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Predictors Of Intense End-Of-Life Care Among Children And Young Adults With Advanced Hematologic Malignancies

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Abstract

Background: Studies suggest that children, adolescents, and young adults (AYAs) with advanced cancer receive intense end-of-life (EOL) care. This is particularly true for patients with hematologic malignancies. Yet, it is unclear who is at highest risk for receiving intense care.

Methods: We used the Premier Healthcare Database to perform a population-based analysis of patients aged 0-39 years at death with hematologic malignancies who died between 2010-2017. We defined intense EOL care as: receipt of cardiopulmonary resuscitation (CPR), intubation, hemodialysis, or tracheostomy within the last 30 days of life; more than one emergency room (ER) visit within the last 30 days of life; receipt of intravenous chemotherapy within the last 14 days of life; dying in the intensive care unit (ICU); and having a terminal admission of ≥ 30 days. We used multivariate logistic regression to identify predictors of having more intense EOL care (i.e., ≥ 2 intensity indicators).

Results: The study cohort included 2,069 decedent patients. The most prevalent intensity indicators were receiving chemotherapy (51.7%) and being intubated (45.9%). 47.2% of the cohort experienced ≥ 2 intensity indicators. In multivariate analyses, compared with those who had leukemia, AYAs with Hodgkin lymphoma (odds ratio [OR]=1.50, 95% confidence interval [CI]: 1.97, 2.31) and non- Hodgkin lymphoma (OR=1.13, 95% CI: 1.02, 1.49) were more likely to receive intense EOL care. Patients treated in larger hospitals were more likely to receive intense care (OR: 1.87; 95% CI: 1.18, 2.97). Longer terminal admissions were associated with greater intensity of EOL care.

Conclusion: Children and AYAs in the United States continue to experience intense EOL care. Patients treated at larger hospitals and those who have longer terminal admissions are at particularly high risk. Further research is needed to determine how to mitigate these risks.

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Introduction

While cancer in children, adolescents, and young adults (AYAs) is relatively rare, it is the leading cause of non-accidental death among children and the leading cause of disease-related death among AYAs in the United States (U.S.)[1]. Hematologic malignancies comprise around 40% of all new cancer cases diagnosed in children aged 0-14 years (leukemia accounts for 29% while lymphomas account for 12%), and leukemia is the second leading cause of cancer death in this age group.[2] Meanwhile, lymphomas make up 20% of cancer cases among AYAs aged 15-39 years and leukemia makes up 13%.[2] Survival rates have been improving over the years, but the grim reality is that an estimated 10-20% of children and AYAs will continue to die of advanced illness.[3]

Unfortunately, research consistently shows that pediatric and AYA patients with advanced cancer often receive intensive treatment at the end of life.[4-6] Intensive care at the end of life is variably defined in the literature but includes measures such as multiple intensive care (ICU) admissions, emergency department (ED) visits, receipt of intravenous chemotherapy, and low hospice referrals during the last month of life.[7,8] The literature also suggests that young adults with cancer who are 18-39 years of age are particularly vulnerable to receiving intense care at the end of life, as they are caught between the worlds of pediatric and adult medical providers and are therefore less likely to access optimal medical and psychosocial services compared to other age groups.[9] However, little is known about the predictors for intense end-of-life (EOL) care patterns among children and AYAs with hematologic malignancies.

Only limited population-based studies have assessed the pattern of EOL care in children and AYAs with cancer.[4] In California, nearly two-thirds of pediatric patients (0-21 years) and 59% of AYAs (15-39 years) dying of cancer experienced intense EOL care.[10] Another southern California study reported that 68% of AYAs with cancer received intensive EOL care. Furthermore, 75% of AYA Medicaid decedents with cancer in New York received at least one aspect of intensive EOL care.[6] Internationally, nearly 80% of children dying of cancer received intense care in Taiwan and Korea[11,12], while 41% of children dying of cancer in Ontario, Canada received intense EOL care.[13]

Given the theory that a diagnosis of hematologic malignancy may be associated with receiving more intense EOL care,[10,14-18] it is critical to further examine this particular population to determine what factors are associated with this type of care. To fill these knowledge gaps, we assessed patterns of EOL care and evaluated the possible factors associated with more intense care among a national cohort of patients in the U.S. with hematologic malignancies who span the entire age range from infancy to young adulthood.

Methods

Study Design

We conducted a population-based retrospective cohort study using the Premier Healthcare Database (PHD). The PHD is a U.S. hospital-based, service-level, all-payer database that contains comprehensive information on inpatient and hospital-based outpatient encounters from geographically diverse hospitals. The database represents approximately 25% of U.S. admissions among private and academic hospitals. These hospitals and healthcare systems submit administrative, healthcare utilization, and financial data from patient encounters. PHD data include: demographics, admission and discharge diagnoses, information on billed services, therapeutic services, and patient disposition and discharge health status. The Yale University Investigational Review Board approved the study and deemed it exempt from Human Subjects Review.

Study Population

We identified patients aged 0 to 39 years at death who died between January 1, 2010 and March 31, 2017 **(Figure 1)**. We evaluated a broader age range to fully capture adolescents and young adults, whom the National Cancer Institute defines to be aged 15-39 years.[19] Death was identified according to the following PHD codes: 20 (expired), 40 (expired at home for hospice care), 41 (expire in medical facility for hospice), and 42 (expired, place unknown, for hospice). These patients also had to have a diagnosis of hematologic malignancy (HM) at their final

encounter, which was identified through ICD-9 and ICD-10 codes. These diagnoses were ultimately grouped into four categories: Hodgkin lymphoma (ICD-9: 201.xx; ICD-10: C81.xx), non-Hodgkin lymphoma (ICD-9: 202.xx; ICD-10: C82.xx – C86.xx), myeloma (ICD-9: 203.xx; ICD-10: C90.xx), leukemia (ICD-9: 204.xx – 208.xx, V10.60; ICD-10: C91.xx – C95.xx), and other HM, not otherwise specified (ICD-9: 238.7x; ICD-10: D47.xx).

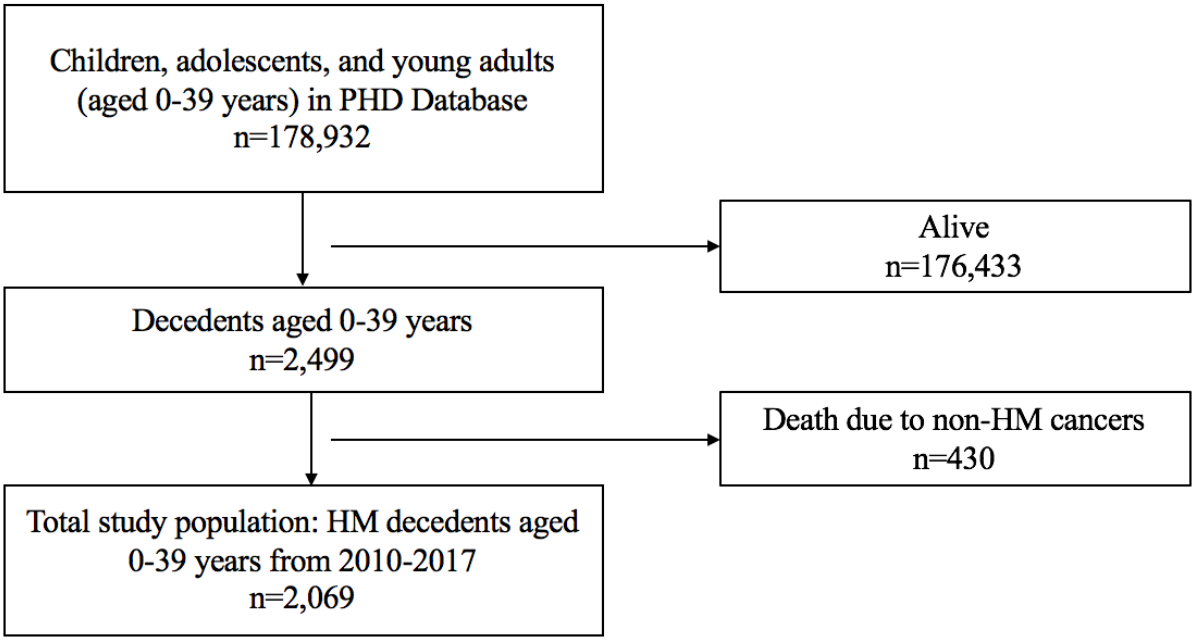

Figure 1

Study Population: Children, adolescents, and young adults between 2010 and 2017 who died of hematologic malignancy at ages 0-39 years.

Measurements of intense end-of-life care

Earle and colleagues developed an approach to identify a set of measures that could be indicative of intense EOL care.[8,20,21] According to this approach, intensive care in the last month of life includes invasive medical procedures (e.g., mechanical ventilation) and cancer-directed therapies (e.g., chemotherapy), multiple hospital and/or ICU admissions, multiple emergency room visits, and in-hospital deaths.[8] These measures have been used extensively in adults to evaluate EOL care patterns, with a goal of improving quality of care.[22] While EOL care measures have not

been formally developed for the pediatric population, Earle's measures have been previously adopted to identify intense EOL care patterns among children and AYAs with cancer.[4,6,10,13,15]

For the purposes of this study, indicators of intense EOL care were having more than 1 emergency room (ER) visit or receiving cardiopulmonary resuscitation (CPR), hemodialysis, tracheostomy placement, or intubation/mechanical ventilation in the last 30 days of life; receiving intravenous chemotherapy in the last 14 days of life; dying in the intensive care unit (ICU); and having a terminal admission of 30 days or greater. ICD-9/ICD-10 and CPT codes were used to identify receipt of CPR, intubation/ventilation, chemotherapy, tracheostomy placement, and hemodialysis (**Appendix: Table 1**).[23] Chemotherapy receipt, death in ICU, and ER admissions were further identified using billing information. We computed the composite number of intensity measures received by each patient.

Data for individual patient encounters did not have exact admission days in the PHD; rather, the PHD only provided the month and year of admission, along with the calendar quarter (e.g., YYYYQMM format). Therefore, intensity measures were tracked by capturing all encounters that fell within one month prior to the patient's final admission (e.g., any encounter between January and February 2012). However, billing data included exact service dates. While there were no precise indicators for ICU admission, we amassed a list of billing codes that indicated a charge master code in the ICU. The charge master code refers to Premier's process of mapping each hospital's charge items to a standard charge item, such that these charges are coded consistently across the entire database.[24]

Predictor variables of interest

We included candidate variables which are available in our database and have been used in research examining EOL care.[4,6,10,13,15] Patient sociodemographic variables included age at death, gender, race/ethnicity, and insurance type. HM diagnosis was categorized as Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, leukemia, and "other" HM (not otherwise specified according to ICD-9/ICD-10 diagnosis codes). The quartiles of the distribution of the patients' length of stay at final admission were used to categorize that particular variable, so as

not to over-represent a particular range of days. Location of death was also noted. Hospital-based variables included the hospital's urbanity/rurality, teaching status, size, and geographic region.

Statistical Analysis

We defined our outcome of interest (i.e., intense EOL care) as receiving 2 or more intensity measures, based on previous literature.[4] Descriptive statistics were calculated for each independent and dependent variable. We used frequency distributions for categorical variables. We used the χ^2 test to assess the statistical significance of differences between patients who received fewer than 2 intensive EOL care measures and patients who received 2 or more intensive EOL care measures for categorical variables. For continuous variables, the statistical significance of unadjusted differences between groups of patients were evaluated by Student t-test.

We conducted univariate analyses to determine factors that are significantly associated with having ≥ 2 intensity indicators. We also constructed multivariable logistic regression models and used backward elimination to produce the final model. All of the independent variables listed above were used when building the model, except for location of death due to the nature of this dataset and having an over-representation of hospital deaths (99.1%), and age because of the stratified analysis. We stratified analyses by age to determine differences in predictors for children versus AYAs. Results were presented in odds ratios and 95% confidence intervals.

All significance tests were two-sided with an α-level of 0.05. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Characteristic of study population

The final study cohort included 2,069 patients with a median age of 30 (interquartile range [IQR]: 22-35) years (**Table 1**). These patients were predominantly male (57.2%), died of leukemia (43.6%), and received Medicaid (46.0%). The median length of stay at the final

admission was 11 (IQR: 2-27) days. Most patients received their care at an urban hospital (94.6%), a teaching hospital (58.6%), or a hospital with at least 200 beds (91.5%).

Compared to those with < 2 intensity indicators, patients with ≥ 2 EOL intensity indicators had longer length of stay at last admission ($p<0.01$), were more likely to die in the hospital ($p<0.01$), and receive care at teaching hospitals ($p=0.04$) and hospitals with at least 500 beds ($p<0.01$). However, patients with ≥ 2 intensity indicators were more likely to be non-Hispanic black ($p=0.05$) and less likely to die of leukemia ($p=0.04$).

Table 1.
Characteristics of decedent pediatric and young adult patients with hematologic malignancies in PHD, 2010-2017.

Characteristic	Overall n (%)	Number of intensity indicators		p
		< 2 n (%)	≥ 2 n (%)	
Age (at death)				
0 – 14	217 (10.5)	114 (10.4)	103 (10.6)	0.93
15 – 39	1852 (89.5)	979 (89.6)	873 (89.4)	
Gender				
Male	1184 (57.2)	616 (56.4)	568 (58.2)	0.40
Female	885 (42.8)	477 (43.6)	408 (41.8)	
Race/Ethnicity				
Non-Hispanic White	1076 (52.0)	594 (54.0)	482 (49.5)	0.05
Non-Hispanic Black	377 (18.2)	178 (16.2)	199 (20.4)	
Hispanic	51 (2.5)	28 (2.6)	23 (2.4)	
Other/unknown	565 (27.3)	293 (27.2)	272 (27.7)	
Length of stay at last admission (in days)				
0 – 2	522 (25.2)	367 (33.6)	155 (15.9)	<0.01
3 – 11	550 (26.6)	372 (34.0)	178 (18.2)	
12 – 27	489 (23.6)	62 (5.7)	427 (43.8)	
≥ 28	508 (24.6)	292 (26.7)	216 (22.1)	
Location of death				
Hospital	2050 (99.1)	1075 (98.4)	975 (99.9)	<0.01
Outside of hospital for hospice care	19 (0.9)	18 (1.6)	1 (0.1)	
Diagnosis				
Hodgkin lymphoma	134 (6.5)	61 (5.6)	83 (8.5)	0.04
Non-Hodgkin lymphoma	421 (20.3)	241 (22.1)	225 (23.1)	
Myeloma	26 (1.3)	14 (1.3)	12 (1.2)	
Leukemia	902 (43.6)	548 (50.1)	439 (45.0)	
Other hematologic malignancies, not otherwise specified	586 (28.3)	229 (21.0)	217 (22.2)	
Insurance Type				

Medicaid	943 (45.6)	473 (43.3)	470 (48.2)	0.39
Managed Care	680 (32.9)	349 (31.9)	331 (33.9)	
Other (Indemnity, Charity, Indigent, Medicare)	446 (21.5)	271 (24.8)	175 (17.9)	
Hospital vicinity to city center				
Urban	1966 (95.0)	1039 (95.1)	927 (95.0)	0.93
Rural	103 (5.0)	54 (4.9)	49 (5.0)	
Teaching status				
Teaching	1262 (61.0)	644 (58.9)	618 (63.3)	0.04
Non-teaching	807 (39.0)	449 (41.1)	358 (36.7)	
Hospital size				
Small, 0-199 beds	156 (7.5)	105 (9.6)	51 (5.2)	<0.01
Medium, 200 – 499 beds	858 (41.5)	452 (41.4)	406 (41.6)	
Large, ≥ 500 beds	1055 (50.0)	536 (49.0)	519 (53.2)	
Geographic region				
Northeast	389 (18.8)	200 (18.3)	189 (19.4)	0.45
Midwest	213 (10.3)	103 (9.4)	110 (11.3)	
West	417 (20.2)	225 (20.6)	192 (19.7)	
South	1050 (50.8)	565 (51.7)	485 (49.6)	

Prevalence of intensive EOL care

As shown in Figure 1, 77% of patients received at least one measure of intense EOL care. Among the 1583 patients who received some form of intense care, 47% experienced two or more measures of intense EOL care. The most common intensity measures (**Table 2**) were receiving intravenous chemotherapy in the last 14 days of life (51.7%, n=1069) and being intubated/mechanically ventilated in the last 30 days of life (45.9%, n=949). Additionally, in the last 30 days of life, 19.4% received CPR, 24% of patients experienced more than 1 ER visit, 13.7% had hemodialysis, and 7.9% received a tracheostomy placement. Furthermore, 22.3% of patients died in the ICU and 21.4% of patients had a terminal admission of 30 days or longer.

Compared to children aged 0-14 years, AYAs were less likely to receive CPR ($p<0.01$), less likely to have more than 1 ER visit ($p=0.02$), more likely to receive intubation/mechanical ventilation ($p<0.01$), and more likely to receive a tracheostomy placement ($p<0.01$) in the last 30 days of life. Furthermore, these patients were more likely to receive chemotherapy in the last 14 days of life ($p<0.01$), but less likely to die in the ICU ($p=0.04$).

Table 2. Prevalence of Intensive End-of-Life Care Measures.

Intensive Care Measure	Overall N (%)	Age		p
		0-14 years N (%)	15-39 years N (%)	
Within 30 days:				
CPR	402 (19.4)	75 (34.6)	327 (17.7)	<0.01
> 1 ER visit	497 (24.0)	61 (28.1)	436 (23.5)	0.02
Hemodialysis	283 (13.7)	23 (10.6)	260 (14.0)	0.10
Intubation/mechanical ventilation	949 (45.9)	84 (38.7)	865 (46.7)	<0.01
Tracheostomy	164 (7.9)	6 (2.8)	158 (8.5)	<0.01
Within 14 days:				
Intravenous chemotherapy	1069 (51.7)	79 (36.4)	990 (53.4)	<0.01
Death in ICU	461 (22.3)	81 (37.3)	380 (20.5)	0.04
Terminal admission ≥ 30 days	433 (21.4)	76 (35.0)	357 (19.3)	0.21

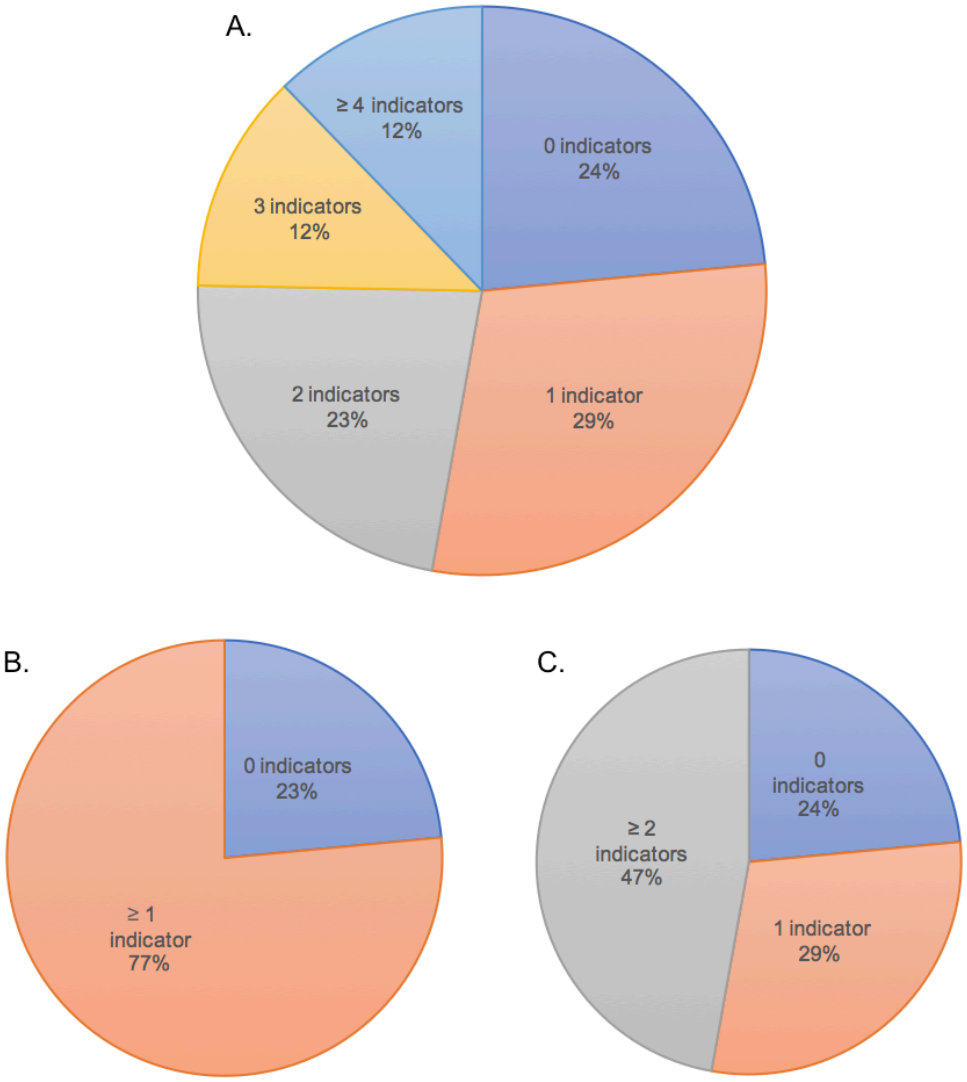

Figure 1. Prevalence of (A) total number of intensity indicators received; (B) at least 1 indicator received; and (C) at least 2 indicators received.

Factors associated with intensive EOL care

Univariate logistic regression results suggested that length of stay at last admission ($p<0.01$), Hodgkin lymphoma diagnosis ($p<0.01$), teaching status of the hospital ($p=0.04$), and size of the hospital ($p<0.01$) were associated with receiving more intense EOL care (**Table 3**). For instance, patients who had a terminal admission of 12-27 days had 9.31 times the odds of receiving ≥ 2 intensity measures (95% CI: 4.78, 15.59) compared to those with a shorter length of stay at the terminal admission (0 to 2 days). Those with a terminal admission of 28 days or greater had 1.75 times the odds (95% CI: 1.35, 2.27). Furthermore, patients diagnosed with Hodgkin lymphoma had higher odds of receiving more intense care compared with patients diagnosed with some form of leukemia (OR: 1.68; 95% CI: 1.16, 2.45). Patients with other diagnoses also tended to have higher odds of receiving more intense care, but these differences were not statistically significant. Patients treated at a non-teaching hospital had lower odds of receiving more intense EOL care (OR: 0.83; 95% CI: 0.70, 0.92). Finally, compared to patients treated at small hospitals (0-199 beds), patients treated at medium-sized hospitals (200-499 beds) had 1.85 times increased odds of receiving more intense EOL care (95% CI: 1.29, 2.65) while patients treated at large hospitals (≥ 500 beds) had 1.99 times increased odds (95% CI: 1.40, 2.85). AYA patients aged 15-39 were slightly less likely to receive more intense EOL care compared to children aged 0 to 14 at death, but this was not statistically significant.

Table 3. Unadjusted Associations Between Patient Characteristics and Receipt of Two or More Intensive End-of-Life Care Measures

Characteristic	OR (95% CI)	p
Age (at death)		
0 – 14	1.00	
15 – 39	0.91 (0.75, 1.21)	0.93
Gender		
Male	1.00	
Female	0.93 (0.78, 1.11)	0.40
Race		
Non-Hispanic White	1.00	
Non-Hispanic Black	1.20 (0.93, 1.56)	0.16
Hispanic	0.89 (0.50, 1.57)	0.68
Other/Unable to Determine	0.87 (0.71, 1.07)	0.20

Length of stay at last admission (in days)		
0 – 2	1.00	
3 – 11	1.13 (0.87, 1.47)	0.35
12 – 27	9.31 (4.78, 15.59)	<0.01
≥ 28	1.75 (1.35, 2.27)	<0.01
Location of Death		
Hospital	1.00	
Outside of hospital for hospice care	0.06 (0.01, 0.46)	0.03
Diagnosis		
Hodgkin Lymphoma	1.68 (1.16, 2.45)	<0.01
Non-Hodgkin Lymphoma	1.25 (0.99, 1.58)	0.06
Myeloma	1.33 (0.59, 2.99)	0.49
Leukemia	1.00	
Other Hematologic Malignancy	1.35 (1.10, 1.67)	<0.01
Insurance Type		
Medicaid	1.00	
Managed Care	1.07 (0.88, 1.29)	0.53
Other (Indemnity, Charity, Indigent, Medicare)	0.91 (0.69, 1.20)	0.51
Hospital vicinity to city center		
Urban	1.00	
Rural	1.02 (0.68, 1.51)	0.93
Teaching status		
Teaching	1.00	
Non-teaching	0.83 (0.70, 0.92)	0.04
Hospital size		
Small, 0-199 beds	1.00	
Medium, 200 – 499 beds	1.85 (1.29, 2.65)	<0.01
Large, ≥ 500 beds	1.99 (1.40, 2.85)	<0.01
Geographic region		
Northeast	1.00	
Midwest	1.13 (0.81, 1.58)	0.47
West	0.91 (0.72, 1.15)	0.42
South	0.90 (0.69, 1.19)	0.47

After backward elimination, the multivariate logistic regression suggested slightly different predictors for the two age groups. Among children aged 0-14 years at death, two variables were associated with receiving ≥ 2 measures of intense EOL care: length of stay at last admission and geographic region of the hospital (**Table 4**). Specifically, length of stay at last admission remained positively associated with intensity of care. Compared to patients who had a terminal admission of 0 to 2 days, those who were in the hospital for 12 to 27 days during their final admission had 9.98 times the odds of receiving two or more intensive EOL care measures (95% CI: 3.64, 17.40). Furthermore, children who were treated in hospitals in the South had much

higher odds of receiving intensive EOL care compared to patients who were treated in the Northeast (OR: 4.04; 95% CI: 1.18, 8.83).

Among AYAs aged 15-39 years at death, three variables were associated with receiving ≥ 2 intensity measures at the end of life: length of stay at last admission, diagnosis, and hospital size. Like children, patients who had a terminal admission of 12 to 27 days had higher odds of receiving more intense EOL care compared to patients with a terminal admission of 0 to 2 days (OR: 7.80; 95% CI: 2.83, 14.86). Patients with a terminal admission of ≥ 28 days also had higher odds, though the magnitude was lower (OR: 1.79; 95% CI: 1.34, 2.39). Furthermore, AYAs who had Hodgkin Lymphoma and non-Hodgkin Lymphoma had higher odds of receiving more intense EOL care compared with AYAs who were diagnosed with a form of leukemia (ORs: 1.50 [95% CI: 1.97, 2.31] and 1.13 [95% CI: 1.02, 1.49], respectively). Finally, patients treated at larger hospitals were more likely to receive intense EOL care. Compared to smaller hospitals, patients treated at medium-sized hospitals had 1.71 times the odds of receiving ≥ 2 measures of intense EOL care (95% CI: 1.18, 2.70), while those treated at large-sized hospitals had 1.87 times the odds (95% CI: 1.18, 2.97).

Table 4. Adjusted Associations Between Patient Characteristics and Receipt of Two or More Intensive End-of-Life Care Measures, Stratified by Age Group

Characteristic	Overall		Age			
			0-14 years		15-39 years	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Length of stay at last admission (in days)						
0 – 2	1.00		1.00		1.00	
3 – 11	1.10 (0.84, 1.43)	0.49	1.87 (0.79, 4.46)	0.16	1.08 (0.82, 1.43)	0.5
12 – 27	8.63 (4.24, 14.73)	<0.01	9.98 (3.64, 17.40)	<0.01	7.80 (2.83, 14.86)	<0.0
≥ 28	1.70 (1.30, 2.22)	<0.01	1.55 (0.72, 3.34)	0.27	1.79 (1.34, 2.39)	<0.0
Diagnosis						
Hodgkin Lymphoma	1.50 (1.10, 2.29)	0.05	-	-	1.50 (1.97, 2.31)	0.0
Non-Hodgkin Lymphoma	1.14 (0.88, 1.48)	0.33	-	-	1.13 (1.02, 1.49)	0.0
Myeloma	1.32 (0.53, 3.30)	0.56	-	-	1.33 (0.53, 3.36)	0.5
Leukemia	1.00		-	-	1.00	
Other Hematologic Malignancy	1.08 (0.85, 1.37)	0.52	-	-	1.08 (0.84, 1.40)	0.5
Hospital size						
Small, 0-199 beds	1.00		-	-	1.00	
Medium, 200 – 499 beds	1.61 (1.07, 2.41)	0.02	-	-	1.71 (1.18, 2.70)	0.0
Large, ≥ 500 beds	1.71 (1.15, 2.55)	<0.01	-	-	1.87 (1.18, 2.97)	<0.0

Geographic region						
Northeast	-	-	1.00		-	-
Midwest	-	-	1.44 (0.64, 3.24)	0.38	-	-
West	-	-	2.36 (0.74, 4.51)	0.15	-	-
South	-	-	4.04 (1.18, 8.83)	0.03	-	-

All variables in the table above were mutually adjusted in the model.

Discussion

Our study found that a majority (76.5%) of children and AYA decedents with hematologic malignancies received at least 1 measure of intensive EOL care, while 47.2% experienced two or more. Children and AYAs who had a longer inpatient stay at the last admission were more likely to receive 2 or more EOL care measures. Among children aged 0-14 years at death, being treated in the South was another significant predictor for receiving 2 or more EOL care measures. Among AYAs, having either Hodgkin or non-Hodgkin Lymphoma were predictors for receiving more intense care, along with being treated at a larger hospital.

We found that a majority of children and AYA decedents with hematologic malignancies received at least 1 measure of intensive EOL care. Similar to our findings, Mack et al. found that 75% of adolescent and young adult Medicaid decedents (aged 15-39 years) with cancer in New York received at least one intensive measure at the end of life.[6] Meanwhile, Johnston et al. found that only 23% of their cohort of patients aged 0-21 years in California[10] and 30% of another cohort of patients aged 15-39 years in the same state[4] experienced 2 or more intensity indicators, compared to our 47.2% across both age groups. These slight variations may be due to differences in the individual measures of intense EOL care chosen for analyses, along with differences in prevalence for individual measures. For instance, the Mack study reported on both ICU admissions and hospitalizations in the last 30 days of life but did not report on specific procedures such as mechanical ventilation, as our study had. Both Johnston studies used hospital death as an intensity measure, while our study did not due to being largely limited to encounters for patients who died in the hospital. Both Johnston studies also included ICU admissions as one of the intensive EOL indictors, which were not available in our study.

Our study observed higher percentages of patients receiving chemotherapy and mechanical ventilation/intubation than previous studies in the US.[4,6] Nearly half of the patients (51.6%) in our study received chemotherapy, whereas only 11% AYA Medicaid decedents in the New York State[6] and 3-4% of pediatric and AYA decedents in California received chemotherapy.[4] The two California studies further reported that 19.9% and 16.2% of their cohorts experienced mechanical ventilation/intubation within 30 days of death,[4,10] compared to our 45.9%. The reasons for these differences are relatively unclear, though one explanation could be that our study included regions of the United States that these other population-based studies in North America had not included. Therefore, it is possible that care patterns tend to be more intensive in this region, which would need to be validated with further research. Another explanation may be that our cohort only included patients with hematologic malignancies, which has previously been found to be a predictor for more intensive EOL care among patients with cancer.[10,15-17] One population-based study examining hospital utilization among pediatric patients in the last year of life in the U.S. found that 53.3% of patients with malignancies received mechanical ventilation during the terminal admission,[25] which is consistent with our findings.

Patients in our cohort also experienced higher rates of intensity measures compared to patients in Ontario. Among pediatric cancer decedents in Ontario, 7.9% received IV chemotherapy in the last 14 days (compared to our 51.6%), 8.6% had more than one ER visit in the last 30 days (compared to our 24%), and 16.7% were mechanically ventilated in the last 14 days (compared to our 45.9% in the last 30 days).[13] Unlike the Ontario study, our study also included young adults who may be more likely to receive more intensive care at the end of life compared to children and adolescents.[26] Other potential explanations for the discrepancy may be differences in healthcare systems and physician practice patterns between the U.S. and Canada.

In our study, there was a higher proportion of white patients who received less intense care, and a higher proportion of black and unknown race patients receiving more intense care. However, our analyses did not suggest a statistically significant difference in EOL care intensity across these racial/ethnic groups. Yet, other studies have previously found that black and Hispanic patients may be more likely to receive intensive measures at the end of life, so this disparity is worth exploring further.[27,28]

Additionally, patients who received intense care were more likely to spend at least 12 days in the hospital at the last admission. Like our multivariable analysis suggested, the odds were particularly high for those with a terminal length of stay between 12 to 27 days. Theoretically, this makes sense, with the hypothesis being that patients who have a lengthier admission are likely hospitalized due to having more serious health complications and are exposed to more therapeutic, and thus intensive, procedures and regimens. Further research is needed to test this hypothesis. Interestingly, the magnitude of risk was lower for patients with a terminal admission of 28 days or greater, though they were still at significantly higher risk for receiving more intense care compared to patients with a terminal admission of 0 to 2 days. This pattern warrants further investigation to determine why the risk peaks at a particular range of days.

Interestingly, our results showed that AYA patients with either Hodgkin or non-Hodgkin lymphomas were significantly more likely to receive highly intense EOL care compared to patients with leukemia; other forms of hematologic malignancy were not significantly associated with intensity of care. Prior studies show that patients with blood cancers are more likely to die without hospice.[29,30] However, none of these studies evaluate the differences in care that patients with lymphomas versus patients with leukemia may experience. Furthermore, diagnosis was not a significant predictor for children as it was for AYAs. Further research is needed to examine why differences in treatment patterns at the end of life may exist between these two groups.

Additionally, geographic region was a significant predictor for intense care among children but not for AYAs. Children treated in the South had higher odds of receiving more intense care compared with children treated in the Northeast. This may be because half (50.8%) of the hospitals in our database were located in the South, but further research on regional variations in care intensity is needed. On the other hand, AYA patients who were treated at larger hospitals were more likely to receive more intense care at the end of life, but the same conclusion could not be made for children. Morden et al. previously found that patients with cancer who were cared for in medium- and large-sized hospitals received more care by almost every measure of intense EOL care compared to patients treated in small hospitals.[31] These suggest that it may be worth further exploring physicians' patterns of practice in larger hospitals, particularly when it

comes to care at the end of life, and compare these patterns to those of physicians in smaller hospitals.

A strength of this study was that it was population-based and we were able to link detailed clinical data as possible predictors for intense EOL care. Our study also has the advantage of being the first to analyze a cohort that includes both pediatric and AYA patients with hematologic malignancies across the country and not just a singular state. By conducting an analysis with a wider range of patients who we already hypothesized to be at higher risk for more intense EOL care due to their diagnoses, we were able to: (a) directly observe potential differences in EOL care intensity between the two age groups, and (b) identify predictors to be mindful of specifically for patients with hematologic malignancies.

However, our study has limitations to consider. The nature of the PHD dataset restricted our analyses to billing and coding data, which come with inherent limitations. For instance, data for individual patient encounters did not have exact admission days; rather, we were only given the month and year of admission, along with the calendar quarter. Therefore, we cannot guarantee that all encounters and intensity measures received in the final 14 and 30 days of life were precisely accounted for. Because claims data are dependent on professional ICD coding, it is also possible that some diagnoses may have been missed, that there may have been different coding patterns across the hospitals represented in the database, and that not all coding may be accurate.[32] Other important intensity markers, such as hospice use and ICU admissions,[8] were not available in sufficient detail in the PHD, which may limit our scope of understanding. Furthermore, we were limited to patients who died in the hospital because the database did not track patients who died at home or any other facility, unless they died somewhere outside the hospital for hospice care. Meanwhile, research shows that around 47% of children with cancer die in the hospital, 45% die at home, and anywhere from 2% to 10% die in hospice.[33] Additionally, AYAs were heavily represented in our cohort compared to children (89.5% versus 10.5%, respectively). Therefore, our results may be more generalizable to AYAs than children with cancer.

Ultimately, it is important to frame the conversation around the public health implications. Dying is inevitable, and while there is no one definition of a "good" death, high levels of patient distress can surely be characteristic of a "bad" death.[34] Our study is suggesting that 47% of children and young adults with HM are receiving two or more measures of intense care at the end of their lives, which may cause undue suffering.[7] Young patients with long terminal hospital admissions are at particularly high risk of receiving more intense care, especially if these patients are being treated at large hospitals, so physicians should remain mindful in taking measures to prevent highly intense care during this time. This could likely come in the form of better integrating palliative care and/or hospice care.[35-38] Future studies should also validate whether these indicators of intense EOL care[8] are as applicable to pediatric and young adult patients, given that they have primarily been used to analyze care patterns for older adults.

Conclusion

Many children, adolescents, and young adults with hematologic malignancies are receiving intense care at the end of their lives, which may cause undue pain and suffering. Patients who have a longer terminal admission, are being treated at larger hospitals, and have Hodgkin lymphoma are at particularly high risk. These are factors that medical teams should be mindful of when providing care for these patients to ensure that they are not suffering physically, emotionally, and financially. Many prior studies have only been conducted in adult populations, so it is imperative that more attention be given to children and young adults who are suffering with cancer to improve end-of-life care.

References

1. *National Center for Health Statisics: Child Health.* Centers for Disease Control and Prevention; 2016.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30.
3. Noone A, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. *Bethesda, MD, based on November.* 2017.
4. Johnston EE, Alvarez E, Saynina O, Sanders L, Bhatia S, Chamberlain LJ. End-of-Life Intensity for Adolescents and Young Adults With Cancer: A Californian Population-Based Study That Shows Disparities. *J Oncol Pract.* 2017;13(9):e770-e781.
5. Johnston EE, Alvarez E, Saynina O, Sanders LM, Bhatia S, Chamberlain LJ. Inpatient utilization and disparities: The last year of life of adolescent and young adult oncology patients in California. *Cancer.* 2018;124(8):1819-1827.
6. Mack JW, Chen K, Boscoe FP, et al. High Intensity of End-of-Life Care Among Adolescent and Young Adult Cancer Patients in the New York State Medicaid Program. *Med Care.* 2015;53(12):1018-1026.
7. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med.* 2000;342(5):326-333.
8. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. *J Clin Oncol.* 2003;21(6):1133-1138.
9. Bleyer A, Barr R. Cancer in Young Adults 20 to 39 Years of Age: Overview. *Seminars in Oncology.* 2009;36(3):194-206.
10. Johnston EE, Alvarez E, Saynina O, Sanders L, Bhatia S, Chamberlain LJ. Disparities in the Intensity of End-of-Life Care for Children With Cancer. *Pediatrics.* 2017;140(4).
11. Tzuh Tang S, Hung Y-N, Liu T-W, et al. Pediatric End-of-Life Care for Taiwanese Children Who Died As a Result of Cancer From 2001 Through 2006. *Journal of Clinical Oncology.* 2011;29(7):890-894.
12. Park JD, Kang HJ, Kim YA, et al. Trends in the aggressiveness of end-of-life care for Korean pediatric cancer patients who died in 2007-2010. *PLoS One.* 2014;9(6):e99888.
13. Kassam A, Sutradhar R, Widger K, et al. Predictors of and Trends in High-Intensity End-of-Life Care Among Children With Cancer: A Population-Based Study Using Health Services Data. *Journal of Clinical Oncology.* 2016;35(2):236-242.
14. Hui D, Didwaniya N, Vidal M, et al. Quality of end-of-life care in patients with hematologic malignancies: a retrospective cohort study. *Cancer.* 2014;120(10):1572-1578.
15. Tang ST, Wu S-C, Hung Y-N, Chen J-S, Huang E-W, Liu T-W. Determinants of Aggressive End-of-Life Care for Taiwanese Cancer Decedents, 2001 to 2006. *Journal of Clinical Oncology.* 2009;27(27):4613-4618.
16. Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC. Trends in the Aggressiveness of End-of-Life Cancer Care in the Universal Health Care System of Ontario, Canada. *Journal of Clinical Oncology.* 2011;29(12):1587-1591.
17. Kirtane K, Downey L, Lee SJ, Curtis JR, Engelberg RA. Intensity of End-of-Life Care for Patients with Hematologic Malignancies and the Role of Race/Ethnicity. *Journal of Palliative Medicine.* 2018;21(10):1466-1471.

18. Martins-Branco DA, Lopes S, Canario R, et al. Factors associated with the aggressiveness of end-of-life care for patients dying of cancer in hospitals: A nationwide cohort study. *Journal of Clinical Oncology.* 2018;36(34_suppl):68-68.
19. Institute NC. Adolescents and Young Adults with Cancer. National Institutes of Health.
20. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol.* 2004;22(2):315-321.
21. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Health Care.* 2005;17(6):505-509.
22. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-742.
23. Barnato AE, Farrell MH, Chang CC, Lave JR, Roberts MS, Angus DC. Development and validation of hospital "end-of-life" treatment intensity measures. *Med Care.* 2009;47(10):1098-1105.
24. *Premier Healthcare Database: Data that Informs and Performs.* Premier Applied Sciences; 2018.
25. Ananth P, Melvin P, Feudtner C, Wolfe J, Berry JG. Hospital Use in the Last Year of Life for Children With Life-Threatening Complex Chronic Conditions. *Pediatrics.* 2015;136(5):938-946.
26. Mack JW, Chen LH, Cannavale K, Sattayapiwat O, Cooper RM, Chao CR. End-of-Life Care Intensity Among Adolescent and Young Adult Patients With Cancer in Kaiser Permanente Southern California. *JAMA Oncol.* 2015;1(5):592-600.
27. Smith AK, McCarthy EP, Paulk E, et al. Racial and ethnic differences in advance care planning among patients with cancer: impact of terminal illness acknowledgment, religiousness, and treatment preferences. *J Clin Oncol.* 2008;26(25):4131-4137.
28. Miesfeldt S, Murray K, Lucas L, Chang CH, Goodman D, Morden NE. Association of age, gender, and race with intensity of end-of-life care for Medicare beneficiaries with cancer. *J Palliat Med.* 2012;15(5):548-554.
29. Odejide OO, Cronin AM, Earle CC, Tulsky JA, Abel GA. Why are patients with blood cancers more likely to die without hospice? *Cancer.* 2017;123(17):3377-3384.
30. Odejide OO, Cronin AM, Condron N, Earle CC, Wolfe J, Abel GA. Timeliness of End-of-Life Discussions for Blood Cancers: A National Survey of Hematologic Oncologists. *JAMA Intern Med.* 2016;176(2):263-265.
31. Morden NE, Chang CH, Jacobson JO, et al. End-of-life care for Medicare beneficiaries with cancer is highly intensive overall and varies widely. *Health Aff (Millwood).* 2012;31(4):786-796.
32. Tyree PT, Lind BK, Lafferty WE. Challenges of using medical insurance claims data for utilization analysis. *Am J Med Qual.* 2006;21(4):269-275.
33. Shah A, Diggens N, Stiller C, Murphy D, Passmore J, Murphy MF. Place of death and hospital care for children who died of cancer in England, 1999-2006. *Eur J Cancer.* 2011;47(14):2175-2181.
34. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA.* 2000;284(19):2476-2482.
35. Osenga K, Postier A, Dreyfus J, Foster L, Teeple W, Friedrichsdorf SJ. A Comparison of Circumstances at the End of Life in a Hospital Setting for Children With Palliative Care Involvement Versus Those Without. *J Pain Symptom Manage.* 2016;52(5):673-680.

36. Ranallo L. Improving the Quality of End-of-Life Care in Pediatric Oncology Patients Through the Early Implementation of Palliative Care. *J Pediatr Oncol Nurs.* 2017;34(6):374-380.
37. Snaman JM, Kaye EC, Lu JJ, Sykes A, Baker JN. Palliative Care Involvement Is Associated with Less Intensive End-of-Life Care in Adolescent and Young Adult Oncology Patients. *J Palliat Med.* 2017;20(5):509-516.
38. Wiesenthal A, Goldman DA, Korenstein D. Impact of Palliative Medicine Involvement on End-of-Life Services for Patients With Cancer With In-Hospital Deaths. *Journal of Oncology Practice.* 2017;13(9):e749-e759.

Appendix

Table 1
ICD-9/ICD-10 codes and CPT codes used to identify diagnoses and EOL care indicators

	ICD-9 Procedure Codes	**ICD-9 Diagnosis Codes**	**ICD-10 Procedure Codes**	**ICD-10 Diagnosis Codes**	**CPT Codes**
Hodgkin Lymphoma		201.xx		C81.xx	
Non-Hodgkin Lymphoma		202.xx		C82.xx – C86.xx	
Multiple myeloma		203.xx		C90.xx	
Leukemia		204.xx – 208.xx		C91.xx – C95.xx; V10.60	
CPR	99.60-99.64, 99.69		5A12012, 5A2204Z		92950, 92992
Intubation/ ventilation	96.01-96.06, 96.70-96.72		09HN7BZ, 09HN8BZ, 0CHY7BZ, 0CH78BZ, 0DH57BZ, 0DH58BZ, 0BH17EZ, 0BH18EZ, 0B717DZ, 0B718DZ, 0BH07DZ, 0BH08YZ, 0BH172Z, 0BH17YZ, 0BH182Z, 0BH18YZ, 0BHK7YZ, 0BHK8YZ, 0BHL7YZ, 0BHL8YZ, 0WQ7YZ, 0DL57DZ, 0DL58DZ, 5A1935Z, 5A1945Z, 5A1955Z		31500, 32550-32555

Chemotherapy	99.25, 99.28, 00.15, 17.70	V58.11, V58.12, V66.62, V67.2	3E03305, 3E04305, XW03351, XW043B3, XW033C3, XW04351, XW043B3, XW043C3	Z51.11, Z51.12	96400-96549, J9000-J9999, Q0083-Q0085
Tracheostomy placement	31.1, 31.2, 31.29	V44.0 (but not listed in our diagnosis dataset)	0B110F4, 0B110Z4, 0B113F4, 0B113Z4, 0B114F4, 0B114Z4	Z93.0 (but not listed in our diagnoses dataset)	31600, 31601
Hemodialysis	39.95	V45.11 (but not listed in our diagnosis dataset)	5A1D70Z 5A1D80Z 5A1D90Z	Z99.2 (but not listed in our diagnoses dataset)	90935-90940