Title

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Journal

Pediatric Blood & Cancer, 66(4)

ISSN

1545-5009

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Publication Date

2019-04-01

DOI

10.1002/pbc.27583

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Pediatr Blood Cancer. 2019 April ; 66(4): e27583. doi:10.1002/pbc.27583.

Comparable On-Therapy Mortality and Supportive Care Requirements in Black and White Patients Following Initial Induction for Pediatric Acute Myeloid Leukemia

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Abstract

Background: Black patients with acute myeloid leukemia (AML) are more likely to present with high acuity and consequently experience higher rates of induction mortality than White patients. Given the consistently identified racial disparities in overall survival (OS) among patients with AML, we aimed to evaluate whether there were sustained on-therapy racial differences in inpatient mortality, intensive care unit (ICU) requirements, or supportive care beyond initial induction.

Procedure: Within a retrospective cohort of 1,239 children diagnosed with AML between 2004 to 2014 in the Pediatric Health Information System (PHIS) database who survived their initial course of induction chemotherapy, we compared on-therapy inpatient mortality, ICU-level care requirements, treatment course duration, cumulative length of hospital stay (LOS), and resource utilization after Induction I by race.

Results: Over the period from the start of Induction II through completion of frontline chemotherapy, there were no significant differences in mortality (adjusted OR 1.01, 95% CI 0.41–2.48), ICU-level care requirements (adjusted OR 0.93, 95% CI 0.69–1.26), LOS (adjusted mean difference 3.2 days, 95% CI −2.3–9.6), or supportive care resource utilization for Black patients relative to White patients. Course-specific analyses also demonstrated no differences by race.

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

Conclusion: Although Black patients have higher acuity at presentation and higher induction mortality, such disparities do not persist over subsequent frontline chemotherapy treatment. This finding allows interventions aimed at reducing disparities to be directed at presentation and induction.

Keywords

AML; outcomes research; chemotherapy; disparities; post induction; mortality; intensive care; race

INTRODUCTION

Black patients with cancer experience lower overall survival than White patients [1–4]. For patients with acute myeloid leukemia (AML), both adult [5–6] and pediatric [7–9] studies demonstrated higher induction mortality and lower overall survival (OS) among Black patients compared to White patients.

Although racial disparities in pediatric AML outcomes have been well documented, factors that contribute to such disparities are not fully understood. Distinct disease biology, lack of access to timely treatment, lower socioeconomic status (SES), differences in health insurance, and poor response to treatment have been suggested as potential mechanisms for these differences [10]. Each of these mechanisms may be relevant at different points in the treatment and post-treatment trajectory. Our previous study focused on early mortality in the initial induction period and the role of acuity at presentation [11]. This study demonstrated that Black patients have higher acuity prior to initiating chemotherapy, which substantially contributed to higher mortality during Induction I. Therefore, we are interested in whether the racial disparity observed in the initial induction course persisted in subsequent frontline chemotherapy courses.

The objective of this study was to evaluate for differences by race in on-therapy inpatient mortality, intensive care unit (ICU) requirements, and supportive care beyond the initial induction course for pediatric patients with AML. As a result of AML therapy being predominantly inpatient and highly standardized, we hypothesized that there would be no racial differences in on-therapy outcomes after Induction I. Confirming this hypothesis would allow interventions for reducing racial disparities to be directed toward management of initial presentation and supportive care during Induction I period.

METHODS

Data Source

PHIS is an administrative database that contains inpatient, emergency department, and observation unit information from over 52 not-for-profit, tertiary care pediatric hospitals. Data include demographics, dates of service, discharge disposition, and daily inpatient billing data for medications, laboratory tests, imaging procedures, clinical services/procedures, and supplies. Quality of submitted data is assured through a joint effort between the Children's Hospital Association, Truven Health Analytics, and participating hospitals. Records are de-identified at the time of submission and are exempt from IRB approval.

Study Population

We previously assembled a cohort of pediatric patients receiving treatment for newly diagnosed AML using data from PHIS [12–13]. In brief, patients receiving standard induction chemotherapy (cytarabine, daunorubicin, etoposide – "ADE") from January 2004 through June 2014 were identified; patients who did not receive ADE in the first course were excluded to minimize inclusion of patients presenting with relapsed disease. Patients with a diagnosis for an alternative malignancy or evidence of bone marrow transplantation within 60 days following the first admission with chemotherapy were also excluded.

This study population was derived from the previous established cohort. We restricted to patients whose race was identified as either White or Black and who survived Induction I. The full follow-up period began at the start of the second course of frontline chemotherapy (Induction II) and continued until 50 days from the start of the last documented consolidation chemotherapy course, 200 days from the start of Induction II, death, or the last date of follow-up in PHIS, whichever occurred first. Course-specific analyses were also performed, where for each course the follow up period began on the first day of chemotherapy in the given course and continued to the earliest of 50 days, the start of the next course, death, or the last date of follow-up in PHIS.

Race

The race of a patient, dichotomized as either Black or White, was identified by contributing hospitals and considered the primary 'exposure' variable. The race variable is contained in the PHIS database and represents data mapped directly from the medical record. Ethnicity was not evaluated as this information was missing in a substantial proportion of patients.

Outcomes

The primary outcome of interest was inpatient mortality during frontline chemotherapy following initial induction. Inpatient deaths were identified based on PHIS discharge status for each hospitalization. ICU-level resources were defined by specific ICD-9-CM procedure codes or clinical resource utilization considered *a priori* as markers of ICU-level care rather than by physical location [14]. ICU-level resource requirements were evaluated by organ system as represented by vasopressor support, mechanical ventilation, renal replacement therapy, and leukapheresis, as well as the need for any of these therapies (versus none). An ICU score was also created with three categories (none, 1 system, and ≥2 systems) based on the number of organ systems requiring ICU-level resources.

Daily utilization rates of antibiotics, antifungals, antivirals, anti-hypertensives, anti-emetics, opioid medications, diuretics, parenteral nutrition, blood products, supplemental oxygen, and granulocyte colony-stimulating factor (GCSF) were determined from billing data. Binary indicators for each resource exposure on each inpatient day were created and summed to obtain the total number of days exposed. Resource utilization rates were designated as days of use per 100 inpatient days.

Covariates

Patient characteristics included age [15, 16], sex [17], insurance type (private, public, or other) [5, 18], and time period of diagnosis (2004–2009 vs. 2010–2014). ICU-level resource utilization during the first 72 hours following admission for initial AML chemotherapy was also included as a covariate, where the timeframe was chosen *a priori* to evaluate clinical acuity at presentation rather than acuity resulting from chemotherapy toxicity [11]. Acuity of presentation was categorized into three groups (none, 1 system, and ≥2 systems) based on the number of organ systems requiring ICU-level resources within the first 72 hours of the diagnostic admission. Patient chemotherapy regimens were categorized as COG-like standard, SJCRH-like standard, and non-standard based on review of the chemotherapy regimen received for each course.

Primary Statistical Analyses

Distributions of patient characteristics were compared using Chi-square tests. Covariates that were significantly associated with race were adjusted in the multivariate models of outcomes. Duration of follow up and LOS during the follow up period were compared using linear regression models and mean differences with 95% confidence intervals (CIs) were reported. Logistic regressions were used to estimate the unadjusted and adjusted odds ratios (OR) for mortality and use of ICU-level care. Resource utilization rates were compared using Poisson regression models with total inpatient days as the offset, and the unadjusted and adjusted rate ratios (RR) with 95% CIs were reported. In all analyses, White patients were used as the reference group and generalized estimating equations with an exchangeable correlation structure were used to obtain robust variance estimates to account for clustering by hospital. Analyses were performed for both the full follow-up period and for each treatment course separately. A two-sided p value of <0.05 was considered statistically significant and no multiplicity adjustment was performed.

Sensitivity Analyses

We were specifically interested in evaluating differences in outcomes during frontline treatment for AML. The occurrence of nonstandard chemotherapy regimens during the follow-up window may indicate the occurrence of refractory or relapsed disease which may differ by race and be associated with worse outcomes. Thus, sensitivity analyses restricted to treatment courses utilizing COG-like standard chemotherapy regimens were performed. Specifically, over the full follow-up analyses, follow-up was truncated at 50 days from the start of the last COG-like standard chemotherapy course, and in the course-specific analyses, patients were excluded from courses-specific analyses once they deviated from a COG-like standard regimen. All analyses were performed using SAS (version 9.2, SAS Institute, Inc., Cary, NC), and a two-sided p value where <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A flow chart depicting the assembly of the study population is presented in Figure 1. Table 1 summarizes the distribution of patient characteristics by race. The study population included

1,239 patients (84% White, 16% Black) diagnosed with *de novo* AML at 42 PHIS-contributing institutions between January 1, 2004 and June 30, 2014 who survived their initial course of induction chemotherapy. The majority of patients received chemotherapy regimens consistent with Children's Oncology Group (COG) or St. Jude Children's Research Hospital (SJCRH) protocols (90%) and the remainder received non-standard regimens. Distributions of sex, age, time period of diagnosis, and non-standard treatment regimen did not differ by race. Black patients were significantly more likely than White patients to be publicly insured (56% versus 37%, p <0.0001). While the proportion of patients with high acuity at initial presentation in the study population was low, Black patients were significantly more likely to have had ICU-level care requirements involving two or more systems within the first 72 hours of the diagnostic admission (6% versus 2%, p=0.006).

Full Follow Up Outcomes

Table 2 presents the unadjusted and adjusted (adjusted for insurance and acuity score at presentation) analyses during the full follow up period. Inpatient mortality was similar between Black and White patients (3.1% vs. 3.3%, adjusted OR 1.01, 95% CI 0.41–2.48, p=0.981). The proportion of Black and White patients requiring any ICU-level care was also similar overall (21.2% vs. 22.4%, adjusted OR 0.93, 95% CI 0.69–1.26, p=0.649) and by organ system. Overall resource utilization following Induction I did not differ significantly between Black and White children, except that Black patients received more antihypertensive medications (adjusted RR 2.17, 95% CI 1.61–2.91, p<0.001) and slightly less antiemetic medications (adjusted RR 0.92, 95% CI 0.87–0.98, p=0.015

Black patients had a longer median duration of follow up than White patients (median 136 days vs. 126 days, adjusted p=0.042), but similar cumulative LOS (median 91 days vs. 85 days, adjusted p=0.260). In the sensitivity analyses restricting to courses that were consistent with COG standard chemotherapy regimens (Supplementary Table S1), duration of follow-up no longer differed for Black patients compared to White patients (median 117 days vs. 133 days, adjusted p=0.981). All other results are consistent with the primary analyses.

Course-Specific Outcomes

Table 3 presents the unadjusted and adjusted analyses for each treatment course separately, with a total of 1,239, 1,117, 864, and 560 patients contributing to the four post-Induction I courses, respectively. Despite attrition at each successive treatment course, the distribution of race is similar across courses; distributions of gender, age, and insurance status by race are also similar across courses (Supplementary Table S2). Black patients had slightly longer course duration than White patients during Induction II (median 39 days vs. 36 days, adjusted p=0.001), but similar duration in other courses and similar cumulative LOS in all courses. Inpatient mortality was similar among Black and White patients in all courses (0% vs. 0.8% in Course 2, 1.1% vs. 0.4% in Course 3, 2.1% vs. 1.5% in Course 4, 1.3% vs. 3.7% in Course 5). While the proportion of patients requiring any ICU-level care during a given course increased from earlier to later courses, there were no differences among Black and White patients in ICU level-care requirement in any specific course. The lack of difference was apparent both overall (any ICU-level care: 3.1% vs. 5.7% in Course 2, 8.6% vs. 7.9% in

Course 3, 12.8% vs. 13.0% in Course 4, 13.8% vs. 13.3% in Course 5) and by organ system. Results of the sensitivity analyses were consistent with the primary analyses (Supplementary Table S3).

DISCUSSION

In a large nationally representative cohort of pediatric patients with AML, Black and White children experienced similar outcomes during the frontline treatment courses that follow Induction I. No difference was observed in mortality, requirement for ICU-level care, or hospital length of stay. Supportive care resource utilization was generally similar between Black and White children, except Black patients received more antihypertensive medications. The difference in anti-emetic medication use was statistically significant, but unlikely to represent a clinically meaningful difference. On-therapy length of follow-up was modestly longer in Black patients; however, this difference resolved upon excluding patients at the time of receipt of chemotherapy that was not consistent with COG frontline regimens. This suggests that Black patients were more likely to receive non-frontline therapies, such as salvage regimens or those targeted at refractory disease that typically have longer course durations due to prolonged myelosuppression.

We previously found a racial disparity in initial induction mortality that was explained in large part by higher acuity at the outset of the diagnostic admission in Black patients compared to White patients [11]. While previous publications have also demonstrated decreased overall survival of Black patients with AML relative to White patients [7–9], few provide insights into possible etiologies or specific details on the timing of deaths. Understanding these details may inform potential mechanisms for differences by race as well as inform possible interventions to resolve these differences. Induction deaths explain a substantial portion of the decrement in overall survival among Black patients and differential mortality at other points post-therapy in the longitudinal disease course likely also contributes to the observed disparities in overall survival. Because pediatric AML therapy is entirely inpatient and relatively standardized, access to care and the associated presentation acuity are not likely major contributors to disparities beyond the initial treatment course. We therefore expected smaller differences in on-therapy mortality during the subsequent frontline chemotherapy courses than during Induction I. Our analyses confirmed this hypothesis and demonstrated that among patients who survive Induction I, Black and White patients have similar mortality rates during the remainder of frontline chemotherapy courses. Similarly, at St. Jude Children’s Research Hospital, no racial differences in AML mortality were detected [20], which may be due to the uniform access to care among those referred.

Following the first course, the requirement for ICU-level care increases with each subsequent course reflecting the intensification of treatment and cumulative chemotherapy toxicities over time. This accumulation of toxicity, as represented by ICU-level care requirements, is similar for Black and White patients during the post-Induction I treatment period. The absence of a persistent disparity in on-therapy outcomes beyond Induction I highlights that the impact of mechanisms that contribute to racial disparities in early mortality, such as differential access to care, do not persist over time. These findings suggest

that once patients are connected to the healthcare system, post-diagnostic treatment and supportive care do not substantially differ by race.

Our results should be viewed in light of study limitations. Although we did not observe significant racial differences in mortality, given the relatively low mortality rate and the inherently small minority population, the power to detect small but possibly meaningful differences is somewhat limited. Therefore the lack of detected difference does not mean the mortality rates between the Black and White populations are necessarily the same. In addition, ethnicity is poorly ascertained in PHIS, thus Hispanic patients are included among the two race groups. If Hispanic patients have worse outcomes compared to White patients and are also proportionally more abundant in the White race group, a true association between race and post-induction mortality or resource utilization may be obscured.

Disparities in SES are associated with survival outcomes for some pediatric cancer patients [21–25]. We used insurance as a crude proxy for SES in this study. Although Black patients were less likely to have private insurance than White patients, the insurance-adjusted and unadjusted associations between race and mortality or race and resource utilization in the post induction period were similar, suggesting that insurance does not have a major impact on these outcomes. However, insurance in PHIS is specified at the admission level and Medicaid can be applied retroactively to charges that occurred while the patient was actually uninsured. Given this potential for misclassification of insurance status and the absence of a more refined measure of SES, we cannot exclude the possibility of resonant confounding.

Another limitation of our study is the absence of laboratory results in PHIS, which prevented an evaluation of biologic risk factors. However, previous studies suggested no difference in clinical characteristics, FAB subtype, cytogenetics, or prognostic molecular markers between Black and White pediatric patients with AML [5, 20]. Lastly, PHIS resource utilization data did not allow for analyses using medication dose or hour-level timing of administration, and similarly comorbidities could not be fully evaluated using available inpatient data.

This study provides reassurance that Black and White patients have similar on-therapy mortality and supportive care requirements following initial induction treatment for pediatric AML. This finding allows interventions aimed at reducing disparities to be directed at presentation and induction. Disparities in OS have been consistently identified, suggesting that the disparity not explained by differences in early mortality are likely driven by mechanisms that present outside of the context of frontline chemotherapy, such as relapse, transplant, and long-term toxicities. Additional studies are needed to further explore the factors and pathways leading to these disparities. Such analyses would require data sources beyond administrative data and integration of various datasets [26] to gain more sophisticated understanding and enable the development of empirical interventions to address racial disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Dr. Winestone's effort was supported by the Abramson Cancer Center's Paul Calabresi Career Development Award for Clinical Oncology (National Cancer Institute K12CA076931). Her research is also supported by a Young Investigator Award from Alex's Lemonade Stand Foundation.

Abbreviation

ADE	cytarabine, daunorubicin, etoposide
AML	acute myeloid leukemia
CI	confidence interval
COG	Children's Oncology Group
GCSF	granulocyte colony-stimulating factor
ICU	intensive care unit
LOS	length of stay
OR	odds ratio
OS	overall survival
PHIS	Pediatric Health Information Systems
RR	rate ratio
SES	socioeconomic status
SJCRH	St. Jude Children's Research Hospital

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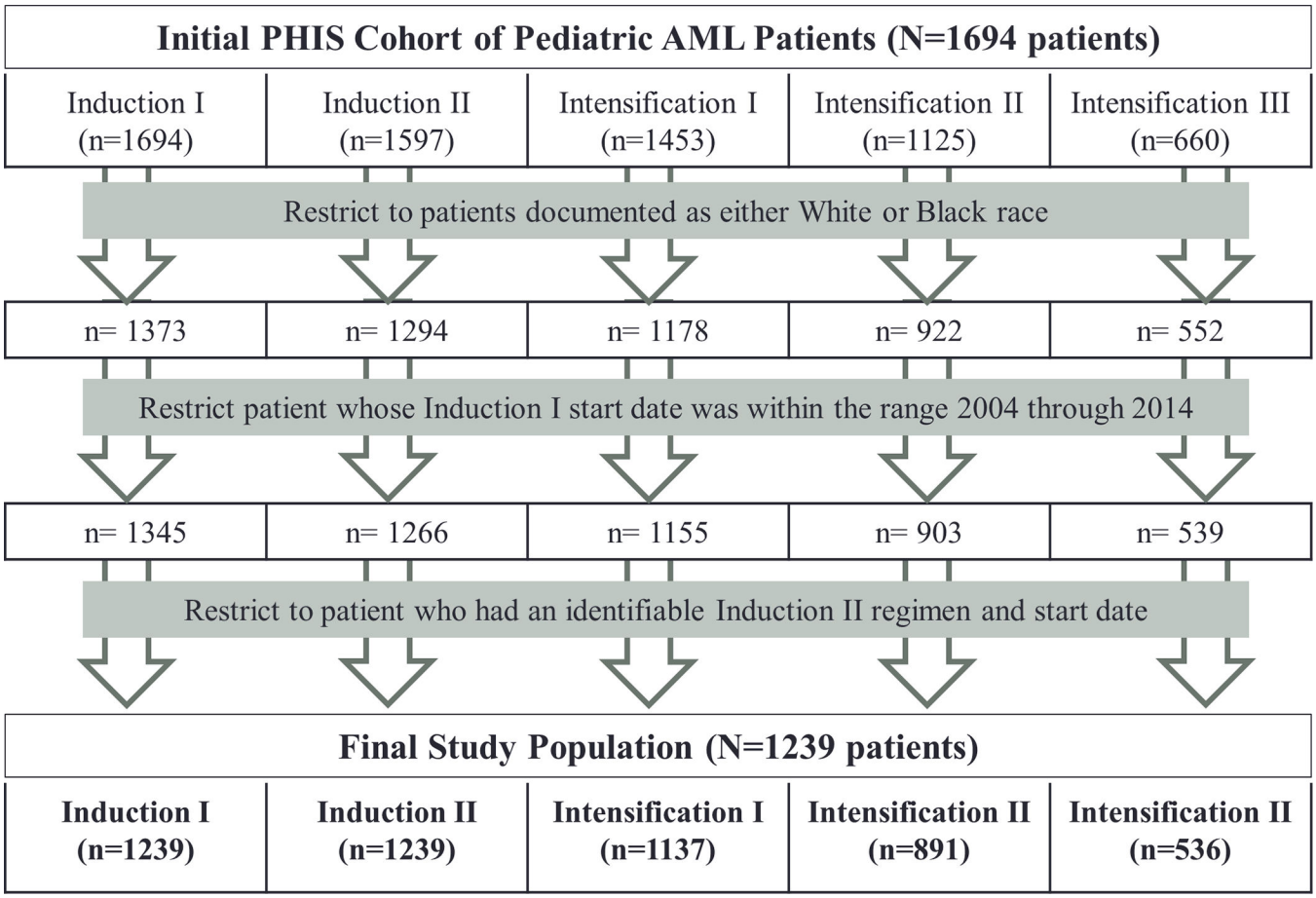

Figure 1. Consort diagram for the study cohort.

A flow chart depicting the assembly of the study population is presented. The cohort was restricted to patients whose race was identified as either White or Black and who survived Induction I. With attrition at each successive course, a total of 1,239, 1,117, 864, and 560 patients contributed to the four post-Induction I courses, respectively.

TABLE 1.

Distribution of patient characteristics by race.

Characteristic, n (%)	Overall (N=1239)	White (N=1046)	Black (N=193)	p-value [a]
Sex				0.852
Male	656 (53)	555 (53)	101 (52)	
Female	583 (47)	491 (47)	92 (48)	
Age (in years)				0.848
<1 year	143 (11)	120 (11)	23 (12)	
1 to <5 years	317 (26)	268 (26)	49 (25)	
5 to <10 years	195 (16)	167 (16)	28 (15)	
10 to <15 years	317 (26)	262 (25)	55 (29)	
15+ years	267 (21)	229 (22)	38 (20)	
Insurance				<0.001
Private	542 (44)	497 (48)	45 (23)	
Public	494 (40)	386 (37)	108 (56)	
Self pay	16 (1.3)	13 (1.2)	3 (1.5)	
Other [b]	187 (15)	150 (14)	37 (19)	
Time Period				0.328
2004–2009	701 (57)	598 (57)	103 (53)	
2010–2014	538 (43)	448 (43)	90 (47)	
Acuity Score in 72 hours of Induction I				0.006
0 – no ICU	1120 (90)	951 (91)	169 (88)	
1 – single organ	85 (7)	73 (7)	12 (6)	
>=2 – multi organ	34 (3)	22 (2)	12 (6)	
Patient chemotherapy group				0.845
COG-like	1036 (84)	872 (83)	164 (85)	
SJCRH-like	80 (6)	69 (7)	11 (6)	
Non-standard	123 (10)	105 (10)	18 (9)	

[a] p-value from Chi-square test, for the comparison of distributions by race.

[b] Other category includes charity care, admissions without charges, and other as specified by the sites.

TABLE 2.

Comparison of outcomes by race, during chemotherapy treatment period post Induction I.

	White (N=1046)	Black (N=193)	Unadjusted association[a] (95% CI)	Unadjusted p-value	Adjusted association[b] (95% CI)	Adjusted p-value
Full follow up duration, median (IQR)	126 (88–162)	136 (103–170)	8.7 (1.3–16.0)	0.021	7.8 (0.3–15.3)	0.042
Cumulative LOS, median (IQR)	85 (58–112)	91 (63–116)	4.5 (−0.9–9.8)	0.104	3.2 (−2.3–9.6)	0.260
Mortality, n (%)	34 (3.25)	6 (3.11)	0.96 (0.40–2.31)	0.919	1.01 (0.41–2.48)	0.981
ICU, n (%)						
Any, all organ	234 (22.4)	41 (21.2)	0.95 (0.71–1.27)	0.729	0.93 (0.69–1.26)	0.649
Any, Cardiovascular	191 (18.3)	32 (16.6)	0.91 (0.65–1.28)	0.577	0.91 (0.64–1.29)	0.592
Any, Respiratory	109 (10.4)	21 (10.9)	1.04 (0.67–1.62)	0.848	1.06 (0.68–1.65)	0.810
Any, Renal	29 (2.8)	4 (2.1)	0.75 (0.27–2.10)	0.579	NA	NA
Score			NA	0.921	NA	NA
0 - no ICU	812 (77.6)	152 (78.8)				
1 - single organ	150 (14.3)	27 (14.0)				
2 - multi organ	84 (8.0)	14 (7.2)				
Resource Utilization [c]						
Antibiotics, total of 5 subclasses	114.5	110.7	0.97 (0.92–1.01)	0.145	0.99 (0.94–1.04)	0.584
Antifungals, total of 3 subclasses	84.6	84.2	0.995 (0.94–1.06)	0.869	0.95 (0.89–1.02)	0.137
Antivirals	15.7	13.6	0.87 (0.65–1.16)	0.329	0.70 (0.48–1.03)	0.074
Anti-hypertensives	8.2	18.7	2.27 (1.77–2.92)	<0.001	2.17 (1.61–2.91)	<0.001
Anti-emetics	47.6	42.7	0.90 (0.85–0.95)	<0.001	0.92 (0.87–0.98)	0.015
Blood Products, total	30.6	27.8	0.91 (0.83–1.00)	0.049	0.92 (0.81–1.04)	0.169
Platelets	18.6	16.8	0.90 (0.81–1.01)	0.068	0.90 (0.78–1.04)	0.169
Packed RBC	11.8	10.8	0.91 (0.84–0.99)	0.030	0.93 (0.81–1.06)	0.281
Fresh frozen plasma	0.4	0.4	1.18 (0.70–2.01)	0.537	1.02 (0.52–2.01)	0.950
Cryoprecipitate	0.1	0.0	0.35 (0.04–3.36)	0.366	NA	NA
Parenteral Nutrition	14.4	14.7	1.02 (0.87–1.20)	0.778	1.08 (0.79–1.47)	0.632
Oxygen Therapy	2.7	3.0	1.09 (0.75–1.60)	0.647	0.84 (0.52–1.36)	0.485
GCSF	6.8	8.9	1.31 (1.08–1.59)	0.006	1.26 (0.87–1.82)	0.228

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	White (N=1046)	Black (N=193)	Unadjusted association[a] (95% CI)	Unadjusted p-value	Adjusted association[b] (95% CI)	Adjusted p-value
Opioid	19.0	17.7	0.93 (0.80–1.09)	0.381	0.92 (0.77–1.10)	0.360
Diuretics	4.8	5.6	1.16 (0.83–1.61)	0.378	1.10 (0.80–1.52)	0.558

[a] Shows mean difference for duration and LOS, OR for mortality and any ICU, and RR for resource utilizations

[b] Adjusted for insurance and acuity score in 72 hours of Induction I

[c] Rates as number of days exposed per 100 hospital days

TABLE 3.

Comparison of outcomes by race, for each of the chemotherapy course

	Induction II (N=1239)				Intensification I (N=117)				Intensification II (N=864)				Intensification III (N=516)			
	White (N=1046)	Black (N=193)	Unadjusted association [a] (95% CI)	Adjusted association [b] (95% CI)	White (N=942)	Black (N=175)	Unadjusted association [a] (95% CI)	Adjusted association [b] (95% CI)	White (N=723)	Black (N=141)	Unadjusted association [a] (95% CI)	Adjusted association [b] (95% CI)	White (N=436)	Black (N=80)	Unadjusted association [a] (95% CI)	Adjusted association [b] (95% CI)
Course Duration,	36	39	2.0	2.1	39	40	0.2	0.4	49	50	1.7	1.6	50	50	2.1	1.7
median (IQR)	(32–42)	(34–47)	(0.8–3.2)	(0.9–3.2)	(34–50)	(33–50)	(−1.2–1.5)	(−1.0–1.8)	(36–50)	(40–50)	(0–3.4)	(−0.2–3.3)	(36–50)	(38–50)	(−0.3–4.5)	(−0.7–4.2)
Cumulative LOS,	26	28	1.2	1.1	27	27	0.7	0.6	32	33	0.6	0.3	33	32	0.03	−0.4
median (IQR)	(23–31)	(23–34)	(−0.1–2.4)	(−0.2–2.4)	(23–31)	(23–33)	(−0.8–2.1)	(−0.9–2.1)	(27–40)	(27–42)	(−1.3–2.5)	(−1.6–2.2)	(27–39)	(27–38)	(−2.4–2.4)	(−2.9–2.1)
ICU, n (%)																
Any, all organ	60	6	0.53	0.50	74	15	1.10	1.08	94	18	0.98	0.96	58	11	1.04	0.97
	(5.7)	(3.1)	(0.22–1.24)	(0.21–1.20)	(7.9)	(8.6)	(0.62–1.96)	(0.59–1.95)	(13)	(12.8)	(0.57–1.68)	(0.55–1.68)	(13.3)	(13.8)	(0.52–2.08)	(0.47–1.98)
Any, Cardiovascular	46	4	0.46	0.44	60	11	0.99	0.99	72	12	0.84	0.84	49	9	1	0.93
	(4.4)	(2.1)	(0.16–1.29)	(0.15–1.24)	(6.4)	(6.3)	(0.51–1.92)	(0.50–1.96)	(10)	(8.5)	(0.44–1.59)	(0.44–1.62)	(11.2)	(11.2)	(0.47–2.13)	(0.43–2.04)
Any, Respiratory	19	4	1.14	1.12	31	9	1.59	1.62	52	9	0.88	0.95	26	4	0.83	0.69
	(1.8)	(2.1)	(0.38–3.40)	(0.37–3.45)	(3.3)	(5.1)	(0.75–3.41)	(0.74–3.56)	(7.2)	(6.4)	(0.42–1.83)	(0.45–2.00)	(6)	(5)	(0.28–2.45)	(0.23–2.13)
Any, Renal	7	2	1.55	1.21	10	3	1.63	1.51	12	1	0.42	0.44	9	0	NA	NA
	(0.7)	(1.0)	(0.32–7.54)	(0.23–6.23)	(1.1)	(1.7)	(0.44–5.97)	(0.40–5.69)	(1.7)	(0.7)	(0.06–3.28)	(0.05–3.46)	(2.1)	(0)		
Score			NA	NA			NA	NA			NA	NA			NA	NA
0 - no ICU	986	187			868	160			629	123			378	69		
	(94.3)	(96.9)			(92.1)	(91.4)			(87.0)	(87.2)			(86.7)	(86.3)		
1 - single organ	46	3			51	9			58	15			37	8		
	(4.4)	(1.6)			(5.4)	(5.1)			(8.0)	(10.6)			(8.5)	(10)		
2 - multi organ	14	3			23	6			36	3			21	3		
	(1.3)	(1.6)			(2.4)	(3.4)			(5.0)	(2.1)			(4.8)	(3.7)		

[a] Shows mean difference for duration and LOS, OR for mortality and any ICU, and RR for resource utilizations

[b] Adjusted for insurance and acuity score in 72 hours of Induction I