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Differential Outcomes by SES in Children Undergoing Treatment for Acute Lymphoblastic Leukemia

Sergio Barrera, Randy Davila, and Emily Roberts
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Mentors: **Dr. Donna Neuberg**, Senior Lecturer on Biostatistics, Dana-Farber Cancer Institute and Harvard T.H. Chan School of Public Health

Traci Blonquist, MS Dana-Farber Cancer Institute

Graduate Mentor: **Joey Antonelli**, Harvard T.H. Chan School of Public Health

Pediatric Acute Lymphoblastic Leukemia: Biology

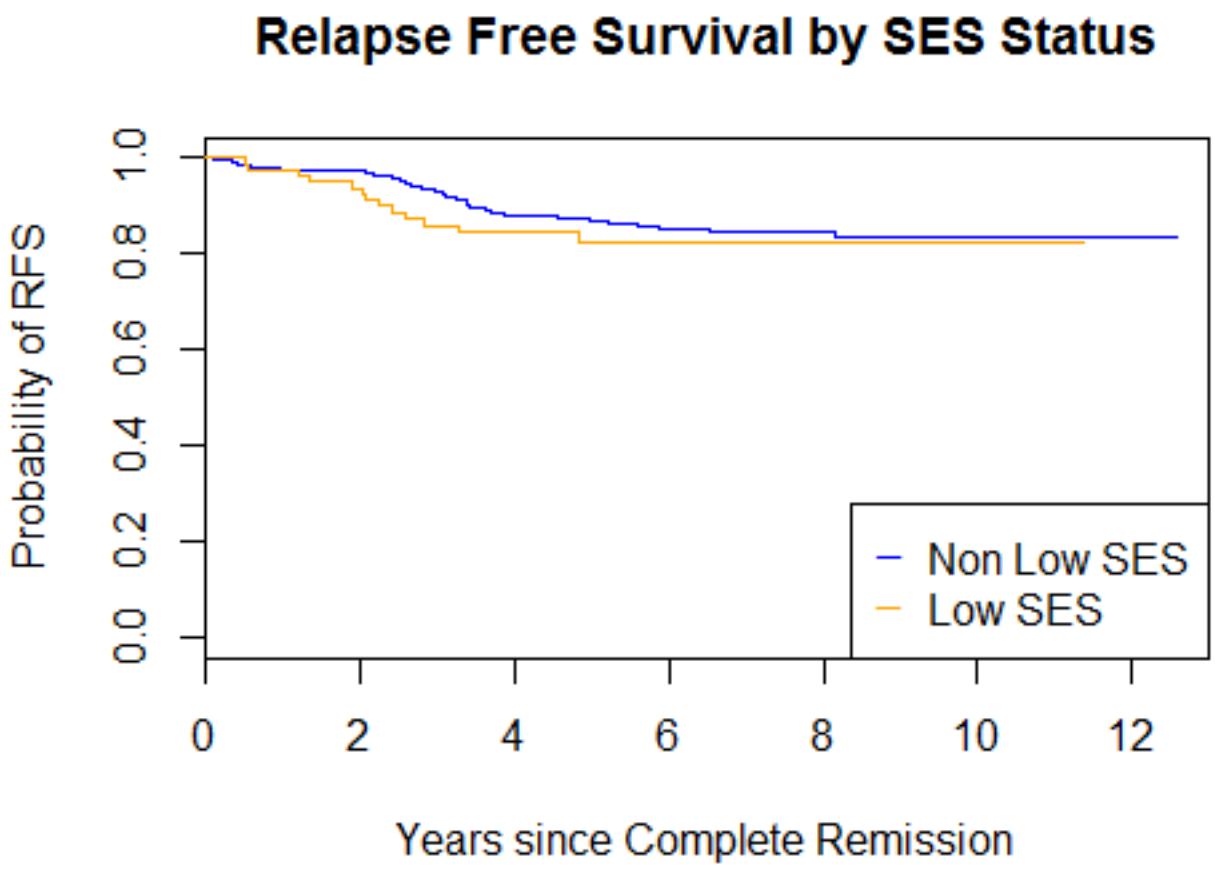
- Disease that affects white blood cell count (increased lymphocyte count)
  - Median age at diagnosis: 5 years
- Increase in survival rates
- Therapy approach: decrease probability of relapse event without affecting the increase of toxicity incidence

Design of the Study

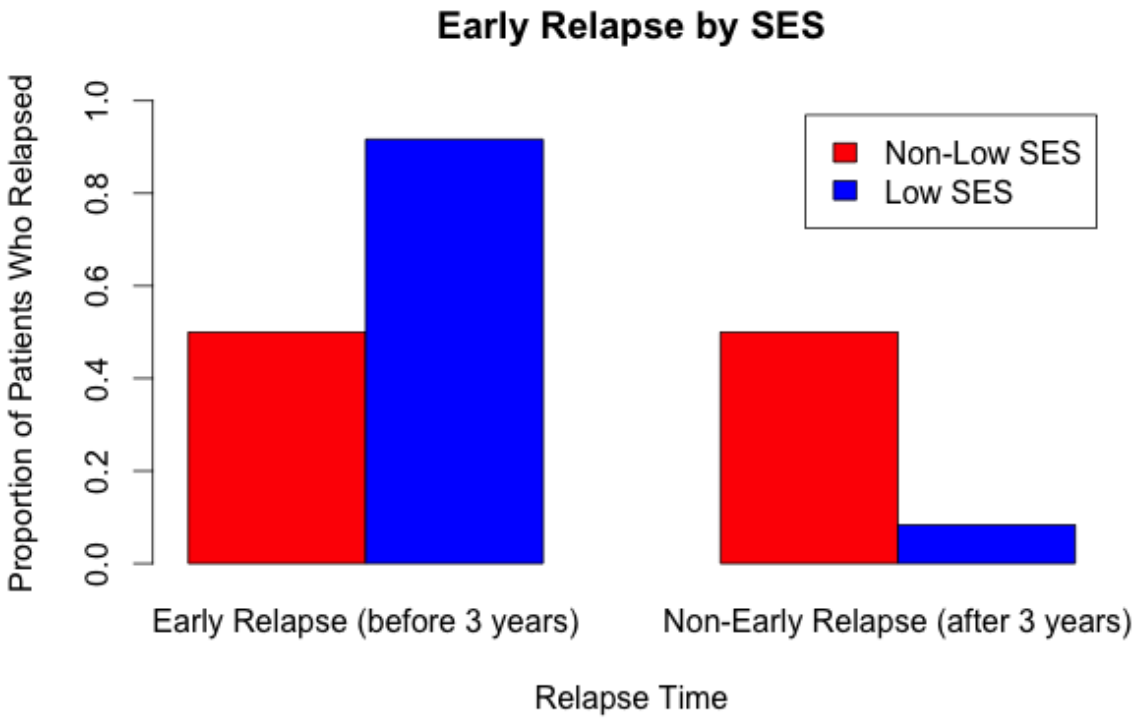
Study Phase	00-001	05-001
Induction	1 month	1 month
Consolidation/ Intensification	5 months	~ 6 months
Continuation	~ 18 months	~ 17 months

- Two protocols: 00-001 and 05-001
  - 00-001 randomized patients to two randomizations:
    - Fixed versus individualized dose
    - Type of steroid post-induction
  - 05-001 randomized drug delivery
  - Goal is to determine efficacy based on event-free survival rate
- Low SES determined by more than 20% of population below poverty level in zip code

Relapse-Free Survival time based on SES



Differential Relapse Time

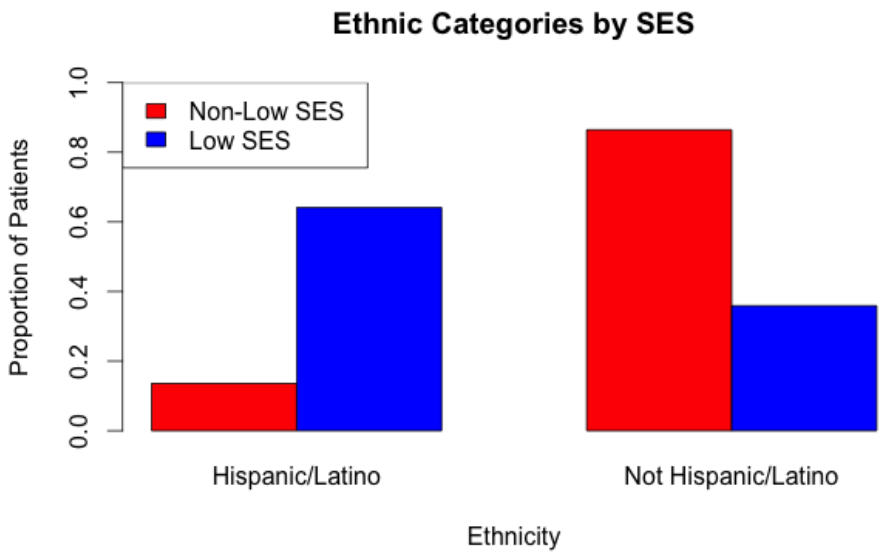


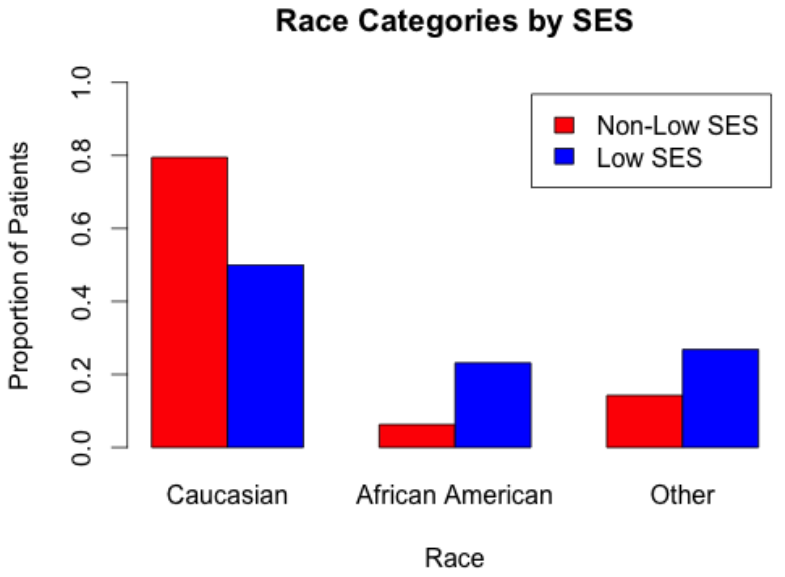
Fisher's Exact p-value 0.009

Hypothesis

- Our question: What is driving a difference in relapse time based on SES?
- Difference in toxicity events based on SES
- Prediction: Greater number of toxicity events in low SES group

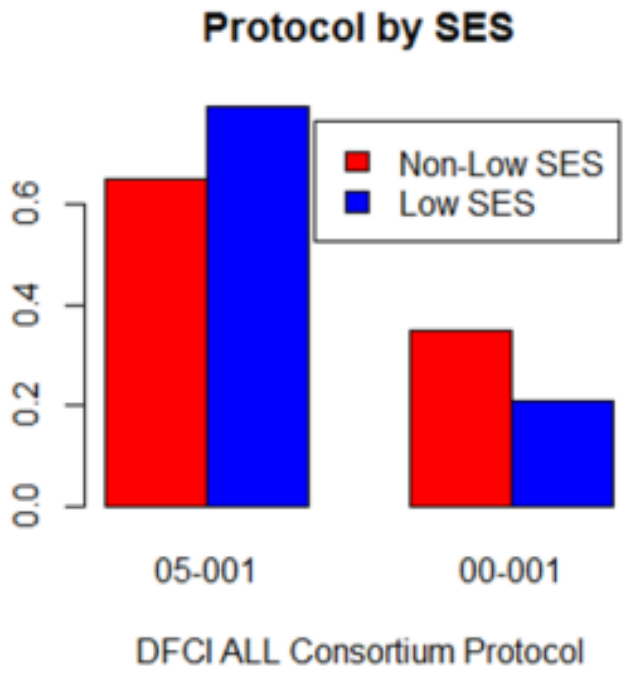
Demographic Variables by SES			
	n Low SES (%)	n Non-Low SES (%)	Fisher's Exact P-Value
Female	30 (36.6)	221 (47.7)	0.07
Ethnicity(Hispanic)	20 (25.6)	53 (13.6)	0.001
White/Caucasian	41 (50)	368 (79.5)	<0.001
African-American	19 (23.2)	29 (6.7)	<0.001
Other (Asian/Other)	22 (26.8)	66 (14.3)	0.008





Risk Stratification (Genotype Characteristics) by SES			
	n Low SES (%)	n Non-low SES (%)	Fisher's Exact P-value
Age(>10 year)	25 (30.5)	109 (23.5)	0.21
Down Syndrome Status	1 (1.2)	23 (4.97)	0.15
Philadelphia Chromosome Status	0 (0)	11 (2.38)	0.38
Standard risk patients	39 (43.8)	203 (47.6)	0.63
T-cell phenotype	9 (11)	42 (9.1)	0.54
White blood cell count greater than 50,000	21 (25.6)	81 (17.5)	0.09

SES Group Proportions Based on Study Design			
Protocol and Study Designation	n Low SES (%)	n Non-Low SES (%)	Fisher's Exact P-value
Patients Not Randomized	20 (24.4)	162 (35.2)	0.06
Patients designated to 2000 study	17 (20.7)	162 (35)	0.01



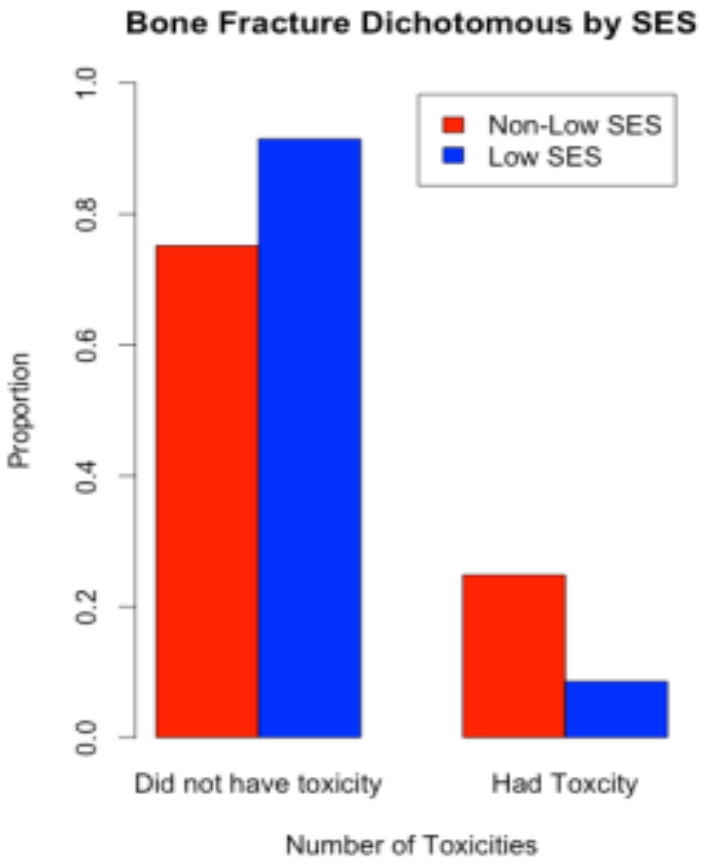
Toxicities

Variables	n Low SES (%)	n Non-Low SES (%)	Fisher's Exact P-Value
Edema	1 (1.2)	0 (0)	0.150
Pancreatitis	9 (11.0)	36 (7.8)	0.381
Allergies	7 (8.5)	53 (11.4)	0.566
Infections	22 (26.8)	118 (25.5)	0.785
Thrombosis	7 (8.5)	34 (7.3)	0.653
Abnormal Blood Lipids	3 (3.6)	25 (5.3)	0.786
Insulin-Requiring Diabetes	0 (0)	2 (0.4)	1.0

- No significant differences by SES found in dichotomous outcomes for these toxicities

Bone Events

Variable	Fisher's Exact P-Value
Avascular Necrosis 1	1.0
Avascular Necrosis 2	0.837
Avascular Necrosis Follow Up	0.845
Avascular Necrosis Dichot.	0.453
Bone Fracture 1	0.625
Bone Fracture 2	0.313
Bone Fracture Follow Up	0.175
Bone Fracture Dichot.	0.0008



- 7 Low SES, 115 Non-Low SES

New Question?

- What could be contributing to higher bone fracture incidence among non-low SES patients?
- To answer this question we performed logistic regression analysis
- In choosing our regression model we
  - Performed Fisher's Exact Tests on explanatory variables
  - Conducted Stepwise and Bayesian Model Averaging

Other Potential Factors

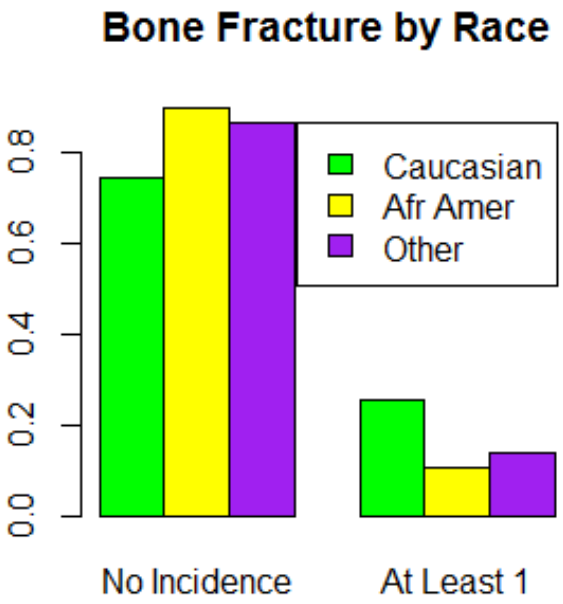
- We know from previous analysis that SES groups differ by
  - Protocol
  - Race
  - Ethnic status
  - Randomization
- Other Variables include:
  - Gender
  - White Blood Cell Count
  - Age
  - Phenotype

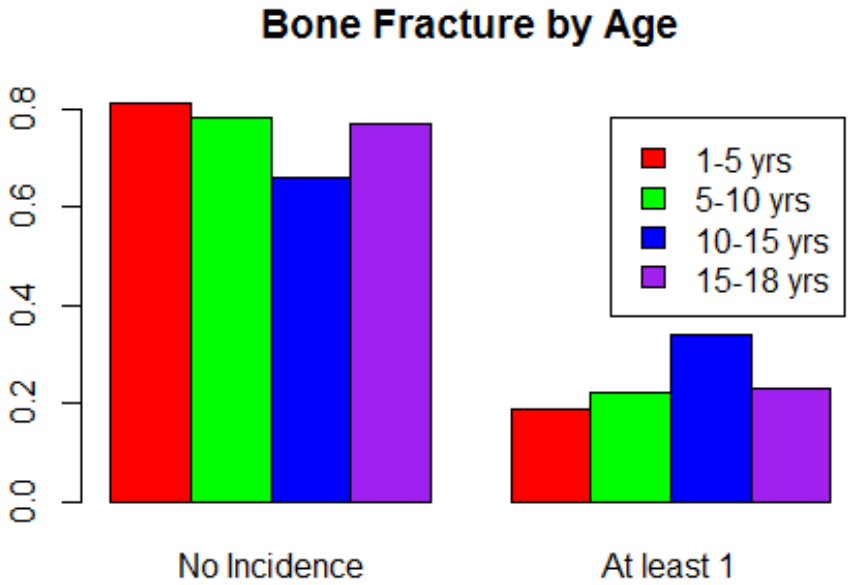
Univariate Analysis of Potential Explanatory Variables for Bone Fracture

Variable	Odds Ratio	Fisher's Exact P-value
Randomization	1.07	0.83
Protocol	1.26	0.32
Gender (1 if Female)	1.28	0.26
Risk Category	1.35	0.15
WBC (1 if >50K)	0.82	0.51
Phenotype	0.72	0.48
Ages 5 and below	0.67	0.064
Ages 5-10	0.97	1.0
Ages 10-15	2.032	0.0091
Ages 15 and up	1.04	0.86
Non-standard Risk <10	0.80	0.44
Hispanic (Ethnic Cat.)	0.70	0.23
Caucasian	2.414	0.001
African American	0.378	0.045
Other Race	0.499	0.036

- There appears to be an association between age and race with bone fracture incidence
- All other variables were not associated with bone fracture incidence

Interesting Differential Results





- Caucasians had a higher incidence of bone fracture compared to other races
- Patients aged between 10-15 years of age also had a higher incidence of bone fracture compared to other age groups

Model Selection

- To overcome model uncertainty we performed the stepwise procedure
- This tests different models and chooses the model with the lowest estimated information loss
- Based off of prior analysis, variables included in stepwise procedure included:
  - Age at diagnosis (categorical)
  - Race Categories (African American, Other)
  - Protocol
  - Risk Status
  - Randomization
  - Ethnic Category (Hispanic/Non Hispanic)

Step-wise Procedure

- The stepwise procedure returned a model which only included SES, race, and age as explanatory variables
- This finding is consistent with our earlier analysis
- Our proposed model then was of the form

$$\ln\left(\frac{p}{1-p}\right) = \widehat{\beta_1} + \widehat{\beta_2} Low\ SES + \widehat{\beta_3} African\ American + \widehat{\beta_4} Other\ Race$$
$$+\widehat{\beta_5} age(5-10) + \widehat{\beta_6} age(10-15) + \widehat{\beta_7} age(15-18)$$

Bayesian Model Averaging

- In order to verify if our model is an appropriate model for our analysis we conducted a BMA analysis
- Reports model of the form

$$\ln\left(\frac{p}{1-p}\right) = \widehat{\beta_1} + \alpha_2\widehat{\beta_2}Low\ SES + \alpha_3\widehat{\beta_3}African\ American + \alpha_4\widehat{\beta_4}Other\ Race$$
$$+\alpha_4\widehat{\beta_5}age(5-10) + \alpha_6\widehat{\beta_6}age(10-15) + \alpha_7\widehat{\beta_7}age(15-18)$$
$$+\alpha_8\widehat{\beta_8}NonStan\ Risk + \alpha_9\widehat{\beta_9}Protocol + \alpha_{10}\widehat{\beta_{10}}Not\ Randomized$$

- Accounts for model uncertainty by averaging over the best models
  - Reports average value of coefficients of best models
  - Reports approximate posterior probability

BMA Results: Hispanic

BMA Model with Ethnic Variable		
	Estimate	%(α =1)
Intercept	-1.134	NA
Low SES	-1.245	95
Age_5-10	0	0
Age_10-15	0.276	39
Age_>15	0.018	3.9
Ethnicity (Hispanic)	0	0
African American	-0.393	32
Other Race	-0.321	35.9
Risk Category	0.028	7.5
Direct Assign	0	0
Protocol B	0	0

- Ethnicity was never selected as an explanatory variable in any of the models
- Therefore we did not include ethnic status in our final models

Logistic Regression Results

Variables	Estimate	P-value
Intercept	-1.199	<.001
Low SES	-1.076	0.011
Age_5-10	0.174	0.51
Age_10-15	0.889	0.002
Age_>15	0.359	0.34
African American	-1.006	0.045
Other Race	-0.699	0.039

- Low SES, age 10-15, being African American and of race "other" were all statistically significant at the 5% level of significance
- Being between the ages 5-10 and being older than 15 were not

Test for Confounding

	Model 1		Model 2: Confounder	
Variables	Estimate	P-value	Estimate	P-value
Intercept	-1.199	<0.001	-1.265	<0.001
Low SES	-1.076	0.011	-1.044	0.014
Age_5-10	0.174	0.51	0.207	0.43
Age_10-15	0.889	0.002	1.002	0.005
Age_>15	0.359	0.34	0.445	0.302
African American	-1.006	0.045	-0.984	0.052
Other Race	-0.699	0.039	-0.77	0.033
Not Standard Risk			-0.082	0.78
Not Randomized			0.09	0.705
Protocol 00-001			0.107	0.641

Model Interpretation

- Socioeconomic status is significant
- Unexpected results in direction
- Highest odds of bone fracture: Non-Low SES (reference group), Caucasian (reference group), age 10-15

Limitations

- Non-optimal measure of SES
- Analysis done of dichotomous outcome
  - No frequency or time component
- Some toxicity events were infrequent

Future Work

- Possible explanations
  - Puberty, athletics, relationship with other toxicities, adherence to steroid medication
- New survey
  - More direct questions about SES

Conclusion

- There are differential outcomes
- Current measure of SES is not informative enough
- Need to address medical and social factors to best treat ALL patients

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Questions?