OS for consistency with past
83 neuroblastoma publications.[2]
84
85 *Covariates*
86 Covariates included sex, race (white, black, or other), ethnicity (Spanish/Hispanic/Latino vs.
87 non-Spanish/non-Hispanic/non-Latino) and diagnostic treatment era. We examined race and
88 ethnicity as distinct constructs, given prior reports of differential health outcomes according to
89 race and/or ethnicity.[21] Treatment eras were defined based on major advances in the standard-
90 of-care for children with high-risk neuroblastoma: 1991-1998 (early treatment era) vs. 1999-
91 2004 (multimodal treatment including ASCT)[5] vs. 2005-2010 (improved supportive care) vs.

92 2011-2015 (immunotherapy)[2] to allow for exploration of the potential interaction between
93 treatment era and SES.
94
95 *Statistical analysis*
96 Descriptive statistics were used to summarize baseline cohort characteristics. Kaplan-Meier
97 curves of OS were generated for the overall cohort and stratified by county- and individual-level
98 variables, as well as insurance for the post-2007 sub-cohort. Overall survival was compared
99 between groups using the log-rank test. Univariate Cox proportional hazards (Cox-PH)
100 regression was used to test the association of each SES variable with OS. The proportional
101 hazards assumption was tested by visually examining log-log plots and by testing the interaction
102 of selected covariates with time. Our results indicated no violation of the proportional hazards
103 assumption.
104
105 Bi-variable Cox-PH regression was used to jointly test the effect of each SES variable with
106 (continuous) treatment era on OS, including SES variables with $p \leq 0.1$ in univariate analyses.
107 Variables with $p \leq 0.1$ in bi-variable analyses were included in multi-variable models with
108 treatment era as an interaction term to test for effect modification (i.e. any difference in change
109 in OS over time between the SES groups). Multi-variable Cox-PH regression tested the SES
110 variable, treatment era, and the interaction of treatment era with the SES variable. If the
111 interaction term was statistically significant, this would provide evidence that there was a
112 significant difference in the change in OS over time between examined SES groups.
113

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 post-hoc 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.[22]

Results:

Study population

The analytic cohort included 1,217 patients (**Figure 1**). 550 patients were diagnosed after 2007 and form 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

137 Median follow-up was 2.75 years [range=0-24.92 years]. OS improved by treatment era
138 (p<0.001) with 2-year OS (±standard error) increasing from 53.0±3.4% to 76.9±2.9% between
139 1991-1998 and 2011-2015 (**Figure 2**). In univariate analysis of OS (**Table 2**), increased hazard
140 of death was seen in patients in high-poverty counties (≥20% of households below 100% FPL)
141 compared to those in low-poverty counties (hazard ratio [HR]=1.74, 95% confidence interval
142 [CI]=1.17-2.60, p=0.007). No other county-level SES factors were found to be statistically
143 significant. In the post-2007 sub-cohort, individuals with any Medicaid experienced increased
144 hazard of death compared to those with other insurance (HR=1.40, 95% CI=1.05-1.86, p=0.02).
145

146 *Multivariable analysis of change in OS by SES factors over time*

147 In multivariable analysis, we included the SES variables that were near significant in bivariable
148 analysis (p≤0.1), treatment era, and SES*treatment era interaction. None of these interactions
149 were statistically significant (interaction p≥0.80), indicating that the changes in OS over time did
150 not differ significantly between these SES groups. Hazard ratios with 95% confidence intervals
151 are displayed in **Figure 3**.
152

153 *Sensitivity analyses*

154 A sensitivity analysis using the 90th percentile as a cut-point to define a high-poverty county,
155 while not statistically significant, did not differ greatly from the primary analysis (HR=1.15, 95%
156 CI=0.89-1.49, p=0.27). In multivariable modeling, the interaction between treatment era and
157 county-level poverty using this cut-point was similarly not statistically significant (p = 0.45).
158

159 *Post hoc multivariable analyses including race and ethnicity in the model*

160 In a multivariable regression model for the entire cohort considering county-based poverty, race,
161 ethnicity, and treatment era, there was an increased hazard of death associated with higher
162 county-based poverty (HR=2.08, p<0.001, **Table 3**) and a lower hazard of death associated with
163 later treatment era (HR=0.78, p<0.001). Race and ethnicity were not significantly associated
164 with survival.
165
166 In the post-2007 sub-cohort, higher county-based poverty (HR=2.38, p=0.001) and any Medicaid
167 insurance (HR=1.38, p=0.04) were statistically significantly associated with increased hazard of
168 death. Race, ethnicity, and treatment era were not statistically significant. Treatment era was
169 included in this second model for consistency although this sub-cohort notably only includes
170 patients diagnosed after 2007, limiting power of this analysis.
171
172 **Discussion:**
173
174 In a representative population of US children with high-risk neuroblastoma, children living in
175 high-poverty counties experienced a 74% increased hazard of death compared to those living in
176 low-poverty counties. In a sub-cohort of children with available insurance data, those with any
177 Medicaid insurance experienced a 40% increased hazard of death compared to those with other
178 insurance. As reported elsewhere[4], overall survival for the entire cohort improved steadily over
179 time (from 53% to 77%). Notably, while SES-related survival disparities persisted over time,
180 they did not widen.
181

182 These findings build on prior work identifying SES-associated survival disparities in children
183 with high-risk neuroblastoma treated on clinical trials[23] by investigating whether outcome
184 disparities have increased with advances in care. Given the resource-intense and highly
185 centralized nature of modern high-risk neuroblastoma treatment, this exemplifies the dual
186 potential of precision medicine to improve outcomes while simultaneously worsening health
187 disparities if these advances are not delivered equitably.[24] Although analyses of this cohort are
188 limited by absence of patient-level treatment data in the SEER database, the equitable survival
189 gains across all groups over time are encouraging and stand in contrast to widening disparities
190 observed in other populations (e.g. asthma, adult cancers).[25,26] These data suggest that access
191 to resource-intensive and highly-centralized treatment advances with known survival benefits has
192 been generally equitable among children with high-risk neuroblastoma, perhaps due to the high
193 reliance on clinical trial enrollment and delivery of protocolized care in pediatric oncology.
194
195 That U.S. children of lower SES with high-risk neuroblastoma continue to die at higher rates
196 than their higher SES counterparts must also be highlighted.[23] Despite focused policy
197 statements and advocacy efforts identifying poverty as a major determinant and predictor of
198 adverse health outcomes in children, we observed persistent and clinically meaningful survival
199 disparities associated with SES. Recent studies in other cancer populations have similarly found
200 insurance and neighborhood (i.e. county-based) poverty to be predictors of inferior outcomes.
201 [27,28] Of note, children with high-risk neuroblastoma receive intensive (largely inpatient)
202 treatment for 18-months at specialized, tertiary care centers. Therefore, this population is in
203 many ways optimally positioned to minimize disparities in care. Our finding that survival
204 disparities persist even in this population suggests that there may be other fundamental

205 mechanisms driving SES-related gaps, warranting exploration of mechanisms beyond access to
206 care.
207
208 Our study benefits from a robust, population-based sample across more than two decades of
209 high-risk neuroblastoma treatment, allowing for analysis of changes in survival over time. The
210 SEER database is uniquely positioned as a population-based registry to provide disparities data
211 as it is intentionally biased to oversample minority populations and those that have traditionally
212 been underrepresented in clinical trials.[29] Interestingly, we did not identify racial and ethnic
213 disparities observed in other neuroblastoma cohorts.[9,30] Importantly, our cohort differs from
214 these previous studies in that we restricted analyses to those with high-risk disease, which is
215 more prevalent in minority populations. As such, our data may thus reflect prior findings that
216 inferior survival observed for Black patients compared to their white counterparts was
217 attributable to their higher prevalence of high-risk disease at diagnosis.[30] Our data build on
218 recent publications demonstrating that SES mediates racial and ethnic survival disparities across
219 pediatric cancer,[9] and that low-SES is associated with inferior survival in the context of
220 modern-era clinical trials.[23] These disparities disproportionately impact children of racial and
221 ethnic minority status who disproportionately live in low-SES households due to structural
222 disadvantages and biases. We importantly find that these disparities are not, however, worsening
223 in the modern era of complex treatment delivery. Future attention to characterizing the
224 relationships between SES and outcomes is essential to begin to narrow the survival gap.
225
226 There are important limitations to our data. Inherent to any large registry, SEER data are limited
227 by missing data/unrecorded variables, coding reliability, and selection bias.[31] We utilized a

228 proxy for high-risk (stage M) neuroblastoma in the absence of histological, genetic, and staging
229 variables in SEER. While this proxy definition approximates elements of modern staging criteria,
230 we may have misclassified children with lower risk disease. We similarly lacked access to
231 patient-level treatment data, though our findings are consistent with SES-associated disparities in
232 the clinical trial setting. Finally, we had access to individual-level (insurance) SES data for only
233 the sub-cohort of patients diagnosed after 2007, limiting our ability to consider the impact of
234 insurance across all treatment eras in this analysis. Given the magnitude of the effect of
235 insurance status on survival, however, similar findings would be expected prior to 2007. SEER
236 also codes patients with Medicaid-only (e.g. based on income eligibility) and Medicaid as a
237 second-insurer identically. Consequently, some patients with Medicaid as a second insurer may
238 have been misclassified as low-SES, an error which would bias toward the null, lending
239 additional weight to our finding of survival disparities according to insurance status.
240
241 While significant SES-related survival disparities exist for children with high-risk neuroblastoma
242 in the United States, these disparities have not widened over time. These findings suggest that
243 the highly centralized and structured care delivery model of pediatric oncology allows for
244 equitable integration of novel therapies into the standard of care. They suggest a model of care
245 that could be applied to other patient populations—in oncology and more generally—for whom
246 novel therapies and other resource-intensive treatment modalities are entering the clinical space.
247 At the same time, low-SES patients continue to die at higher rates than their higher-SES
248 counterparts, and efforts to reduce this inequity are essential. The complex interplay between
249 poverty and other social factors, race/ethnicity, and cancer begs for clearer understanding so that
250 we might better address differences in healthcare access and outcomes. Future investigations

251 should focus on both elucidating mechanisms underlying SES-related disparities among
252 oncology patients accessing complex but standardized treatments, as well as designing targeted
253 interventions to improve overall survival in vulnerable groups.

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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 and (B) High-poverty county in multivariate analyses controlling for treatment era and SES*treatment era interaction on overall survival. CI, confidence interval