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Association of social disorganization index with time to first septic shock event in children with acute myeloid leukemia

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Abstract

Background—Pediatric acute myeloid leukemia (AML) chemotherapy increases the risk of life-threatening complications including septic shock (SS). We hypothesized an area-based measure of social determinants of health, the Social Disorganization Index (SDI), would be associated with SS and SS-associated death (SS-death).

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Conflict of Interest

The rest of the co-authors have no conflict of interests to disclose.

Ethical Approval: Ethical approval was not required as study did not meet criteria for human subject research.

Methods—Children treated for de novo AML on two Children's Oncology Group (COG) trials at institutions contributing to the Pediatric Health Information System (PHIS) database were included. SDI was calculated using residential ZIP code data from the US Census Bureau. SS was identified using PHIS resource utilization codes. SS-death was defined as death within 2 weeks of an antecedent SS event. Patients were followed from 7 days after start of chemotherapy until the first of: end of front-line therapy, death, relapse, or removal from study. Multivariable-adjusted Cox regressions estimated hazard ratios (HR) comparing time to first SS by SDI groups.

Results—The assembled cohort included 700 patients with 207 (29.6%) sustaining at least one SS event. There were 233 (33%) in SDI-5 group (highest disorganization). Adjusted time to incident SS did not statistically significantly differ by SDI [reference = SDI-1; SDI-2 HR 0.84 (95% Cl 0.51, 1.41); SDI-3 HR 0.70 (95% Cl 0.42, 1.16); SDI-4 HR 0.97 (95% CI 0.61, 1.53); and SDI-5 HR 0.72 (95% CI 0.45, 1.14)]. Nine (4.4%) patients with SS experienced SS-death; 7 (78%) were in SDI-4 or 5.

Conclusions—In a large, nationally representative cohort of trial-enrolled pediatric patients with AML, there was no significant association between SDI and time to septic shock.

Precis:

Time to first septic shock event was not associated with the social disorganization index (SDI), an area-based measure of social determinant of health, in children with acute myeloid leukemia treated on two COG trials. Septic shock-associated mortality is rare in children with AML and differences by SDI were not able to be detected.

Keywords

Pediatric AML; Septic Shock; Social Disorganization Index; SDOH; COG

INTRODUCTION

Severe infections occur frequently in children with acute myeloid leukemia (AML) receiving intensive chemotherapy. Population-based cancer studies consistently identify infection as the leading cause of treatment-related morbidity and mortality.[1] A life-threatening complication of severe infections is septic shock (SS), defined as sepsis with cardiovascular organ dysfunction.[2] Interventions to monitor patients more closely, intensify supportive care, or reduce treatment intensity can improve outcomes.[3,4] Previous studies detected increased risk for infection-related mortality in Black children with AML,[5] and increased odds of severe sepsis in Hispanic children with AML[6] compared to white children. Additionally, mortality was higher among children from minoritized backgrounds who have cancer[5,7–9] and among hospitalized children without cancer.[10,11] However, race is an inconsistently defined and applied social construct and is often used in research as a proxy for other social determinants of heath (SDOH).[12] Children living in disorganized environments can sustain early toxic stress with subsequent altered immune responses and increased risk for adverse health outcomes.[13,14] We hypothesize this prior exposure of chronically altered immune response from a disorganized environment may impact infectious complications, like SS, in children with leukemia regardless of where they receive treatment. Further investigation is

warranted to better understand the relationship between SDOH and SS outcomes in children with AML.

Individual-level SDOH have not been routinely collected in administrative databases or clinical trials. However, neighborhood-level data have been used as proxies for individual SDOH and have been associated with individual health outcomes.[15,16] There are multiple composite neighborhood indexes[17,18] comprised of different component domains of SDOH and validated at varying levels of census-based geographic granularity. The Social Disorganization Index (SDI)[19] measures neighborhood disorganization, which is driven in part by structural racism resulting in policies and laws driving differential access to resources and opportunities.[20] This index is validated at the ZIP code level and has been used to proxy neighborhood SDOH in investigating teen alcohol use[19], syphilis infection[21], and neurodevelopment in infants[22] outcomes. To our knowledge, neighborhood disorganization has not been evaluated in association with SS incidence or outcomes in children with AML. The SDI may allow us to risk stratify patients and guide the development of interventions.

The primary objective of this study was to determine whether neighborhood disorganization, measured by the SDI, was associated with time to SS for children with AML treated on two Children's Oncology Group (COG) trials. Our secondary objective was to determine whether neighborhood disorganization was associated with septic shock-associated mortality (SS-death). We hypothesized that higher neighborhood disorganization would be associated with higher hazards of SS and SS-death.

METHODS

Data sources

The Pediatric Health Information System (PHIS) is an administrative database that contains inpatient, emergency department, and observation unit information from over 50 not-for-profit, tertiary care pediatric hospitals.[23] Data include demographics, dates of service, discharge disposition and vital status, diagnosis codes, and daily inpatient billing data for medications, laboratory tests, imaging procedures, clinical services/procedures, and supplies. Data are deidentified at the time of submission. Quality of submitted data is ensured through a joint effort between the Children's Hospital Association, Truven Health Analytics, and participating hospitals.

COG is a pediatric cooperative oncology group funded by the National Cancer Institute with over 200 participating centers in the United States, Canada, Europe, New Zealand, and Australia. We have merged COG AAML0531 and AAML1031 trial data with PHIS administrative data.[24,25] AAML0531 randomized 1,028 eligible patients to standard chemotherapy ± gemtuzumab for treatment of *de novo* AML from August 2006 to June 2010.[26] AAML1031 trial randomized 1,231 eligible patients to standard chemotherapy ± bortezomib from February 2011 and January 2016.[27] Both studies captured extensive diagnostic, leukemia biology, and outcomes data.

Study population

This study used a previously assembled cohort of pediatric patients with *de novo* AML aged 0–19 years, who enrolled on COG AAML0531 or AAML1031 trial and received treatment at a PHIS participating institution[24,25,28] from 2006–2015. Patients with Down syndrome, those with an enrollment date before their treating hospital started contributing inpatient data to PHIS, those who transferred care after treatment initiation, those with incomplete billing data or less than 7 days of therapy, or those with an invalid or non-residential ZIP code (e.g., PO box and/or areas not defined by the Census) were excluded. Patients who did not survive 7 days after start of chemotherapy were excluded.

Social Disorganization Index (SDI)

The primary exposure was the SDI, an area-based composite measure of SDOH domains. We calculated the SDI with data from the 2013 Census Bureau's American Community Survey (ACS) and validated for 5-digit ZIP Code Tabulation Areas (ZCTA). ACS data were first reported in 2011, however this 2011 version had fewer questions and less comprehensive geographic coverage.[29] Given that ACS data provide 5-year estimates,[29] 2013 ACS 5-year estimates were used to calculate the SDI as this year would encompass both clinical trial periods (2006–2010 and 2011–2016) and allow for comparison. The SDI is calculated as the sum of the following proportions: overall unemployment, households receiving public assistance, low-income persons (<100% and at 100–149% poverty level), high school dropouts, female-headed households, renter-occupied houses, and moved households within the last year.[19] For this analysis, patients' 5-digit home ZIP code recorded on first admission, using COG data, was used to link to the ZCTA-level SDI. To define their exposures to neighborhood disorganization at the ZIP code level, patients were grouped into one of 5 SDI categories (SDI-1 being least and SDI-5 being most disorganized) based on their US nationally normed SDI.

Outcomes

The primary outcome of interest was time from 7 days after start of first course of chemotherapy to first SS event during front-line chemotherapy. We did not assess SS during the first 6 days of therapy due to potential overlap with severity of presentation at diagnosis that may be misclassified. We used our previously developed and validated method to detect SS events in PHIS.[30] Our algorithm for SS detection incorporates PHIS resource utilization (RU) codes (Figure 1) with comparable sensitivity and positive predictive value to published papers using diagnostic (ICD-9) codes.[31–33] Unlike approaches based on diagnosis codes alone,[33] our augmented approach using diagnosis and RU codes allows for determination of the date of onset of SS. PHIS data only provide information on whether a medication was ordered and billed; not whether it was administered to the patient. By design, our cohort used a permissive definition of septic shock, including fluid-responsive shock, as fluid-sensitive shock is clinically relevant and likely indicative of significant infectious or inflammatory events. Thus, our algorithm is designed to capture both fluid-sensitive and fluid-refractory SS.

The secondary outcome of interest was time to SS-death, defined as death within 2 weeks of an antecedent SS event and without evidence of relapse.[34] This analysis was restricted to patients with a first SS event.

Covariates

Patient characteristics using COG data included age,[35,36] sex,[37] insurance type (private, public, or other),[38,39] race-ethnicity [Hispanic, non-Hispanic (NH)-Black, NH-white, and other],[40] COG study and risk group by COG study.

Statistical analyses

Differences in demographic characteristics by SDI group were assessed using Fisher's exact test. To evaluate potential confounding, each covariate's association with exposure and outcome was evaluated and those demonstrated associations with both exposure ($P<0.2$ or absolute difference in proportion >10%) and outcome ($P<0.2$ or HR >1.5 or HR <0.67) were retained in the final adjusted model.

Time to SS event (primary outcome) and time to SS-death (secondary outcome) by SDI group were evaluated using the Kaplan-Meier method and compared by SDI group using log-rank tests. Patients were censored at the first of: relapse, death, completion of therapy or removal from the study due to induction failure or patient or clinician preference; all these dates were obtained from COG data. Cox proportional hazard regression was used to estimate unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for both outcomes. The proportional hazards assumption was assessed by visual inspection of the log-log plot and by the score test using the Schoenfeld residuals.

Stratified analysis by trial was performed as a post-hoc sensitivity analysis to accommodate potential heterogeneity between trials. Additionally, sensitivity analyses were performed restricting follow-up to end of course 1, as previous studies have demonstrated disparities in outcomes during induction.[40] Finally, we performed sensitivity analysis collapsing the SDI categories into 3 groups: low (SDI 1 and 2), medium (SDI 3) and high (SDI 4 and 5). All analyses were performed using STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The study was considered exempt by the Children's Hospital of Philadelphia Institutional Review Board.

RESULTS

Patient characteristics

The initial eligible cohort included 771 patients diagnosed with de novo AML between October 18, 2006 and December 31, 2015. Excluded patients included patients with Down syndrome (n=2), patients who enrolled on study at hospitals not participating in PHIS and then transferred care to PHIS hospitals (n=33), and patients with incomplete billing data (n=20). Nine patients were excluded due to no ZIP code reported, invalid ZIP code, or absent ZCTA. Only patients who enrolled in either trial and started therapy (2 enrolled and never started therapy) and had at least 7 days of treatment (5 had less than 7 days) were included in the final analysis. The final study population for analysis included 700

patients. Table 1 summarizes the distribution of patient characteristics by SDI group. Higher proportions of Hispanic (37.8%) and NH-Black (17.2%) patients were in SDI-5 compared to the other SDI group ($p<0.001$). A higher proportion of publicly insured patients (48.1%) were in SDI-5 compared to the other SDI groups ($p<0.001$). Distributions of age, sex, trial participation, and AML risk groups were more comparable across SDI groups.

Follow up time and distribution of events

The median on-therapy follow-up for the cohort was 167 days [interquartile range (IQR) 133, 214], and was similar by SDI groups (Table 1).

There were 207 (29.6%) patients with a SS event before completing follow-up or experiencing a censoring event. There were 33 (4.7%) patients censored for relapse [SDI-1 n=2 (1.9%), SDI-2 n=6 (5.8%), SDI-3 n=4 (3.5%), SDI-4 n=8 (5.4%), and SDI-5 n=13 (5.8%)] and two patients (one each in SDI-3 and SDI-4) died without an antecedent SS event. Competing risk analyses for relapse and non-relapse mortality were not performed given the small numbers of competing events in each SDI group and similar distribution across SDI groups.

Association of SDI with first septic shock event

Figure 2 shows Kaplan-Meier estimates for time to first SS according to neighborhood disorganization. SDI was not significantly associated with time to first SS event (log rank, $p=0.54$).

Table 2 presents unadjusted and adjusted (adjusting for confounders: race-ethnicity and insurance status) HRs and 95% Cls for first SS event by SDI group. There was no evidence that the proportional hazards assumption was violated either by formal statistical tests ($p>0.5$) or visual inspection of Schoenfeld residuals.

Septic shock-associated mortality in relation to patient characteristics and SDI

Table 3 summarizes the distribution of patient characteristics for the subset of patients (n=207) in the cohort that had at least one SS event by SDI group. The distribution of patients by SDI group was: 15% SDI-1, 13.5% SDI-2, 14.5% SDI-3, 24.2.0% SDI-4 and 32.9% SDI-5. Similar to the full cohort, most patients (32.9%) were in SDI-5.

There were 9 SS-deaths. Due to the limited number of events, Kaplan-Meier estimates and Cox regression models were not performed. Table 4 summarizes the distribution of patient characteristics who had SS-deaths by SDI group. Seven of the 9 patients (78%) belonged in SDI-4 or 5, and 7 out of 9 patients (78%) were NH white. Five out of 9 patients (56%) had SS-death in cycle 1 of therapy.

Sensitivity Analysis

Primary analyses were repeated by trial (AAML0531 and AAML1031). Supplemental Figure 1 and supplemental Figure 2 shows Kaplan-Meier estimates for time to first SS according to SDI by trial. SDI was not significantly associated with time to first SS event for AAML0531 (log rank, $p=0.264$) or for AAML1031 (log rank, $p=0.117$). In our adjusted

model for AAML0531 there is a decreased hazard of SS for SDI-2–5 when compared to SDI-1 that approaches statistical significance. In contrast, the adjusted HR for SDI-2–5 compared to SDI-1 for AAML1031 were not statistically significant (Supplemental Tables 1–4). Additionally, SDI was not significantly associated with time to first SS event when we restricted follow up to end of cycle 1 nor was there a significant association when we collapsed the SDI categories into 3 groups.

DISCUSSION

In a large, nationally representative cohort of trial-enrolled pediatric patients with AML, there was no significant association between SDI and time to SS in children treated on two COG trials. Thus, the SDI was not a useful metric to risk stratify these patients. This study is the first to investigate the relationship of neighborhood disorganization proxied by the SDI, an area-based measure of SDOH, and frequency of SS in children with AML.

The general pediatric literature has mixed findings on the association of area-based measures of SDOH and infection-related outcomes, including sepsis. One study found no significant association between neighborhood social vulnerability and prolonged lengths of intensive care unit stays for children with severe sepsis and underlying medical complexity, not restricted to patients with cancer.[41] Nationally, roughly 80% of pediatric patients receive AML care in the inpatient setting.[42] Therefore, we assume most of our population of patients with AML was already admitted to the hospital following receipt of chemotherapy. Once hospitalized, disparities in access to medical care may be less impactful; thus, the care our study population received at large children's hospitals might mitigate the impact of neighborhood SDOH on SS outcomes. In contrast, in a cohort of infants presenting to medical care for fever and infection evaluation, patients exposed to a high neighborhood poverty status had higher rates of bacterial infection compared to patients from low poverty neighborhoods.[43]

An adult study found that sepsis-related mortality was higher among patients living in low-income neighborhoods compared to patients from higher income neighborhoods and that neighborhood poverty, lack of insurance, and lower formal education status were independently associated with sepsis-related mortality.[44] This study used community data for the city of Baltimore, creating a more demographically granular area of measurement. This method differs from ours, which used a less granular 5-digit ZIP-code based measure with a higher risk of misclassification, which may have biased our results towards the null.

Fifty-four percent of the patients in our cohort came from neighborhoods assigned to SDI-4 or 5 (more disorganized neighborhoods), and this finding was similar across the two trials. To our knowledge, this is the first time this has been reported in a pediatric AML population. There are some studies that applied the area deprivation index in pediatric acute lymphoblastic leukemia[45] and pediatric central nervous system tumors[46] populations, and their cohorts had proportionate numbers of patients by area deprivation index quartiles. Further investigation is needed to understand the distribution of social disorganization among trial-enrolled pediatric AML patients.

There were 9 SS-deaths events in the cohort, and 78% (n=7) of them were in SDI-4 or SDI-5 (highest disorganization). Seven out of 111 NH-white patients and zero out of 27 NH-Black patients had a SS-death, which contrasts with an older study that showed NH-Black patients had higher mortality from infection.[5] Our SS definition was based on resource utilization codes,[30] while the previous study used clinical trial adverse event reporting, which can be inaccurate.[47] A previous study showed higher acuity of presentation in NH-Black children with AML compared to NH-white children, which was associated with increased mortality during Induction[40]. Since our study excluded the first 7 days of treatment to differentiate acuity of initial presentation from chemotherapy-associated toxicities, our study intentionally excludes sepsis present at the time of AML diagnosis. Septic shock-associated mortality is rare in children with AML receiving intensive chemotherapy, and differences by SDI were not able to be detected in this cohort.

Our stratified analysis showed evidence of heterogeneity by trial. The trials had similar clinical demographics including similar number of patients (340 for AAML0531 and 360 for AAML1031), a similar distribution of patients by SDI, and a similar proportion of patients had our primary outcome. Methodologically we used 2013 ACS 5-year estimates to calculate SDI for both trials to allow for comparison. We suspect that the heterogeneity between trials may be due to the small numbers of events across the 5 SDI groups.

The majority of studies investigating SDOH as they relate to cancer outcomes use area-based measures.[48] However, individual measures of SDOH may be more useful in developing targeted patient-centered interventions. Although there was no association between SDI and hazard of SS, individual-level measures of SDOH likely play a role in pediatric cancer outcomes. Acknowledging the importance of these key risk factors, COG and the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium have incorporated individual assessments of SDOH in recent[50] and upcoming phase 3 trials (clinicaltrials.gov ID: NCT03020030 and NCT03914625).

This study has several important limitations to note. First, it used an area-based measure to calculate neighborhood disorganization. Populations comprising ZIP codes and ZCTAs tends to be more heterogenous than other census geographies, such as block groups. ZIP codes and ZCTAs are large in area, and assignment of an SDI group to an individual patient or patient's family using 5-digit ZIP code data is more vulnerable to misclassification than using SDI groups derived using data from a more granular measurement such as block groups. Additionally, only patients with a valid U.S. 5-digit zip code were included in this analysis, thus our results cannot be applied to populations outside the United States or in certain rural areas unmapped to ZIP codes. To compare results by trial, we calculated the SDI using 2013 ACS 5-year estimates, which ensures the same methodology in calculating our exposure but risks misclassification if there were changes in SDI during the early and late years of AAM0531 and AAML1031 respectively. In this dataset, we were not able to distinguish which patients were discharged early from those who remained inpatient through count nadir and recovery and thus were not able to evaluate if early discharge was associated with time to first SS. Our SS outcome is defined by an intentionally inclusive algorithm that includes fluid-responsive SS and thus may result in higher number of SS events. Finally, our study only captures patients enrolled on a clinical trial and treated at PHIS participating

institutions, which are limited to free-standing academic children's hospitals. Patients treated off trial and/or treated in a community hospital were not captured and thus our results may not include those with the greatest barriers to accessing care.

This study found no statistically significant association between an SDI derived from 5-digit ZIP code areas and hazard of SS in children being treated for AML. Additional studies are needed to further explore individual-level and other neighborhood-level measures of SDOH and SS in children undergoing cancer treatment. It may be necessary to leverage more granular measures of SDOH to identify differential risk for poor outcomes among pediatric cancer populations. The potential impact of SDOH on patient outcomes may be mitigated by care provided in the inpatient setting. Therefore, possible association between SDOH and clinical outcomes may be more apparent in cohorts of children with a cancer that is managed in the outpatient setting such as acute lymphoblastic leukemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

Data is available on request from authors.

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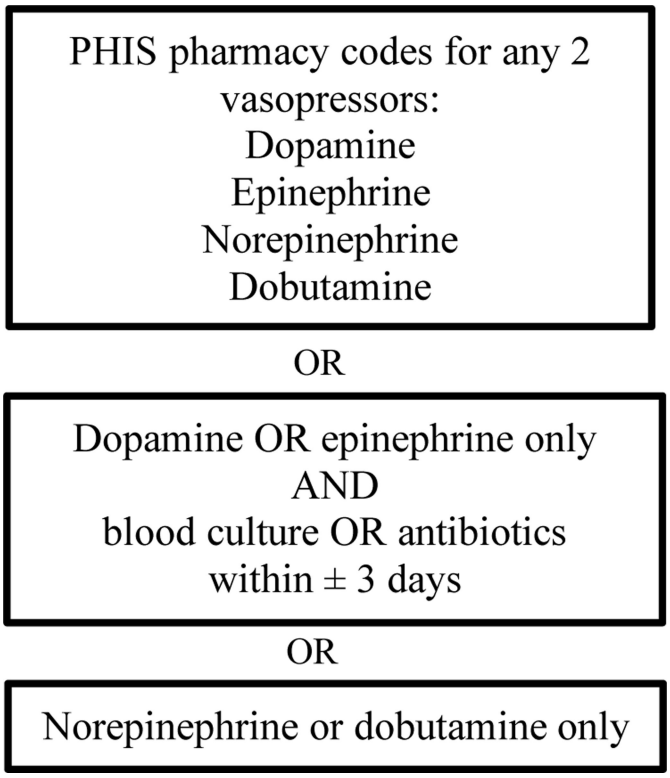
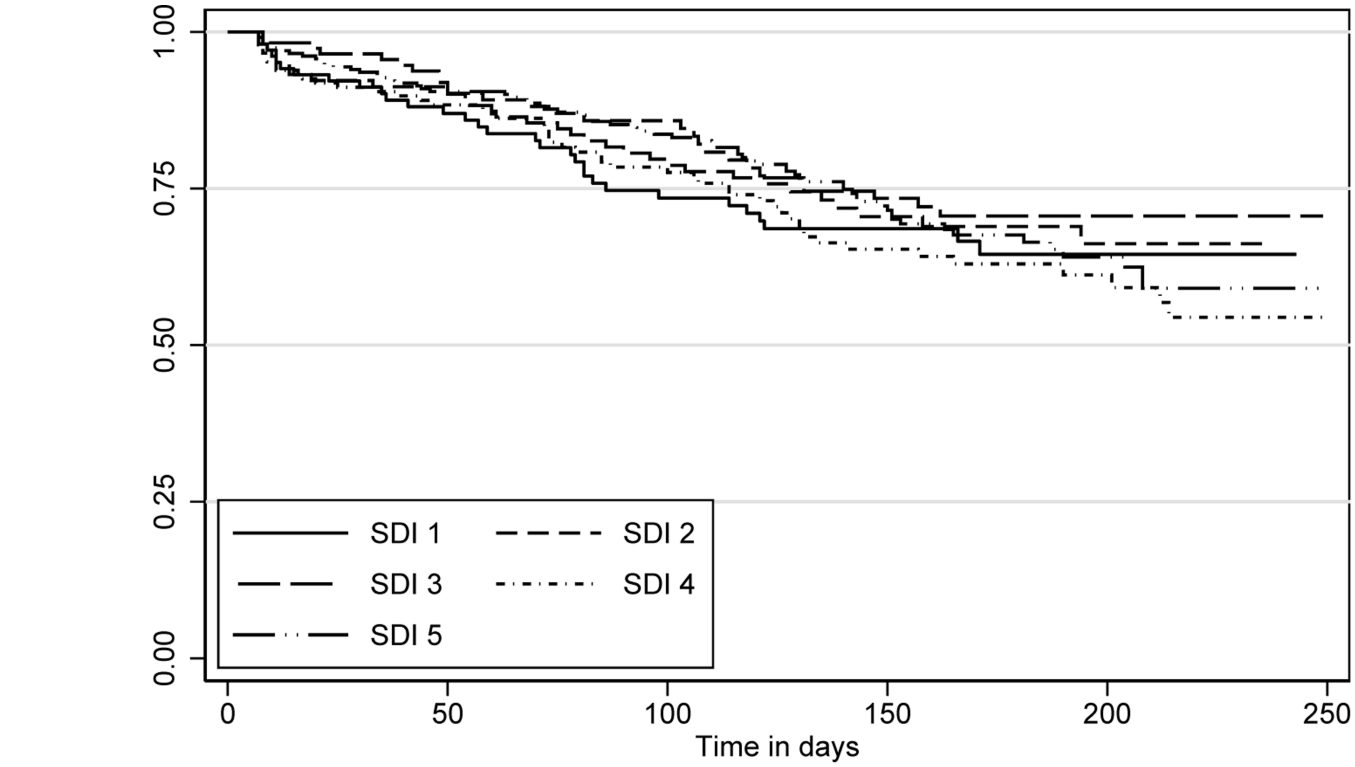


Figure 1: Septic shock identification.

Vasopressor RU patterns were used to identify SS events in PHIS cohorts. Note: single-agent epinephrine with asparaginase within ± 3 days was considered anaphylaxis, not septic shock.



RISK TABLE

SDI 1	103	81	61	46	17	3
SDI 2	103	87	71	48	21	3
SDI 3	114	100	81	63	30	9
SDI 4	147	125	93	60	30	7
SDI 5	233	200	161	102	45	11

Figure 2:

Kaplan-Meier time to first septic shock event estimates for children with acute myeloid leukemia according to Social Disorganization Index (SDI). X-axis indicated time since start of chemotherapy + 7 days, in days. Y-axis indicates probability of being septic shock free. Line pattern indicates SDI group. Solid line: SDI 1 (least disorganized); small dash : SDI 2; long dash : SDI 3; short dash dot: SDI 4; long dash dot dot: SDI 5 (most disorganized).

Table 1.

Characteristics of children with acute myeloid leukemia according to Social Disorganization Index (SDI).

	Lowest <<< <<>> >>> Highest disorganization disorganization						
	Total	**SDI 1**	**SDI 2**	**SDI 3**	**SDI 4**	**SDI 5**	**p-value[a]**
	N=700 (100)	n=103 (14.7)	n=103 (14.7)	n=114 (16.3)	n=147 (21.0)	n=233 (33.3)	
Age in yrs, n (%)							0.62
<1	64 (9.1)	4 (3.9)	11 (10.7)	11 (9.6)	14 (9.5)	24 (10.3)	
1–2	132 (18.9)	16 (15.5)	14 (13.6)	23 (20.2)	29 (19.7)	50 (21.5)	
3–9	169 (24.1)	33 (32.0)	22 (21.4)	22 (19.3)	36 (24.5)	56 (24.0)	
10–15	173 (24.7)	24 (23.3)	27 (26.2)	30 (26.3)	36 (24.5)	56 (24.0)	
15+	162 (23.1)	26 (25.2)	29 (28.2)	28 (24.6)	32 (21.8)	47 (20.2)	
Sex, n (%)							0.44
Female	336 (48)	50 (48.5)	45 (43.7)	63 (55.3)	66 (44.9)	112(48.1)	
Male	364 (52)	53 (51.5)	58 (56.3)	51 (44.7)	81 (55.1)	121(51.9)	
Race-ethnicity, n (%)							<0.001
Hispanic	136 (19.4)	8 (7.8)	8 (7.8)	12 (10.5)	20 (13.6)	88 (37.8)	
NH[b] Black	66 (9.4)	2 (1.9)	1 (1.0)	7 (6.1)	16 (10.9)	40 (17.2)	
NH White	421 (60.1)	81 (78.6)	80 (77.7)	81 (71.1)	94 (63.9)	85 (36.5)	
Other	77 (11)	12 (11.7)	14 (13.6)	14 (12.3)	17 (11.6)	20 (8.6)	
Insurance[*], n (%)							<0.001
Private	386 (55.1)	78 (75.7)	74 (71.8)	64 (56.1)	82 (55.8)	88 (37.8)	
Public	224 (32.0)	14 (13.6)	19 (18.4)	34 (29.8)	45 (30.6)	112(48.1)	
Other	90 (12.9)	11 (10.7)	10 (9.7)	16 (14.0)	20 (13.6)	33 (14.2)	
COG trial, n (%)							0.41
AAML 0531	340 (48.6)	59 (57.3)	48 (46.6)	52 (45.6)	68 (46.3)	113(48.5)	
AAML 1031	360 (51.4)	44 (42.7)	55 (53.4)	62 (54.4)	79 (53.7)	120(51.5)	
Risk Group, n (%)							0.39
0531 Low	75 (10.8)	14 (13.7)	11 (10.8)	7 (6.1)	17 (11.6)	26 (11.2)	
0531 Intermediate	206 (29.6)	35 (34.3)	30 (29.4)	38 (33.3)	36 (24.7)	67 (28.8)	
0531 High	59 (8.5)	10 (9.8)	7 (6.9)	7 (6.1)	15 (10.3)	20 (8.6)	
1031 Low	285 (40.9)	40 (39.2)	41 (40.2)	53 (46.5)	60 (41.1)	91 (39.1)	
1031 High	72 (10.3)	3 (2.9)	13 (12.7)	9 (7.9)	18 (12.3)	29 (12.4)	
Missing	3 (0.4)	1 (1)	1 (1)	0 (0)	1 (0.7)	0 (0)	
Median follow up times in days (IQR[**])							
	167 (133,214)	173 (141,221)	168 (122,202)	170 (139,221)	170 (115,217)	165 (132,210)	

[a] Categorical variables compared by Fisher's exact test

[b] NH= Non-Hispanic

*Public insurance includes Medicaid, Medicare, and no means of payment (no insurance); Private insurance includes Medicare and private insurance (together), military sponsored, private insurance, and veterans sponsored insurance; Other insurance includes categories other, self-pay, and unknown.

**IQR= interquartile range

Table 2.

Hazard ratio and 95% CI for septic shock event in children with AML according to SDI group.

SDI group	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
SDI 1	Reference	Reference
SDI 2	0.85 (0.51–1.42)	0.84 (0.51–1.41)
SDI 3	0.77 (0.46–1.28)	0.70 (0.42–1.16)
SDI 4	1.12 (0.71–1.75)	0.97 (0.61–1.53)
SDI 5	0.91 (0.59–1.39)	0.72 (0.45–1.14)

Abbreviations: SDI, social disorganization index; AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio.

*Adjusted for patient's race-ethnicity and insurance status

Table 3.

Characteristics of children with acute myeloid leukemia who had at least one septic shock event according to group of Social Disorganization Index (SDI).

	Lowest <<<	<<>>	>>> Highest disorganization disorganization				
	Total	**SDI 1**	**SDI 2**	**SDI 3**	**SDI 4**	**SDI 5**	**p-value[a]**
	N=207 (100)	n=31 (15.0)	n=28 (13.5)	n=30 (14.5)	n=50 (24.2)	n=68 (32.9)	
Age in yrs, n (%)							0.49
<1	10 (4.8)	1 (3)	3 (11)	1 (3)	3 (6)	2 (3)	
1–2	27 (13)	2 (6)	0 (0)	6 (20)	8 (16)	11 (16)	
3–9	43 (21.8)	8 (26)	6 (21)	5 (17)	13 (26)	11 (16)	
10–15	54 (26.1)	6 (19)	9 (32)	7 (23)	10 (20)	22 (32)	
15+	73 (35.3)	14 (45)	10 (36)	11 (37)	16 (32)	22 (32)	
Sex, n (%)							0.49
Female	99 (47.8)	14 (45)	13 (46)	19 (63)	22 (44)	31 (46)	
Male	108 (52.2)	17 (55)	15 (54)	11 (37)	28 (56)	37 (54)	
Race-ethnicity, n (%)							<0.001
Hispanic	46 (22.2)	6 (19)	2 (7)	4 (13)	6 (12)	28 (41)	
NH[b] Black	27 (13.0)	1 (3)	1 (4)	3 (10)	7 (14)	15 (22)	
NH White	111 (53.6)	20 (65)	21 (75)	20 (67)	31 (62)	19 (28)	
Other	23 (11.1)	4 (13)	4 (14)	3 (10)	6 (12)	6 (9)	
Insurance[*], n (%)							0.002
Private	105 (50.7)	20 (65)	19 (68)	19 (63)	27 (54)	20 (29)	
Public	64 (30.9)	4 (13)	7 (25)	6 (20)	14 (28)	33 (49)	
Other	38 (18.4)	7 (23)	2 (7)	5 (17)	9 (18)	15 (22)	
COG trial, n (%)							0.037
AAML 0531	100 (48.3)	19 (61)	10 (36)	13 (43)	18 (36)	40 (59)	
AAML 1031	107 (51.7)	12 (39)	18 (64)	17 (57)	32 (64)	28 (41)	
Risk Group, n (%)							0.44
0531 Low	22 (10.7)	8 (26)	2 (7)	0 (0)	4 (8)	8 (12)	
0531 Intermediate	63 (30.7)	10 (32)	7 (26)	11 (37)	11 (22)	24 (35)	
0531 High	15 (7.3)	1 (3)	1 (4)	2 (7)	3 (6)	8 (12)	
1031 Low	83 (40.5)	9 (29)	12 (44)	17 (57)	23 (47)	22 (32)	
1031 High	22 (10.7)	3 (10)	5 (19)	0 (0)	8 (16)	6 (9)	
Missing	2 (1)	0 (0)	1 (4)	0 (0)	1 (2)	0 (0)	

[a] Categorical variables compared by Fisher's exact test

[b] NH= Non-Hispanic

[*] Public insurance includes Medicaid, Medicare, and no means of payment (no insurance); Private insurance includes Medicare and private insurance (together), military sponsored, private insurance, and veterans sponsored insurance; Other insurance includes categories other, self-pay, and unknown.

Table 4.

Characteristics of children with acute myeloid leukemia who had septic shock-associated mortality according to group of Social Disorganization Index (SDI).

	Total	SDI 1	SDI 2	SDI 3	SDI 4	SDI 5
	N=9 (100)	n=0 (0)	n=1 (11)	n=1 (11)	n=3 (33)	n=4 (44)
Age in yrs, n (%)						
<10	6 (67)	0 (0)	0 (0)	1 (100)	2 (67)	3 (75)
10+	3 (33)	0 (0)	1 (100)	0	1 (33)	1 (25)
Sex, n (%)						
Female	6 (67)	0 (0)	1 (100)	0 (0)	1 (33)	4 (100)
Male	3 (33)	0 (0)	0 (0)	1 (100)	2 (67)	0 (0)
Race-Ethnicity, n (%)						
Hispanic	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)
NH Black	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NH White	7 (78)	0 (0)	1 (100)	1 (100)	2 (67)	3 (75)
Other	1 (11)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
Insurance, n (%)						
Private	6 (67)	0 (0)	0 (0)	1 (100)	3 (100)	2 (50)
Public	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)
Other	2 (22)	0 (0)	1 (100)	0 (0)	0 (0)	1 (25)
Trial, n (%)						
AAML0531	5 (56)	0 (0)	0 (0)	0 (0)	1 (33)	4 (100)
AAML1031	4 (44)	0 (0)	1 (100)	1 (100)	2 (67)	0 (0)
Course number, n (%)						
1	5 (56)	0 (0)	1 (100)	0 (0)	2 (50)	2 (50)
>1	4 (44)	0 (0)	0 (0)	0 (0)	2 (50)	2 (50)