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Complications preceding early deaths in Black and White children with acute myeloid leukemia

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Abstract

Black patients have a twofold increased risk of induction mortality compared to White patients with acute myeloid leukemia (AML). We reviewed diagnosis and billing data from Pediatric Health Information System for 28 AML Induction I deaths to investigate conditions preceding death in White and Black patients. Half of deaths occurred within 10 days of initial diagnostic admission. Respiratory, cardiac, renal, and infectious complications were common prior to both White and Black deaths. Deaths in White patients were more commonly preceded by intracranial hemorrhage compared to deaths in Black patients. Future studies should assess management approaches of complications by race to identify modifiable processes that reduce mortality.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Keywords

AML; disparities; intensive care; mortality; outcomes research; race

1 | INTRODUCTION

In the last four Children's Oncology Group studies, Black children with acute myeloid leukemia (AML) had lower overall survival than White children with the most recent study showing a twofold increased risk of death in Black children.^{1–3} Early death, defined as occurring within 42 days of diagnosis, accounts for more than 10% of mortality in pediatric patients with AML.⁴ Early deaths have previously been associated with low performance status, French–American–British type M4 and M5, hyperleukocytosis,^{5,6} thrombocytopenia,⁷ and older age.^{4,8} We recently demonstrated that induction mortality among Black children with AML was more than twice that of White children.⁹ This disparity was associated with increased frequency of multiorgan system failure and increased requirement for Intensive Care Unit (ICU) level resources within 72 hr of initial admission. While early deaths in pediatric patients with AML have previously been examined,^{4,8,10} racial disparities have not been explicitly assessed. We aimed to describe the similarities and differences in clinical trajectory among a series of White and Black AML patients who died during Induction I. The results of this granular assessment can identify target areas for future research and interventions to reduce outcome disparities.

2 | METHODS

We present a case series of patients with newly diagnosed AML between January 2004 through June 2014 who died during Induction I. These deaths were identified from an AML cohort in the Pediatric Health Information System (PHIS) database assembled by a previously validated process.¹¹ The source cohort excluded patients who did not receive standard AML induction chemotherapy or had race identified as neither Black nor White. Cases were limited to those deaths that occurred before the start of Induction II chemotherapy or within 50 days from initial diagnostic admission, whichever came first. PHIS data are deidentified at the time of submission and thus this study is exempt from Institutional Review Board approval.

International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes and resource utilization data including Clinical Transaction Classification (CTC) codes as well as pharmacy bills from the start of initial admission until death were reviewed in each case to describe the clinical course of those patients who died in Induction I. Administrative data elements were used to construct a timeline of events leading up to death for each patient (Supplementary Table S1). Median time to death was compared using the log rank test. For each patient, all recorded ICD-9 diagnosis codes were grouped according to specific systems (e.g., cardiac, respiratory, renal) and billing data and ICD-9 procedure codes were used to assess ICU-level resources utilized (e.g., vasopressors, dialysis). The frequency (%) of system-based complications and resource requirements were compared between Black and White patients who died using the chi-square test (Table 1).

3 | RESULTS

There were 28 deaths (9 Black and 19 White) identified during Induction I from a cohort inclusive of 183 Black and 939 White children with newly diagnosed AML. The median time from admission to death was similar for Black (8 days, interquartile range [IQR]: 5–29) and White (10 days, IQR: 6–20) patients. The median time from admission to start of chemotherapy was 2 days (IQR: 1–3.5) and from chemotherapy start to death was 6.5 days (IQR: 4–17.5). These time frames were similar between Black and White patients who died (Fig. 1). Demographic characteristics were similar between Black and White patients who died with the exception of age: Black patients who died were older at the time of diagnosis ($P < 0.006$, Supplementary Table S2).

Specific details regarding preexisting conditions and complications sustained by each patient prior to death are shown in Table S1. Cardiac, renal, respiratory, neurologic, and infectious complications were present in greater than 50% of both White and Black deaths with no detectable differences between the two groups (Table 1). There were higher rates of intracranial hemorrhage, based on ICD-9 codes, among White patients compared with Black patients who died during induction (47 vs. 0%, $P = 0.012$). All but two patients were billed for vasopressors prior to their death and 86% of patients had a bill for mechanical ventilation; four patients had Extracorporeal Membrane Oxygenation (ECMO) bills and seven had CTC or ICD-9 procedure codes for cardiopulmonary resuscitation. Nine patients had dialysis CTC or procedure codes and five patients were billed for apheresis procedures (Table 1).

4 | DISCUSSION

This report describes complications observed in a series of Black and White patients' deaths during Induction I among a cohort of children with newly diagnosed AML. In light of our previous finding of increased induction mortality among Black children,⁹ we sought to further explore similarities and differences in clinical course between Black and White patients who died. Overall, more than half of deaths occurred within a week of chemotherapy initiation and deaths were often preceded by respiratory, cardiac, renal, and infectious complications as well as the need for intensive care resources (such as vasopressors and mechanical ventilation). Interestingly, there were no significant differences between Black and White patients' deaths with regard to time to death or utilization of intensive care resources.

Black patients tended to be older at the time of death. The difference in age distribution observed among those patients who died is consistent with our previous finding that age is a confounder in the association between race and mortality.⁹ Importantly, a number of the White patients who died had congenital heart disease or prematurity, while the profile of preexisting conditions for Black patients who died included asthma and autism (Table S1). The two most common causes of death in AML are hemorrhage and infection.⁶ We observed intracranial hemorrhage more frequently among White children who died than among Black children who died. None of the Black patients in our cohort had documented intracranial hemorrhage. Differences in infectious burden or types of antibiotics administered were not

observed in this series of Black and White patients who died. Not surprisingly, infections (and treatment for infections) were ubiquitous in this population of critically ill newly diagnosed leukemia patients. Moreover, the severity of infection could not be discerned from the available administrative data. These factors may have obscured detection of infection-related mortality.

There are well-documented issues with sensitivity and specificity of ICD-9 codes.^{12–14} In addition, diagnosis codes do not provide insight into temporal relationships between diagnoses. However, the use of resource utilization information in combination with diagnoses codes sheds some light on temporal associations. PHIS data do not contain laboratory or imaging results or specific information about cause of death so the actual events leading to each patient's death can only be inferred; however, cause of death is difficult to discern even in traditional chart reviews.¹⁵ In addition, while this series is among the largest descriptions of pediatric AML induction mortality, our power to detect statistically significant differences between the Black and White populations is limited by how rarely early deaths occur.

While we did not identify factors, other than age-related comorbidities and intracranial bleeding, which varied between Black and White patients' deaths, our approach of using administrative data to examine individual patients' clinical trajectory is unique and highlights the richness of the information contained in the PHIS database (Table S1). Understanding the detailed clinical experience of patients who died during Induction I AML therapy provides direction to compare how complications that frequently precede death, such as infectious, cardiac, neurologic, renal, and respiratory complications, are managed when they are present during the course of therapy in White and Black patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

Dr. Brian Fisher receives research funding from Pfizer and Merck for projects unrelated to this research.

Abbreviations

AML	acutemyeloid leukemia
CTC	Clinical Transaction Classification
ICD-9	International Classification of Diseases, Ninth Revision
ICU	Intensive Care Unit

IQR	interquartile range
PHIS	Pediatric Health Information System

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FIGURE 1.
Pattern of intensive care utilization (in relation to admission, chemotherapy initiation, and death) by race

TABLE 1

Occurrence of specific diagnoses (n, %) and resource utilization among patients with AML who died during induction, overall and by race

Diagnosis category	ICD-9 codes/CTC codes	Total		White		Black		P-value ^a
		n	(%)	n	(%)	n	(%)	
Bleeding	286.6–286.9, 578.1–578.9, 773.2, 784.7, 920–924, 998.11, E870.5	20	65	14	74	6	67	0.70
Cardiac	423.9–429.9, 745.11–747.83	16	57	10	53	6	66	0.48
Clotting	444.81–453.89	3	11	1	5	2	22	0.17
Cytopenias	284.1–285.9, 287.5–288.09, 776.1–776.7	22	79	16	84	6	67	0.29
Electrolytes	251.2–277.88, 775.5, 790.29–790.6	19	68	13	68	6	67	0.93
GI	570–571.8, 751.4, 782.4, 787.91–789.59, 997.4	13	46	9	47	4	44	0.89
Infection	041.89–112.84, 382.9, 462–466.11, 480.1–491.8, 599.0, 771.7, 780.6–780.61, 998.59	18	64	11	58	7	78	0.31
Leukemia	205–207.80, 288.6–288.8	28	100	19	100	9	100	1.0
Neurologic	253.5, 331.4–348.5, 431–434.91, 768.7, 780.03–780.39, 997.09	15	54	11	63	3	33	0.14
Intracranial Hemorrhage	431 and 432.9	9	32	9	47	0	0	0.01
Renal	401.9–405.99, 584–593.9, 599.7	17	61	11	58	6	67	0.66
Respiratory	478.74, 493.9–518.82, 769–770.3, 786.09–786.30, 799.02	27	96	18	95	9	100	0.48
Sepsis	038.0–038.9, 458.9, 771.81, 780.65, 785.50–785.52, 995.91–996.62	14	50	9	50	5	50	0.67
Other		20	71	13	68	7	78	0.61
Resource category	ICD-9 codes/CTC codes	Total		White		Black		P-value ^a
		n	(%)	n	(%)	n	(%)	
Mechanical ventilation	521161, 521166	24	86	16	84	8	89	0.74
Vasopressors	131111, 131305, 131311, 131321.20, 131351	26	93	17	89	9	100	0.31

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Dialysis	39.95, 5252221, 525201	9	32	5	26	4	44	0.23
Apheresis	99.71, 99.72, 355012	5	16	4	21	1	11	0.52
Total		28	19				9	

^a Chi-square test was used to evaluate for statistically significant differences.