Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Jason M. Stevenson, M.D. Date

Evaluating the Impact of Race, Ethnicity, and Social Deprivation on the Incidence and Severity of Adverse Events in Children with Acute Lymphoblastic Leukemia

By

Jason M. Stevenson, M.D.
Master of Science
Clinical Research

_____
Jordan Kempker, M.D., M.Sc.
Advisor

_____
Amita Manatunga, Ph.D.
Co-Advisor

_____
D. John Bergsagel, M.D.
Committee Member

_____
Tamara P. Miller, M.D., M.S.C.E.
Committee Member

Accepted:

_____
Kimberly Jacob Arriola, Ph.D., MPH
Dean of the James T. Laney School of Graduate Studies

_____
Date

Evaluating the Impact of Race, Ethnicity, and Social Deprivation on the Incidence and Severity of Adverse Events in Children with Acute Lymphoblastic Leukemia

By

Jason M. Stevenson
B.S., Ouachita Baptist University, 2014
M.D., University of Arkansas for Medical Sciences, 2018

Advisor: Jordan Kempker, M.D., M.Sc.
Co-Advisor: Amita Manatunga, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2025

Abstract

Evaluating the Impact of Race, Ethnicity, and Social Deprivation on the Incidence and Severity of Adverse Events in Children with Acute Lymphoblastic Leukemia

By Jason M. Stevenson, M.D.

Background: Therapies used to treat pediatric acute lymphoblastic leukemia (ALL) lead to high cure rates but can cause significant adverse events (AEs). Children from racial and ethnic minority groups with oncologic diagnoses, , have increased acuity of illness at presentation, higher rates of relapse, and decreased overall survival (OS). These disparities are multifactorial and may be influenced by differences in AE incidence, yet the relationship between race, ethnicity, social deprivation, and AE development has not been comprehensively evaluated.

Objective: Compare the incidence and severity of clinically-significant AEs during induction therapy for *de novo* pediatric ALL by race and ethnicity, social deprivation level, and the combined effect of these factors.

Methods: This is a single-institution retrospective cohort study of pediatric patients diagnosed with *de novo* ALL at Children's Healthcare of Atlanta between January 1, 2010 and September 1, 2022. Incidence and severity, defined as the highest grade of each AE per National Cancer Institute Common Terminology Criteria for Adverse Events definitions, were manually abstracted following a detailed chart abstraction guide. Addresses at diagnosis were mapped to the Social Deprivation Index (SDI) by census tract. The association of (a) race and ethnicity and (b) SDI quintiles with the incidence and severity of each AE was analyzed using multivariable binary logistic regression, adjusting for age at diagnosis, sex, and leukemia risk classification.

Results: Of the 728 patients in the cohort, 156 (21.4%) were non-Hispanic Black, 189 (30.0%) were Hispanic, and 348 (47.8%) were non-Hispanic White. Compared to non-Hispanic White patients, non-Hispanic Black patients had significantly lower odds of ileus, neuropathy, and sepsis, while Hispanic patients had a significantly lower odds of ileus and neuropathy. Non-Hispanic Black patients had a 1.96 times higher odds (95% CI 1.07-3.57) of severe hyperglycemia compared to non-Hispanic White patients. There was no statistically significant interaction between SDI quintile, race, and ethnicity.

Conclusions: Non-Hispanic Black race was an independent risk for severe hyperglycemia during induction highlighting a targetable group for early prevention and intervention. Higher rates of relapse and decreased OS previously described in racial and ethnic minority groups may not be attributable to AEs experienced during ALL induction.

Evaluating the Impact of Race, Ethnicity, and Social Deprivation on the Incidence and Severity of Adverse Events in Children with Acute Lymphoblastic Leukemia

By

Jason M. Stevenson
B.S., Ouachita Baptist University, 2014
M.D., University of Arkansas for Medical Sciences, 2018

Advisor: Jordan Kempker, M.D., M.Sc.
Co-Advisor: Amita Manatunga, Ph.D.

A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2025

Acknowledgements

I would like to express my sincere thanks and appreciation to my mentorship team: Tamara P. Miller, MD, MSCE, Sharon Castellino, MD, MSc, Xu Ji, PhD, MSPH, Heeju Sohn, PhD, and Karen Wasilewski-Masker, MD, MSc. Their endless support and guidance over the course of this project has been invaluable. I would also like to thank my fellowship leadership team, Drs. Kathryn Sutton, Dan Weschler, Gary Woods, and Megan Brown, for their support of my participation in the Master of Science in Clinical Research (MSCR) program. I am grateful for the knowledge, skills, and feedback provided by MSCR faculty, which has prepared me for both this project and my future as an independent clinical investigator. Next, I would like to thank my thesis advisor, Dr. Jordan Kempker, for all of his assistance as I conducted by project and prepared my oral and written thesis. Finally, I would like to thank the patients and families of the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta that I have had the privilege of caring for during my training.

Support:

This research was supported by the Georgia Clinical and Translational Science Alliance and the National Center for Advancing Translational Sciences of the National Institutes of Health and was made possible through the Emory University MSCR program. Additional support was received from the Aflac Cancer and Blood Disorders Center.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

A. Background

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer accounting for approximately 30% of all pediatric cancer diagnoses [1, 2]. ALL is defined as a clonal proliferation of lymphoblasts arising from the bone marrow with the subtype of lymphoblast (B cell, T cell, or mixed lineage) determining the type of ALL [3]. Children with ALL are stratified into National Cancer Institute (NCI) classifications of standard risk or high risk based on their risk of relapse. The prognostic factors included in the risk classification include white blood cell count at diagnosis, age, and cytogenetics [4].

Therapy for *de novo* ALL is largely standardized amongst patients in the United States and compromised of multiple chemotherapy courses that take from 1 month to 1.5 years to complete. The first course, known as induction, lasts approximately 1 month. In the most commonly used regimens by the Children's Oncology Group, standard risk patients receive a 3 chemotherapy drug induction (glucocorticoid, vincristine, and asparaginase), while high risk patients receive a 4 chemotherapy drug induction (glucocorticoid, vincristine, asparaginase, and doxo/daunorubicin) [3, 4]. Mortality for children with ALL has improved significantly over the past 40 years due to advancements in treatments with overall survival now greater than 90% [2]. However, the treatments children receive can cause clinically-significant adverse events (AEs) that can impact both short- and long-term health.

Adverse Events in Pediatric Acute Lymphoblastic Leukemia

The NCI Common Terminology Criteria for Adverse Events (CTCAE) is an NCI mandated set of definitions for reporting AEs in clinical trials. The current version of the CTCAE (version 5) includes more than 800 AEs [5]. Definitions for each grade of each AE are included in the CTCAE, and these grades overall follow a parallel approach between AEs. Grade 1 is asymptomatic, mild symptoms, or diagnostic observations, such as abnormal laboratory values. Grade 2 is minimal or moderate symptoms that may require local or noninvasive interventions. Grade 3 is severe or medically significant symptoms that are not immediately life-threatening. Grade 3 AEs may require hospitalization or prolongation of hospitalization and may be disabling or limiting activities of daily living (ADLs). Grade 4 is life-threatening symptoms that may require urgent intervention, such as intensive care level support. Grade 5 is death due to the AE [5].

Multiple studies have demonstrated that AEs are underestimated and misreported on clinical trials, which leads to an incomplete understanding of the safety and tolerability of our current chemotherapy regimens [6-8]. Inaccurate AE reporting and data ascertainment is likely multifactorial, including time limitations, limited resources available for AE reporting, and the complexity of the AEs. Adverse event reporting in clinical trials is typically conducted by clinical research associates, who may have limited training in AE assessment and balance multiple research responsibilities, further impacting the accuracy and completeness of AE documentation.[6]. As AEs can impact the ability to give adequate and timely chemotherapy as well as lead to organ toxicity or death, mitigating the incidence and severity of AEs is critical to improving outcomes. To do to, it is crucial to identify those at highest risk for developing AEs during therapy and plan effective prevention and early intervention. If associations

between race, ethnicity, socioeconomic status, and the development of AEs are identified, these findings could enhance our understanding of AE-related outcomes and inform more personalized treatment strategies.

Racial and Ethnic Disparities in Pediatric Oncology

Prior studies show that children from racial and ethnic minority groups with oncologic diagnoses have inferior outcomes, including decreased overall survival, higher rates of relapse, and increased acuity of illness at presentation [9-17]. Winestone and colleagues demonstrated a significantly greater risk of induction mortality and ICU-level resource requirement at presentation in Black patients with acute myeloid leukemia (AML) compared to White patients [15]. Additionally, Kehm and colleagues showed statistically significant racial and ethnic disparities in survival independent of socioeconomic status in multiple childhood cancers, including ALL. These studies highlight the complex interplay of patient-level, healthcare system, community, and societal factors contributing to these differences. [18].

A relationship between these patient-level, healthcare system, community, and societal factors has been proposed by Ji and colleagues (Figure 1) [19]. This framework considers multiple levels of outcome drivers, including patient, family, and healthcare system levels, all nested within broader societal and cultural factors that have been shaped by a history of legalized racial discrimination and segregation. To achieve equitable health outcomes, these multi-level barriers (patient, family, healthcare system, and structural) must be transformed into modifiable drivers. While Ji and colleagues focused on overall survival, another outcome potentially influenced by these drivers is AEs, which may, in turn, impact survival. [19].

Social Deprivation Index

As proposed by Ji X, et al., we must consider community and societal factors when examining differences amongst different races and ethnicities [19]. One approach is to assess the level of social deprivation of the neighborhood where patients reside. The Social Deprivation Index (SDI) is a measure of the socioeconomic disadvantage of a neighborhood, which has been linked to adverse health outcomes, including age-adjusted mortality, infant mortality, low birth weight, and diabetes prevalence [20]. The SDI includes seven factors associated with socioeconomic disadvantage including income level, education, employment, housing conditions, household crowding, access to transportation, and single-parent household status. The SDI does not include race and ethnicity as a factor of social deprivation. The average proportions from each of the factors are used to calculate the SDI score (Table 1). Scores range from 1 to 100 with higher scores indicating a higher level of social deprivation [21].

A 2022 study by Thomson J, et al. showed that medically complex pediatric patients living in areas with a greater socioeconomic disadvantage, as measured by the SDI, were more likely to miss healthcare appointments [22]. This study did not, however, evaluate the differences in racial and ethnic minorities that may also be contributing to different health outcomes. When examining neighborhood poverty levels, Acharya S, et al, found that pediatric patients with ALL residing in neighborhoods with the highest poverty rate had a 1.8-fold increase in mortality compared with patients residing in neighborhoods with the lowest poverty rate [17].

Specific factors associated with socioeconomic disadvantage may also influence the incidence and severity of AEs in therapy for pediatric ALL.

Is Race, Ethnicity, and Social Deprivation associated with AEs?

While multiple studies have evaluated the association of race, ethnicity, and socioeconomic status on outcome disparities including rates of survival and relapse, data are lacking regarding how these factors affect AEs [9-15, 17]. In addition to providing novel insight into the impact of race, ethnicity, and social deprivation on AEs, this study provides patient-level, comprehensive data on the incidence and severity of AEs during ALL induction.

This study aims to examine the association between race, ethnicity, and social deprivation with the incidence and severity of AEs. As a secondary aim, this study examined the impact of social deprivation concomitantly with race on the incidence and severity of AEs to determine any interaction. It is hypothesized that non-white children and children living in areas of greater social deprivation would have an increased overall incidence and incidence of severe AEs during induction therapy for ALL.

The goal of this study is to help identify groups that are the highest risk for the development of AEs to provide providers with data that can be used for clinical decision making and educating patients, and families about what to expect during treatment. In addition, any associations of race, ethnicity, socioeconomic status, and the development of AEs identified may enhance our understanding of AE-related outcomes and inform more personalized treatment strategies to help improve outcome disparities in these groups.

B. Methods

Study Aims

1. Compare the overall incidence and incidence of severe AEs in pediatric ALL induction by race and ethnicity
2. Compare the overall incidence and incidence of severe AEs in pediatric ALL induction by (a) social deprivation and (b) social deprivation and race and ethnicity combined.

Study Design

This is a single-institution retrospective study that included patients treated at Children's Healthcare of Atlanta (CHOA), which is one of the largest pediatric oncology programs in the country with approximately 500 new cancer diagnoses per year. The study was reviewed and approved by the CHOA Institutional Review Board (CHOA00000404).

Sample

All children aged 0-21 years who were diagnosed with *de novo* ALL between January 1, 2010 and September 1, 2022 and treated at CHOA were eligible for inclusion. Patients were identified using the CHOA Cancer Registry, which is a manually-identified database of all patients with cancer treated at CHOA. Patients diagnosed and treated at an outside institution, those who transferred to another hospital prior to completion of their induction therapy, and those lacking detailed EHR data due to treatment before the current EHR system was in place were excluded. Patients missing race and/or ethnicity and those unable to be geocoded to their respective census-tract were also

excluded. A total of 728 eligible subjects were identified as eligible for this study (Figure 2).

Study Measures

The primary exposure variables were patient-reported race and ethnicity and SDI score. Patient-reported race and ethnicity were extracted in an automated way from the EHR and categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic, and other. Non-Hispanic Asian and Non-Hispanic American Indian and Alaska Natives were collapsed into "other" due to the small number of patients (n=35). Patients' addresses, determined by the primary caregiver's/guardian's address at time of diagnosis, were extracted from the EHR. Using patients' addresses of residence at time of diagnosis, the cohort of eligible patients was linked to their respective census tract using Decentralized Geomarker Assessment for Multi-Site Studies (DeGAUSS) v 3.3.0 [23]. The patient's census tract was then matched to the census tract-level database of the SDI for each year during 2010-2021 to generate an SDI score. SDI scores were categorized into quintiles with quintile 1 representing the areas of lowest social deprivation and quintile 5 representing the areas of highest social deprivation. The SDI includes seven factors associated with socioeconomic disadvantage including (1) percent of population with incomes less than 100% Federal Poverty Level, (2) percent of population 25 years or older with less than 12 years of education, (3) percent of non-employed population between 16-64 years of age, (4) percent of households living in renter-occupied housing units, (5) percent of households living in crowded housing units, (6) percent of single parent families with dependents less than 18 years of age, (7) percent of households with

no vehicle. The average proportions from each of the seven factors are used to calculate the census-tract level SDI score ranging from 1 to 100 (Table 1) [21].

Incidence and severity (highest grade per CTCAE v5 definitions) of AEs, including acute respiratory distress syndrome (ARDS), constipation, hyperglycemia, ileus, infection, neuropathy, pancreatitis, seizure, sepsis, stroke, thromboembolic event (TE), and typhlitis was manually abstracted from the EHR into a secure REDCap™ database. Severity was determined by the grade as per CTCAE v5 definitions. A detailed chart abstraction guide for each AE was created and chart abstractors received rigorous training on how to abstract AEs to ensure consistency. AEs were only included if they started or worsened after the start of chemotherapy. AEs that began prior to the start of induction therapy and did not worsen were excluded. To ensure the reliability and validity of the recorded AEs, 10% of the AE data for each condition were re-abstracted by a second reviewer. This adjudication process involved cross-checking the original data entries with the re-abstracted information to identify any discrepancies. Any inconsistencies were resolved through discussion with the abstractors and final decisions were made by the study principal investigator. Severe AEs were defined as Grade 3 or higher per CTCAE v5 definitions. Individual AEs were categorized as present (1) or absent (0) for both overall incidence of AE and incidence of severe AEs. Additionally, patients were categorized as present (1) or absent (0) for incidence of one or more severe AEs.

For all eligible subjects, demographic information (sex, race, ethnicity), age at diagnosis, leukemia type, and leukemia risk classification were extracted from the EHR. Confounders, as laid out in the conceptual model (Figure 3), included age at diagnosis,

sex, and leukemia risk classification. Covariates were selected using a priori criteria and research expertise.

Statistical Analysis

Descriptive statistics were conducted on all study variables including frequencies and percentages for categorical variables and medians and interquartile ranges (IQR) for non-parametric continuous variables. We compared the distribution in baseline demographic and clinical characteristics by race and ethnicity. Bivariate analyses were performed to assess the relationship between individual AEs and quintiles of SDI by race and ethnicity, using chi-square tests for categorical or binary variables.

For specific aim one, multivariable binary logistic regression was performed to assess the association of race and ethnicity with individual AE incidence and incidence of individual severe (Grade 3+) AEs, controlling for the aforementioned confounders. Each AE was analyzed as a binary outcome with the overall incidence (Yes/No) and incidence of severe (Yes/No) as separate dependent variables. Non-Hispanic white was assigned as the referent group. The two final models (one model for each AE incidence and one model for each severe AE incidence) were as below:

$$\text{logit}\big(\text{P(Adverse Event=1)}\big) = \beta_0 + \beta_1 Race/Ethnicity + \beta_2 Age + \beta_3 Sex + \beta_4 NCI\ Risk$$

$$\text{logit}\big(\text{P(Severe Adverse Event=1)}\big) = \beta_0 + \beta_1 Race/Ethnicity + \beta_2 Age + \beta_3 Sex + \beta_4 NCI\ Risk$$

For specific aim two, multivariable binary logistic regression was performed to assess the association of SDI quintile with individual AE incidence and incidence of individual severe (Grade 3+) AEs, controlling for age, sex, leukemia risk classification,

and race and ethnicity. Each AE was analyzed as a binary outcome with the overall incidence (Yes/No) and incidence of severe (Yes/No) as separate dependent variables. For SDI Quintile, polychotomous nominal exposure was used, and SDI quintile 1 was assigned as the referent group. The two final models (one model for each AE incidence and one model for each severe AE incidence) were as below:

$$\text{logit}\big(\text{P(Adverse Event=1)}\big) = \beta_0 + \beta_1 \textit{SDI Quintile} + \beta_2 \textit{Race/Ethnicity} + \beta_3 \textit{Age} + \beta_4 \textit{Sex} + \beta_5 \textit{NCI Risk}$$

$$\text{logit}\big(\text{P(Severe Adverse Event=1)}\big) = \beta_0 + \beta_1 \textit{SDI Quintile} + \beta_2 \textit{Race/Ethnicity} + \beta_3 \textit{Age} + \beta_4 \textit{Sex} + \beta_5 \textit{NCI Risk}$$

Additionally, multivariable binary logistic regression modeling was performed to assess for an interaction between (a) SDI quintile and (b) race and ethnicity with a model for each individual AE incidence and incidence of individual severe (Grade 3+) AEs, controlling for the aforementioned confounders. The two final models (one model for each AE incidence and one model for each severe AE incidence) were as below:

$$\text{logit}\big(\text{P(Adverse Event=1)}\big) = \beta_0 + \beta_1 \textit{SDI Quintile} + \beta_2 \textit{Race/Ethnicity} + \beta_3 \textit{SDI Quintile*Race/Ethnicity} + \beta_4 \textit{Age} + \beta_5 \textit{Sex} + \beta_6 \textit{NCI Risk}$$

$$\text{logit}\big(\text{P(Severe Adverse Event=1)}\big) = \beta_0 + \beta_1 \textit{SDI Quintile} + \beta_2 \textit{Race/Ethnicity} + \beta_3 \textit{SDI Quintile*Race/Ethnicity} + \beta_4 \textit{Age} + \beta_5 \textit{Sex} + \beta_6 \textit{NCI Risk}$$

Finally, multivariable binary logistic regression was performed to assess the association of (a) race and ethnicity and (b) SDI quintile with the incidence of any severe (Grade 3+) AEs, controlling for the aforementioned confounders. The final model was as below:

$$\text{logit}\big(\text{P(Severe Adverse Event=1)}\big) = \beta_0 + \beta_1 SDI\ Quintile + \beta_2 Race/Ethnicity + \beta_4 Age + \beta_5 Sex + \beta_6 NCI\ Risk$$

For chi-square tests and interaction terms, a p-value of <0.05 was considered statistically significant. For multivariable binary logistic regression, statistical significance was determined using 95% confidence intervals (CIs), where intervals that did not include the null value (1) were considered statistically significant. All statistical analyses were performed using R (version 4.3.2, R Core Team, Vienna, Austria).

C. Results

Patient Characteristics

In this retrospective cohort study, 766 patients were assessed for inclusion. Four patients had missing data on race and/or ethnicity in the EHR and 34 patient addresses were unable to be mapped to the SDI due to missing addresses in the EHR or inaccurate geocoding. This resulted in a cohort of 728 patients with complete data available for analysis. Median (IQR) age at diagnosis was 6.0 years (3.0-11.0). The cohort was predominantly male (n=401, 55.1%). The overall patient cohort was racially and ethnically diverse: 47.8% (n=348) were non-Hispanic White, 21.4% (n=156) were non-Hispanic Black, 26.0% (n=189) were Hispanic, and 4.8% (n=35) were non-Hispanic Asian and other racial and ethnic backgrounds (Table 2).

The SDI was non-normally distributed (Figure 4) with a median of 52.5 (IQR 27-79). There were 521 unique census tracts for the 728 patients with an even distribution amongst the varying levels of social deprivation (Figure 5). Patient race and ethnicity were compared by SDI quintiles and chi-square tests were conducted (Table 2). There was a statistically significant difference in the distribution of SDI quintile by patient race and ethnicity ($p<0.001$). The proportion of non-Hispanic White patients in SDI quintile 1 (area of lowest social deprivation) was 27.0% (n=94) compared to 10.9% (n=17) for non-Hispanic Black and 13.8% (n=26) for Hispanic patients. The proportion of non-Hispanic White patients in SDI quintile 5 (area of highest social deprivation) was 8.9% (n=31) compared to 26.9% (n=42) for non-Hispanic Black and 34.9% (n=66) for Hispanic patients (Table 2).

Incidence of AEs

When considering all CTCAE grades, constipation and hyperglycemia were the most common AEs with 58.2% (n=424) of patients experiencing constipation and 98.5% (n=717) of patients experiencing hyperglycemia. When considering all CTCAE grades, ARDS, ileus, pancreatitis, seizure, stroke, TE, and typhlitis were rare, occurring in 1.0-5.5% (n=7-40) of patients (Table 3). Incidence of each AE was compared by race and ethnicity using chi-square tests with statistically significant differences noted in the incidence of ileus and neuropathy (p=0.023 and p=0.006, respectively).

AE rates were stratified by CTCAE grade of AE (Table 4). Per the CTCAE, ARDS, sepsis, and typhlitis do not have definitions for grades 1 and 2, while Pancreatitis does not have a definition for grade 1. The majority of events for constipation, hyperglycemia, ileus, infection, neuropathy, and TE were low grade (grade 1-2). The majority of events for pancreatitis, seizure, and stroke were severe (grade 3+). As ARDS, sepsis, and typhlitis are only recorded as grade 3+, all events were severe.

Association of Race and Ethnicity with AE Incidence and Severity

Separate unadjusted and adjusted binary logistic regression models were used to evaluate the association of race and ethnicity and the overall incidence and incidence of severe AEs individually. As there were a total of 12 individual AEs, this equated to 24 separate models with 12 for the overall incidence of AEs and 12 for the incidence of severe AEs. In the unadjusted models, the odds ratios (ORs) of neuropathy and sepsis in non-Hispanic Black patients was 0.47 (95% confidence interval [CI]=0.30-0.72) and 0.45

(95% CI 0.22-0.86), respectively, compared to non-Hispanic White patients. In the unadjusted models, the odds of ileus was lower in non-Hispanic Black and Hispanic patients (vs. non-Hispanic White) with ORs 0.14 (95% CI 0.01-0.72) and 0.24 (95% CI 0.04-0.85), respectively (Table 5).

After adjusting for age at diagnosis, sex, and leukemia risk classification, non-Hispanic Black patients had lower odds of ileus (adjusted OR 0.15, 95% CI 0.01-0.73), neuropathy (adjusted OR 0.42, 95% CI 0.27-0.66), and sepsis (adjusted OR 0.45, 95% CI 0.22-0.86) compared to non-Hispanic White patients. In the adjusted models, Hispanic patients had a lower odds of ileus (adjusted OR 0.24, 95% CI 0.04-0.85) and neuropathy (adjusted OR 0.67, 95% CI 0.45-0.98) (Table 5). There were no other statistically significant associations of race and ethnicity with overall individual AE incidence (Figure 6).

In the unadjusted models for severe (grade 3+) AEs, non-Hispanic Black patients had a 2.02 times higher odds (95% CI 1.14-3.57) of severe hyperglycemia compared to non-Hispanic White patients. Additionally, non-Hispanic Black patients had a 0.38 times lower odds (95% CI 0.13-0.92) of neuropathy when compared to non-Hispanic White patients (Table 6). After adjusting for age at diagnosis, sex, and leukemia risk classification, the odds of hyperglycemia and neuropathy in non-Hispanic Black patients remained similar with an adjusted OR 1.96 (95% CI 1.07-3.57) and 0.37 (95% CI 0.12-0.90), respectively (Table 6). There were no other statistically significant associations of race and ethnicity with severe individual AE incidence (Figure 7).

Association of SDI Quintile with AE Incidence and Severity

Separate unadjusted and adjusted binary logistic regression models were used to evaluate the association of SDI quintile and the overall incidence and incidence of severe AEs individually. As there were a total of 12 individual AEs, this equated to 24 separate models with 12 for the overall incidence of AEs and 12 for the incidence of severe AEs. In the unadjusted models, there were no statistically significant associations between SDI quintile and overall individual AE incidence (Table 7).

After adjusting for race and ethnicity, age at diagnosis, sex, and leukemia risk classification, there remained no statistically significant associations of SDI quintile with overall individual AE incidence (Table 7; Figure 8).

In the unadjusted models for severe (grade 3+) AEs, patients living in SDI quintile 3 had a 6.21 times higher odds (95% CI 1.04-118.15) of severe pancreatitis compared to those living in SDI quintile 1, or areas of lowest social deprivation (Table 8). There were no additional statistically significant associations. After adjusting for race and ethnicity, age at diagnosis, sex, and leukemia risk classification, there were no statistically significant associations of SDI quintile with severe individual AE incidence (Table 8; Figure 9).

Interaction between Race, Ethnicity, and SDI Quintile

Each of the 48 models were assessed for a statistically significant interaction term between (a) race and ethnicity and (b) SDI. There were no statically significant interaction terms noted in any of the models with p-values ranging from 0.08 to 1.00.

D. Discussion

Despite significant improvements in outcomes in pediatric oncology over the past several decades, racial and ethnic minorities continue to have inferior outcomes when compared to their peers [9-16]. The etiology for these disparities is poorly understood, but may be due in part to the various drivers that nested within society and cultural factors that have been shaped by a history of legalized racial discrimination and segregation [19]. These drivers may also affect the incidence and severity of clinically-significant AEs experienced during ALL therapy, which may in turn affect survival outcomes. In this large single-institution retrospective analysis, we aimed to 1) compare the overall incidence and incidence of severe AEs in pediatric ALL induction by race and ethnicity and 2) compare the overall incidence and incidence of severe AEs in pediatric ALL induction by (a) social deprivation and (b) social deprivation and race and ethnicity combined.

To our knowledge, this is the first study to comprehensively examine patient-level associations between AE incidence and severity and race, ethnicity, and social deprivation in pediatric ALL. We found that SDI quintile proportions varied significantly by race and ethnicity ($p<0.001$) with a larger majority of non-Hispanic Black and Hispanic patients living in the areas of highest social deprivation (SDI quintile 5) when compared to non-Hispanic White patients (26.9 and 34.9% vs. 8.9%; Table 2). Additionally, a larger percentage of non-Hispanic White patients lived in the areas of lowest social deprivation (27% vs 10.9% and 13.8%; Table 2). Given the strong correlation between race, ethnicity, and social deprivation, no statistically significant interaction terms were observed ($p>0.05$).

Based on our findings, the previously reported higher rates of relapse and decreased overall survival (OS) among racial and ethnic minorities groups may not be due to AEs experienced during ALL induction. The significantly lower incidence of neuropathy experienced in non-Hispanic Black and Hispanic patients may be explained by genetic variation in CYP3A5 polymorphisms, which alters the metabolism of vincristine [24]. Prior studies have shown differences in both CYP3A5 polymorphisms and development of neuropathy by race. Non-Hispanic Black patients are more likely to express functional CYP3A5 alleles, leading to increased vincristine clearance and, consequently, a lower risk of neurotoxicity. As non-Hispanic White patients have higher expression of CYP3A5 variants that lead to poor metabolism of vincristine, this leads to an increase incidence of vincristine accumulation and subsequent neurotoxicity in this group [24, 25]. The lower odds of neuropathy in addition to ileus and sepsis experienced by non-Hispanic Black patients may also be representative of lower efficacy of chemotherapy as studies have shown greater progression-free survival in oncology patients with greater toxicities [26]. When examining differences among racial and ethnic groups, it is important to note that race is a social construct used to perpetuate the false historical narrative that there are inherent biological differences between racial groups [27]. While genetic variation exists within racial and ethnic groups, these differences are largely influenced by structural inequities and geographic location rather than inherent biological distinctions [28]. However, there may be genetic variations more common in racial and ethnic minority groups that contribute to a reduced incidence of AEs and, consequently, lower chemotherapy efficacy. Identifying these variations could inform

protocol modifications aimed at optimizing treatment and improving survival outcomes.

Although there was no statistically significant higher odds of development of hyperglycemia, non-Hispanic Black patients were noted to have a 1.96 times higher odds (95% CI 1.07-3.57) of severe hyperglycemia when compared to non-Hispanic White patients, after adjusting for age at diagnosis, sex, and leukemia risk classification (Table 6). There was, however, no statistically significant increased odds of the incidence of hyperglycemia when evaluating all CTCAE grades (Table 6). Given that low-grade hyperglycemia was extremely common (98.6% of patients), this may have affected our ability to detect differences. Prior studies have shown increased prevalence and severity of diabetes in non-Hispanic Black patients, which partially aligns with our findings of increased odds of severe hyperglycemia [29]. In pediatric ALL, an analysis by Savage B, et al., found that black children were 37% more likely than White children to develop hyperglycemia and that residing in areas where annual median income was below $5400 was associated with a 1.4 times increased odds of hyperglycemia when compared to wealthier areas [30]. This study differed from ours as it was conducted as a secondary analysis on a national database of hospitalizations, which may lead to an inaccurate estimation of true rates of hyperglycemia and reported race and ethnicity. Our finding highlights a potentially targetable group for early hyperglycemic prevention and intervention. As severe hyperglycemia is defined as the need for additional medications, such as insulin administration, and possible hospitalization this presents a significant burden for both patients and families [5].

Although not well studied, hyperglycemia during therapy has the potential to lead to additional health problems post-therapy [31].

Unexpectedly, we found no significant association between SDI quintile and the incidence or severity of adverse events. We hypothesized that patients from higher deprivation areas (SDI quintile 5) would experience a greater burden of AEs due to disparities in healthcare access, baseline health status, and social determinants of health. However, the increased resources and support provided to these populations in the pediatric care setting may mitigate these effects. Additionally, many patients remain hospitalized or have close follow-up throughout the induction period, which may also negate the effects of their social environment on AE development. Future analysis of additional chemotherapy courses where patients are not hospitalized may show differences not observed during induction. Finally, while the SDI provides a composite of many factors associated with social determinants of health, it may not fully capture the complex, multifaceted aspects of the patient's social environment, such as family support, transportation access, or health literacy, which could play a role in AE incidence and severity. Future studies incorporating patient-reported outcomes and additional socioeconomic indicators may provide a more nuanced understanding of these relationships.

There are many strengths of this study. First, this study provides comprehensive data on the incidence and severity of AEs during therapy for ALL, which has shown to be under and misreported in clinical trials [6-8]. It is also novel in examining the impact of race, ethnicity, and social deprivation on the incidence of severities of AEs. While previous studies have described outcomes by race and ethnicity alone, this

study importantly incorporates social and neighborhood level characteristics into this examination. The racially, ethnically, and socially diverse population cared for at CHOA also provides an ideal and likely generalizable population for this study.

This study has several limitations. First, its retrospective design limits our ability to establish causality between race, ethnicity, and social deprivation and AE development. While we adjusted for key confounders, residual confounding remains possible due to unmeasured factors such as nutritional status, comorbidities, or medication adherence. Second, there is also a chance that inconsistent or incomplete documentation of AEs both by providers documenting in the EHR and by abstractors could affect the accuracy of the incidence and severity rates, potentially underestimating the true burden of AEs. In addition, we only captured AEs that started or worsened after initiation of chemotherapy. The exclusion of AEs that started prior to induction and persisted throughout induction if they did not worsen in severity may also underestimate the true burden of AEs by focusing in this study on incidence rather than prevalence. We have mitigated these limitations by excluding patients with incomplete EHR documentation, creating robust chart abstraction guides, and requiring that all abstractors complete a rigorous training process including successful completion of test patients prior to beginning abstractions. We also implemented a 10% recheck of the AE data for each condition to identify any discrepancies and ensure quality and consistency. Third, while the SDI is a validated measure used widely in health disparities research to examine differences amongst areas of social deprivation, it may not fully capture the intricacies and variability of social determinants of health experienced by our patients at an individual level. For

example, two patients living in the same census tract may have vastly different socioeconomic experiences, family support structures, or access to resources, which could influence AE outcomes. As address at time of diagnosis was used to calculate the SDI score, we cannot account for patients that move during treatment. Although, it is unlikely for patients to move during the first month of therapy.

The goal of this study is to provide guidance to patients, families, and healthcare providers by improving understanding of AE risks during therapy. For families, these findings can help set realistic expectations regarding the potential for AEs during treatment and offer reassurance about their management if they do occur. Clear communication about risks and supportive care strategies may also improve adherence to treatment and reduce anxiety. For healthcare providers, these data can inform clinical decision-making by identifying patients at higher risk for severe AEs, allowing for earlier intervention and proactive management strategies. Providers can use this information to tailor supportive care measures, optimize monitoring plans, and guide shared decision-making with families. Additionally, these findings can influence the design of future clinical trials by highlighting patient populations that may benefit from targeted interventions to reduce treatment-related toxicity.

Future directions for this study include the abstraction of ten additional clinically-significant AEs. We will also expand the analysis to include all courses of *de novo* chemotherapy. Given differences in the setting of therapy and the specific chemotherapies used, there is a possibility that associations may emerge in later chemotherapy courses that were not observed during induction. Unlike induction, where many patients remain hospitalized or have close follow-up, subsequent courses

of therapy are primarily outpatient, requiring patients to seek medical care when AEs occur. Delays in accessing care due to transportation barriers or other factors may influence the severity and outcomes of AEs in these settings. Future studies are needed to evaluate the association of AEs during therapy with the development of long-term health effects in the post-therapy, or survivorship, period.

In conclusion, our study identifies non-Hispanic Black race and ethnicity as an independent risk factor for severe hyperglycemia during ALL induction, highlighting a potential target for early intervention. Future research should assess whether interventions, such as continuous glucose monitoring, can mitigate severe hyperglycemia in this patient population. The absence of significant associations between SDI quintile and AE incidence and severity suggest that the structured and resource-intensive nature of pediatric oncology care may mitigate some social deprivation-related disparities. However, broader investigations across all treatment phases and multiple institutions are needed to fully assess long-term outcomes. Our findings suggest that the disparities in survival and relapse rates previously reported among racial and ethnic minority groups and patients living areas of social deprivation may not be attributable to differences in adverse events during induction. This aligns with the fact that induction therapy is typically administered at full intensity regardless of toxicities, with providers prioritizing treatment completion. Dose modifications, when necessary, are more commonly made in later phases of therapy, which may be where disparities in treatment intensity and outcomes emerge. Future studies to explore additional disparities among racial and ethnic minorities and individuals living in areas of high social deprivation to better understand the

underlying factors driving differences in adverse event incidence, treatment tolerance, and long-term outcomes in pediatric ALL are needed.

E. References

1. Iacobucci, I. and C.G. Mullighan, *Genetic Basis of Acute Lymphoblastic Leukemia*. J Clin Oncol, 2017. **35**(9): p. 975-983.
2. Siegel, D.A., et al., *Pediatric cancer mortality and survival in the United States, 2001-2016*. Cancer, 2020. **126**(19): p. 4379-4389.
3. Rabin KR, G.M., Margolin JF, Poplack DG, *Chapter 19: Acute Lymphoblastic Leukemia*, in *Principles and Practice of Pediatric Oncology*. 2016, Lippincott Williams & Wilkins: Philidelphia, PA.
4. Schultz, K.R., et al., *Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG)*. Blood, 2007. **109**(3): p. 926-35.
5. Institute, N.C., *Common terminology criteria for adverse events (CTCAE) Version 5*, U.S.D.o.H.a.H. Services, Editor. 2017.
6. Miller, T.P. and R. Aplenc, *Evolution of Hematology Clinical Trial Adverse Event Reporting to Improve Care Delivery*. Curr Hematol Malig Rep, 2021. **16**(2): p. 126-131.
7. Miller, T.P., et al., *Rates of laboratory adverse events by course in paediatric leukaemia ascertained with automated electronic health record extraction: a retrospective cohort study from the Children's Oncology Group*. Lancet Haematol, 2022. **9**(9): p. e678-e688.
8. Miller, T.P., et al., *Accuracy of Adverse Event Ascertainment in Clinical Trials for Pediatric Acute Myeloid Leukemia*. J Clin Oncol, 2016. **34**(13): p. 1537-43.
9. Bhatia, S., *Disparities in cancer outcomes: lessons learned from children with cancer*. Pediatr Blood Cancer, 2011. **56**(6): p. 994-1002.
10. Bhatia, S., et al., *Racial and ethnic differences in survival of children with acute lymphoblastic leukemia*. Blood, 2002. **100**(6): p. 1957-64.
11. Henderson, T.O., et al., *Racial and ethnic disparities in risk and survival in children with neuroblastoma: a Children's Oncology Group study*. J Clin Oncol, 2011. **29**(1): p. 76-82.
12. Kadan-Lottick, N.S., et al., *Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia*. JAMA, 2003. **290**(15): p. 2008-14.
13. Kahn, J.M., et al., *Survival by Race and Ethnicity in Pediatric and Adolescent Patients With Hodgkin Lymphoma: A Children's Oncology Group Study*. J Clin Oncol, 2019. **37**(32): p. 3009-3017.
14. Li, Y., et al., *Comparable on-therapy mortality and supportive care requirements in Black and White patients following initial induction for pediatric acute myeloid leukemia*. Pediatr Blood Cancer, 2019. **66**(4): p. e27583.
15. Winestone, L.E., et al., *The role of acuity of illness at presentation in early mortality in black children with acute myeloid leukemia*. Am J Hematol, 2017. **92**(2): p. 141-148.
16. Aristizabal, P., et al., *Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents With Cancer*. Am Soc Clin Oncol Educ Book, 2021. **41**: p. e315-e326.

17. Acharya, S., et al., *Effects of Race/Ethnicity and Socioeconomic Status on Outcome in Childhood Acute Lymphoblastic Leukemia*. J Pediatr Hematol Oncol, 2016. **38**(5): p. 350-4.
18. Kehm, R.D., et al., *Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival?* Cancer, 2018. **124**(20): p. 4090-4097.
19. Ji, X., et al., *Moving Beyond Patient-Level Drivers of Racial/Ethnic Disparities in Childhood Cancer*. Cancer Epidemiol Biomarkers Prev, 2022. **31**(6): p. 1154-1158.
20. Butler, D.C., et al., *Measures of social deprivation that predict health care access and need within a rational area of primary care service delivery*. Health Serv Res, 2013. **48**(2 Pt 1): p. 539-59.
21. Care, R.G.C.-P.S.i.F.M.P. *Social deprivation index (SDI)*. 2018 [cited 2024 January 29]; Available from: https://www.graham-center.org/rgc/maps-data-tools/sdi/social-deprivation-index.html.
22. Thomson, J., et al., *Neighborhood Socioeconomic Deprivation and Health Care Utilization of Medically Complex Children*. Pediatrics, 2022. **149**(4).
23. Brokamp, C., et al., *Decentralized and reproducible geocoding and characterization of community and environmental exposures for multisite studies*. J Am Med Inform Assoc, 2018. **25**(3): p. 309-314.
24. van de Velde, M.E., et al., *Genetic Polymorphisms Associated with Vincristine Pharmacokinetics and Vincristine-Induced Peripheral Neuropathy in Pediatric Oncology Patients*. Cancers (Basel), 2022. **14**(14).
25. Sims, R.P., *The effect of race on the CYP3A-mediated metabolism of vincristine in pediatric patients with acute lymphoblastic leukemia*. J Oncol Pharm Pract, 2016. **22**(1): p. 76-81.
26. Abola, M.V., V. Prasad, and A.B. Jena, *Association between treatment toxicity and outcomes in oncology clinical trials*. Ann Oncol, 2014. **25**(11): p. 2284-2289.
27. Bryant, B.E., A. Jordan, and U.S. Clark, *Race as a Social Construct in Psychiatry Research and Practice*. JAMA Psychiatry, 2022. **79**(2): p. 93-94.
28. Jorde, L.B. and S.P. Wooding, *Genetic variation, classification and 'race'*. Nat Genet, 2004. **36**(11 Suppl): p. S28-33.
29. Health, O.o.M. *Diabetes and Black/African Americans*. 2023 [cited 2025; Available from: https://minorityhealth.hhs.gov/diabetes-and-blackafrican-americans#:~:text=In%202023%2C%20non%2DHispanic%20Black,National%20Diabetes%20Surveillance%20System%20.
30. Savage, B., P.D. Cole, and H. Lin, *Racial and Economic Differences in the Risk of Hyperglycemia in Children Hospitalized With Acute Lymphoblastic Leukemia*. J Pediatr Oncol Nurs, 2021. **38**(5): p. 277-284.
31. Abu-Ouf, N.M. and M.M. Jan, *Metabolic syndrome in the survivors of childhood acute lymphoblastic leukaemia*. Obes Res Clin Pract, 2015. **9**(2): p. 114-24.

F. Tables and Figures

Table 1. Social Deprivation Index (SDI) components and formula

SDI Component Description	SDI Component Formula
Percent Population Less Than 100% FPL	(Population < 0.99 FPL) / (Total Population)
Percent Population 25 Years or More With Less Than 12 Years of Education	(Population < 12 years of education) / (Total Population)
Percent Non-Employed for Population 16-64 years	(Not in Labor Force + Unemployed Between 16-64 Years) / (Civilian + Not in Labor Force between 16-64 years)
Percent Households Living in Renter-Occupied Housing Units	(Renter Occupied) / (Owner Occupied + Renter Occupied)
Percent Households Living in Crowded Housing Units	(Tenure by Occupants Per Room - (Owner Occupied + Renter Occupied)) / (Total Occupied Housing Units)
Percent Single Parent Families With Dependents < 18 years	(Single Parent Households With Dependent Children < 18 Years) / (Total Families)
Percent Households With No Vehicle	(Households Without a Vehicle) / (Total Occupied Housing Units)

*Adapted from Robert Graham Center [21]

Table 2. Patient characteristics stratified by race and ethnicity

	Non-Hispanic White (N=348)	Non-Hispanic Black (N=156)	Hispanic (N=189)	Other (N=35)	Overall (N=728)	p-value
Age (years) Median [IQR]	5 [3, 10]	6 [3, 12]	7 [3, 12]	4 [3, 9]	6 [3, 11]	
Sex						
Male	198 (56.9%)	80 (51.3%)	105 (55.6%)	18 (51.4%)	401 (55.1%)	
Female	150 (43.1%)	76 (48.7%)	84 (44.4%)	17 (48.6%)	327 (44.9%)	
SDI Quintile						<0.001
1	94 (27.0%)	17 (10.9%)	26 (13.8%)	9 (25.7%)	146 (20.1%)	
2	83 (23.9%)	27 (17.3%)	24 (12.7%)	12 (34.3%)	146 (20.1%)	
3	83 (23.9%)	31 (19.9%)	27 (14.3%)	5 (14.3%)	146 (20.1%)	
4	57 (16.4%)	39 (25.0%)	46 (24.3%)	3 (8.6%)	145 (19.9%)	
5	31 (8.9%)	42 (26.9%)	66 (34.9%)	6 (17.1%)	145 (19.9%)	

Other: Non-Hispanic Asian and Non-Hispanic American Indian and Alaskan Native; IQR: Interquartile Range; SDI: Social Deprivation Index

Table 3. Incidence of AEs experienced during induction stratified by race and ethnicity

	Non-Hispanic White (N=348)	Non-Hispanic Black (N=156)	Hispanic (N=189)	Other (N=35)	Overall (N=728)	p-value
ARDS	5 (1.4%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	7 (1.0%)	0.602
Constipation	211 (60.6%)	88 (56.4%)	106 (56.1%)	19 (54.3%)	424 (58.2%)	0.655
Hyperglycemia	343 (98.6%)	151 (96.8%)	189 (100%)	34 (97.1%)	717 (98.5%)	0.096
Ileus	15 (4.3%)	1 (0.6%)	2 (1.1%)	0 (0.0%)	18 (2.5%)	**0.023**
Infection	133 (38.2%)	46 (29.5%)	69 (36.5%)	12 (34.3%)	260 (35.7%)	0.300
Neuropathy	127 (36.5%)	33 (21.2%)	55 (29.1%)	10 (28.6%)	225 (30.9%)	**0.006**
Pancreatitis	11 (3.2%)	5 (3.2%)	7 (3.7%)	1 (2.9%)	24 (3.3%)	0.986
Seizure	9 (2.6%)	2 (1.3%)	3 (1.6%)	2 (5.7%)	16 (2.2%)	0.363
Sepsis	50 (14.4%)	11 (7.1%)	27 (14.3%)	4 (11.4%)	92 (12.6%)	0.118
Stroke	3 (0.9%)	2 (1.3%)	1 (0.5%)	0 (0.0%)	6 (0.8%)	0.826
TE	19 (5.5%)	11 (7.1%)	9 (4.8%)	1 (2.9%)	40 (5.5%)	0.707
Typhlitis	6 (1.7%)	3 (1.9%)	0 (0.0%)	0 (0.0%)	9 (1.2%)	0.252

AEs: Adverse Events; Other: Non-Hispanic Asian and Non-Hispanic American Indian and Alaskan Native; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event

Table 4. Rates of AEs experienced during induction stratified by CTCAE grade

	Low Grade AEs		Severe AEs		
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
ARDS	-	-	1 (14.3%)	5 (71.4%)	1 (14.3%)*
Constipation	101 (23.0%)	319 (72.7%)	19 (4.3%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	628 (87.6%)	5 (0.70%)	84 (11.7%)	0 (0.0%)	0 (0.0%)
Ileus	1 (5.6%)	9 (50%)	7 (38.8%)	1 (5.6%)	0 (0.0%)
Infection	20 (5.3%)	196 (51.7%)	144 (38.0%)	14 (3.7%)	5 (1.3%)* †
Neuropathy	58 (25.8%)	119 (52.9%)	48 (21.3%)	0 (0.0%)	0 (0.0%)
Pancreatitis	-	9 (37.5%)	10 (41.7%)	5 (20.8%)	0 (0.0%)
Seizure	0 (0.0%)	1 (5.9%)	9 (52.9%)	7 (41.2%)	0 (0.0%)
Sepsis	-	-	66 (68.7%)	23 (24.0%)	7 (7.3%)
Stroke	0 (0.0%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	2 (33.3%)*
TE	1 (2.5%)	30 (75%)	7 (17.5%)	2 (5%)	0 (0.0%)
Typhlitis	-	-	5 (55.6%)	3 (33.3%)	1 (11.1%)*

AEs: Adverse Events; CTCAE: Common Terminology Criteria for Adverse Events; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event

*10 unique patient deaths among the 16 grade 5 AEs: 2 patients with grade 5 infection alone, 3 patients with grade 5 sepsis alone, 1 patient with grade 5 stroke alone, 1 patient with grade 5 ARDS, 2 separate lung infections, and sepsis, 1 patient with grade 5 sepsis and lung infection, 1 patient with grade 5 sepsis and stroke, and 1 patient with grade 5 sepsis and typhlitis

†4 unique patients among the 5 grade 5 infections: 1 with candidal lung infection, 1 with a presumed unspecified fungal and staphylococcus capitis lung infection, 1 with a staphylococcus aureus lung infection, and 1 with a lung infection with no causal organism identified

Table 5. Unadjusted and Adjusted models estimating odds of development of AEs during induction by race and ethnicity

	Univariable Analysis	Multivariable Analysis
	OR (95% CI)	**OR (95% CI)**
ARDS		
Non-Hispanic Black	-	-
Hispanic	0.73 (0.10-3.44)	0.56 (0.08-2.70)
Other	-	-
Non-Hispanic White	REF	REF
Constipation		
Non-Hispanic Black	0.84 (0.57-1.23)	0.83 (0.57-1.22)
Hispanic	0.83 (0.58-1.19)	0.82 (0.57-1.18)
Other	0.77 (0.38-1.57)	0.78 (0.39-1.58)
Non-Hispanic White	REF	REF
Hyperglycemia		
Non-Hispanic Black	0.44 (0.12-1.60)	0.33 (0.08-1.28)
Hispanic	-	-
Other	0.50 (0.08-9.64)	0.43 (0.06-8.64)
Non-Hispanic White	REF	REF
Ileus		
Non-Hispanic Black	0.14 (0.01-0.72)	**0.15 (0.01-0.73)**
Hispanic	0.93 (0.64-1.34)	**0.24 (0.04-0.85)**
Other	-	-
Non-Hispanic White	REF	REF
Infection		
Non-Hispanic Black	0.68 (0.45-1.01)	0.70 (0.46-1.05)
Hispanic	0.93 (0.64-1.43)	0.97 (0.67-1.41)
Other	0.84 (0.39-1.72)	0.82 (0.38-1.68)
Non-Hispanic White	REF	REF
Neuropathy		
Non-Hispanic Black	0.47 (0.30-0.72)	**0.42 (0.27-0.66)**
Hispanic	0.71 (0.49-1.04)	**0.67 (0.45-0.98)**
Other	0.70 (0.31-1.46)	0.70 (0.31-1.48)
Non-Hispanic White	REF	
Pancreatitis		
Non-Hispanic Black	1.01 (0.32-2.84)	0.91 (0.28-2.60)
Hispanic	1.18 (0.43-3.04)	1.00 (0.36-2.64)
Other	0.90 (0.05-4.85)	0.96 (0.05-5.44)
Non-Hispanic White	REF	REF
Seizure		
Non-Hispanic Black	0.49 (0.07-1.93)	0.47 (0.07-1.85)
Hispanic	0.61 (0.13-2.06)	0.58 (0.13-1.97)
Other	2.28 (0.34-9.33)	2.57 (0.38-10.79)
Non-Hispanic White	REF	REF
Sepsis		
Non-Hispanic Black	0.45 (0.22-0.86)	0.45 (0.22-0.86)
Hispanic	0.99 (0.59-1.64)	1.00 (0.59-1.65)
Other	0.77 (0.22-2.05)	0.75 (0.22-2.00)
Non-Hispanic White	REF	REF

Stroke		
Non-Hispanic Black	1.49 (0.20-9.10)	1.41 (0.18-8.62)
Hispanic	0.61 (0.03-4.81)	0.59 (0.03-4.71)
Other	-	-
Non-Hispanic White	REF	REF
TE		
Non-Hispanic Black	1.31 (0.59-2.79)	1.27 (0.56-2.74)
Hispanic	0.87 (0.37-1.90)	0.83 (0.35-1.85)
Other	0.51 (0.03-2.58)	0.58 (0.03-3.05)
Non-Hispanic White	REF	REF
Typhlitis		
Non-Hispanic Black	1.12 (0.23-4.29)	1.11 (0.23-4.29)
Hispanic	-	-
Other	-	-
Non-Hispanic White	REF	REF

*Covariates controlled for in the regression model: age at diagnosis, sex, and leukemia risk classification

AEs: Adverse Events; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event; OR: odds ratio; CI: confidence interval; REF: referent; -: unable to be calculated due to low incidence of event (ARDS, Ileus, Stroke, and Typhlitis) or failure to converge (Hyperglycemia)

Table 6. Unadjusted and Adjusted models estimating odds of development of severe (grade 3+) AEs during induction by race and ethnicity

	Univariable Analysis	Multivariable Analysis
	OR (95% CI)	**OR (95% CI)**
ARDS		
Non-Hispanic Black	-	-
Hispanic	0.73 (0.10-3.44)	0.56 (0.08-2.70)
Other	-	-
Non-Hispanic White	REF	REF
Constipation		
Non-Hispanic Black	0.22 (0.01-1.15)	0.22 (0.01-1.17)
Hispanic	1.11 (0.37-3.03)	1.12 (0.38-3.08)
Other	2.05 (0.31-8.19)	2.02 (0.30-8.13)
Non-Hispanic White	REF	REF
Hyperglycemia		
Non-Hispanic Black	2.02 (1.14-3.57)	**1.96 (1.07-3.57)**
Hispanic	1.62 (0.91-2.84)	1.47 (0.81-2.66)
Other	1.37 (0.39-3.75)	1.64 (0.44-4.87)
Non-Hispanic White	REF	REF
Ileus		
Non-Hispanic Black	-	-
Hispanic	0.26 (0.01-1.47)	0.25 (0.01-1.42)
Other	-	-
Non-Hispanic White	REF	REF
Infection		
Non-Hispanic Black	0.86 (0.50-1.44)	0.87 (0.51-1.46)
Hispanic	1.06 (0.66-1.68)	1.08 (0.67-1.72)
Other	0.83 (0.28-2.07)	0.81 (0.27-2.02)
Non-Hispanic White	REF	REF
Neuropathy		
Non-Hispanic Black	0.38 (0.13-0.92)	**0.37 (0.12-0.90)**
Hispanic	0.84 (0.41-1.64)	0.81 (0.39-1.60)
Other	0.69 (0.11-2.45)	0.73 (0.11-2.61)
Non-Hispanic White	REF	REF
Pancreatitis		
Non-Hispanic Black	1.50 (0.38-5.33)	1.39 (0.35-4.96)
Hispanic	1.87 (0.58-6.05)	1.67 (0.51-5.46)
Other	-	-
Non-Hispanic White	REF	REF
Seizure		
Non-Hispanic Black	0.49 (0.07-1.93)	0.47 (0.07-1.85)
Hispanic	0.61 (0.13-2.06)	0.58 (0.13-1.97)
Other	2.28 (0.34-9.33)	2.57 (0.38-10.79)
Non-Hispanic White	REF	REF
Sepsis		
Non-Hispanic Black	0.45 (0.22-0.86)	0.45 (0.22-0.86)
Hispanic	0.99 (0.59-1.64)	1.00 (0.59-1.65)
Other	0.77 (0.22-2.05)	0.75 (0.22-2.00)
Non-Hispanic White	REF	REF

Stroke		
Non-Hispanic Black	0.74 (0.04-5.85)	0.72 (0.04-5.74)
Hispanic	-	-
Other	-	-
Non-Hispanic White	REF	REF
TE		
Non-Hispanic Black	1.69 (0.33-7.74)	1.57 (0.31-7.24)
Hispanic	0.46 (0.02-3.12)	0.41 (0.02-2.84)
Other	2.53 (0.13-17.71)	2.67 (0.13-19.02)
Non-Hispanic White	REF	REF
Typhlitis		
Non-Hispanic Black	1.12 (0.23-4.29)	1.11 (0.23-4.29)
Hispanic	-	-
Other	-	-
Non-Hispanic White	REF	REF

*Covariates controlled for in the regression model: age at diagnosis, sex, and leukemia risk classification

AEs: Adverse Events; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event; OR: odds ratio; CI: confidence interval; REF: referent; -: unable to be calculated due to low incidence of event (ARDS, Ileus, Stroke, and Typhlitis)

Table 7. Unadjusted and Adjusted models estimating odds of development of AEs during induction by SDI Quintile

	Univariable Analysis	Multivariable Analysis
	OR (95% CI)	**OR (95% CI)**
ARDS		
SDI Quintile		
5 [most]	-	-
4	-	-
3	-	-
2	-	-
1 [least]	REF	REF
Constipation		
SDI Quintile		
5 [most]	1.17 (0.73-1.86)	1.30 (0.80-2.12)
4	1.35 (0.85-2.15)	1.44 (0.89-2.33)
3	1.15 (0.72-1.82)	1.19 (0.75-1.90)
2	1.49 (0.93-2.38)	1.54 (0.96-2.48)
1 [least]	REF	REF
Hyperglycemia		
SDI Quintile		
5 [most]	-	-
4	-	-
3	-	-
2	-	-
1 [least]	REF	REF
Ileus		
SDI Quintile		
5 [most]	0.67 (0.09-4.08)	1.25 (0.15-8.13)
4	1.01 (0.18-5.52)	1.39 (0.25-7.77)
3	2.76 (0.78-12.81)	2.98 (0.83-13.97)
2	0.66 (0.09-4.05)	0.73 (0.09-4.50)
1 [least]	REF	REF
Infection		
SDI Quintile		
5 [most]	0.87 (0.52-1.41)	0.92 (0.55-1.55)
4	1.14 (0.71-1.84)	1.15 (0.70-1.88)
3	1.37 (0.86-2.21)	1.40 (0.87-2.26)
2	0.86 (0.52-1.39)	0.84 (0.51-1.37)
1 [least]	REF	REF
Neuropathy		
SDI Quintile		
5 [most]	0.58 (0.34-0.95)	0.74 (0.43-1.28)
4	0.95 (0.59-1.54)	1.15 (0.69-1.92)
3	0.66 (0.40-1.08)	0.74 (0.44-1.24)
2	0.91 (0.56-1.48)	1.03 (0.62-1.69)
1 [least]	REF	REF

Pancreatitis		
SDI Quintile		
5 [most]	1.70 (0.41-8.43)	1.63 (0.36-8.62)
4	0.67 (0.09-4.08)	0.69 (0.09-4.41)
3	2.40 (0.65-11.31)	2.61 (0.69-12.54)
2	2.40 (0.65-11.31)	2.77 (0.73-13.31)
1 [least]	REF	REF
Seizure		
SDI Quintile		
5 [most]	0.50 (0.07-2.59)	0.61 (0.08-3.41)
4	0.75 (0.15-3.46)	1.07 (0.20-5.19)
3	1.00 (0.23-4.30)	1.11 (0.25-4.89)
2	0.74 (0.14-3.44)	0.84 (0.16-3.95)
1 [least]	REF	REF
Sepsis		
SDI Quintile		
5 [most]	1.14 (0.57-2.27)	1.34 (0.65-2.78)
4	1.01 (0.50-2.04)	1.11 (0.54-2.27)
3	1.06 (0.53-2.13)	1.15 (0.57-2.31)
2	0.94 (0.46-1.91)	0.98 (0.48-2.00)
1 [least]	REF	REF
Stroke		
SDI Quintile		
5 [most]	-	-
4	-	-
3	0.50 (0.02-5.24)	0.46 (0.02-4.92)
2	1.51 (0.25-11.60)	1.39 (0.22-10.92)
1 [least]	REF	REF
TE		
SDI Quintile		
5 [most]	1.42 (0.56-3.76)	1.42 (0.52-4.03)
4	0.62 (0.18-1.89)	0.71 (0.20-2.28)
3	0.87 (0.30-2.48)	0.83 (0.28-2.43)
2	1.13 (0.42-3.10)	1.33 (0.48-3.74)
1 [least]	REF	REF
Typhlitis		
SDI Quintile		
5 [most]	0.33 (0.02-2.62)	0.44 (0.02-3.93)
4	0.33 (0.02-2.62)	0.35 (0.02-2.93)
3	1.34 (0.29-6.92)	1.27 (0.27-6.69)
2	-	-
1 [least]	REF	REF

*Covariates controlled for in the regression model: age at diagnosis, sex, and leukemia risk classification

AEs: Adverse Events; SDI: Social Deprivation Index; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event; OR: odds ratio; CI: confidence interval; REF: referent; -: unable to be calculated due to low incidence of event (ARDS, Stroke, and Typhlitis) and failure to converge (Hyperglycemia)

Table 8. Unadjusted and Adjusted models estimating odds of development of severe (grade 3+) AEs during induction by SDI quintile

	Univariable Analysis	Multivariable Analysis
	OR (95% CI)	**OR (95% CI)**
ARDS		
SDI Quintile		
5 [most]	-	-
4	-	-
3	-	-
2	-	-
1 [least]	REF	REF
Constipation		
SDI Quintile		
5 [most]	1.52 (0.25-11.68)	1.73 (0.27-13.85)
4	2.04 (0.39-14.90)	2.37 (0.44-17.65)
3	3.09 (0.70-21.30)	3.44 (0.77-23.92)
2	2.03 (0.39-14.80)	2.06 (0.39-15.16)
1 [least]	REF	REF
Hyperglycemia		
SDI Quintile		
5 [most]	0.84 (0.36-1.94)	0.61 (0.24-1.50)
4	1.93 (0.95-4.08)	2.06 (0.94-4.64)
3	1.72 (0.83-3.66)	1.76 (0.81-3.93)
2	1.26 (0.58-2.76)	1.47 (0.65-3.38)
1 [least]	REF	REF
Ileus		
SDI Quintile		
5 [most]	2.03 (0.19-43.92)	5.10 (0.45-115.02)
4	2.03 (0.19-43.92)	3.42 (0.31-75.67)
3	2.01 (0.19-43.62)	2.42 (0.23-52.84)
2	1.00 (0.04-25.45)	1.20 (0.05-30.88)
1 [least]	REF	REF
Infection		
SDI Quintile		
5 [most]	1.41 (0.77-2.61)	1.51 (0.80-2.89)
4	1.29 (0.70-2.41)	1.31 (0.70-2.48)
3	1.16 (0.62-2.19)	1.18 (0.63-2.23)
2	0.69 (0.34-1.38)	0.69 (0.34-1.37)
1 [least]	REF	REF
Neuropathy		
SDI Quintile		
5 [most]	1.14 (0.42-3.12)	1.44 (0.51-4.17)
4	0.74 (0.24-2.20)	0.89 (0.28-2.70)
3	1.69 (0.69-4.38)	1.95 (0.78-5.12)
2	1.54 (0.62-4.05)	1.76 (0.70-4.66)
1 [least]	REF	REF

Pancreatitis		
SDI Quintile		
5 [most]	3.06 (0.39-62.33)	2.27 (0.27-47.80)
4	1.01 (0.04-25.63)	0.83 (0.03-21.60)
3	6.21 (1.04-118.15)	6.01 (0.99-115.19)
2	5.14 (0.82-99.17)	5.59 (0.87-108.85)
1 [least]	REF	REF
Seizure		
SDI Quintile		
5 [most]	0.50 (0.07-2.59)	0.61 (0.08-3.41)
4	0.75 (0.15-3.46)	1.07 (0.20-5.19)
3	1.00 (0.23-4.30)	1.11 (0.25-4.89)
2	0.74 (0.14-3.44)	0.84 (0.16-3.95)
1 [least]	REF	REF
Sepsis		
SDI Quintile		
5 [most]	1.14 (0.57-2.27)	1.34 (0.65-2.78)
4	1.01 (0.50-2.04)	1.11 (0.54-2.27)
3	1.06 (0.53-2.13)	1.15 (0.57-2.31)
2	0.94 (0.46-1.91)	0.98 (0.48-2.00)
1 [least]	REF	REF
Stroke		
SDI Quintile		
5 [most]	-	-
4	-	-
3	0.50 (0.02-5.24)	0.48 (0.02-5.22)
2	0.50 (0.02-5.24)	0.49 (0.02-5.32)
1 [least]	REF	REF
TE		
SDI Quintile		
5 [most]	0.33 (0.02-2.62)	0.30 (0.01-2.68)
4	0.33 (0.02-2.62)	0.34 (0.02-2.90)
3	0.33 (0.02-2.60)	0.33 (0.02-2.68)
2	1.00 (0.18-5.48)	1.01 (0.18-5.67)
1 [least]	REF	REF
Typhlitis		
SDI Quintile		
5 [most]	0.33 (0.02-2.62)	0.44 (0.02-3.93)
4	0.33 (0.02-2.62)	0.35 (0.02-2.93)
3	1.34 (0.29-6.92)	1.27 (0.27-6.69)
2	-	-
1 [least]	REF	REF

*Covariates controlled for in the regression model: age at diagnosis, sex, and leukemia risk classification

AEs: Adverse Events; SDI: Social Deprivation Index; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event; OR: odds ratio; CI: confidence interval; REF: referent; -: unable to be calculated due to low incidence of event (ARDS, Stroke, and Typhlitis)

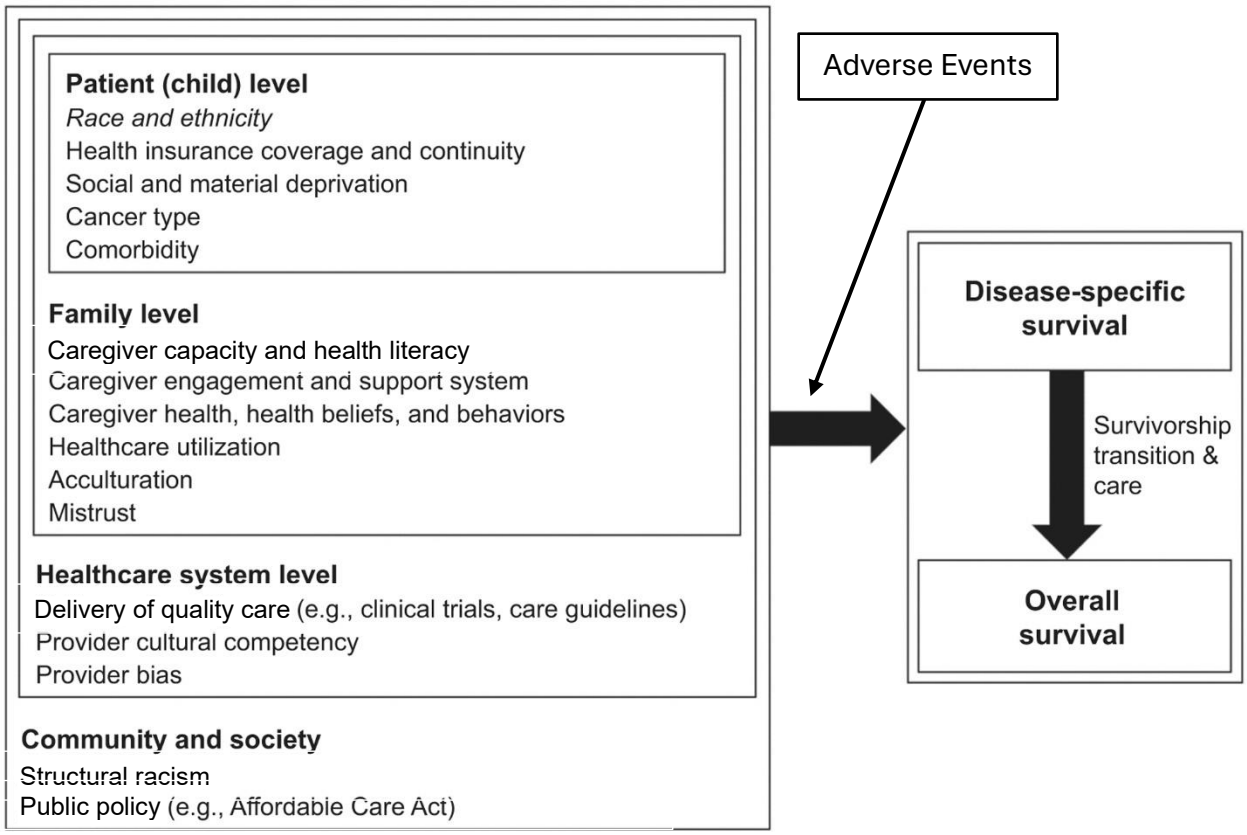
Table 9. Unadjusted and Adjusted models estimating odds of development of any severe (grade 3+) AEs during induction by race, ethnicity, and SDI quintile

Variables	Univariate Analysis	Multivariate Analysis
	OR (95% CI)	**OR (95% CI)**
Race and Ethnicity		
Non-Hispanic Black	1.06 (0.72-1.57)	0.98 (0.65-1.48
Hispanic	1.24 (0.87-1.78)	1.16 (0.79-1.70)
Other	0.66 (0.30-1.38)	0.69 (0.30-1.46)
Non-Hispanic White	REF	REF
SDI Quintile		
5 [most]	1.14 (0.71-1.82)	1.10 (0.67-1.82)
4	1.10 (0.69-1.77)	1.11 (0.68-1.81)
3	1.15 (0.72-1.85)	1.20 (0.74-1.95)
2	0.89 (0.55-1.43)	0.95 (0.58-1.54)
1 [least]	REF	REF
Age	1.06 (1.03-1.09)	**1.06 (1.03-1.09)**
Sex		
Female	1.38 (1.02-1.87)	**1.51 (1.11-2.05)**
Male	REF	REF

*Covariates controlled for in the regression model: age at diagnosis, sex, and leukemia risk classification

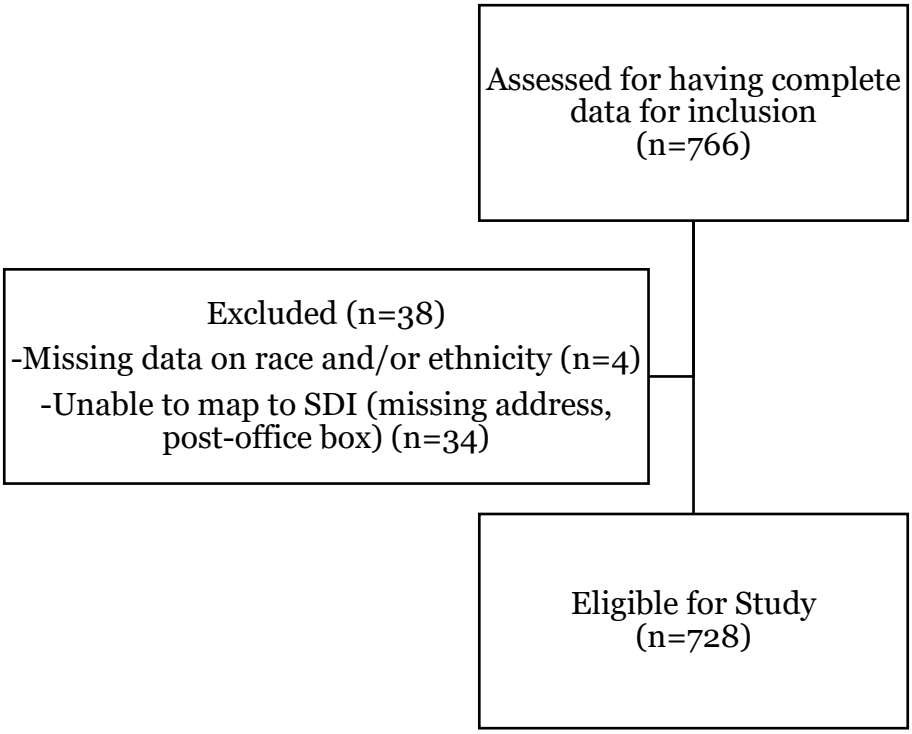
AEs: Adverse Events; SDI: Social Deprivation Index; OR: odds ratio; CI: confidence interval; REF: referent

Figure 1. Multi-level drivers that affect the association between race/ethnicity and survival among children diagnosed with cancer



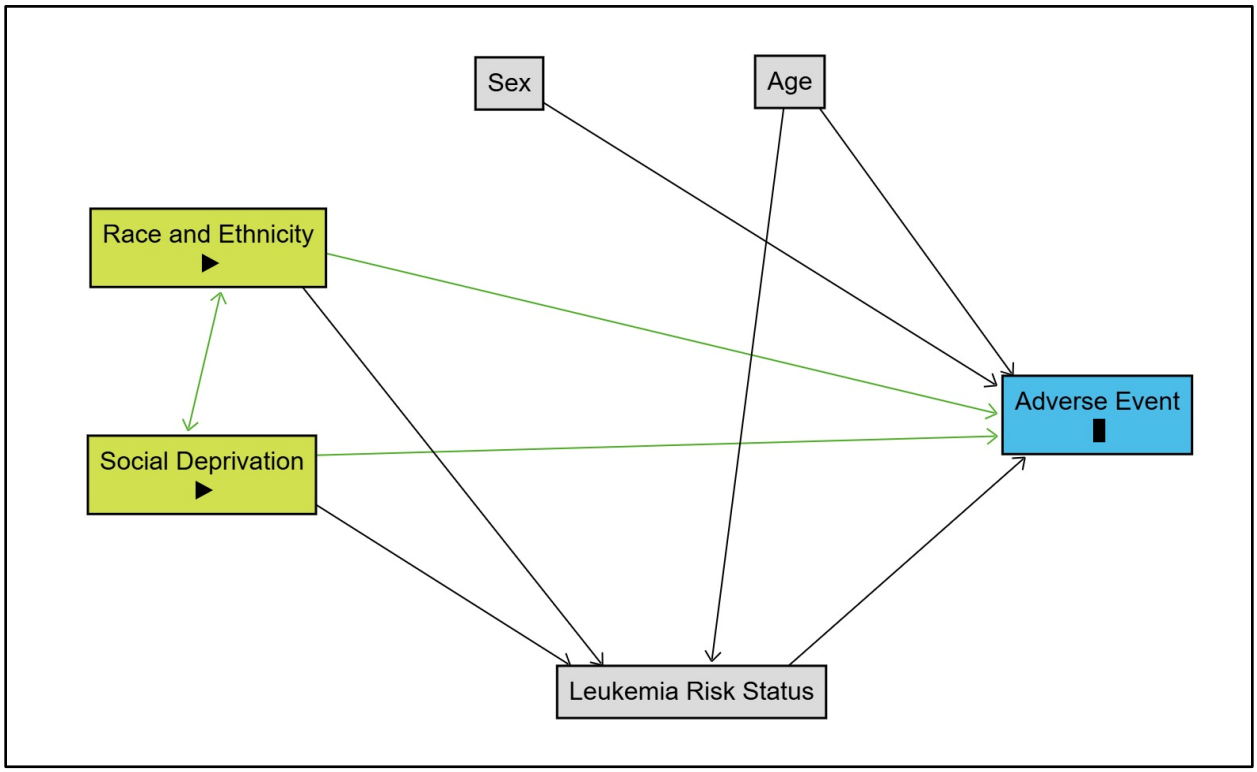
*Adapted from Ji, X., et al [19].

Figure 2. CONSORT diagram describing exclusion criteria



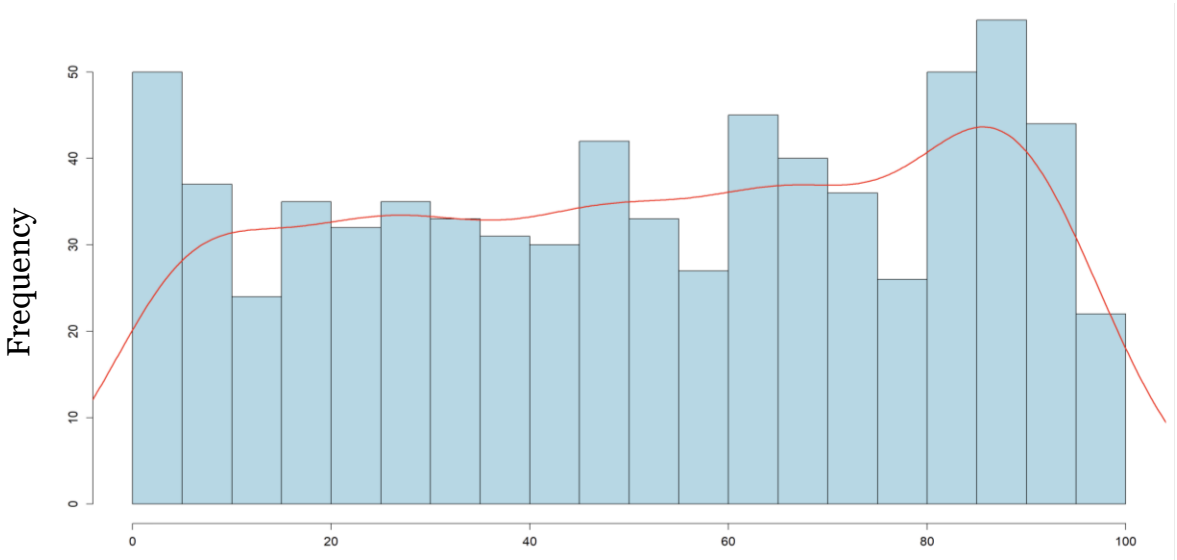
CONSORT: Consolidated Standards of Reporting Trials; SDI: Social Deprivation Index

Figure 3. Conceptual model of the association between race, ethnicity, and social deprivation and adverse events



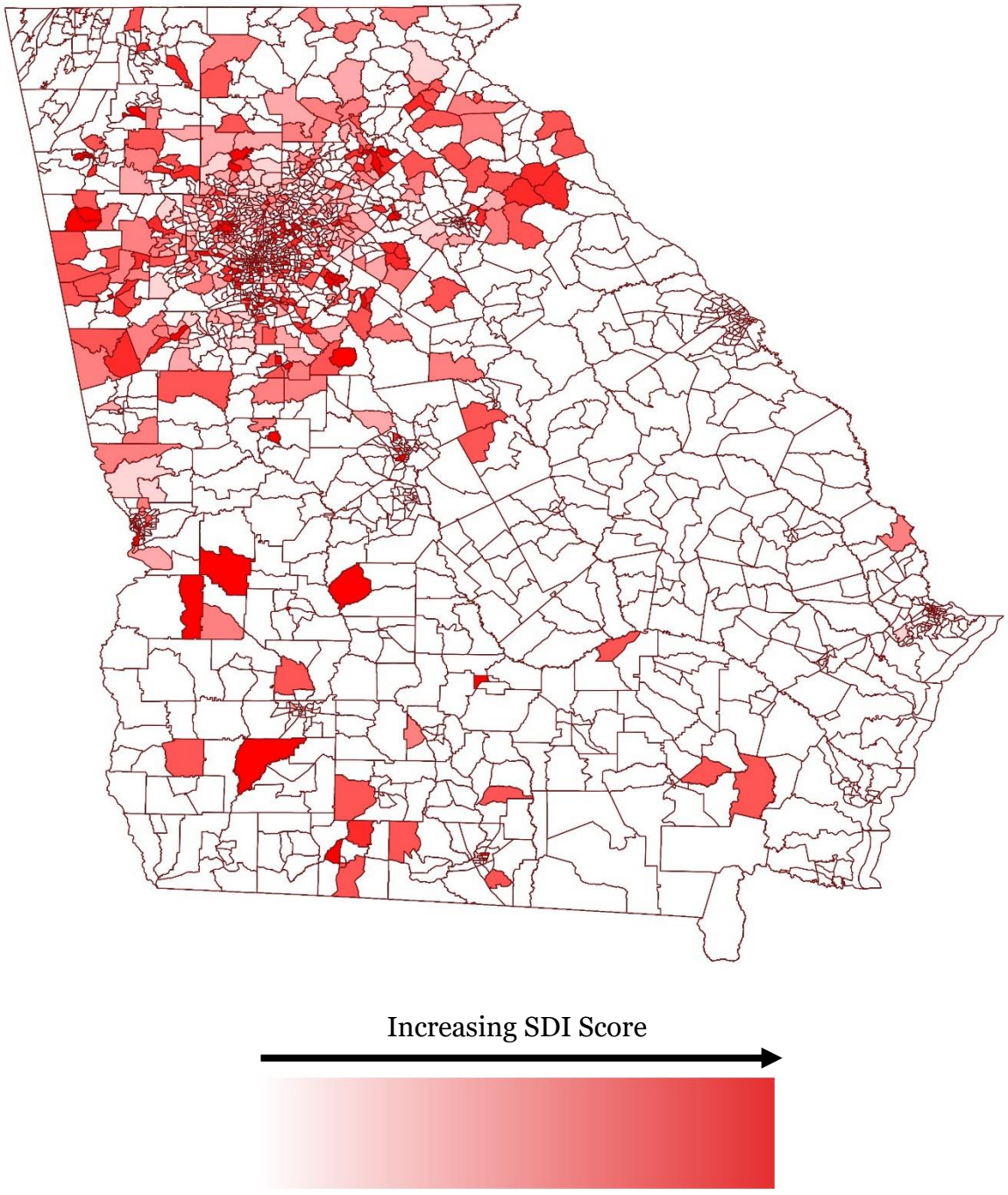
▶: Exposure; ▮: Outcome

Figure 4. SDI score distribution in cohort of patients included in the study



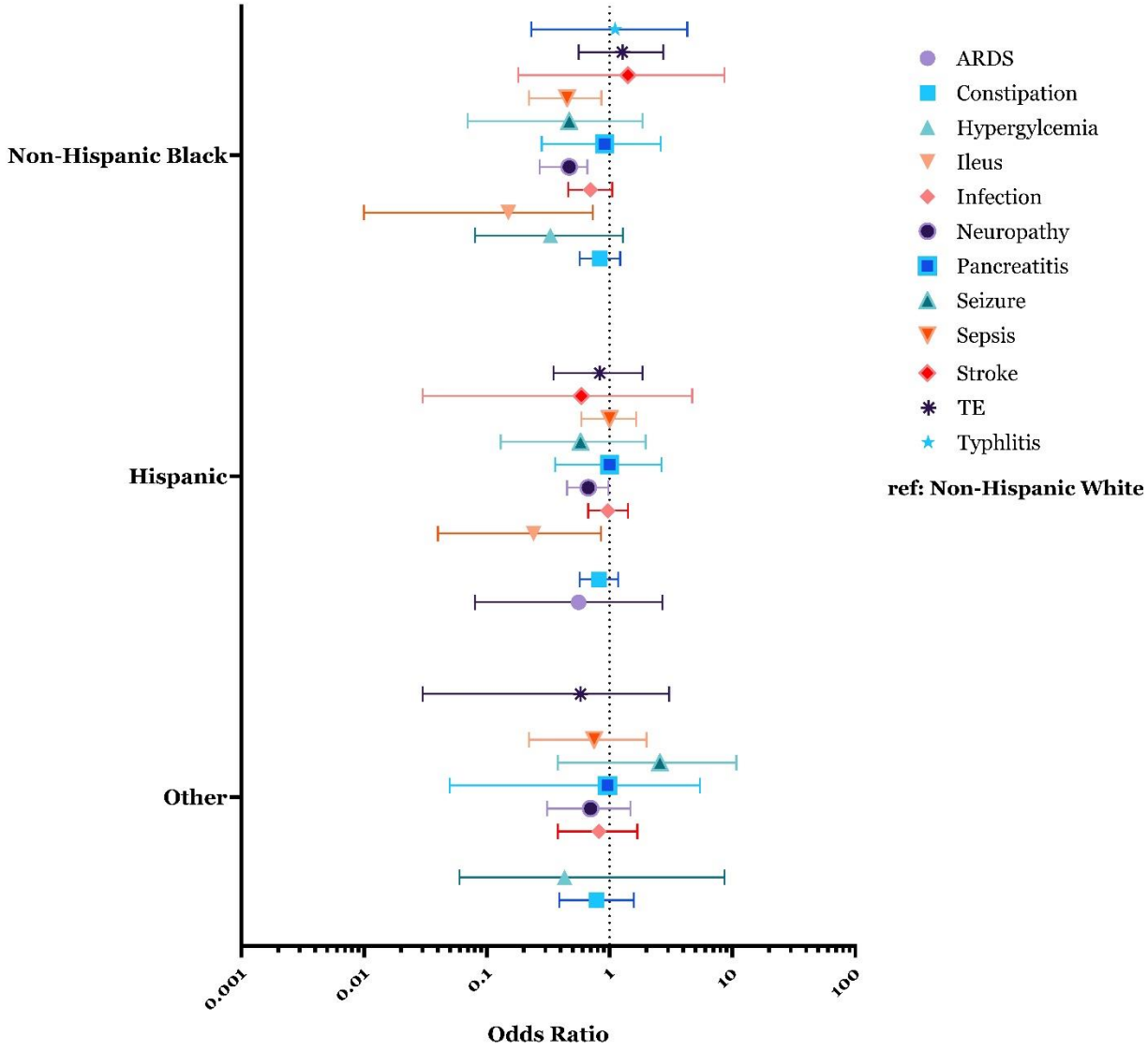
SDI: Social Deprivation Index; IQR: Interquartile Range

Figure 5. Distribution of SDI census tract for patients in the cohort



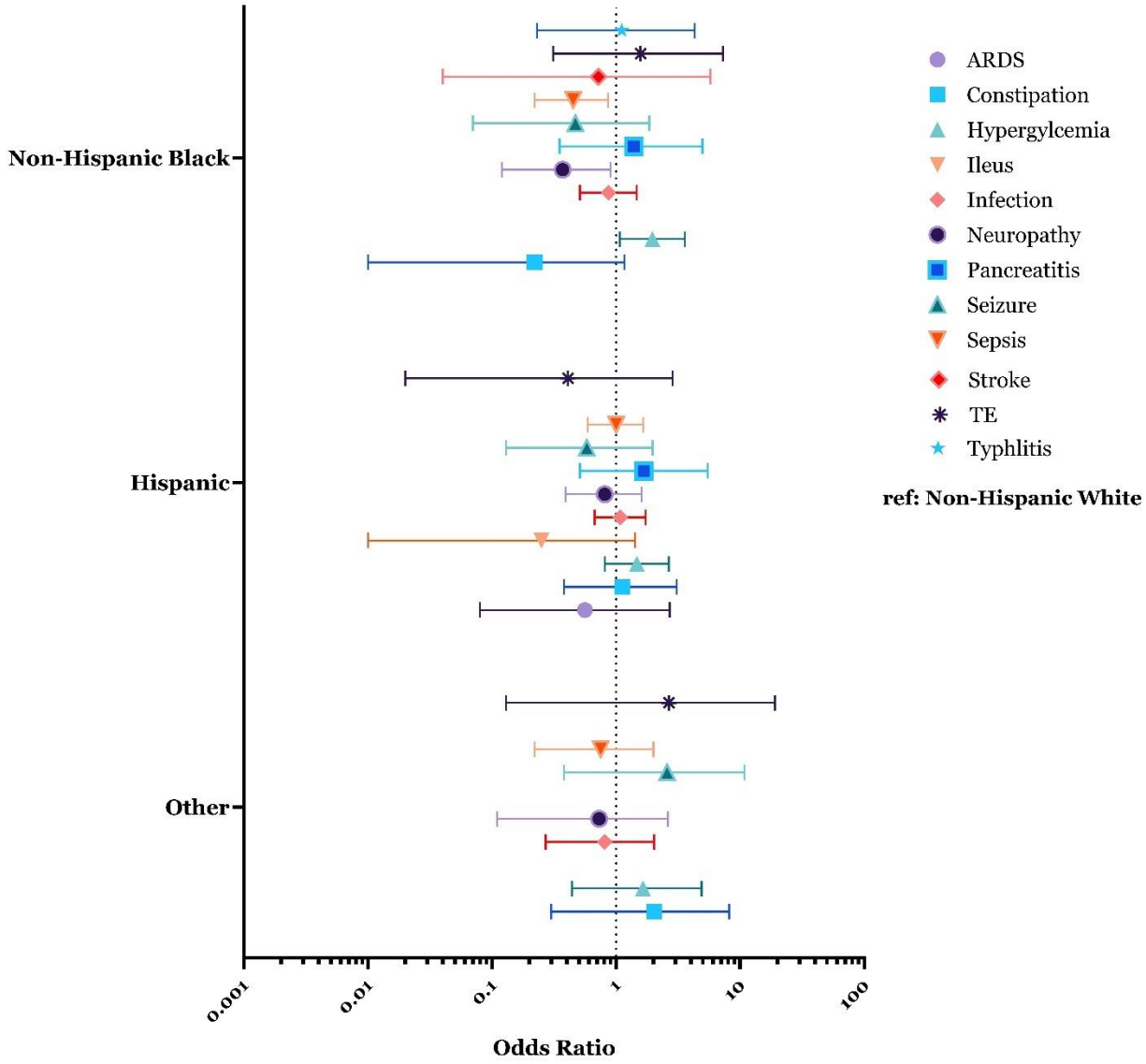
Red-Shaded Census Tracts – represent areas where patients in the cohort reside; Unshaded (White) Census Tracts – represent areas without patients in the cohort; SDI: Social Deprivation Index

Figure 6. Odds of development of AEs during induction by race and ethnicity



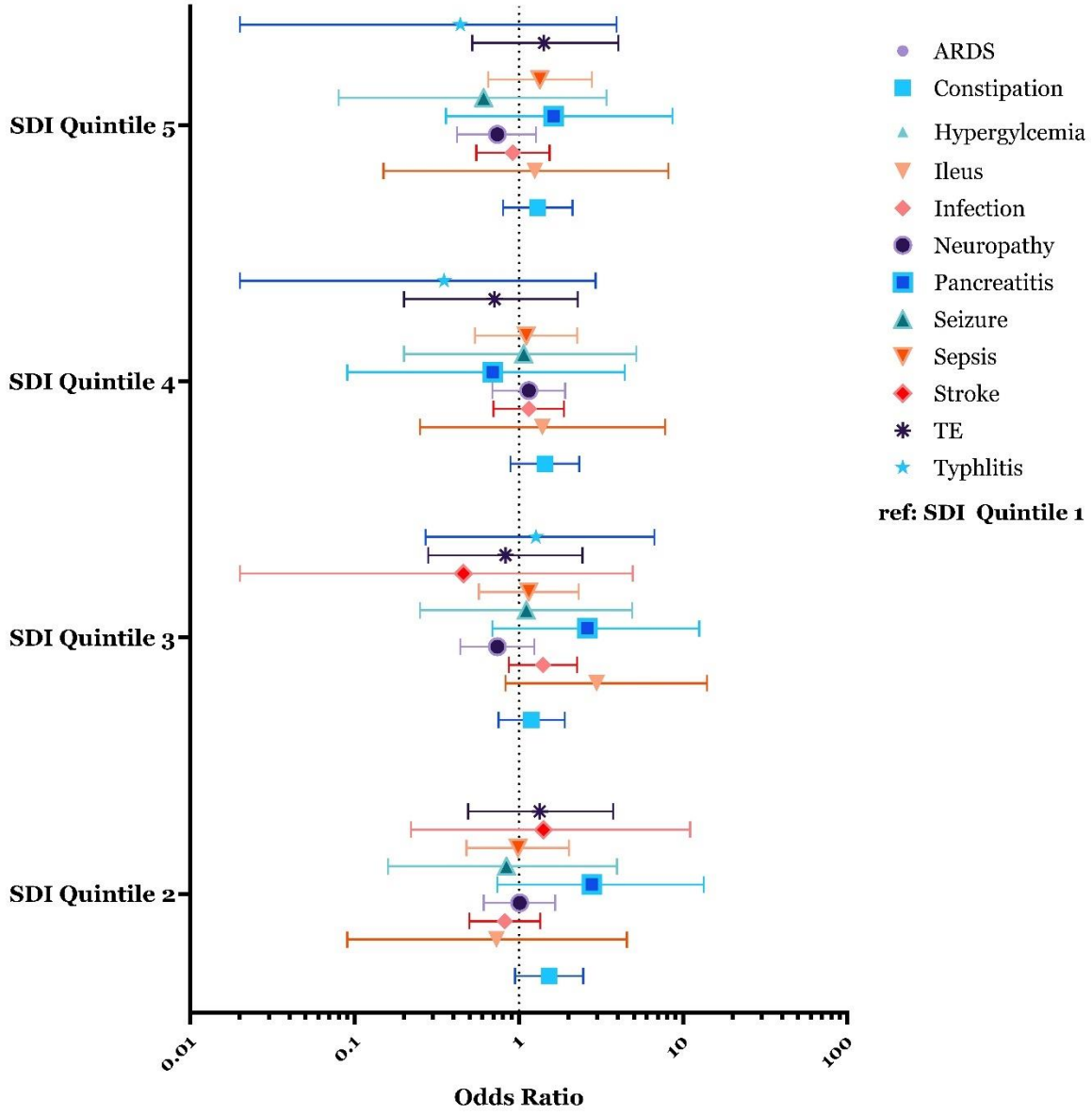
AEs: Adverse Events; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event

Figure 7. Odds of development of severe (grade 3+) AEs during induction by race and ethnicity



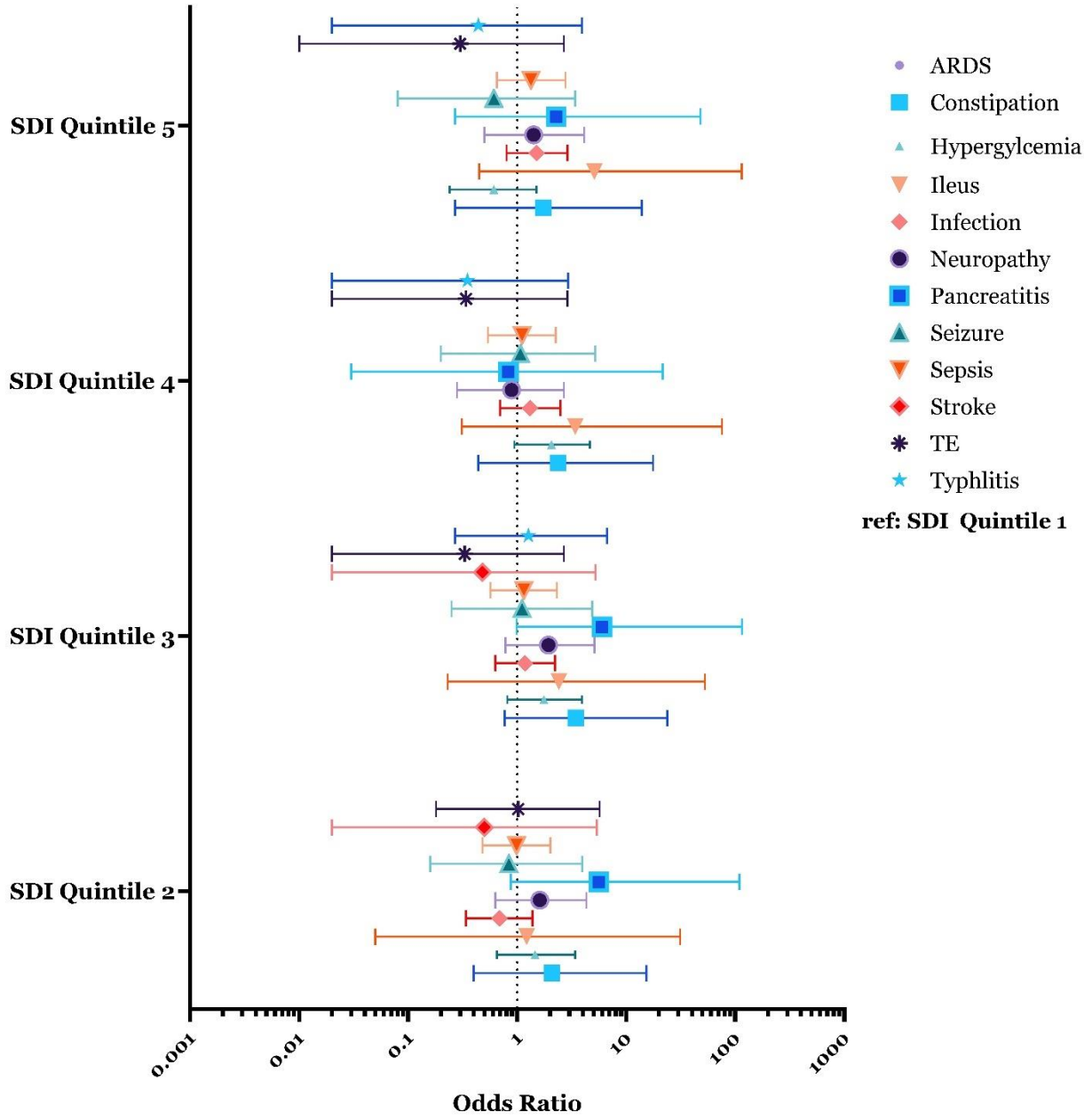
AEs: Adverse Events; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event

Figure 8. Odds of development of AEs during induction by SDI quintile



SDI: Social Deprivation Index; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event

Figure 9. Odds of development of severe (grade 3+) AEs during induction by SDI quintile



AEs: Adverse Events; SDI: Social Deprivation Index; ARDS: Acute respiratory distress syndrome; TE: Thromboembolic event