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William Blum, Emory University
M Rebechi, The Ohio State University Wexner Medical Center
J Kohlschmidt, The Ohio State University Comprehensive Cancer Center
K Mrózek, The Ohio State University Comprehensive Cancer Center
D Nicolet, The Ohio State University Comprehensive Cancer Center
AS Mims, The Ohio State University Comprehensive Cancer Center
JS Blachly, The Ohio State University Comprehensive Cancer Center
S Orwick, The Ohio State University Comprehensive Cancer Center
KT Larkin, The Ohio State University Wexner Medical Center
CC Oakes, The Ohio State University Wexner Medical Center

Only first 10 authors above; see publication for full author list.

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Association of social deprivation with survival in younger adult patients with AML: an Alliance study

Melanie Rebechi,1 Jessica Kohlschmidt,2,3 Krzysztof Mrózek,2 Deedra Nicolet,2,3 Alice S. Mims,2,4 James S. Blachly,2,4 Shelley Orwick,4 Karilyn T. Larkin,1,2 Christopher C. Oakes,1,2 Andrew Hantel,5 Andrew J. Carroll,6 William G. Blum,7 Bayard L. Powell,8 Geoffrey L. Uy,9 Richard M. Stone,5 Richard A. Larson,10 John C. Byrd,11 Electra D. Paskett,12 Jesse J. Plascak,12,* and Ann-Kathrin Eisfeld2,4,*

1Department of Internal Medicine, The Ohio State University, Columbus, OH; 2Clara D. Bloomfield Center for Leukemia Outcomes Research, The Ohio State University Comprehensive Cancer Center, Columbus, OH; 3Alliance Statistics and Data Management Center, The Ohio State University Comprehensive Cancer Center, Columbus, OH; 4Division of Hematology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; 5Department of Medical Oncology, Dana-Farber/Partners CancerCare, Boston, MA; 6Department of Genetics, University of Alabama at Birmingham, Birmingham, AL; 7Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; 8Department of Internal Medicine, Section on Hematology and Oncology, Comprehensive Cancer Center of Wake Forest Baptist Health, Winston-Salem, NC; 9Division of Oncology, Washington University School of Medicine, St. Louis, MO; 10Department of Medicine, University of Chicago, Chicago, IL; 11Department of Internal Medicine, University of Cincinnati, Cincinnati, OH; and 12Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, OH

Cancer health disparities are differences in health outcomes observed across population groups, including patients with acute myeloid leukemia (AML), characterized by various social factors such as race, ethnicity, education, or environmental exposure.1-5 Patients living in areas characterized by higher social deprivation (SD) experience worse health outcomes because of public and private disinvestment, leading to exposure to various health-adverse factors.6,7 Notably, SD is an extrinsic factor that can be changed by measures taken at the community level, and/or overcome by individuals. To our knowledge, no large study of adult AML has hitherto evaluated the impact of SD within large, multicenter clinical trials conducted with standardized treatments to reduce confounding bias owing to health care access.

We analyzed 1893 adults diagnosed with de novo AML (except acute promyelocytic leukemia), including 1233 patients aged <60 years and 660 aged ≥60 years, who were treated on the Cancer and Leukemia Group B/Alliance for Clinical Trials in Oncology frontline treatment protocols (supplemental Figure 1). All patients provided written informed consent to participate in treatment studies, of which protocols were in accordance with the Declaration of Helsinki and approved by institutional review boards at each center.

We calculated zip code–level social deprivation index (SDI), a well-validated metric of zip code SD6 (supplemental Data). We divided patients with AML into quartiles based on SDI (trend test, P = .81) and then defined 2 SDI groups: low (patients in quartile 1) and high (patients in quartiles 2-4). Low SDI comprised the lowest 25% of SDI scores and included 323 younger patients and 172 patients aged ≥60 years. High SDI included the upper 75% of SDI scores and included 910 younger and 488 older patients. Figure 1A shows the geographic distribution of patients’ residential zip code SDI.

The mutational status of 80 protein-coding genes was retrospectively determined centrally at The Ohio State University via companion protocol CALGB 20202.8-10 Experimental details are provided in the supplemental Data.

The baseline characteristics of patients with high and low SDI scores are shown in supplemental Table 1. Most clinical characteristics did not differ significantly between the high- and low-SDI groups. However, Black patients were more frequent in the high-SDI group (9% vs 1%, P < .001).
Among patients aged <60 years, those in the high-SDI group had lower percentages of BCOR (3% vs 7%, \( P = .03 \)), IDH1 (6% vs 11%, \( P = .03 \)), and STAG2 (2% vs 5%, \( P = .02 \)) mutations, of mutations in genes belonging to the cohesin complex (11% vs 18%, \( P = .03 \)) and methylation-related (36% vs 46%, \( P = .03 \)) groups, and a higher percentage of mutations in genes encoding
tumor suppressors (18% vs 11%, \( P = .02 \)) than patients in the low-SDI group, suggesting differences in the disease biology (supplemental Tables 2 and 3).

Younger patients in the high-SDI group had shorter disease-free survival (DFS; median, 1.5 vs 2.8 years; \( P = .02 \)) and overall survival (OS; median, 1.9 vs 3.0 years; \( P = .005 \)), and more of them died during follow-up (65% vs 55%; \( P = .004 \)) compared with younger patients in the low-SDI group (Table 1; supplemental Figures 1A-B). Notably, fewer patients residing in the high SDI areas underwent off-protocol hematopoietic stem cell transplantation in first complete remission (CR) than patients in low SDI areas (12% vs 17%, \( P = .04 \)).

In multivariable analyses, high SDI score associated independently with shorter OS both in the entire cohort of younger patients (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.06-1.55; \( P = .001 \)) and in the subset of younger patients with available molecular information (HR, 1.43; 95% CI, 1.10-1.86; \( P = .008 \); Figure 1C; supplemental Table 4). However, because both BCOR\(^{11-13} \) and IDH\(^{11,14} \) mutations have been reported to adversely affect prognosis of younger adults with AML, the lower frequency of these mutations in high SDI-group patients, whose outcomes are worse, makes it less likely that the observed survival disparities can be explained by underlying biology of the disease.

Importantly, there were no significant differences in CR or relapse rates between SDI groups (Table 1), suggesting that response to induction was not inherently different. There was also no significant difference in early death rate, indicating that a delay in diagnosis and/or starting therapy might not be a factor driving differences in survival outcomes. Similarly, there was no difference in the number of consolidation cycles received that would support differences in post-CR consolidation intensity.

Notably, high SDI score, compared with low SDI score, was associated with shorter DFS (5-year rates: 48% vs 60%; \( P = .05 \); supplemental Figure 2B) and OS (5-year rates: 56% vs 73%; \( P = .004 \); Figure 1D) in patients belonging to the 2017 European LeukemiaNet\(^{15} \) favorable-risk group (supplemental Table 5). No significant impact of SDI scores on DFS or OS was seen in patients belonging to either the 2017 European LeukemiaNet intermediate-risk or adverse-risk groups (supplemental Figure 3).

The association of SD with outcomes within the favorable genetic-risk group is especially concerning, because patients in this genetic-risk group have the highest likelihood of being cured with chemotherapy alone. Because these patients are generally not offered allogeneic hematopoietic stem cell transplantation in first CR, transplant availability does not seem to have played a major role in the observed survival disparities. In contrast, the higher percentage of patients in the high-SDI group who died during follow-up, may suggest that impediments to, or delay of, care and support after completion of protocol treatment might have contributed to survival disparities.

Given the previously reported shorter survival of non-Hispanic Black patients with AML,\(^{16,17} \) we analyzed the survival of Black and White patients separately with respect to the assigned SDI group. In White patients, belonging to the high-SDI group (compared with those in the low-SDI group) was associated with shorter DFS (median: 1.5 years vs 2.3 years; \( P = .04 \); supplemental Figure 2C) and OS (median: 2.0 vs 2.9 years; \( P = .01 \); Figure 1E and supplemental Table 6), whereas no direct analysis of the impact of SDI could be made in Black patients because of the very low number (\( n = 3 \)) of Black patients in the low-SDI group. However, Black patients belonging to the high-SDI group had comparable DFS (median: 1.0 vs 1.5 years; \( P = .45 \)) and OS (median: 1.7 vs 2.0 years; \( P = .27 \)) to those of White patients who lived in areas with high SDI.

In contrast to younger patients, we found no significant differences in the frequency distribution of AML-associated gene mutations (\( n = 660 \); supplemental Table 7) or survival between the SDI groups in older patients, both among patients treated with chemotherapy and those receiving treatment with decitabine with or without bortezomib\(^{18} \) (supplemental Table 8). This is not surprising, because older patients are known to have worse outcomes\(^{15} \); thus, any potentially negative impact of SDI would be more difficult to detect in this age group.

### Table 1. Outcome of adult patients with AML aged <60 years with respect to SDI-group assignment

<table>
<thead>
<tr>
<th>End point</th>
<th>Patients with low SDI, ( n = 269 )</th>
<th>Patients with high SDI, ( n = 800 )</th>
<th>( P ) value(^{\text{c}} )</th>
<th>OR/HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early death, n (( n^1 ))</td>
<td>11 (3)</td>
<td>41 (5)</td>
<td>.52</td>
<td>0.73 (0.37-1.43)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>235 (73)</td>
<td>681 (75)</td>
<td>.46</td>
<td>1.11 (0.84-1.48)</td>
</tr>
<tr>
<td>Relapse rate, n (%)</td>
<td>97 (53)</td>
<td>321 (56)</td>
<td>.49</td>
<td>1.13 (0.81-1.57)</td>
</tr>
<tr>
<td>Patients who died, n (%)</td>
<td>149 (55)</td>
<td>522 (65)</td>
<td>.004</td>
<td>1.51 (1.14-2.00)</td>
</tr>
<tr>
<td>DFS</td>
<td>.02</td>
<td></td>
<td>1.58 (1.23-2.03)</td>
<td></td>
</tr>
<tr>
<td>Median, y</td>
<td>2.8</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate at 5 y (95% CI)</td>
<td>45 (37-52)</td>
<td>37 (33-41)</td>
<td>.005</td>
<td>1.31 (1.05-1.62)</td>
</tr>
<tr>
<td>OS</td>
<td>.005</td>
<td></td>
<td>1.31 (1.05-1.62)</td>
<td></td>
</tr>
<tr>
<td>Median, y</td>
<td>3.0</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate at 5 y (95% CI)</td>
<td>46 (40-52)</td>
<td>37 (34-41)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR, odds ratio.

\(^{\text{a}}\)P values for categorical variables are from Fisher exact test; \( P \) values for the time-to-event variables are from the log-rank test.

\(^{\text{b}}\)Early death is defined as death within 30 days after start of induction therapy, regardless of cause.

\(^{\text{c}}\)For early death and complete remission analyses the denominator included patients who received an allogeneic hematopoietic stem cell transplantation in first CR (patients with low SDI, \( n = 323 \); patients with high SDI, \( n = 910 \)). All other outcome analyses excluded patients receiving an allogeneic hematopoietic stem cell transplantation in first CR.
Limitations of our study include the fact that we analyzed only patients enrolled on frontline clinical treatment protocols, which means that patients who are disadvantaged by lack of trial access were omitted. Representativeness in AML clinical trials has been recently identified as an important contributor to research disparities, including both SD and racial-ethnic identity. In this study, we used zip codes and Eastern Cooperative Oncology Group performance status as validated surrogates for SDI determination and patient comorbidities, respectively. However, this highlights the need to collect such data prospectively in future clinical trials.

We believe that our results uncover a potentially modifiable risk factor, which, if addressed, might improve outcomes of patients with favorable-risk AML without changes in treatment modality or intensity, and shows the necessity to investigate possible additional risk factors in patients with AML.

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ORCID iDs: A.S.M., 0000-0002-1898-9836; G.L.U., 0000-0002-7809-0996; R.A.L., 0000-0001-9168-3203.

Correspondence: Ann-Kathrin Eisfeld, The Ohio State University Comprehensive Cancer Center, 460 West 12th Ave, Room 850, Columbus, OH 43210-1228; email: Ann-Kathrin.Eisfeld@osumc.edu; Jessica Kohlschmidt, The Ohio State University Comprehensive Cancer Center, OSU Medical Center, Room 353, 650 Ackerman Rd, Columbus, OH 43202-4500; email: Jessica.Kohlschmidt@osumc.edu; Krzysztof Mrózek, The Ohio State University Comprehensive Cancer Center, OSU Medical Center, Room 351, 650 Ackerman Rd, Columbus, OH 43202-4500; email: Krzysztof.Mrozek@osumc.edu; and Jesse J. Plascak, Division of Cancer Prevention and Control, Department of Internal Medicine, College of Medicine, The Ohio State University, 1590 N High St, Ste 525, Columbus, OH 4320; email: Jesse.Plascak@osumc.edu.

References


