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ORIGINAL REPORT

End-of-Life Care Intensity in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation: A Population-Level Analysis

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A B S T R A C T

Purpose

Intensity of end-of-life care receives much attention in oncology because of concerns that high-intensity care is inconsistent with patient goals, leads to worse caregiver outcomes, and is expensive. Little is known about such care in those undergoing allogeneic hematopoietic cell transplantation (HCT), a population at high risk for morbidity and mortality.

Patients and Methods

We conducted a population-based analysis of patients who died between 2000 and 2013, within 1 year of undergoing an inpatient allogeneic HCT using California administrative data. Previously validated markers of intensity were examined and included: hospital death, intensive care unit (ICU) admission, and procedures such as intubation and cardiopulmonary resuscitation at end of life. Multivariable logistic regression models determined clinical and sociodemographic factors associated with: hospital death, a medically intense intervention (ICU admission, cardiopulmonary resuscitation, hemodialysis, intubation), and ≥ two intensity markers.

Results

Of the 2,135 patients in the study population, 377 were pediatric patients (age ≤ 21 years), 461 were young adults (age 22 to 39 years), and 1,297 were adults (age ≥ 40 years). The most common intensity markers were: hospital death (83%), ICU admission (49%), and intubation (45%). Medical intensity varied according to age, underlying diagnosis, and presence of comorbidities at time of HCT. Patients with higher-intensity end-of-life care included patients age 15 to 21 years and 30 to 59 years, patients with acute lymphoblastic leukemia, and those with comorbidities at time of HCT.

Conclusion

Patients dying within 1 year of inpatient allogeneic HCT are receiving medically intense end-of-life care with variations related to age, underlying diagnosis, and presence of comorbidities at time of HCT. Future studies need to determine if these patterns are consistent with patient and family goals.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only curative option for many malignant and nonmalignant diseases, leading to a steady increase in allogeneic HCTs in the United States in the last two decades.[1] However, HCT continues to be associated with high morbidity and mortality. Therefore, understanding end-of-life care in those undergoing allogeneic HCT is critical.

For oncology patients treated with conventional chemotherapy, medically intense end-of-life care may be inconsistent with patient and family wishes[2,3] and associated with worse bereaved family outcomes.[4,5] The American Society of Clinical Oncology and other professional organizations advocate for a palliative approach to end-of-life care.[6-9] Validation of markers of intensity of end-of-life care in oncology has enabled standardization of this outcome across studies; these markers include: intensive care unit (ICU) admission, intubation, hemodialysis, and cardiopulmonary resuscitation (CPR) in the last month of life, and hospital death.[10-12] Many medical intensity markers have been adopted by the National Quality Forum (NQF) as end-of-life quality markers in oncology.[13] Although the NQF has endorsed the markers for all oncology patients, it is unclear if they are as applicable to patients with hematologic

ASSOCIATED CONTENT

Appendix
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malignancies as those with solid tumors,[14,15] let alone if they are applicable to patients undergoing HCT. Nonetheless, these markers could provide a starting point for discussing end-of-life care with patients undergoing HCT and uncovering what disparities exist in the population; however, there are no population-level studies addressing this topic in those undergoing allogeneic HCT. We have addressed this gap by conducting a systematic evaluation of the intensity of end-of-life care in those undergoing allogeneic HCT at a population level.

PATIENTS AND METHODS

Study Design and Oversight

We conducted a retrospective population-based analysis using the California Office of Statewide Health Planning and Development (OSHPD) Private Patient Discharge Data Database and Vital Statistics Death Certificate Data.[16] All California hospitals, except federal facilities, must submit discharge information to OSHPD, including demographics, residence zip codes, payers, and up to 24 International Classification of Diseases (ninth revision; ICD-9) codes. The discharge database is linked to the death certificate database with unique record linkage numbers. The Stanford University Institutional Review Board and the California Committee for Protection of Human Subjects approved the study. Administrative data study reporting guidelines were followed.[17]

Study Population

The study population included patients who died between 2000 and 2013 and underwent an inpatient HCT within 1 year of death, as determined by first appearance of allogeneic HCT administration ICD-9 code (Fig 1). Patients who died as a result of accidents (except medical errors) or peripartum events and patients without an ICD-9 code associated with a known indication for allogeneic HCT were excluded. Patients were divided into pediatric (age 0 to 21 years), young adult (YA; age 22 to 39 years), and adult (age $\geq$ 40 years) cohorts for age-stratified analyses.

Dependent Variables

Markers of intensity included ICU admission, intubation/mechanical ventilation, hemodialysis, CPR within 30 days of death, and hospital death.[10-12] ICD-9 codes for intensity have been previously described[10] and used in OSHPD.[18,28] ICD-9 codes pertain to an entire admission; a patient was considered to have received an intervention if it was coded during an admission that occurred entirely within 30 days of death or during a terminal admission. Additionally, a terminal admission of $\geq$ 30 days was considered an intensity marker, because days at home at end of life have been suggested to be a quality marker.[20] Location of death was determined from death certificates or hospital disposition of death.

Independent Variables

Sociodemographic variables included payer, death age, sex, race/ethnicity, median household income (zip code–level median income and the 2004 federal poverty level), and metropolitan service area.[21,22] Data were abstracted from death certificate information when available and otherwise abstracted from last hospital admission. Clinical variables included underlying diagnosis, allogeneic HCT year, HCT admission comorbidities/complications, and location of final hospital admission. Two adult and two pediatric transplantation physicians reviewed and grouped a previously published list of indications for allogeneic HCT[23]: acute lymphoblastic leukemia (ALL), acute myeloid leukemia or myelodysplastic syndrome (AML/MDS), lymphoma, other malignant conditions, and nonmalignant conditions. Elixhauser's enhanced comorbidity score was chosen because it was developed with the OSHPD database and included oncology patients.[24,25] Patients received one comorbidity point for each nononcology or nonhematologic comorbidity category coded during their HCT admission. The final hospital site was categorized as the same hospital as the HCT hospital, different hospital than HCT but an oncology specialty center (National Cancer Institute–designated cancer center or Children's Oncology Group center), or different hospital than HCT but a nonspecialty center.

Statistical Analysis

The number of inpatient days and number of admission between transplantation and death were calculated for each patient. Descriptive statistics were calculated for each independent and dependent variable.

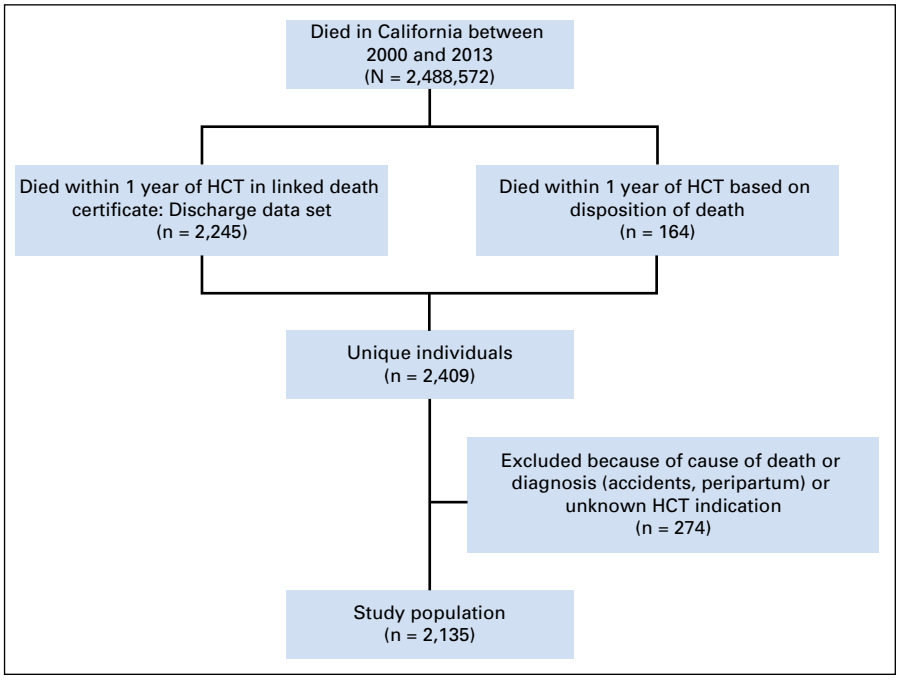

Fig 1. CONSORT diagram showing the study population. The study population included all patients who died between 2000 and 2013 in California and underwent an inpatient hematopoietic cell transplantation (HCT) within 1 year of death who did not die as a result of peripartum events or trauma (N = 2,135).

Predictors of medically intense end-of-life care. Multivariable logistic regression models were constructed to determine factors associated with hospital death, a medically intense intervention (CPR, ICU admission, intubation, hemodialysis), and ≥ two intensity markers.

Sensitivity analysis. Regression models excluding patients who died during their HCT admission were conducted to ensure patients who unexpectedly decompensated in the immediate post-HCT period were not skewing results. SAS software (version 9.1; SAS Institute, Cary, NC) was used.

RESULTS

Study Population Characteristics

The 2,135 patients included 377 pediatric patients, 461 YA patients, and 1,297 adults (Table 1). Overall, 57% of the study population was non-Hispanic white, but only 32% of the pediatric cohort was non-Hispanic white, whereas 67% of adults were non-Hispanic white. The most common diagnoses varied by age; ALL was the most common diagnosis (45%) in the pediatric cohort, but AML/MDS was the most common in the YA (36%) and adult (52%) cohorts. A majority (82%) of patients underwent their HCT and final admission at the same hospital. Thirty percent died during their HCT admission. The most common comorbidities/complications included mucositis, infection (ie, *Clostridium* and cytolomegalovirus), hypertension, renal failure, and respiratory failure.

End-of-Life Hospital Utilization

The patients had an average of 105 hospital days (standard deviation [SD], 52 days) in their last year of life and were readmitted an average of 1.3 times (SD, 0.6 times) after their HCT admission before they died (Table 1). Although all cohorts averaged 1.3 readmissions in the last year, the pediatric cohort had the most hospital days in the last year: 133 days (SD, 61 days).

Intensity Rates

The four most common intensity markers were hospital death (83%), ICU admission (49%), intubation (45%), and hospitalization for the entire last 30 days of life (43%; Fig 2). Fifty-three percent had at least one medically intense intervention, and 57% had ≥ two intensity markers. The pediatric, YA, and adult cohorts were generally similar in the prevalence of intensity markers, as shown by the following respective rates: hospital death, 87%, 84%, and 82%; ≥ one medically intense intervention, 57%, 57% and 51%; and ≥ two intensity markers, 60%, 61%, and 54%. The rates were lower in patients who died during their HCT admission (Appendix Fig A1, online only).

Predictors of Intense End-of-Life Care

Hospital death. The probability of a hospital death varied by age at death, insurance, and presence of comorbidities/complications (Table 2). Adolescents and middle-aged adults were more likely to have a hospital death (age 15 to 21 years: odds ratio [OR], 3.9; 95% CI, 1.8 to 8.3; age 30 to 39 years: OR, 1.9; 95% CI, 1.2 to 3.0; age 40 to 49 years: OR, 1.5; 95% CI, 1.0 to 2.3; age 50 to 59 years: OR, 1.5; 95% CI, 1.0 to 2.1; reference, age ≥ 60 years). Patients with health maintenance

Table 1. Clinical and Sociodemographic Characteristics of Study Cohort

Characteristic	No. (%)			
	Overall (N = 2,135)	Pediatrics* (n = 377)	YAs† (n = 461)	Adults‡ (n = 1,297)
Age, years				
< 5	79 (3.7)	79 (21.0)		
5-9	69 (3.2)	69 (18.3)		
10-14	90 (4.2)	90 (23.9)		
15-21	139 (6.5)	139 (36.9)		
22-29	188 (8.8)		188 (40.8)	
30-39	273 (12.8)		273 (59.2)	
40-49	417 (19.5)			417 (32.2)
50-59	508 (23.8)			508 (39.2)
≥ 60	372 (17.4)			372 (28.7)
Sex				
Female	916 (42.9)	158 (41.9)	185 (40.1)	573 (44.2)
Male	1,219 (57.1)	219 (58.1)	276 (59.9)	724 (55.8)
Race/ethnicity				
Non-Hispanic white	1,209 (56.6)	119 (31.6)	220 (47.7)	870 (67.1)
Black	83 (3.9)	18 (4.8)	22 (4.8)	43 (3.3)
Hispanic	575 (26.9)	181 (48.0)	163 (35.4)	231 (17.8)
Other	268 (12.6)	59 (15.7)	56 (12.2)	153 (11.8)
Diagnosis				
AML/MDS	955 (44.7)	113 (30.0)	165 (35.8)	677 (52.2)
ALL	478 (22.4)	169 (44.8)	148 (32.1)	161 (12.4)
Lymphoma	328 (15.4)	24 (6.4)	81 (17.6)	223 (17.2)
Other malignant	83 (3.9)	0 (0.0)	< 10§	79 (6.1)
Nonmalignant	291 (13.6)	71 (18.8)	63 (13.7)	157 (12.1)
Insurance				
HMO	270 (12.7)	44 (11.7)	61 (13.2)	165 (12.7)
Private, non-HMO	1,071 (50.2)	115 (30.5)	216 (46.9)	740 (57.1)
Public, self	794 (37.2)	218 (57.8)	184 (39.9)	392 (30.2)
Income, × FPL				
< 2	333 (15.6)	90 (23.9)	96 (20.8)	147 (11.3)
2-4	1,302 (61.0)	230 (61.0)	267 (57.9)	805 (62.1)
> 4	393 (18.4)	44 (11.7)	65 (14.1)	284 (21.9)
Year of HCT				
1999-2004	801(37.5)	196 (52.0)	181 (39.3)	424 (32.7)
2005-2009	741 (34.7)	124 (32.9)	165 (35.8)	452 (34.9)
2010-2013	593 (27.8)	57 (15.1)	115 (25.0)	421 (32.5)
MSA status				
Rural	137 (6.4)	19 (5.0)	23 (5.0)	95 (7.3)
Urban	1929 (90.4)	350 (92.8)	416 (90.2)	1,163 (89.7)
Hospital (HCT and final)				
Different, last = community	194 (4.9)	17 (4.5)	43 (9.3)	134 (10.3)
Different, last = specialty	98 (4.4)	35 (9.3)	23 (5.0)	40 (3.1)
Same	1,843 (82.1)	325 (86.2)	395 (85.7)	1,123 (86.6)
No. of comorbidities at time of HCT				
0	378 (17.7)	80 (21.2)	92 (20.0)	206 (15.9)
1	576 (27.0)	108 (28.6)	138 (29.9)	330 (25.4)
≥ 2	1,181 (55.3)	189 (50.1)	231 (50.1)	761 (58.7)
Utilization in last year				
Died during HCT admission	633 (29.6)	142 (37.7)	137 (29.7)	354 (27.3)
Length of stay, No. Of days (SD)	105 (52)	133 (61)	116 (49)	101 (48)
No. of readmissions (SD)	1.3 (0.6)	1.3 (0.7)	1.3 (0.5)	1.3 (0.6)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FPL, federal poverty level; HCT, hematopoietic cell transplantation; HMO, health maintenance organization; MDS, myelodysplastic syndrome; MSA, metropolitan statistical area; SD, standard deviation; YA, young adult.
*Age 0 to 21 years.
†Age 22 to 39 years.
‡Age ≥ 40 years.
§Per state regulation, cannot report cell sizes < 13.

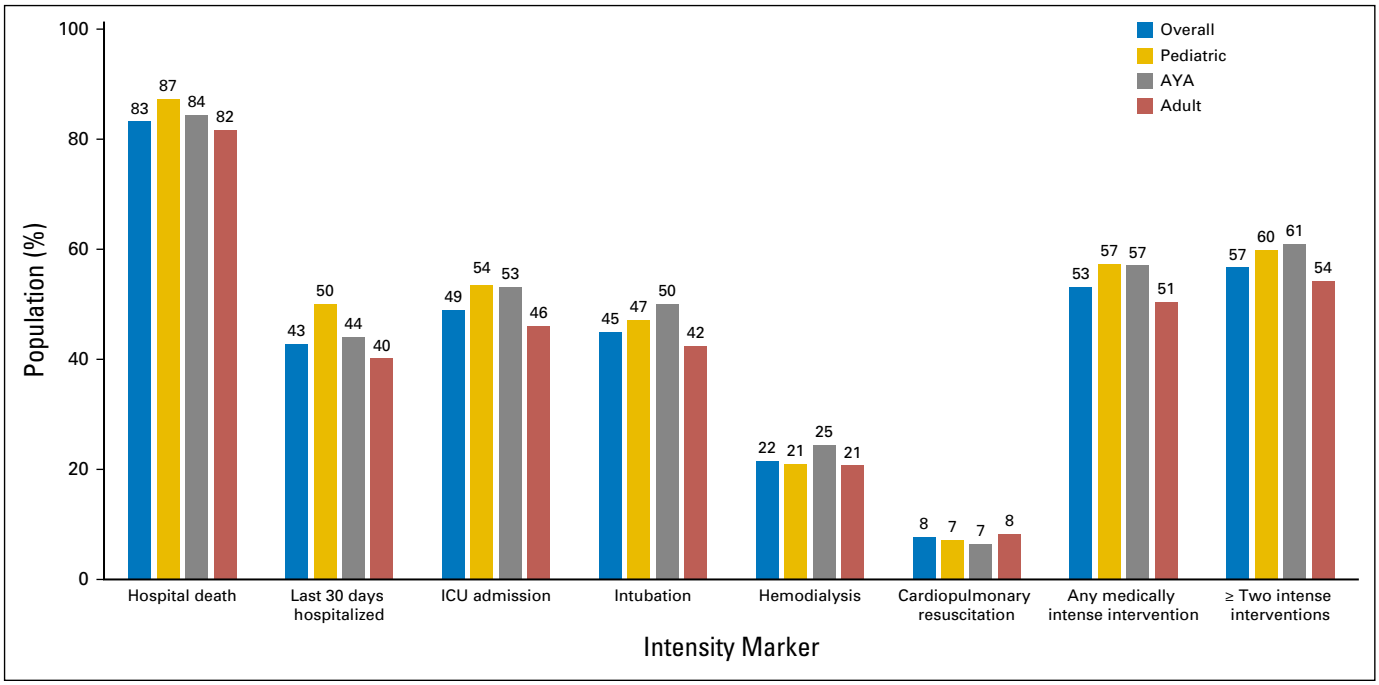

Fig 2. Rates of intense end-of-life care by age category (overall, pediatric [age 0 to 21 years], adolescent and young adult [AYA; age 22 to 39 years], and adult [age ≥ 40 years]).

organization (HMO) insurance were less likely to have a hospital death (HMO: OR, 0.6; 95% CI, 0.4 to 0.8; reference, public). Patients with comorbidities/complications during HCT admission were more likely have a hospital death (one comorbidity: OR, 1.6; 95% CI, 1.1 to 2.2; ≥ two comorbidities: OR, 2.3; 95% CI, 1.7 to 3.1; reference, zero comorbidities). In age-stratified analyses, comorbidities were associated with hospital death in all three groups (Appendix Tables A1 to A3, online only). In the pediatric and adult cohorts, those with HMO insurance had lower odds of hospital death than those with public insurance. Additional findings in the stratified analyses included lower odds of hospital death associated with rural residence in pediatric patients, AML/MDS and lymphoma in YAs, and age ≥ 60 years in adults.

Medically intense intervention. Receipt of a medically intense intervention varied by age at death, underlying diagnosis, HCT year, location of care, and comorbidities (Table 2). Patients age 15 to 21 years (OR, 2.6; 95% CI, 1.6 to 4.1), 30 to 39 years (OR, 1.8; 95% CI, 1.2 to 2.6), and 40 to 49 years (OR, 1.4; 95% CI, 1.0 to 1.9) were more likely to receive a medically intense intervention than those age ≥ 60 years. Patients with AML/MDS were less likely (OR, 0.7; 95% CI, 0.6 to 0.9) to receive a medically intense intervention than those with ALL. Patients undergoing transplantation between 2000 and 2004 were less likely (OR, 0.7; 95% CI, 0.5 to 0.8) to receive a medically intense intervention than those undergoing transplantation between 2010 and 2013. Patients who changed hospitals between HCT and death were less likely to receive a medically intense intervention if they went to a nonspecialty hospital (OR, 0.3; 95% CI, 0.2 to 0.5) or a specialty hospital (OR, 0.4; 95% CI, 0.3 to 0.7). Finally, those with comorbidities/complications (one comorbidity: OR, 1.6; 95% CI, 1.2 to 2.1; ≥ two comorbidities: OR, 2.5; 95% CI, 2.0 to 3.3; reference, zero comorbidities) were more likely to receive a medically intense intervention. Changing hospitals between HCT and death and fewer comorbidities were associated with lower odds of receiving a medically intense intervention in all three age cohorts. Additionally, age 15 to 21 years in pediatric patients and age 40 to 49 and 50 to 59 years in adults were associated with higher odds of receiving a medically intense intervention. Other findings in the age-stratified analysis included lower odds of receiving a medically intense intervention associated with HMO insurance in YAs and adults, underlying diagnosis of AML/MDS in YAs, undergoing an HCT before 2010, and rural residency in adults (Appendix Tables A1 to A3).

≥ Two intensity markers. Age at death, underlying diagnosis, location of care, and comorbidities were associated with ≥ two intensity markers (Table 2). Compared with those age ≥ 60 years at death, patients age 15 to 21 (OR, 2.9; 95% CI, 1.8 to 4.7), 22 to 29 (OR, 1.6; 95% CI, 1.1 to 2.4), 30 to 39 (OR, 1.8; 95% CI, 1.3 to 2.8), 40 to 49 (OR, 1.7; 95% CI, 1.3 to 2.4), and 50 to 59 years (OR, 1.5; 95% CI, 1.1 to 2.0) were more likely to have ≥ two intensity markers. Patients with AML/MDS were less likely (OR, 0.7; 95% CI, 0.6 to 0.9) to have ≥ two intensity markers than those with ALL. Patients with their final hospitalization at a different hospital than their HCT were less likely to have ≥ two intensity markers, whether the final hospital was a nonspecialty (OR, 0.3; 95% CI, 0.2 to 0.4) or specialty hospital (OR, 0.3; 95% CI, 0.2 to 0.5). Patients with a comorbidity/complication were more likely to have ≥ two intensity markers than those without any comorbidities/complications (one comorbidity: OR, 1.7; 95% CI, 1.3 to 2.3; ≥ two comorbidities: OR, 3.1; 95% CI, 2.3 to 4.0). In age-stratified analyses, changing hospitals between HCT and fewer comorbidities at time of HCT were associated with lower odds of receiving ≥ two intensity markers in all three cohorts (Appendix Tables A1 to A3). Additionally, AML/MDS in YAs was associated with lower odds of

Table 2. Factors Associated With Hospital Death, Medically Intense Intervention, and ≥ Two Intensity Markers

Characteristic	OR (95% CI)		
	Hospital Death	Medically Intense Intervention	≥ Two Intensity Markers
Age, years			
< 5	1.9 (0.8 to 4.3)	1.2 (0.7 to 2.1)	1.1 (0.6 to 2.0)
5-9	1.8 (0.8 to 4.0)	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.5)
10-14	0.9 (0.4 to 1.7)	1.5 (0.9 to 2.6)	1.4 (0.8 to 2.3)
15-21	3.9 (1.8 to 8.3)*	2.6 (1.6 to 4.1)*	2.9 (1.8 to 4.7)*
22-29	1.2 (0.7 to 2.0)	1.4 (0.9 to 2.0)	1.6 (1.1 to 2.4)†
30-39	1.9 (1.2 to 3.0)‡	1.8 (1.2 to 2.6)‡	1.9 (1.3 to 2.8)*
40-49	1.5 (1.0 to 2.3)†	1.4 (1.0 to 1.9)†	1.7 (1.3 to 2.4)*
50-59	1.5 (1.0 to 2.1)†	1.3 (1.0 to 1.8)	1.5 (1.1 to 2.0)†
≥ 60	Ref	Ref	Ref
Sex			
Female	Ref	Ref	Ref
Male	1.0 (0.8 to 1.3)	1.1 (0.9 to 1.4)	1.2 (1.0 to 1.4)
Race/ethnicity			
Non-Hispanic white	Ref	Ref	Ref
Black	1.7 (0.8 to 3.6)	1.4 (0.9 to 2.4)	1.1 (0.7 to 1.9)
Hispanic	1.1 (0.8 to 1.4)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)
Other	1.1 (0.7 to 1.6)	1.0 (0.7 to 1.4)	1.0 (0.8 to 1.4)
Diagnosis			
AML/MDS	0.8 (0.6 to 1.2)	0.7 (0.6 to 0.9)†	0.7 (0.6 to 0.9)†
ALL	Ref	Ref	Ref
Lymphoma	1.0 (0.6 to 1.5)	0.9 (0.6 to 1.2)	1.0 (0.7 to 1.4)
Other malignant	0.9 (0.5 to 1.7)	0.8 (0.5 to 1.3)	0.6 (0.4 to 1.1)
Nonmalignant	1.5 (0.9 to 2.5)	1.2 (0.9 to 1.7)	1.4 (1.0 to 1.9)
Insurance			
HMO	0.6 (0.4 to 0.8)‡	0.9 (0.7 to 1.2)	1.0 (0.7 to 1.4)
Private, non-HMO	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.3)	0.9 (0.7 to 1.1)
Public, self	Ref	Ref	Ref
Income, × FPL			
< 2	1.2 (0.8 to 1.9)	1.1 (0.8 to 1.5)	0.9 (0.6 to 1.3)
2-4	1.0 (0.7 to 1.4)	1.1 (0.8 to 1.4)	1.0 (0.8 to 1.2)
> 4	Ref	Ref	Ref
Year of HCT			
2000-2004	1.2 (0.9 to 1.6)	0.7 (0.5 to 0.8)‡	0.9 (0.7 to 1.1)
2005-2009	1.0 (0.7 to 1.4)	0.8 (0.6 to 1.0)	0.9 (0.7 to 1.2)
2010-2013	Ref	Ref	Ref
MSA status			
Rural	0.7(0.5 to 1.2)	0.6 (0.4 to 0.9)†	0.7 (0.5 to 1.1)
Urban	Ref	Ref	Ref
Hospital (HCT and final)			
Different, last = community	0.7 (0.5 to 1.0)	0.3 (0.2 to 0.5)*	0.3 (0.2 to 0.4)*
Different, last = specialty	0.8 (0.4 to 1.3)	0.4 (0.3 to 0.7)*	0.3 (0.2 to 0.5)*
Same	Ref	Ref	Ref
No. of comorbidities at time of HCT			
0	Ref	Ref	Ref
1	1.6 (1.1 to 2.2)‡	1.6 (1.2 to 2.1)‡	1.7 (1.3 to 2.3)*
≥ 2	2.3 (1.7 to 3.1)*	2.5 (2.0 to 3.3)*	3.1 (2.3 to 4.0)*

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FPL, federal poverty level; HCT, hematopoietic cell transplantation; HMO, health maintenance organization; MDS, myelodysplastic syndrome; OR, odds ratio; Ref, reference.
*$P < .001$.
†$P < .05$.
‡$P < .01$.

having ≥ two intensity markers, and age 15 to 21 years in pediatric patients and age 40 to 49 and 50 to 59 years in adults were associated with increased odds of having of ≥ two intensity markers.

Sensitivity analyses. The sensitivity analyses generally decreased the magnitude of association and increased the width of 95% CIs, rendering some previously significant findings insignificant. In particular, the association between hospital death and comorbidities/complications was reduced in magnitude; the association between receipt of a medically intense intervention and rural residence, location of care, and comorbidities was also mitigated. Finally, the association between location of care and comorbidities and ≥ two intensity markers decreased in magnitude.

DISCUSSION

This comprehensive analysis of end-of-life care of patients undergoing allogeneic HCT describes rates of and disparities in intensity of end-of-life care, clarifies research priorities for this population, and informs policy conversations. The most common intensity markers were hospital death, ICU admission, and intubation. More than 80% died in the hospital, more than 40% spent the last 30 days of life in the hospital, and more than 45% were admitted to the ICU near the end of life, with 105 hospital days in their last year of life. These intensity rates are much higher than those found in general oncology patients. For instance, 19% to 22% of adolescents and YAs (AYAs) with cancer are admitted to the ICU in the last month of life compared with the 53% in this study,[18,26,27] and 63% of children die in the hospital compared with the 82% of children dying in the hospital in this study.[28] These findings delineate those undergoing allogeneic HCT as a subset of patients for whom end-of-life care research is vitally important and can help guide resource allocation and end-of-life care conversations in this population.

There were differences in the rates of intensity of end-of-life care related to age at death, underlying diagnosis, location of end-of-life care, and comorbidities/complications. Those age 15 to 21 and 30 to 59 years constituted the highest-intensity age groups in the HCT population. Oncology patients age 15 to 21 years have previously been shown to have higher-intensity end-of-life care than their younger counterparts.[28] Palliative care is associated with lower-intensity end-of-life care for AYA oncology patients receiving conventional chemotherapy,[29] and palliative care integration into the inpatient HCT team results in improvement in symptoms and psychological distress.[30,31] Because of the shortage of palliative care physicians in the United States, even at cancer centers,[32,33] strategic use of palliative care resources is needed. Although not widely used, adolescent patients undergoing allogeneic HCT may benefit from automatic (triggered) palliative care involvement.

Despite the high intensity of end-of-life care in AYAs with cancer, there is a dearth of literature on end-of-life care for such patients.[34] Because AYAs with cancer lag behind other age groups in survival improvements, the National Cancer Institute and the Lance Armstrong Foundation partnered to determine the special research and cancer care needs of this population.[19] This work uncovered addressable issues that contribute to the survival gap; AYAs with cancer lack access to specialty centers and trials.[21,22,35,36] It seems that AYA end-of-life outcomes also require special attention. Our study not only highlights the need to better

understand end-of-life care for AYA patients, but also suggests some starting points. Community hospitals have been associated with higher-intensity end-of-life care for AYA patients than specialty centers for currently unknown reasons,[18] even as AYA patients are increasingly admitted to community hospitals as death approaches.[37] However, this study shows that YAs who went to a community hospital at end of life had less-intense end-of-life care than those who stayed at the HCT center. Therefore, there is a subgroup of YA patients for whom community hospitals provide lower-intensity end-of-life care than specialty centers. When patients undergoing HCT transfer back to their referring centers, many HCT centers remain in close contact with those referring centers; this relationship may guide the end-of-life care YAs at community centers receive after HCT. Studying this subset of YA patients receiving end-of-life care and the systems that allow community centers to provide them lower-intensity end-of-life care may inform future AYA program development at community hospitals.

Other high-intensity groups identified in this study differed from the high-intensity groups found in conventionally treated oncology patients.[38-43] First, patients who changed hospitals between HCT and death received less-intense end-of-life care than those who remained at the HCT center. Location of care has previously been shown to affect end-of-life care for children and AYAs with cancer; patients at community hospitals received more-intense end-of-life care than those at specialty centers.[18,28] However, patients who changed from their HCT hospital to either a community or specialty hospital had less medically intense care than those who stayed at the HCT hospital. This may be because some patients know they are dying and choose to forgo further curative therapy, instead transferring to a community hospital closer to home for comfort care. Therefore, the population of the community hospital would be enriched for those who selected comfort care. Second, many studies of end-of-life care in conventional therapy recipients show minorities receiving more-intense end-of-life care,[18,28,38,41-43] but our study did not show disparities related to race/ethnicity. These differences deserve in-depth examination, particularly to determine if these systems are providing low-intensity and goal-concurrent care to populations traditionally receiving high-intensity end-of-life care and what factors allow them to do so.

Most importantly, concordance (or lack thereof) between the intensity of end-of-life care and the patient's wishes remains undetermined. One single-institution study showed that 69% of patients undergoing allogeneic HCT with an advance directive did not want to prolong life if terminally ill.[44] Multi-institutional studies and studies of patients without advance directives are needed to understand what their end-of-life goals are, whether they are receiving goal-concordant care, whether this high-intensity end-of-life care is goal concordant or determined by factors such as timing of end-of-life conversations,[45-47] how end-of-life wishes are enacted,[48,49] and what hospital practices are regarding end-of-life care.[10,50] Such studies of end-of-life care preferences must include the high-intensity populations identified in our study. Additionally, our study included patients who died as a result of transplantation-related mortality and disease relapse. The two groups may have different end-of-life care goals and end-of-life wishes, necessitating separate exploration of the groups.

As the value-based payment portions of the Affordable Care Act are implemented, evidence to inform what constitutes value-based repayments in HCT at end of life is important. Intensity of end-of-life care could be part of value-based repayment, because many markers of intensity of end-of-life care are already endorsed by the NQF in oncology,[12] but the markers have not been validated in the HCT population. This study shows higher rates of medically intense end-of-life care in those undergoing allogeneic HCT than in conventional oncology patients. More work is needed to determine if the intensity markers traditionally used in the oncology setting are appropriate quality markers of end-of-life care in patients undergoing HCT.

As with any study, there are limitations to consider. First, population-based studies using administrative data have limitations related to data collection and reporting. Because all hospitals are required to report accurate information to the state, and the state cleans and links the data, the OSHPD database is considered reliable and complete. Additionally, we identified patients based on the first occurrence of an allogeneic HCT within 1 year of death using the inpatient ICD-9 code for allogeneic HCT; therefore, we missed outpatient HCTs. OSHPD links the patient discharge database with the vital statistics database, using probabilistic linkage that relies heavily on social security numbers, leading to underrepresentation of children and immigrants. Additionally, our data set was unable to distinguish HCT-related mortality from relapse-related mortality, which have different end-of-life implications. This study was performed with data from Californian patients, with a unique health care system and patient demographics, potentially limiting generalizability. However, it establishes methodology and baseline rates that can be used in future studies. Finally, there are other markers of end-of-life care, such as emergency department use, that were not available to us. Instead, we focused on inpatient intensity, which has important implications for health care finances and evaluation of goal concordance of end-of-life care.

In conclusion, patients dying within 1 year of allogeneic HCT are receiving medically intense end-of-life care, with variations related to age, underlying diagnosis, location of care, and comorbidities. We need to determine if these patients are receiving goal-concurrent care. Additionally, it is important to begin to consider what constitutes value-based repayment in HCT end-of-life care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Table A1. Factors Associated With Hospital Death, Medically Intense Intervention, and ≥ Two Intensity Markers in Pediatrics (age 1-21 years)

Characteristic	OR (95% CI)		
	Hospital Death	Medically Intense Intervention	≥ Two Intensity Markers
Age, years			
< 5	0.7 (0.2 to 2.4)	0.8 (0.4 to 1.8)	0.8 (0.4 to 1.8)
5-9	Ref	Ref	Ref
10-14	0.4 (0.2 to 1.2)	1.1 (0.5 to 2.3)	1.0 (0.5 to 2.1)
15-21	2.0 (0.7 to 5.9)	2.1 (1.0 to 4.1)*	2.2 (1.1 to 4.5)*
Sex			
Female	Ref	Ref	Ref
Male	0.6 (0.3 to 1.2)	1.4 (0.9 to 2.4)	1.3 (0.8 to 2.2)
Race/ethnicity			
Non-Hispanic white	Ref	Ref	Ref
Black	4.0 (0.4 to 38.4)	3.0 (0.8 to 11.0)	1.5 (0.4 to 5.2)
Hispanic	1.4 (0.6 to 3.2)	1.1 (0.6 to 2.0)	0.8 (0.4 to 1.5)
Other	1.1 (0.3 to 3.4)	1.3 (0.6 to 2.7)	1.0 (0.5 to 2.3)
Diagnosis			
AML/MDS	2.2 (0.9 to 5.7)	1.0 (0.5 to 1.7)	1.1 (0.6 to 1.9)
ALL	Ref	Ref	Ref
Lymphoma	0.9 (0.2 to 3.8)	0.8 (0.3 to 2.1)	1.4 (0.5 to 4.1)
Other malignant	NA	NA	NA
Nonmalignant	2.3 (0.8 to 6.8)	1.7 (0.8 to 3.5)	1.8 (0.9 to 3.7)
Insurance			
HMO	0.3 (0.1 to 0.8)*	1.7 (0.7 to 4.2)	1.5 (0.6 to 3.8)
Private, non-HMO	0.7 (0.3 to 1.6)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.5)
Public, self	Ref	Ref	Ref
Income, × FPL			
< 2	0.3 (0.1 to 1.4)	1.3 (0.5 to 3.3)	1.0 (0.4 to 2.4)
2-4	0.4 (0.1 to 1.6)	0.9 (0.4 to 1.9)	0.9 (0.4 to 2.0)
> 4	Ref	Ref	Ref
Year of HCT			
2000-2004	1.0 (0.4 to 3.1)	1.0 (0.5 to 2.0)	1.0 (0.5 to 2.0)
2005-2009	0.8 (0.3 to 2.5)	1.1 (0.5 to 2.3)	1.0 (0.5 to 2.2)
2010-2013	Ref	Ref	Ref
MSA status			
Rural	0.2 (0.1 to 0.8)*	0.6 (0.2 to 1.9)	0.5 (0.2 to 1.7)
Urban	Ref	Ref	Ref
Hospital (HCT and final)			
Different, last = community	0.5 (0.1 to 1.9)	0.3 (0.1 to 0.8)*	0.1 (0 to 0.5)†
Different, last = specialty	1.6 (0.5 to 5.1)	0.2 (0.1 to 0.6)†	0.2 (0.1 to 0.5)†
Same	Ref	Ref	Ref
No. of comorbidities at time of HCT			
0	Ref	Ref	Ref
1	1.9 (0.8 to 4.6)	2.0 (1.0 to 4.1)*	2.8 (1.4 to 5.7)†
≥ 2	3.8 (1.6 to 9.2)†	4.4 (2.4 to 8.3)‡	4.9 (2.6 to 9.2)‡

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FPL, federal poverty level; HCT, hematopoietic cell transplantation; HMO, health maintenance organization; MDS, myelodysplastic syndrome; NA, not applicable; OR, odds ratio; Ref, reference.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table A2. Factors Associated With Hospital Death, Medically Intense Intervention, and ≥ Two Intensity Markers in Young Adults (age 22-39 years)

Characteristic	OR (95% CI)		
	Hospital Death	Medically Intense Intervention	≥ Two Intensity Markers
Age, years			
22-29	Ref	Ref	Ref
30-39	1.7 (0.9 to 2.9)	1.3 (0.9 to 2.1)	1.2 (0.8 to 1.9)
Sex			
Female	Ref	Ref	Ref
Male	0.6 (0.3 to 1.0)	1.0 (0.6 to 1.5)	1.0 (0.6 to 1.6)
Race/ethnicity			
Non-Hispanic white	Ref	Ref	Ref
Black	0.8 (0.2 to 3.3)	1.2 (0.4 to 3.6)	1.1 (0.4 to 3.1)
Hispanic	0.7 (0.4 to 1.4)	0.7 (0.5 to 1.2)	0.9 (0.5 to 1.4)
Other	0.9 (0.4 to 2.1)	0.7 (0.4 to 1.5)	0.8 (0.4 to 1.5)
Diagnosis			
AML/MDS	0.4 (0.2 to 0.9)*	0.4 (0.2 to 0.7)†	0.4 (0.2 to 0.6)†
ALL	Ref	Ref	Ref
Lymphoma	0.4 (0.2 to 1.0)*	0.5 (0.2 to 0.9)*	0.6 (0.3 to 1.2)
Other malignant	NA	NA	NA
Nonmalignant	0.6 (0.2 to 1.6)	0.7 (0.4 to 1.5)	0.7 (0.4 to 1.5)
Insurance			
HMO	0.6 (0.3 to 1.4)	1.8 (0.9 to 3.6)	1.6 (0.8 to 3.2)
Private, non-HMO	1.0 (0.5 to 2.0)	1.7 (1.0 to 2.8)*	1.4 (0.9 to 2.3)
Public, self	Ref	Ref	Ref
Income, × FPL			
< 2	1.1 (0.4 to 3.1)	1.3 (0.6 to 2.6)	1.0 (0.5 to 2.1)
2-4	0.8 (0.4 to 1.8)	1.5 (0.8 to 2.7)	1.2 (0.7 to 2.3)
> 4	Ref	Ref	Ref
Year of HCT			
2000-2004	1.3 (0.6 to 2.7)	0.7(0.4 to 1.2)	0.9 (0.5 to 1.6)
2005-2009	1.6 (0.8 to 3.4)	1.3 (0.7 to 2.3)	1.4 (0.8 to 2.5)
2010-2013	Ref	Ref	Ref
MSA status			
Rural	0.7 (0.2 to 2.1)	1.2 (0.5 to 3.1)	1.2 (0.5 to 3.1)
Urban	Ref	Ref	Ref
Hospital (HCT and final)			
Different, last = community	0.5 (0.2 to 1.2)	0.5 (0.2 to 1.0)*	0.4 (0.2 to 0.9)*
Different, last = specialty	0.9 (0.3 to 3.1)	0.9 (0.3 to 2.2)	0.6 (0.2 to 1.6)
Same	Ref	Ref	Ref
No. of comorbidities at time of HCT			
0	Ref	Ref	Ref
1	2.0 (1.0 to 4.1)*	1.3 (0.7 to 2.3)	1.1 (0.6 to 2.0)
≥ 2	3.1 (1.6 to 6.1)‡	2.8 (1.6 to 4.9)†	2.9 (1.7 to 5.1)†

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FPL, federal poverty level; HCT, hematopoietic cell transplantation; HMO, health maintenance organization; MDS, myelodysplastic syndrome; NA, not applicable; OR, odds ratio; Ref, reference.

*$P < .05$.

†$P < .001$

‡$P < .01$.

Table A3. Factors Associated With Hospital Death, Medically Intense Intervention, and ≥ Two Intensity Markers in Adults (age ≥ 40 years)

Characteristic	OR (95% CI)		
	Hospital Death	Medically Intense Intervention	2 or More Intensity Markers
Age, years			
40-49	1.5 (1.0 to 2.3)*	1.5 (1.1 to 2.1)*	1.8 (1.3 to 2.5)†
50-59	1.5 (1.0 to 2.1)*	1.4 (1.0 to 1.9)*	1.5 (1.1 to 2.1)‡
≥ 60	NS	Ref	Ref
Sex			
Female	Ref	Ref	Ref
Male	1.2 (0.9 to 1.7)	1.1 (0.9 to 1.4)	1.2 (0.9 to 1.5)
Race/ethnicity			
Non-Hispanic white	Ref	Ref	Ref
Black	1.9 (0.6 to 5.5)	1.3 (0.6 to 2.6)	1.1 (0.5 to 2.3)
Hispanic	1.0 (0.7 to 1.6)	1.0 (0.7 to 1.3)	1.0 (0.7 to 1.4)
Other	1.1 (0.7 to 1.7)	1.0 (0.7 to 1.5)	1.1 (0.8 to 1.7)
Diagnosis			
AML/MDS	0.8 (0.5 to 1.3)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.3)
ALL	Ref	Ref	Ref
Lymphoma	1.1 (0.6 to 2.0)	1.2 (0.7 to 1.8)	1.1 (0.7 to 1.7)
Other malignant	0.8 (0.4 to 1.7)	0.8 (0.5 to 1.5)	0.7 (0.4 to 1.2)
Nonmalignant	2.0 (1.0 to 4.2)	1.3 (0.8 to 2.1)	1.5 (0.9 to 2.6)
Insurance			
HMO	0.6 (0.4 to 0.9)*	0.6 (0.4 to 0.9)*	0.8 (0.5 to 1.1)
Private, non-HMO	0.9 (0.6 to 1.3)	0.9 (0.7 to 1.1)	0.8 (0.6 to 1.0)
Public, self	Ref	Ref	Ref
Income, × FPL			
< 2	1.4 (0.8 to 2.5)	1.1 (0.7 to 1.7)	0.9 (0.6 to 1.5)
2-4	1.1 (0.8 to 1.6)	1.1 (0.8 to 1.4)	1.0 (0.7 to 1.3)
> 4	Ref	Ref	Ref
Year of HCT			
2000-2004	1.2 (0.8 to 1.9)	0.6 (0.4 to 0.8)‡	0.9 (0.6 to 1.2)
2005-2009	0.9 (0.6 to 1.3)	0.7 (0.5 to 1.0)*	0.8 (0.6 to 1.1)
2010-2013	Ref	Ref	Ref
MSA status			
Rural	1.0 (0.5 to 1.7)	0.5 (0.3 to 0.8)‡	0.7 (0.4 to 1.1)
Urban	Ref	Ref	Ref
Hospital (HCT and final)			
Different, last = community	0.8 (0.5 to 1.3)	0.3 (0.2 to 0.5)†	0.2 (0.1 to 0.4)†
Different, last = specialty	0.6 (0.3 to 1.2)	0.5 (0.2 to 1.0)*	0.3 (0.2 to 0.7)‡
Same	Ref	Ref	Ref
No. of comorbidities at time of HCT			
0	Ref	Ref	Ref
1	1.4 (0.9 to 2.1)	1.5 (1.0 to 2.2)	1.7 (1.2 to 2.5)‡
≥ 2	1.9 (1.3 to 2.8)‡	2.1 (1.5 to 3.0)†	2.8 (1.9 to 3.9)†

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; FPL, federal poverty level; HCT, hematopoietic cell transplantation; HMO, health maintenance organization; MDS, myelodysplastic syndrome; OR, odds ratio; Ref, reference.

*$P < .05$.

†$P < .001$.

‡$P < .01$.

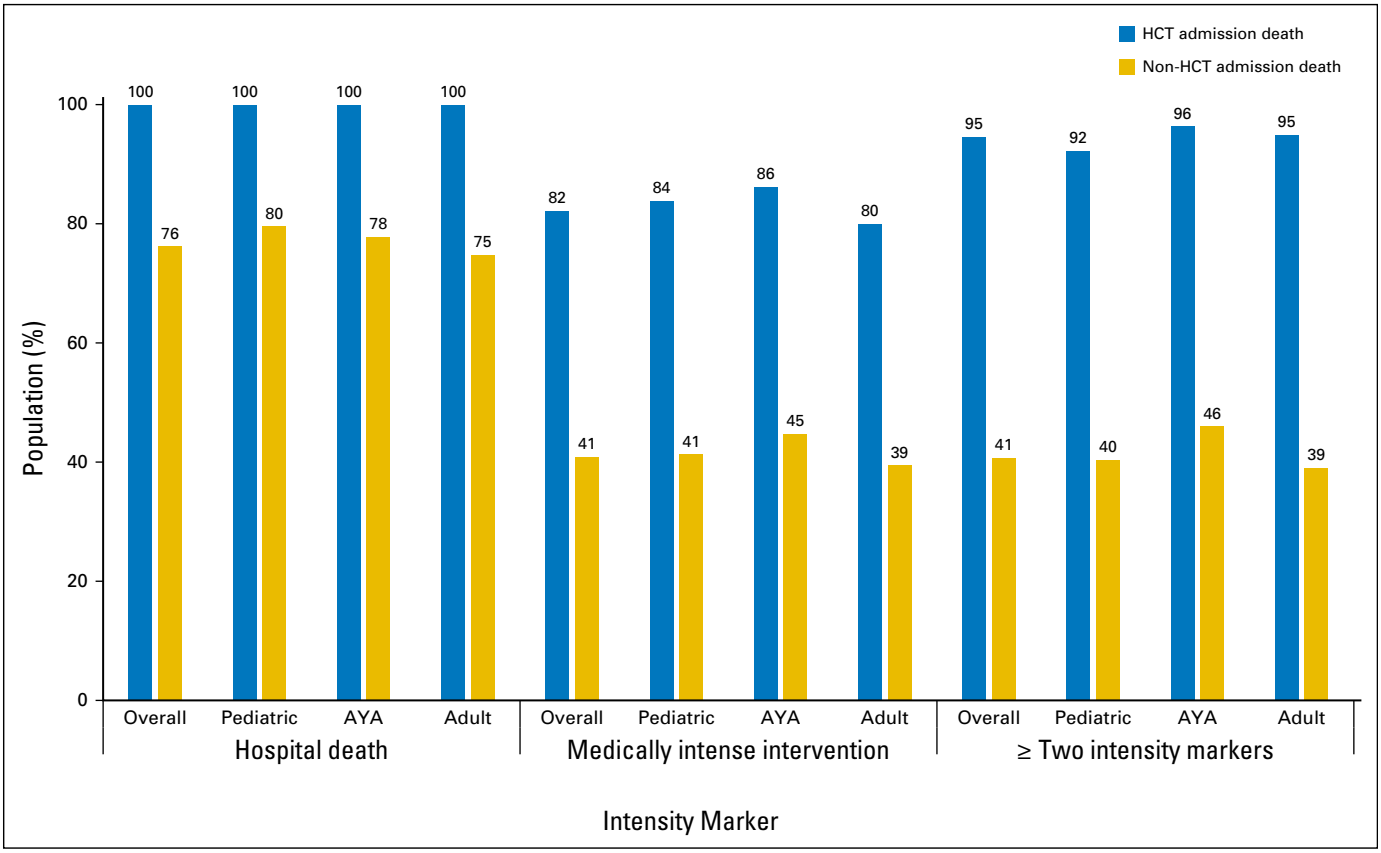

Fig A1. Rates of intense end-of-life care by timing of death (during hematopoietic cell transplantation [HCT] admission or not) for the three primary outcomes: hospital death, receipt of a medically intense intervention, and presence of ≥ two intensity markers. The rates are broken down by age category (overall, pediatric, adolescent and young adult [AYA], and adult).