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# Residence in a Latinx Enclave and End-Induction Minimal Residual Disease Positivity among Children with Acute Lymphoblastic Leukemia

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## Abstract

Racial and ethnic inequities in survival persist for children with acute lymphoblastic leukemia (ALL). In the US, there are strong associations between SES, race/ethnicity, and place of residence. This is evidenced by ethnic enclaves: neighborhoods with high concentrations of ethnic residents, immigrants, and language isolation. The Latinx enclave index (LEI) can be used to investigate how residence in a Latinx enclave is associated with health outcomes. We studied the association between LEI score and minimal residual disease (MRD) in 142 pediatric ALL patients treated at Texas Children's Hospital. LEI score was associated with end-induction MRD positivity (OR per unit increase 1.63, CI 1.12–2.46). There was also a significant trend towards increased odds of MRD positivity among children living in areas with the highest enclave index scores. MRD positivity at end of induction is associated with higher incidence of relapse and lower overall survival among children with ALL; future studies are needed to elucidate the exact causes of these findings and to improve ALL outcomes among children residing within Latinx enclaves.

### Keywords

ALL; Latinx enclave; MRD; health inequities

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Conflict of Interest

The authors declare that there is no conflict of interest.

## Introduction

Acute lymphoblastic leukemia (ALL) remains a leading cause of cancer death in children and adolescents.[1,2] ALL is a cancer with well-described ethnic inequities; in particular, Latinx children bear the dual burden of higher incidence and poorer prognosis, relative to other groups.[3] Delavar et al[3], for example, showed that Latinx pediatric patients had a 1.6-fold increased hazard of death relative to non-Latinx White patients for high-survival cancers such as ALL. It is unclear to what extent these inequities stem from biological factors, social-environmental factors, or a combination of the two, but our group and others have shown an association between low neighborhood socioeconomic status (SES) and worse overall survival (OS) for pediatric ALL patients.[2–14]

In the US, there are strong associations between SES, race/ethnicity, and place of residence. This is evidenced by the existence of clear clusters of high/low SES neighborhoods as well as ethnic enclaves: neighborhoods with high concentrations of ethnic residents, immigrants, and language isolation. The Latinx enclave index (LEI), based on factors such as the proportion of residents in a neighborhood who are Latinx, foreign born, and recent immigrants, has been widely used to investigate how residence in a Latinx enclave affects health outcomes.[15–25] However, no studies have evaluated the effect of residence in a Latinx enclave and outcomes for children with ALL. The primary objective of this study was to determine whether there is an association between residence in a Latinx enclave and end-induction MRD positivity, a strong predictor of relapse and overall survival in childhood ALL.[26]

## Methods

### Study Population and Design

This was an IRB-approved, single-center, retrospective study of individuals diagnosed with B-cell ALL at Texas Children's Hospital between 2007–2018 who were less than 18 years of age at the time of diagnosis (N=142). This population was previously described by our group.[12] Notably, it was purposefully enriched for MRD-positive individuals. Patients were enrolled in and treated according to the Children's Oncology Group (COG) frontline ALL trials as indicated for their disease type and National Cancer Institute (NCI) risk group. Race and ethnicity were self-reported and categorized as non-Latinx White, non-Latinx Black, Latinx, or other Non-Latinx/unknown. The primary study outcome was end-induction MRD status, defined as ≥0.01% leukemic blasts detected in bone marrow by flow cytometry at day 29 of therapy.

### Latinx Enclave Designation

Methods for calculating Latinx enclave index scores have previously been described in detail.[27] Briefly, we computed LEI scores for each patient by principal components analysis (PCA) of the following U.S. Census and American Community Survey data elements: percent of residents who are Hispanic in the individual's census tract, percent who are Hispanic and foreign born, percent households that are linguistically isolated, and percent of Spanish language-speaking households that are linguistically isolated. Linguistically isolated

households are those in which all members in a household aged ≥14 years speak a non-English language and speak English less than “very well”. Each individual’s transformed LEI score was then assigned to a quartile, based on the distribution of scores for all census tracts in Texas: lowest (LEI-1), lower-middle (LEI-2), higher-middle (LEI-3), and highest (LEI-4). A higher LEI score means that the individual lives in a more ethnically distinct neighborhood (i.e. an “ethnic enclave”).

### Statistical Analysis

To assess potential demographic differences by quartile of LEI score, chi-squared tests and Fisher’s exact test were used. We conducted both crude and adjusted logistic regression analysis to estimate the odds ratio (OR) of MRD positivity according to LEI score. The lowest quartile (LEI-1: non-enclave) was used as the referent. All statistical analyses were conducted in R v3.6.0 (R Foundation; Vienna, Austria). For all tests, p-values < 0.05 were considered statistically significant. The following variables were included in adjusted logistic regression analyses: sex (male, female), weight (overweight/obese vs. not), age at diagnosis, unfavorable cytogenetics (defined as *BCR-ABL1* fusion, *KMT2A* rearrangement, hypodiploidy, or intrachromosomal amplification of chromosome 21 [iAMP21] at diagnosis), and NCI risk group (standard, high).

## Results

### Patient Demographics

Information on the 142 patients included in the analysis are presented in Table 1. A majority of the population was male (58.5%), and 62% of the population identified as Latinx. The proportions of NCI high risk and MRD-positive patients were also high (44.4% and 37.3%, respectively). The distribution of LEI scores skewed toward the higher quartiles. When assessing the demographic differences between MRD-negative and MRD-positive groups, there were no statistically significant differences except by NCI risk category and age at diagnosis (Table 1). NCI high risk status was significantly more frequent in the MRD-positive group (58.5%, p=0.01), and children ≥ 10 years old were also more frequent in the MRD-positive group (43.4%, p=0.02).

When evaluating demographics by LEI quartiles, several findings emerged. First, as expected, there were higher proportions of Latinx patients and primary Spanish speakers residing in the two highest LEI quartiles (63.9% and 90.3%, p < 0.001 for Latinx patients; 27.8% and 37.1%, p=0.003 for primary Spanish speakers; see Supplemental Table 1). There were no statistically significant differences in sex, age, NCI risk, cytogenetics, or MRD status according to enclave residence. Of note, there was a statistically significantly greater prevalence of overweight and obesity among patients in the higher LEI quartiles (p=0.03, see Supplemental Table 1). Multiple studies have shown a higher prevalence of obesity in Latinx children compared to their non-Latinx peers, including in Texas.[28–30]

### Latinx Enclave Index Score and MRD

Increasing LEI scores, measured continuously, were associated with a statistically significant increased risk of MRD positivity in both the crude (OR 1.30, CI 1.07–1.59) and adjusted

(OR 1.63, CI 1.12–2.46) models. There was a statistically significant trend towards increased odds of MRD positivity with increasing quartile of LEI scores in unadjusted and adjusted models (Table 2). While not significant, there was evidence that males were more likely to be MRD-positive (OR 1.61, 95% CI 0.75–3.54), as well as those in the NCI high risk group (OR 3.09, 95% CI 0.98–9.79). Further adjustment for overweight/obesity and age did not meaningfully change the associations between LEI quartile and MRD.

## Discussion

As studies continue to show health inequities based on race, ethnicity, and SES, it is critically important to understand the social-environmental correlates of these inequities to improve cancer survival in underserved populations. This report suggests an association between living in a Latinx enclave and MRD positivity. Specifically, LEI score was associated with MRD positivity, and there was a significant trend towards increased odds of MRD positivity among children living in areas with the highest enclave index scores. MRD positivity at end of induction is associated with higher incidence of relapse and lower overall survival among children with ALL[26,31]; therefore, our findings have important implications for long-term outcomes.

There are several potential explanations for our findings. There was an association with higher LEI quartiles and obesity. There are some studies that suggest an association between obesity and worse ALL outcomes, including MRD.[32,33] However, in this study, LEI score was still associated with end-induction MRD after controlling for overweight/obesity. In addition, living in an ethnic enclave may indicate poorer access to care, which could directly impact time to diagnosis, choice of treatment center, or clinical trial participation. Factors such as financial burden, effect of diagnosis/treatment on parent employment status, effect on family income, and lack of social support systems may lead to delays, lapses, or non-adherence to therapy. Moreover, language barriers may lead to poorer communication of the diagnosis, timeline of protocol, and importance of adherence to the treatment plan.[23,24] Latinx families may contend with the additional stress and fear that interactions with the healthcare system may lead to legal consequences or deportation, causing delayed presentation or attrition. Finally, the exposures associated with living in an ethnic enclave (e.g. chronic stress, environmental contaminants, etc.) may lead to epigenomic alterations, which could affect prognosis.[34]

There are several strengths of this study. This patient population comes from one of the most racially, ethnically, and socioeconomically diverse metropolitan areas in the country (Houston, TX). All patients were treated on or according to contemporary Children's Oncology Group protocols. On the other hand, sample size was limited, so the interaction between neighborhood SES and ethnic enclave scores could not be assessed. This single-center study oversampled MRD-positive patients, so the sample may not be comparable to the general population of children with ALL.[12]

Racial and ethnic inequities in childhood ALL are well documented, but there is scant literature on the pathways that connect these characteristics to treatment outcomes. Moreover, recent data suggest that racial and ethnic inequities may be increasing despite

advances in overall survival.[3] Therefore, it is critically important that studies address persistent inequities in childhood cancer outcomes. Our findings suggest that living in a Latinx enclave is associated with MRD positivity, which is a strong predictor of relapse and mortality. It may be important to assess neighborhood social-environmental factors at the time of diagnosis, as some of the deleterious effects of residence in those areas may be amenable to intervention. Possible interventions include increased outreach and engagement by cancer centers with Latinx enclaves. This may help ensure access to adequate resources to successfully navigate treatment, including basic needs screening and provision, and ensuring clear communication with the patient and family in their preferred language. Future work is needed to identify and modify risk factors experienced by patients living in ethnic enclaves, to create better treatment strategies, and to ensure equitable outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations:

| | |
|---|---|
| **ALL** | Acute lymphoblastic leukemia |
| **SES** | Socioeconomic status |
| **MRD** | Minimal residual disease |
| **OS** | Overall survival |
| **LEI** | Latinx enclave index |
| **OR** | Odds ratio |
| **CI** | Confidence Interval |

## References

1. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. 2015; 373(16):1541–1552. [PubMed: 26465987]
2. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol. 2010; 28(15):2625–2634. [PubMed: 20404250]

3. Barrington-Trimes JL, Cockburn M, Metayer C, Guaderman WJ, Wiemels J, McKean-Cowden R. Rising rates of acute lymphoblastic leukemia in Hispanic children: trends in incidence from 1992 to 2011. Blood. 2015; 125(19):3033–4. [PubMed: 25953979]
4. Delavar A, Barnes JM, Wang X, Johnson KJ. Associations between race/ethnicity and US childhood and adolescent cancer survival by treatment amenability. JAMA Pediatr. 2020; 174(5):1–9.
5. Wang L, Bhatia S, Gomez SL, Yasui Y. Differential inequality trends over time in survival among US children with acute lymphoblastic leukemia by race/ethnicity, age at diagnosis, and sex. Cancer Epidemiol Biomarkers Prev. 2015; 24(11):1781–1788. [PubMed: 26377194]
6. Tai EW, Ward KC, Bonaventure A, Siegel DA, Coleman MP. Survival among children diagnosed with acute lymphoblastic leukemia in the United States, by race and age, 2001 to 2009: findings from the CONCORD-2 study. Cancer. 2017; 123(Suppl 24):5178–5189. [PubMed: 29205314]
7. Kent EE, Sender LS, Largent JA, Anton-Culver H. Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. Cancer Causes Control. 2009; 20(8):1409–1420. [PubMed: 19496000]
8. Abrahao R, Lichtensztajn DY, Ribeiro RC, et al. Racial/ethnic and socioeconomic disparities in survival among children with acute lymphoblastic leukemia in California, 1988–2011: a population based observational study. Pediatr Blood Cancer. 2015; 62(10):1819–1825. [PubMed: 25894846]
9. Erdmann F, Feychting M, Mogensen H, Schmiegelow K, Zeeb H. Social inequalities along the childhood cancer continuum: an overview of evidence and a conceptual framework to identify underlying mechanisms and pathways. Front Public Health. 2019; 7:84. [PubMed: 31106186]
10. Scheurer ME, Lupo PJ, Schuz J, et al. An overview of disparities in childhood cancer: report on the Inaugural Symposium on Childhood Cancer Health Disparities, Houston, Texas, 2016. Pediatr Hematol Oncol. 2018; 35(2):95–110. [PubMed: 29737912]
11. Bona K, Blonquist TM, Neuberg DS, Silverman LB, Wolfe J. Impact of socioeconomic status on timing of relapse and overall survival for children treated on Dana-Farber Cancer Institute ALL Consortium Protocols (2000–2010). Pediatr Blood Cancer. 2016; 63(6):1012–1018. [PubMed: 26913850]
12. Schraw JM, Junco JJ, Brown AL, Scheurer ME, Rabin KR, Lupo PJ. Metabolomic Profiling Identifies Pathways Associated with Minimal Residual Disease in Childhood Acute Lymphoblastic Leukaemia. EBioMedicine, vol. 48, 2019, pp. 49–57. [PubMed: 31631039]
13. Schraw JM, Peckham-Gregory EC, Rabin KR, Scheurer ME, Lupo PJ, Oluyomi A. Area deprivation is associated with poorer overall survival in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020; 67:e28525. [PubMed: 32573920]
14. Bona K, Blonquist TM, Neuberg DS, Silverman LB, Wolfe J. Impact of Socioeconomic Status on Timing of Relapse and Overall Survival for Children Treated on Dana-Farber Cancer Institute ALL Consortium Protocols (2000–2010). Pediatric Blood & Cancer, 2016; vol. 63, no. 6, pp. 1012–1018. [PubMed: 26913850]
15. Durazo EM, Mbassa RS, Albert MA. Ethnic Enclaves and Type II Diabetes: a Focus on Latino/Latinx Americans. Current Cardiovascular Risk Reports, 2016; vol. 10, no. 11.
16. Eschbach K, Ostir GV, Patel KV, Markides KS, Goodwin JS. Neighborhood context and mortality among older Mexican Americans: is there a barrio advantage? Am J Public Health. 2004; 94(10):1807–12 [PubMed: 15451754]
17. Osypuk TL, Diez Roux AV, Hadley C, Kandula NR. Are immigrant enclaves healthy places to live? The Multi-ethnic Study of Atherosclerosis. Soc Sci Med. 2009; 69:110–20. [PubMed: 19427731]
18. Logan JR, Zhang W, Alba RD. Immigrant enclaves and ethnic communities in New York and Los Angeles. Am Sociol Rev. 2002; 67(2):299–322.
19. Morales LS, Lara M, Kington RS, Valdez RO. Socioeconomic, cultural, and behavioral factors affecting Latinx health outcomes. J Health Care Poor Underserved. 2002; 13(4):477–503. [PubMed: 12407964]
20. Finch BK, Vega WA. Acculturation stress, social support, and self-rated health among Latinos in California. J Immigr Health. 2003; 5(3):109–17. [PubMed: 14512765]
21. Mulvaney-Day NE, Alegria M, Sribney W. Social cohesion, social support, and health among Latinos in the United States. Soc Sci Med. 2007; 64(2):477–95. [PubMed: 17049701]

22. Viruell-Fuentes E, Morenoff JD, Williams DR, House JS. Contextualizing nativity status, Latino social ties, and ethnic enclaves: an examination of the 'immigrant social ties hypothesis'. Ethn Health. 2013; 18(6):586–609. [PubMed: 23947776]

23. Salas-Wright CP, Robles EH, Vaughn MG, Córdova D, Pérez-Figueroa RE. Toward a typology of acculturative stress: results among Latinx immigrants in the United States. Latinx J Behav Sci. 2015; 37(2):223–42.

24. Nobari TZ, Wang M-C, Chaparro MP, et al. Immigrant enclaves and obesity in preschool-aged children in Los Angeles County. Soc Sci Med. 2013; 92:1–8. [PubMed: 23849273]

25. Shariff-Marco S, Gomez SL, Canchola AJ, et al. Nativity, ethnic enclave residence, and breast cancer survival among Latinas: Variations between California and Texas. Cancer, 2020; 126(12), 2849–2858. [PubMed: 32181892]

26. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood, 2008;111(12), 5477–5485. [PubMed: 18388178]

27. Shariff-Marco S, Lin K, Meltzer D, et al. Developing measures of Asian American and Hispanic/Latino ethnic enclave for five states using U.S. Census and American Community Survey data. University of California San Francisco, San Francisco, CA; October 2021.

28. Wang Y Disparities in Pediatric Obesity in the United States. Advances in Nutrition, Volume 2, Issue 1, January 2011, Pages 23–31. [PubMed: 22211187]

29. Hoelscher DM, Butte NF, Barlow S, et al. Childhood Obesity. Feb 2015.71–91. [PubMed: 25555188]

30. "2021 Report: From Crisis to Opportunity." The State of Childhood Obesity, Robert Wood Johnson Foundation, Oct. 2021, https://stateofchildhoodobesity.org/2021report/.

31. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood, 2015; 126(8), 964–971. [PubMed: 26124497]

32. Eissa HM, Zhou Y, Panetta JC, et al. The effect of body mass index at diagnosis on clinical outcome in children with newly diagnosed acute lymphoblastic leukemia. Blood Cancer J. 2017 Feb 17;7(2):e531. [PubMed: 28212374]

33. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood. 2014 Dec 18;124(26):3932–8. [PubMed: 25349177]

34. Johnstone SE, Baylin SB. Stress and the epigenetic landscape: a link to the pathobiology of human diseases? Nat Rev Genet, 2010 Nov; 11 (11): 806–812. [PubMed: 20921961]

**TABLE 1.**

Patient demographics by MRD status.

| | MRD negative | MRD positive | p-value |
|---|---|---|---|
| *Sex* | | | 0.16 |
| Female | 41 (46.1%) | 18 (34.0%) | |
| Male | 48 (53.9%) | 35 (66.0%) | |
| *Race/ethnicity* | | | 0.16 |
| Latinx | 51 (57.3%) | 37 (69.8%) | |
| Non-Latinx White | 30 (33.7%) | 10 (18.9%) | |
| Non-Latinx Black or Other | 8 (9.0%) | 6 (11.3%) | |
| *Overweight status* | | | 0.26 |
| Not Overweight/Obese | 65 (73.6%) | 34 (64.2%) | |
| Overweight/Obese | 21 (23.6%) | 17 (32.1%) | |
| Unknown or NA | 3 (3.4%) | 2 (3.8%) | |
| *NCI risk group* | | | 0.01 |
| Standard | 57 (64.0%) | 22 (41.5%) | |
| High | 32 (36.0%) | 31 (58.5%) | |
| *Primary Language* | | | 0.31 |
| English | 69 (77.5%) | 37 (69.8%) | |
| Spanish | 20 (22.5%) | 16 (30.2%) | |
| *Cytogenetic category* | | | 0.44 |
| Favorable or neutral | 78 (87.6%) | 44 (83.0%) | |
| Unfavorable | 11 (12.4%) | 9 (17.0%) | |
| *Latinx Enclave Index Quartiles* | | | 0.18 |
| LEI-1 (Lowest LEI Scores) | 12 (13.5%) | 4 (7.5%) | |
| LEI-2 | 18 (20.2%) | 6 (11.3%) | |
| LEI-3 | 27 (30.3%) | 15 (28.3%) | |
| LEI-4 (Highest LEI Scores) | 32 (36.0%) | 28 (52.8%) | |
| *Age at Diagnosis* | | | 0.02* |
| Infant (<1 year) | 0 (0.0%) | 1 (1.9%) | |
| Child (1–9 years) | 66 (74.2%) | 29 (54.7%) | |
| Adolescent (≥10 years) | 23 (25.8%) | 23 (43.4%) | |

All p-values were obtained with the Chi-Squared test, except for *, which was obtained using the Fisher's Exact Test.

**TABLE 2.**

Regression analysis of Latinx enclave index scores and MRD positivity.

| | **Crude OR (95% CI)** | **Adjusted OR (95% CI)**[b] |
|---|---|---|
| Latinx Quartile | p=0.03[a] | p=0.01[a] |
| LEI-1 (Lowest) | 1.00 (Ref) | 1.00 (Ref) |
| LEI-2 | 1.00 (0.23–4.62) | 0.69 (0.14–3.54) |
| LEI-3 | 1.67 (0.48–6.79) | 1.55 (0.41–6.68) |
| LEI-4 (Highest) | 2.62 (0.81–10.24) | 2.91 (0.85–11.96) |
| Male (vs Female) | 1.66 (0.83–3.41) | 1.61 (0.75–3.54) |
| High NCI Risk (vs Standard) | 2.51 (1.26–5.09) | 3.09 (0.98–9.79) |
| Unfavorable Cytogenetics (vs favorable or neutral) | 1.45 (0.55–3.77) | 1.13 (0.37–3.27) |

[a] p-for-trend.

[b] Adjusted for sex (male, female), overweight/obesity (not shown), age at diagnosis (not shown), unfavorable cytogenetics (defined as *BCR-ABL1* fusion, *KMT2A* rearrangement, hypodiploidy, or iAMP21 at diagnosis), and NCI risk group (standard, high).