ELSEVIER

Blood 142 (2023) 2828–2830

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Development of a Novel Methotrexate-Related Neurotoxicity Risk Score in Pediatric Acute Leukemia: A Report from the Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium

Rachel Harris[1], *Olga Taylor*[1], *Melanie Brooke Bernhardt, MS,PharmD*[1], *Ashley Chavana*[1], *Mark Zobeck, MD MPH*[2], *Philip J. Lupo, PhD*[3], *Karen R. Rabin, MDPhD*[4], *Michael E. Scheurer, PhD MPH, FACE*[5], *Austin L Brown, PhD*[1]

[1] Baylor College of Medicine, Houston, TX
[2] Department of Pediatrics, Division of Hematology-Oncology, Baylor College of Medicine, Houston
[3] Division of Hematology-Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, TX
[4] Department of Pediatrics, Baylor College of Medicine, Baylor College of Medicine TX Children's Cancer Center, Houston, TX
[5] Department of Pediatrics, Baylor College of Medicine, Houston, TX

Introduction: Methotrexate (MTX) chemotherapy is a critical component of contemporary pediatric acute lymphoblastic leukemia (ALL) treatment regimens. However, intrathecal (IT) and intravenous (IV) MTX can result in dose-limiting acute neurotoxicity, which has been associated with an increased risk of ALL relapse. Emerging data suggest the likelihood of MTX neurotoxicity is elevated in Latino patients and those diagnosed at older age or treated with high-dose MTX (> 1g/m2); however, there are no established methods for identifying those at greatest risk. Therefore, we used machine learning algorithms to develop a neurotoxicity risk prediction model in a diverse, multi-ethnic cohort of pediatric patients with ALL.
Methods: The Reducing Ethnic Disparities in Acute Leukemia (REDIAL) Consortium enrolls patients diagnosed with ALL from six participating treatment centers in the Southwestern U.S. This interim analysis included pediatric patients (age <20 years) diagnosed and treated for ALL at Texas Children's Hospital (2005-2019). Individuals diagnosed with infant leukemia (<1 year of age) and/or with preexisting neurologic disease were excluded. We retrospectively reviewed medical records to identify clinical, sociodemographic, and Common Terminology Criteria for Adverse Events (CTCAE) grading of toxicities such as transaminitis and hyperbilirubinemia. Address information at the time of diagnosis was geocoded and aligned to the American Community Survey at the census-tract level to define residential social determinants of health (SDOH). Cases of MTX neurotoxicity were identified by manual review of records for any patient who underwent brain MRI imaging during ALL therapy. Cases of acute MTX neurotoxicity were defined following Ponte di Legno Delphi Consensus definitions as neurologic episodes (e.g., seizure, stroke-like symptoms, altered mental status) occurring within 21 days of IV or IT MTX with no other identifiable underlying cause. Demographic and clinical factors were compared between cases of acute MTX-related neurotoxicity and controls using logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI). The dataset was randomly split with 80% of observations used in the training stage and 20% reserved for testing. Random forest algorithms with boosting and down sampling were grown using 5-repeat, 10-fold cross validation to optimize tuning parameters. Model performance was evaluated using test and train error rate, area under the curve of the receiver operating characteristic (AUC-ROC), sensitivity, and specificity.
Results: A total of 770 patients were eligible and met inclusion criteria. Patients were a mean age of 7.0 years at diagnosis, 54% male, 55% Latino and 45% treated with high-risk protocols. Acute MTX neurotoxicity developed in 134 (17.4%) of patients. In logistic regression models, neurotoxicity odds increased with older age at diagnosis (OR = 1.20, 95% CI: 1.15-1.26), Latino ethnicity (OR = 2.14, 95% CI: 1.38-3.38), treatment on high-risk protocols (OR=4.32, 95% CI: 2.75-6.99), obesity at diagnosis (vs normal weight, OR = 2.54, 95% CI: 1.51-4.22), and CTCAE grade 3 or higher transaminitis (OR = 2.02, 95% CI: 1.03-4.47) or hyperbilirubinemia (OR = 4.71, 95% CI: 1.21-18.41) during induction therapy. Overall, the random forest machine learning algorithm resulted in an AUC-ROC of 0.79 with an error rate of 0.26 in both the training and test sets. The overall sensitivity was 0.71, with a specificity of 0.67. Recognizing ethnic disparities in MTX neurotoxicity may exist, random forest models were generated stratifying on ethnicity (Figure 1), which yielded slightly better performance in non-Latino patients (AUC-ROC = 0.77) than Latino patients (AUC-ROC = 0.73).
Conclusions: This interim analysis of data from the REDIAL Consortium demonstrates the potential utility of machine learning algorithms to develop a novel risk prediction model for acute MTX-related neurotoxicity. Efforts to expand this work within the

larger REDIAL cohort (n>2,000) and incorporate inherited genetic data are ongoing. Ultimately, this work may inform efforts to preemptively risk-stratify patients and deliver targeted interventions to vulnerable individuals.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189986

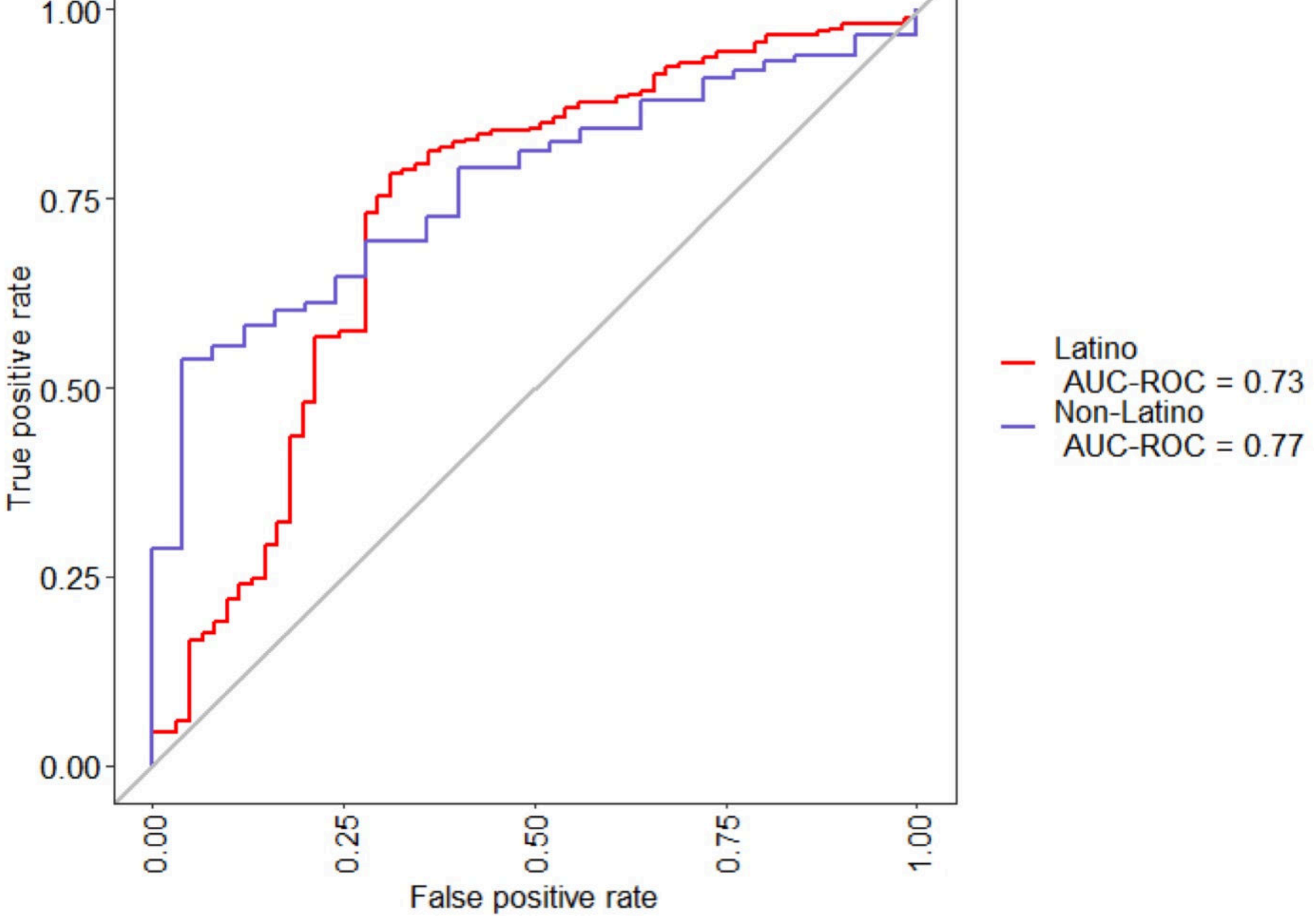

Figure 1. Random forest predictive performance (AUC-ROC) for MTX neurotoxicity stratifying on ethnicity