IMPACT: Prevalence and Predictors of High-Intensity End-of-Life Care Among Adolescents and Young Adults with Cancer in Ontario

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ABSTRACT

Adolescents and young adults (AYA) with cancer may experience disproportionate rates of high-intensity (HI) end-of-life (EOL) care. We conducted a population-based linkage study examining a decedent cohort of all Ontario AYA aged 15-21 years diagnosed with six primary cancers between 1992-2012. The primary composite outcome (HI-EOL care) included any of: intravenous chemotherapy ≤14 days from death; >1 emergency department visit; >1 hospitalization; or any intensive care unit (ICU) admission ≤30 days from death. Secondary outcomes included hospital deaths and measures of most invasive (MI)-EOL care. The outcome prevalence trends were examined, as were the predictors using regression models. Of 483 patients, 292 (60.5%) experienced HI-EOL care. AYA with hematological malignancies and relapsed disease experienced the highest and lowest odds of all outcomes, respectively. The prevalence of MI-EOL care may be increasing, especially for pediatric patients. This work is the first to identify LOC-based disparities in AYA EOL care.

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CONTRIBUTIONS

Drs. Franco Momoli and Sumit Gupta co-supervised this thesis work. Both contributed to the study design, statistical analysis plan, and thesis review. Dr. Momoli provided additional expertise as a methodologist and biostatistician. Dr. Gupta provided additional expertise as a pediatric oncologist and health services researcher.

Dr. Adam Rapoport served as a thesis advisory committee member. He contributed to the study design and thesis review, as well as provided his expertise as a pediatric palliative care specialist.

Ms. Chenthila Nagamuthu contributed as the designated ICES research analyst for this project. She assisted in finalizing the data creation plan and created the datasets allowing for the assembly of the initial cohort and all predictor variables and outcomes. She provided expertise in SAS coding and statistical analysis.

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Dr. Hallie Coltin led the study design, SAS coding, data analysis, and thesis writing. She was funded by the University of Ottawa Clinician Investigator Program and a Canadian Graduate Scholarship from the Canadian Institutes of Health Research.

LIST OF ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
AYA	Adolescents and Young Adults
CI	Confidence Interval
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
COPD	Chronic Obstructive Pulmonary Disease
CNS	Central Nervous System
CPR	Cardiopulmonary Resuscitation
DA	Dissemination Area
ED	Emergency Department
EFS	Event-Free Survival
EOL	End-of-Life
HI	High-Intensity
HR	Hazard Ratio
ICES	Institute for Clinical Evaluative Sciences
ICU	Intensive Care Unit
IKN	Individual Key Number
IMPACT	Initiative to Maximize Progress in Adolescent and Young Adult Cancer Therapy
IQR	Interquartile Range
IV	Intravenous
LR	Logistic Regression
MI	Most Invasive

NACRS	National Ambulatory Care Reporting System
NCI	National Cancer Institute
OCR	Ontario Cancer Registry
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
ORGD	Office of Registrar General Database
OS	Overall Survival
PHIPA	Personal Health Information Protection Act
POGO	Pediatric Oncology Group of Ontario
POGONIS	Pediatric Oncology Group of Ontario Network Information System
RR	Risk Ratio
RPDB	Registered Persons Database
SEER	Surveillance, Epidemiology and End Results
SD	Standard Deviation
SDS	Same Day Surgery
SE	Standard Error
SES	Socioeconomic Status
SPE	Single-Person Equivalent

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1. INTRODUCTION

1.1. Adolescents and Young Adults with Cancer

The definition of the adolescent and young adult (AYA) population is controversial. In oncology, the definition is age-based and varies by reporting body and country.[1] The 2006 Surveillance, Epidemiology and End Results (SEER) program in the United States defined AYA as 15-29 years.[2] The Canadian Cancer Society defines AYA as 15-29 years while the range of 15 to 24 years is used in Australia.[3,4] Many countries participating in the European Cancer Registry (EUROCARE) have defined AYA as 15-24 years. [5] The Teenage Cancer Trust charity in the United Kingdom is dedicated to serving the 13-24 year population within their clinical units.[6] The currently accepted range by the National Cancer Institute (NCI) and by the Journal of Adolescent and Young Adult Oncology is 15-39 years.[7-9] Some experts have advocated for the subdivision of the NCI definition into early young adulthood (15-18 years), young adulthood (19-24 years), and late young adulthood (25-39 years) to better reflect the evolving physiological and psychosocial needs of these patients.[1] Other authors have supported a fluid definition depending on the particular research question.[1,10]

In high-income countries, cancer represents the most common cause of disease-related death in AYA.[11] Improvements in overall survival for AYA with many cancer types lag behind the successes observed in children and adult populations.[5,11-15] The difficulties in treating AYA with cancer are rooted in the unique spectrum of malignancies seen in this population,[11] delay in diagnosis,[16] tumor and patient biology,[17] psychosocial needs,[18] low clinical trial enrolment

rates,[10] and disparate treatment approaches among pediatric and adult centres.[15,19] In the United States, most AYA are treated in the community rather than at specialized cancer centres.[7] In Ontario, oncology care for AYA is scattered across the pediatric, community, and adult domains; they lack a medical home.[20,21] In the Initiative to Maximize Progress in Adolescent and Young Adult Cancer Therapy (IMPACT) cohort, the majority (57%) of 15-21-year-olds in Ontario with leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, bone sarcoma, or testicular cancer, were treated in adult Regional Cancer Centres (RCC), 19% in pediatric oncology centres, and the remaining 24% in community hospitals.[22] An earlier study reported that 46% of adolescents aged 15-17 years with cancer in Ontario were treated in a pediatric centre.[23]

Recent work has identified that the locus of care (LOC) in which AYA with cancer are treated may impact cancer outcomes.[24] Factors that may contribute to survival disparities across various loci of care include disease-specific expertise, differences in treatment protocols, clinical trial access, and patient volume.[25-28] The definition of LOC has varied across studies. Some studies have compared cancer outcomes between specialized and nonspecialized cancer centres while others have examined differences between pediatric and adult settings. In the AYA leukemia literature, treatment at a specialized centre may be associated with improved outcomes.[29,30] The authors hypothesized that superior supportive and multidisciplinary care, and improved treatment delivery that is often found at specialized centres may have contributed to the improved outcomes.[29,30] These studies did not capture biological prognosticators nor types of treatment protocols used which may have introduced confounding from imbalanced baseline characteristics among groups.[29,30]

The positive impact of treatment at pediatric versus adult hospitals for AYA with ALL on cancer outcomes have been reported in two population-based studies. The first study by Gupta et al. controlled for demographic, disease, and treatment variables and reported that treatment at an adult centre was associated with an inferior overall survival (OS) compared to treatment at a pediatric centre [hazard ratio (HR) 2.54, 95% CI 1.06-6.10, P = 0.04]. Survival differences between pediatric and adult centres remained despite accounting for the type of treatment protocol used.[24] Muffly et al. also reported significantly higher OS (HR 0.53, 95% CI 0.37-0.76) for AYA treatment in pediatric hospitals compared to adult hospitals after adjusting for age, sex, and ethnicity. The survival advantage was not seen when the analysis was restricted to AYA treated in adult facilities to compare the effect of pediatric versus adult chemotherapy protocols.[28] These two studies highlighted potential survival advantages of treatment in a pediatric setting for AYA with leukemia despite controlling for treatment approaches.

The AYA sarcoma literature has not investigated LOC-based disparities according to age to the same extent as the leukemia literature.[31] One possible explanation is that the surgical and radiation oncologists involved in AYA sarcoma management often work in both pediatric and adult centres, leading to relative uniformity in clinical management regardless of the setting.[31] A retrospective Canadian study of 29 pediatric patients (median age 13.4 years, range 0.29-16.2) treated at The Hospital for Sick Children and 24 adult patients (median age 26.1 years, range 16.7-66.5) treated at Mount Sinai Hospital with localized Ewing sarcoma showed a trend towards improved 3-year event-free survival ± standard deviation (SD) (pediatric 70% ± 9% versus adult 43% ± 13%, P = 0.10) and significantly improved 3-year OS (± SD) (pediatric 81% ± 7.7% versus adult 59% ± 12%, P = 0.02) for the pediatric patients.[26] However, the two groups

did not receive comparable chemotherapy doses and the pediatric patients experienced a shorter time to local therapy (3.7 months versus 7.4 months, P = 0.0003).[26] This study was not limited to AYA and the crude survival comparison between children and adults was challenging as baseline characteristics were inherently different.[26]

The AYA oncology literature concerned with LOC-based disparities has focused on survival outcomes such as OS. However, in addition to survival, LOC likely impacts the type of care received by AYA both during and following treatment. For example, the need to study health outcomes related to the locus of survivorship care has been identified in a recent review.[32] There remains a gap in the literature describing how LOC may impact the other phases of the cancer journey such as survivorship and at the end-of-life (EOL).

1.2. EOL Care for Patients with Cancer

The transition from curative intent to EOL is challenging for oncology patients, their families, and the healthcare team.[33] However, the appropriate and timely planning for EOL can help patients identify realistic goals of care, avoid interventions or costly healthcare resources that may not offer any clinical benefit, minimize distress, and ease the bereavement process for caregivers.[33] One example is discussing the limited benefit and significant harm of performing cardiopulmonary resuscitation (CPR) at the EOL for a patient with terminal cancer and instituting a do-not-resuscitate order.

Quality EOL care has been described by patients, caregivers, and healthcare providers. Five domains of quality EOL care were identified via survey by adult patients as "receiving adequate pain and symptom management, avoiding inappropriate prolongation of dying, achieving a sense of control, relieving burden, and strengthening relationships with loved ones."[34] Goals of care for the dying patient have been grouped into the following categories: comfort measures, psychological care, religious and spiritual support, communication with loved ones, communication with the primary healthcare team, and ensuring the goals are understood by the patient and family.[35] The goals of care of an individual patient are likely influenced by the age of the patient, sex, ethnicity, socioeconomic status, religious and spiritual beliefs, value, and the understanding of prognosis.[33]

1.3. High-Intensity End-Of-Life (HI-EOL) Care May Be Detrimental to Patients and Their Caregivers

The use of administrative data to evaluate the quality of EOL care received by cancer patients has been pioneered by Craig Earle and colleagues. In 2003, Earle et al. identified indicators of poor quality EOL care for oncology patients through literature review, focus groups, and expert consultation.[36] Three themes of poor quality EOL care for cancer patients emerged that could be determined using administrative data: 1) overuse of chemotherapy: either the initiation of new agents or the continuation of therapies; 2) potential misuse of treatment resulting in frequent unplanned medical encounters: high number of visits to the emergency department (ED), intensive care unit (ICU), or inpatient hospital admissions; and 3) underuse of hospice: high number of patients either never enrolled in hospice or enrolled a few days prior to death, or dying

in an acute-care setting.[36,37] In a subsequent study these themes were coalesced into a composite measure of "aggressive care" consisting of the following indicators: last chemotherapy dose within 14 days of death, new chemotherapy less than 30 days before death, more than one ED visit or hospital admission or ICU admission in the month before death, spending more than 14 days in hospital in the month before death, or death in an acute-care hospital.[38] These indicators of aggressive care were evaluated using administrative data (NCI SEER registries and the Centers for Medicare and Medicaid Services Medicare claims data) in a cohort of 28,777 patients ages 65 years and older in the United States who died within one year of their cancer diagnosis.[38] Over the study time period (1993-1996), there was a trend towards more aggressive EOL care among these cancer decedents, especially in areas with fewer hospice services.[38] This study was updated in 2008 to include 215,484 patients ages 65 years and older captured by a SEER registry who died of any malignancy between 1991 and 2000 in the United States and also demonstrated that most measures of aggressive EOL care continued to increase over time.[39]

Earle et al. developed benchmarking standards of intensive EOL care by evaluating Medicare claims of 48,906 cancer patients in the United States who died between 1991 and 1996.[37,40] Using the pared-mean method,[40] the following six health systems benchmarks of "not providing aggressive care" were determined to be the following: less than 10% of patients receiving chemotherapy in the last 14 days of life, less than 2% starting new chemotherapy in the last 30 days of life, less than 4% having multiple hospitalizations, ED visits, or ICU admissions in the last month of life, and less than 17% dying in an acute care setting.[37] In addition, at least 55% of patients would receive hospice care before death from cancer; and less than 8% of these patients would be admitted within three days of death.[37] The accuracy, reliability, and completeness of

the indicators were determined by comparing administrative data (billing claims) with 150 medical records from an academic hospital system, treating the medical records as gold standard.[37,40] The administrative data were deemed accurate if they identified the events within one calendar day of the medical record documentation.[37] The six indicators of aggressive EOL care were sensitive (range 82-96%), specific (range 94-100%), and accurate (range 85-97%), whereas the hospice use indicators were inconsistently captured; with the exception of hospice services, the aggressiveness of EOL care was underestimated by administrative data.[37] One limitation of this study was that the administrative databases were restricted to patients over the age of 65 years living in specific geographic locations; the benchmarks therefore may not have been appropriate for younger cancer patients if the type and frequency of care usage was different.[37]

Grunfeld et al. established that certain administrative data indicators of quality EOL care were feasible, valid, and reliable in Ontario.[41] The validity of the indicators was assessed after analyzing the administrative databases for completeness and accuracy against abstracted patient charts of a random sample of the population-based cohort of decedent women from breast cancer as the gold standard.[41] Based on the above work, Ho et al. developed a composite measure of high-intensity (HI)-EOL care consisting of at least one of the following indicators: last dose of chemotherapy received within 14 days of death; more than one ED visit or hospitalization within 30 days of death; or at least one ICU admission within 30 days of death.[42]

HI-EOL care in terminal adult cancer patients may represent “poor-quality care” for patients and caregivers.[39] The continuation of chemotherapy or the introduction of new chemotherapy agents

close to death may result in more toxicity than benefit, and may inappropriately replace important yet difficult discussions of prognosis and advance directives.[36] Improved supportive care at home or in hospice could prevent many emergency department visits and hospital admissions.[36] Given that most adult oncology patients prefer to die at home or in hospice, in-hospital deaths are often considered poor-quality care for this population.[36]

Prospective cohort studies of adult oncology decedents have reported that HI-EOL care may negatively impact patients and their caregivers. In one study, ICU admission, mechanical ventilation, resuscitation, chemotherapy near death, and feeding tube use were associated with inferior quality of life measures compared to those who did not receive this care.[43] The caregivers of these patients had higher odds of developing major depressive disorder and themselves reported poorer quality of life scores.[43] In the same cohort, patients who died in hospital or the ICU reported significantly lower quality of life scores and measures of physical comfort compared to patients who died at home.[44] Chemotherapy administered close to the EOL, in-hospital death, and late involvement of hospice was associated with poor satisfaction ratings among caregivers of decreased women with metastatic breast cancer.[39,45,46]

Similar findings of the potential for increased symptom burden at the EOL for patients receiving HI-EOL care exist in the pediatric and AYA literature. In the seminal paper by Wolfe et al. published in the New England Journal of Medicine in 2000, 89% of 103 decedent children of cancer reported high rates of suffering from at least one symptom (fatigue, pain, dyspnea, etc.) at the EOL.[47] This study was at risk of recall bias (the interviews with parents were conducted on average 3.1 years following the child's death), single institution nature of the study, and small

sample size.[47] However, the characterization of the high symptom burden of pediatric patients at the EOL provided an important foundation for future studies. Another study reported that 61% of parents of decedent children with cancer felt that cancer-directed therapy (chemotherapy, radiation, surgery) at the EOL was associated with suffering among their children.[48] Lastly, a retrospective chart review of 61 decedent children by Schindera et al. reported increased rates of dyspnea among children who received IV chemotherapy or were hospitalized in the last month of life.[49] Though limited by small sample sizes and single institution data, this work provided exploratory data to suggest that patients who experienced indicators of HI-EOL care (IV chemotherapy, admission to hospital) may have had higher likelihood of physical suffering at the EOL.

The above-mentioned work spanning the adult, AYA, and pediatric literature has demonstrated that HI-EOL care may be associated with increased suffering for patients and their loved ones at the EOL through mechanisms such as increased symptom burden and decreased quality of life.

1.4. The Prevalence of HI-EOL Care May Be Increasing

In adults with cancer, the trends in and predictors of HI-EOL care are well described. Rates of HI-EOL care for adults with advanced cancer have increased over time.[39,42,50] Various patient, malignancy, and health system factors have been associated with higher rates of HI-EOL care. Patient factors have included male sex,[39,42,51] younger age,[42,52,53] minority group status,[54-56] low socioeconomic status,[54,55] living in a rural location,[42] and the presence of comorbidities.[42,53,54] Hematological malignancies have repeatedly shown to be associated with higher rates of HI-

EOL care compared to other malignancy groups.[39,42,52,56-58] From a health systems perspective, receipt of care at an academic hospital,[39] and lack of palliative care involvement have been associated with higher rates of HI-EOL care.[59,60]

In children dying of cancer, HI-EOL care is also prevalent.[47,61-66] Population-based studies examining location of death for children with cancer have identified high prevalence rates of in-hospital death,[65,67,68] however there is conflicting evidence regarding the rates over time of hospice and hospital deaths.[65,67-69] Table 1 outlines the details and findings of relevant population-based pediatric oncology studies of HI-EOL care.

Table 1. Population-Based Studies of HI-EOL Care in Children with Cancer

First Author, Publication Year	**Location**	**Years**	**Demographics**	**Data Sources**	**Main Findings**	**Limitations**
Revon-Rivière, 2019[70]	France	2014-2016	1,899 cancer decedents 0-25 years at death	National hospital database (medical and administrative)	61.4% and 28.8% experienced HI- and MI-EOL* care, respectively Predictor of HI- or MI-EOL care: hematological malignancy, comorbidities, specialty center, decreased odds with palliative care	Did not distinguish between pediatric and adult LOC May represent cohort biased towards HI-EOL care since patients who died at home excluded Did not exclude patients who died shortly after diagnosis Short period of study

						limiting trend analyses
Johnston, 2017[61]	California (USA)	2000-2011	3,732 cancer decedents 0-21 years at death	OSHPD private discharge database Vital Statistics	65% experienced at least 1 HI-EOL indicator Predictor of HI-EOL care: hematological malignancy	Administrative data only Limited clinical information Different definition of HI-EOL care compared to published literature
Kassam, 2017[63]	Ontario (Canada)	2000-2012	815 cancer decedents 0-18 years at death	Provincial cancer registry Health services databases	40.6% experienced composite HI-EOL measure Predictor of HI-EOL care: hematological malignancy Predictor of ICU admission and MV: female, hematological malignancy, death in later periods	Inability to capture palliative care involvement
Park, 2014[71]	Korea	2007-2010	696 cancer decedents 0-17 years at death	National cancer registry Health services databases	Decrease in chemotherapy use, CPR; increase in prolonged admissions in last month of life	Did not examine predictors Did not exclude patients who died shortly after diagnosis
Tang, 2011[64]	Taiwan	2001-2006	1,208 cancer decedents 0-18 years at death	National cancer registry National health services databases	78.8% died in hospital In last month of life: 52.5% had chemotherapy, 14.3% had >1	Did not examine predictors Did not exclude patients who

					ED visit, 32.5% had >1 admission, 57% ICU admission, 48.2% MV Trends over time stable except decreased intubation	died shortly after diagnosis

CPR: cardiopulmonary resuscitation; EOL: end-of-life; HI: high intensity; ICU: intensive care unit; LOC: locus of care; MI: most invasive; MV: mechanical ventilation; OSHPD: Office of Statewide Health Planning and Development
*MI-EOL care defined as the occurrence of at least one of the following indicators: intubation and/or mechanical ventilation, cardiopulmonary resuscitation, and hemodialysis in the last 30 days of life

Among these studies, the participant ages, definitions of HI-EOL care, and inclusion of trend analyses have varied. Few studies included AYA participants.[61,70] The prevalence of HI-EOL care ranged from 40.6% to over 65.0%. Predictors of HI-EOL care included AYA age,[61] female sex,[63] hematological malignancies,[61,63,70] comorbidities,[70] care at a specialty centre[70], and dying in the later period of study.[61,63] The involvement of palliative care was associated with decreased odds of HI-EOL care in one study.[70]

Population-based Ontario pediatric data has been published by Kassam et al.[63] In this study, all Ontario children (815 patients) diagnosed with a primary cancer at <15 years of age who died over a 12-year period at ≤18 years of age were included.[63] A detailed provincial cancer registry was linked with health services databases to examine the composite measure of HI-EOL care which was defined as any one of the following indicators: IV chemotherapy within 14 days of death, more than one ED visit within 30 days of death, more than one hospitalization within 30

days of death, or any ICU admission within 30 days of death.[63] Mechanical ventilation within 14 days of death and in-hospital death were other outcomes of interest.[63] In this study, 40.6% experienced the composite measure of HI-EOL care, 16.7% were mechanically ventilated, and 43.4% died in hospital.[63] In multivariate modeling of the primary composite outcome, the only significant predictor was hematologic malignancy in comparison to solid tumors (OR 2.5, 95% CI 1.8-3.6); hematologic malignancy was also associated with increased odds of experiencing ICU admission (OR 5.1, 95% CI 3.3-8.0), mechanical ventilation (OR 5.1, 95% CI 3.1-8.3), and in-hospital death (OR 2.7, 95% CI 1.9-4.0).[63] Female sex, in addition to dying in the middle (2005-2008) and later (2009-2012) time periods, compared to the earliest period (2000-2004), were associated with increased odds of ICU admission, mechanical ventilation, and in-hospital death.[63] While palliative care involvement was not captured, the strengths of this study included the availability of detailed clinical data and the ability to identify patients who died of treatment-related causes.[63]

As described above, the pediatric oncology literature has identified similar demographic, disease, and health systems factors associated with receipt of HI-EOL care as described in the adult oncology literature. International pediatric population-based studies included large patient numbers and largely described elevated HI-EOL care prevalence among cancer decedents. Some challenges that limited comparisons between studies included variability in how HI-EOL care was defined, inconsistent capture of palliative care involvement, and the inclusion of AYA patients without distinguishing which patients were treated in pediatric versus adult settings.

1.5. The Preferences of Adolescents and Young Adults with Cancer at the EOL Are Poorly Understood

The type of EOL care patients receive may be influenced by the setting in which such care is provided in addition to the patients' preferences, values, and beliefs.[16,72] However, AYA are often not included in discussions of prognoses and EOL care.[16,73] The exclusion of AYA in EOL discussions conflicts with recent literature demonstrating that AYA often desire honest communication and wish to participate in decision-making at the EOL.[16,74,75] The wish to receive cancer-directed therapy at the EOL as well as preferred location of death is not uniform among AYA. In a Japanese study of 349 AYA with cancer, 53% wished to receive chemotherapy for incurable cancer despite significant toxicity.[72] Maintaining an open discourse becomes challenging if the patient is incapacitated at the EOL, potentially leading to decisions that may not reflect the wishes of the patient.[16] AYA with cancer at the EOL who have not been included in decision-making may also be more distressed and experience increased physical symptoms such as pain.[76] The failure to engage AYA with cancer in discourse at the EOL may result in the delivery of care that is incongruent with their wishes, as well as unnecessary physical and emotional suffering.[76] Recent work has outlined the importance of exploring the care preferences of AYA at the EOL as the majority of AYA have strong preferences regarding place of death, ability to communicate their wishes with loved ones, and value time spent being comfortable and free from pain.[76]

1.6. HI-EOL Care for AYA with Cancer

The trends and predictors of HI-EOL care for AYA with cancer are less clear than for adult and pediatric populations. Fewer studies restricted to the AYA age group exist, and many studies failed to report AYA findings separately in the case of mixed age groups. Population-based studies examining the location of death for both children and young adults have demonstrated that AYA died more often in hospital and demonstrated trends toward HI-EOL care compared to younger children.[63,67,68] Studies of AYA and adults with cancer demonstrated that younger patients also died more often in hospital and were more likely to receive HI-EOL care.[42,52,57,77]

The findings of published population-based studies of HI-EOL care in AYA with cancer are summarized in Table 2.

Table 2. Population-Based Studies of HI-EOL in AYA with Cancer

First Author, Publication Year	Location	Years	Demographics	Data Sources	Main Findings	Limitations
Johnston, 2018[78]	California (USA)	2000-2011	12,883 cancer decedents 15-39 years at death	OSHPD private discharge database Vital Statistics	Mean of 40 days admitted in last year of life; majority admitted in last 6 months of life Highest utilization in: younger age, minority, hematological malignancy, specialty centre, later death year	Administrative data only Limited clinical information

Rajeshuni, 2017[79]	California (USA)	1989-2011	30,573 cancer decedents 15-39 years at death	OSHPD private discharge database Vital Statistics	57% died in hospital; stable rate since 1995 Associations with hospital death: younger age, minority, hematological malignancy, close to specialty centre	Administrative data only Limited clinical information Risk of misclassification bias from inaccurate cause of death
Johnston, 2017[80]	California (USA)	2000-2011	12,938 cancer decedents 15-39 years at death	OSHPD private discharge database Vital Statistics	59% received at least 1 intensive EOL care interventions Associations with intensive EOL care: younger age, non-white, hematological malignancy, treatment at non-specialty centre	Administrative data only Limited clinical information No information on emergency department use
Mack, 2015[81]	California (USA)	2001-2010	663 cancer decedents with relapse or stage IV 15-39 years at death	KPSC clinical database and cancer registry	68% received at least 1 HI-EOL care measure Decreased intensive EOL care: bone/soft tissue, GI malignancies	Dually-insured and uninsured patients not captured
Mack, 2015[82]	New York (USA)	2004-2011	705 cancer decedents 15-29 years at diagnosis	NYSCR Medicaid database	75% received at least 1 HI-EOL measure Associations with intensive EOL care: older age, stage IV	Limited to patients enrolled in Medicaid program

AYA: adolescents and young adults; GI: gastrointestinal; KPSC: Kaiser Permanente Southern California; NYSCR: New York State Cancer Registry; OSHPD: Office of Statewide Health Planning and Development

In population-based AYA decedent oncology studies, the prevalence rates of HI-EOL care have been reported to be between 59.0% and 75.0%, with trends toward decrease or stability. In-hospital deaths have been reported between 53.0% and 65.0%, with trends toward decrease. The following predictors of HI-EOL care have been reported: younger age at death,[79,80] older age at death,[82] hematologic malignancy,[79-81] comorbidities,[80] minority status,[79,80] living close to a specialty centre[79] or hospital,[80] care at a non-specialty centre,[80] decreased socioeconomic status,[81] and private insurance.[80] Overall, the above literature suggests that the receipt of HI-EOL care is prevalent among decedent AYA with cancer.

1.7. Palliative Care Involvement May Improve the EOL Course

There is strong evidence in the adult literature that palliative care services may be associated with an improved EOL course. A meta-analysis of 23 studies including 37,561 adult patients with advanced illness (predominantly advanced cancer) and 4,042 caregivers demonstrated that home palliative care services was associated with an increased odds of dying at home and reduced symptom burden at the EOL.[83] In the adult oncology literature, palliative care involvement has been associated with decreased rates of hospitalization and aggressive EOL care,[54,84] dying in the patient's preferred location,[85] improved quality of life scores,[84,86] decreased rates of depressive symptoms,[84,86] and decreased health care costs in the last month of life.[87]

The pediatric literature surrounding the impact of palliative care for children with cancer is less extensive and at times conflicting.[88] One retrospective study found an increase in the number of hospital and emergency room admissions for children who were followed by pediatric palliative care services.[89] Other studies have shown that specialized pediatric palliative care involvement is associated with increased rates of home deaths,[90,91] improved symptom identification and management,[90,92,93] improved communication between the family and healthcare providers,[92] and lower intensity care at the EOL.[70,94-96] Widger et al. conducted a population-based cohort study of children in Ontario who died of cancer between 2000 and 2012 and received care at an institution with a specialized pediatric palliative care team to examine the impact of palliative care involvement on the receipt of HI-EOL care.[94] In this study, the primary measure of HI-EOL care was ICU admission in the last month of life.[63,94] Among 572 patients, 166 (29.0%) received care from a specialized pediatric palliative care team greater than 30 days before death, 100 (17.5%) were categorized as having received general palliative care (defined as palliative care services provided by physicians without palliative care training), and 306 (53.5%) did not receive palliative care.[94] Patients with hematological malignancies (OR 0.3, 95% CI 0.3-0.4; reference solid tumors), lower income quintiles, and living farther from the tertiary centre experienced lower odds of receiving specialized pediatric palliative care; compared to the earliest period of death (2000-2004), patients who died in the latest period (2009-2012) had the greatest odds of receiving specialized pediatric palliative care services (OR 43.1, 95% CI 2.9-636).[94] Significant predictors of ICU admission in the last month of life in multivariate analysis included specialized pediatric palliative care involvement (OR 0.2, 95% CI 0.1-0.4; reference no palliative care involvement), hematologic malignancy (OR 5.7, 95% CI 4.2-7.7; reference solid tumors), lower income quintiles (OR range 0.3-0.4), longer distance to tertiary care centre (OR 0.5, 95%

CI 0.4-0.7), and middle and late time periods of death (OR range 1.9-2.0; reference early time period of death).[94]

Population-based studies focusing on EOL care for AYA with cancer have not examined the prevalence and impact of palliative care consultation. Retrospective reviews of small patient numbers have reported that palliative care involvement was associated with decreased odds of ICU death,[97,98] mechanical ventilation near death,[98] and receipt of medical procedures near death[98] and increased odds of AYA dying in their preferred location.[99] Recommendations from Canadian working groups have included the development of AYA-specific multidisciplinary palliative care teams that work in both pediatric and adult settings as well as in patients' homes to bridge the gaps between pediatric and adult oncology practices.[100,101]

1.8. Limitations of Previous Studies Examining HI-EOL Care for AYA with Cancer

Many of the published studies examining EOL care in AYA with cancer have important methodological limitations including narrative analyses susceptible to recall bias,[72,102] single centre reviews with small patient numbers,[73,97,98,103,104] and multisite studies at risk of selection bias.[105,106] Studies which have included both pediatric and AYA populations may have limited generalizability to the AYA experience.[61,63,67,68,70,73] As previously described, the age definition of AYA has varied across the oncology literature resulting in large discrepancies in ages included.

Population-based studies using health services data have minimized recall and selection biases and have allowed authors to examine the trends and predictors of HI-EOL care over extensive periods of time. Population-based studies of HI-EOL care are limited, however, by the data captured within administrative databases; the databases were not constructed for research purposes and therefore may lack relevant clinical information such as disease stage and relapse data.[36] These challenges can be mitigated when administrative health data are linked with detailed cancer registry data, which is not always possible. Missing data on ED use in the last month of life can limit the comprehensive measurement of HI-EOL care and can limit the comparison of study findings when different HI-EOL care definitions are used.[61,80] In the use of death certificates to determine location of death, authors have raised methodological concerns that this practice may result in misclassification bias.[61,67,79,80,107] Many administrative databases do not contain billing data, which can further contribute to misclassification bias.[61] For example, using surrogate markers for ICU admissions such as mechanical ventilation could underestimate ICU admission rates as not all admissions result in mechanical ventilation.[61,80] Other methodological challenges include the failure of studies to distinguish between AYA who die from cancer versus AYA with cancer who die of treatment complications such as infection, when HI-EOL care might very well be appropriate.[61,80] In a similar vein, use of population-based studies are unable to capture clinical symptoms at the EOL such as pain and dyspnea (shortness of breath), nor the substance of clinical interactions between patients and their caregivers, which are known to influence how and where patients receive EOL care.[36]

From a health care systems perspective, population-based studies from the United States may lack generalizability to Canadian populations. The structure of the United States healthcare

system and insurance programs places AYA at high risk of being uninsured and unable to seek appropriate care at the EOL.[21,61,80,108-110] Importantly, studies of HI-EOL care in AYA with cancer have not examined the impact of LOC either for cancer-directed care or care at the EOL; this question is especially relevant for AYA who receive care in the pediatric, adult, and community settings.

This thesis will address a number of limitations and will specifically shed light on the relationship between LOC, both during oncology treatment and at the EOL, and HI-EOL care through the linkage of population-based detailed clinical data with comprehensive administrative health databases in Ontario.

2. STUDY RATIONALE AND OBJECTIVES

2.1. Study Rationale

We have captured population-based data from all healthcare settings, including pediatric oncology, adult oncology, and community hospitals in order to describe the relationship between LOC (both for oncology treatment and at the EOL) and the receipt of HI-EOL care.[22] This methodology has allowed us to identify potential disparities at the EOL for AYA with cancer according to LOC, which have not been reported previously. Using complete and granular population-based data, we therefore aim to describe the prevalence and predictors of HI-EOL care among AYA with cancer in Ontario, with the goal of promoting targeted support and improved advocacy for this vulnerable population.

2.2. Study Objectives

1. To determine the prevalence of HI-EOL care among AYA with specific cancers in Ontario diagnosed between 1992-2012.
2. To determine the prevalence of MI-EOL care and in-hospital death among AYA with specific cancers in Ontario diagnosed between 1992-2012.
3. To determine the predictors of HI-EOL care among AYA with specific cancers in Ontario diagnosed between 1992-2012.
4. To determine the predictors of MI-EOL care and in-hospital death among AYA with specific cancers in Ontario diagnosed between 1992-2012.

3. METHODOLOGY

3.1. Study Design

This is a population-based historical cohort study of Ontario AYA aged 15-21 years at the time of diagnosis with one of six primary cancers (leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, bone sarcoma, or testicular cancer), who died within five years of their initial diagnosis (a decedent cohort). The diagnostic, treatment, and outcome data for patients treated at pediatric institutions were obtained from a population-based pediatric cancer registry, while data concerning patients treated at adult institutions were from a new AYA cancer registry derived from medical records.[22] These clinical data were subsequently linked to population-based administrative health data housed at ICES (formerly named the Institute for

Clinical Evaluative Sciences).[22] The observation window in which the outcomes were evaluated occurred in the 30 days before and including the date of death. Ethics approval was obtained from the Research Ethics Boards of CHEO, The Ottawa Hospital Research Institute, The Hospital for Sick Children, and Sunnybrook Health Sciences Centre.

3.2. Data Sources

Data on the disease, treatment, and clinical outcomes of AYA patients treated in pediatric centres were obtained through the Pediatric Oncology Group of Ontario Network Information System (POGONIS), where data had been collected prospectively.[22] In the case of AYA patients treated at adult centres, patients were identified from the Ontario Cancer Registry (OCR); disease, treatment, and outcome data were obtained through retrospective chart review of hospital records, operative and pathology reports, and discharge summaries by trained data abstractors with experience in cancer research.[22] The validity, completeness, and consistency of the abstracted data were ensured through training sessions, mock chart abstraction, and review of the data by study team members.[22]

ICES houses previously collected health administrative databases. Data security and confidentiality procedures are governed by section 45 of Ontario's *Personal Health Information Protection Act* (PHIPA).[111] Using patient-specific identifiers, including provincial health insurance number and an encrypted Individual Key Number (IKN), the cohort was linked with administrative databases housed at ICES.[22]

A number of health services databases were used to define the cohort, outcomes, and predictor variables. The death date in the Registered Persons Database (RPDB) was used to identify deceased patients. The cause of death found in the ORGD was used to exclude patients who died of external causes such as motor vehicle accidents, poisonings, and suicides (see below for details). The outcomes, such as receipt of HI-EOL care, were defined using the following databases: Ontario Health Insurance Plan (OHIP), National Ambulatory Care Reporting System (NACRS), and Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). The predictor variables were defined using the following databases: POGONIS, RPDB, Institution Information System (INST), OHIP, CIHI DAD, and NACRS. Table 3 outlines the clinical and health services data sources, the data elements, and how the databases were used in this study.

Table 3. Clinical and Administrative Health Databases

Database	**Data Elements**	**Use in Study**
Pediatric Oncology Group of Ontario Networked Information System (POGONIS)	Date of diagnosis Cancer type Locus of care Relapse information	Cohort creation Predictor variable definition
Ontario Cancer Registry (OCR)	Cancer type Date of diagnosis	Cohort creation Predictor variable definition
Registered Persons Database (RPDB)	Demographic information Date of death	Cohort creation Study exclusions Predictor variable definition
Office of the Registrar General – Deaths (ORGD)	Date of death Cause of death	Cohort creation Study exclusions
Ontario Health Insurance Plan (OHIP)	ED visits ICU admissions Mechanical ventilation Chemotherapy and radiation administration codes	Outcome variable definition Predictor variable definition
National Ambulatory Care Reporting System (NACRS)	ED visits Chemotherapy and radiation administration codes	Outcome variable definition Predictor variable definition

Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Hospitalizations In-hospital death Death in ICU Chemotherapy and radiation administration codes	Outcome variable definition Predictor variable definition
Institution Information System (INST)	Institution names associated with service codes	Predictor variable definition

ED: emergency department; ICU: intensive care unit

Pediatric Oncology Group of Ontario Networked Information System (POGONIS)

POGONIS contains detailed clinical data on diagnosis, treatment, complications, and long-term outcomes of all patients treated for cancer at the five pediatric oncology institutions in Ontario since 1985.[112] Ninety-six percent of children with cancer aged 0-14 years are captured in POGONIS compared to 46% of adolescents aged 15-17 years.[23] Patients treated outside of pediatric centres are not captured.[23] Accrual occurs through active registration at the pediatric oncology centres and uses a histology based classification system (International Classification of Childhood Cancer system).[23] The data are reviewed by a pediatric oncology nurse-data manager at the Pediatric Oncology Group of Ontario (POGO) for accuracy prior to entry into the database.[23]

Ontario Cancer Registry (OCR)

The OCR has captured all incident cancers in Ontario since 1964 with 95% reported completeness.[22,23,113] Registration in the OCR occurs via passive linkage and is based upon hospital discharge and day surgery summaries, pathology reports, records emanating from

specialized cancer institutions, and death certificates which mention cancer.[114] The main data elements include: patient demographics, cancer diagnosis details, and death information.[114]

Registered Persons Database (RPDB)

The RPDB contains demographic information for any person holding an Ontario health card.[115] The information captured is enriched by the Ministry of Health and includes dates of birth and death, sex, date of last contact, periods of OHIP eligibility, and postal codes.[115]

Office of the Registrar General – Deaths (ORGD)

ORGD contains information on all deaths, including cause of death, registered in Ontario since January 1, 1990.[116] Deterministic and probabilistic data linkage with the RPDB is used to assign IKNs to the ORGD records as the dataset does not contain health card numbers but rather direct identifiers such as name and postal code; the linkage rate is 95.9%.[116] Beginning in 2000, causes of death are coded using ICD-10, unlike the OCR which uses ICD-9.[116] However, there is strong agreement among causes of death between the two sources.[116]

Ontario Health Insurance Plan (OHIP)

The OHIP database contains most claims made by health care providers (physicians, groups, laboratories, out-of-province providers) for insured services.[117] Approximately 95% of specialists and 50% of primary care physicians in Ontario are paid on a fee-for-service basis and

claims are submitted for reimbursement.[117] For physicians paid by alternative plans, shadow claims are mandated, thus ensuring capture of most physician encounters.[63,117] Missing services from OHIP claims data include some laboratory services, provincial psychiatric hospital services, and health service organizations.[117] Each record represents a single service.[117] The main data elements are: encrypted patient and physician identifiers, service provided (code, date, associated diagnosis), and fee paid.[117]

National Ambulatory Care Reporting System (NACRS)

NACRS captures patient visits to hospital and ambulatory facilities including day surgery, outpatient clinics, and emergency departments.[118] The main data elements are: demographic data, clinical data, administrative data, financial data, and service-specific data.[118] Beginning in April 2003, the Same Day Surgery (SDS) datasets are derived from NACRS.[118] The SDS datasets capture patient-level records for day surgery centres in Ontario, with each record corresponding to a single same-day surgery or procedure event.[118] The main data elements are: demographic data, clinical data, administrative data, financial data, and service-specific data.[118]

Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)

The CIHI DAD provides patient-level inpatient data in the form of one record per hospital stay (acute, rehabilitation, chronic, and day surgery institutions) from 1988 onwards, regardless of the disposition (home, transfer to another hospital, death).[119] All Ontario Hospital Medical Records departments submit data to CIHI directly and the datasets are available by fiscal year.[119] The data

elements contain clinical information (diagnoses, procedures, physician), demographic information (sex, date of birth, postal code, country code, residence code), and administrative information (institution, length of stay, disposition).[119] The diagnosis fields are complex and changed in the fiscal year 2002.[119] Until 2001, the ICD-9 coding system was used and each record contained up to 16 diagnosis codes; the first code corresponded to the diagnosis responsible for most of the hospital stay and the others represented pre- or post-admission diagnoses, external cause of injury, morphology code, and hospital-specific codes.[119] Starting in 2002, the ICD-10 coding system was implemented and each record contains between 1 and 25 diagnoses.[119] The DAD also contains procedure/intervention codes which were modified starting in 2002.[119]

Institution Information System (INST)

The INST database contains linkable datasets containing information about Ontario care institutions funded by the Ministry of Health and Long-Term Care.[120] Each institution is assigned a unique institution number that can be linked to the administrative dataset.[120]

3.3. Eligibility Criteria

All AYA aged 15-21 years diagnosed with leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, bone sarcoma, and testicular cancer between January 1, 1992-December 31, 2012 were identified through POGONIS and OCR to create the IMPACT cohort.[22] There are no other comparable AYA oncology cohorts in Ontario. Patients were eligible for the

current study if they were included in the IMPACT cohort, had a death date present in RPDB, and if the death date was ≤ 5 years from the primary cancer diagnosis. This restricted time period between the diagnosis and death dates was implemented in order to increase the likelihood of death being from the cancer itself and not from late effects of cancer therapy, or a non-cancer event.[63,94] EOL care received as a result of the late effects of cancer treatment or a non-cancer event were expected to be different from the EOL care received in the context of an anticipated death from progressive or relapsed cancer.[63]

3.4. Exclusion Criteria

Of the decedent patients in the IMPACT cohort identified above, patients were excluded if they met any of the following criteria:

1. Patients who died of external causes: Patients with an underlying cause of death as determined in the ORGD beginning with "E" were excluded as these were patients who died of injuries (such as motor vehicle or suicide) or poisonings, and not from cancer.
2. Invalid IKN and/or missing sex in the RPDB.
3. Missing date of death in RPDB.
4. Patients who were not Ontario residents.
5. Patients who were < 15 or > 21 years at the time of diagnosis with their primary cancer: This was determined using the RPDB.

6. Patients who died ≤ 30 days from their primary cancer diagnosis: These patients were excluded because their deaths were likely acute complications of their recently diagnosed cancer, where HI-EOL care was warranted.[22,63,94]

3.5. Outcome Definition

The primary outcome was the receipt of HI-EOL care, defined as in previous pediatric and adult studies:[39,42,63,121] any one or more of the following:

1. More than one ED visit ≤ 30 days from death
2. ICU admission ≤ 30 days from death
3. More than one hospitalization ≤ 30 days from death
4. Intravenous chemotherapy ≤ 14 days from death

Secondary outcomes included the individual measures above as well as the following measures:

1. Measures of the MI-EOL care[63]
    a. Death in ICU
    b. Mechanical ventilation ≤ 14 days from death
2. In-hospital death

Tables 4 and 5 outline the definitions used to derive each measure of HI-EOL, MI-EOL care, and in-hospital death. The corresponding diagnoses and procedures associated with the diagnostic and procedure codes, respectively, are outlined in Appendix I and II.

Table 4. Definitions Used to Derive Each Measure of HI-EOL Care

Measures	**Definition**
More than one ED visit ≤ 30 days from death	1. Before 2002: in OHIP emergency claims, more than one ED visit within 30 days of death date **OR** 2. 2002 and later: in NACRS emergency claims, more than one ED visit within 30 days of death date
ICU admission ≤ 30 days from death	OHIP fee codes G400, G401, G402, G405, G406, G407, G557, G558, G559 with service date within 30 days of death date
More than one hospitalization ≤ 30 days from death	In DAD, more than one acute care hospital admission within 30 days of death date
IV chemotherapy ≤ 14 days from death	1. OHIP fee codes G281, G339, G345, G359, G381, G390, H530 with service date within 14 days of death date **OR** 2. Before 2002: in DAD, hospital procedure code 1355 with service date within 14 days of death date **OR** 3. 2002 and later: in DAD, hospital intervention codes 1ZZ35HAM0, 1ZZ35HAM1, 1ZZ35HAM2, 1ZZ35HAM3, 1ZZ35HAM4, 1ZZ35HAM5, 1ZZ35HAM9 with service date within 14 days of death date

ED: emergency department; ICU: intensive care unit; IV: intravenous

Table 5. Definitions Used to Derive Each Measure of MI-EOL Care and In-Hospital Death

Measures	**Definition**
Death in ICU	1. Before 2002: in DAD, value of 1 or 2 for "DTHSCU" variable 1 = Patient died ≤ 48 hours of admission to the unit 2 = Patient died > 48 hours of admission to the unit

	OR 2. 2002 and later: in DAD, value of Y for "DTHSCU" variable Y = Yes
Mechanical ventilation ≤ 14 days from death	OHIP fee codes G557, G558, G559, G405, G406, G407 within 14 days of death
In-hospital death	In DAD, record encompassing date of death or with discharge disposition of death

DTHSCU: death in special care unit; ICU: intensive care unit

3.6. Predictor Variable Definitions

The following demographic, disease-related, and health system variables were explored as potential predictors of HI-EOL care:

3.6.1. Health System Variables

1. **Locus of Care (LOC) for Cancer Therapy:** This predictor variable aimed to capture the predominant setting of cancer-directed care. This three-level categorical variable (Pediatric/RCC/Community) was defined in a stepwise approach using POGONIS, OHIP, DAD, and NACRS data:
    a. **Pediatric:** Patients were categorized as Pediatric if their records were obtained from POGONIS, meaning their oncology care took place at one of the five pediatric centres in Ontario. The exception to this categorization was if the POGONIS "LR_Code" (Limited Registry) variable had a value of 4 (Diagnosis In POGO Program, But Referred To Adult Service) or 8 (Interlink Patients, Age ≤ 17 Years, Treated/Seen At An Adult Facility); these values indicated that the patients did not receive oncological care at a pediatric institution and therefore the

categorization for these patients followed the algorithm for patients treated in adult institutions.

b. **Adult (RCC or Community):** For patients not meeting the criteria for Pediatric classification, all chemotherapy and radiation codes during the year before death were identified (Appendix III and IV) along with corresponding institutions for each of the associated claims. The institution associated with the most codes was designated as the main treating institution. This institution was classified as an RCC or community hospital based on its classification by Cancer Care Ontario (Appendix V).[122] If the main treating institution was considered an RCC, then the patient's LOC for cancer therapy was classified as RCC, and as Community for the remaining patients.

2. **Locus of Care Near Death:** Some patients who received their initial oncology care at a pediatric centre (LOC for cancer therapy = Pediatric) may have received their EOL care at an adult institution. For example, some patients may have experienced relapse of their primary cancer after the age of transition to adult care and thus received subsequent oncology and/or EOL care at an adult institution. Examining the LOC near death aimed to capture the transition of some pediatric patients who were initially diagnosed in a pediatric institution but received EOL care at an adult institution. The LOC near death predictor variable was dichotomized (Pediatric/Adult) and defined in a stepwise approach:

    a. **Patients who received their cancer therapy at an adult institution remained as adult for LOC near death:** Given the unlikely scenario of a patient receiving

their initial oncology care at an adult centre and EOL care at a pediatric centre (transitioning from adult to pediatric), all patients who were classified as receiving their initial oncology care in an adult institution (LOC for cancer therapy = RCC or Community) were classified as having received EOL care in an adult setting as well (LOC near death = Adult).

b. **Patients who received their cancer therapy in a pediatric institution:** For the patients who received their cancer therapy in a pediatric institution (LOC for cancer therapy = Pediatric), all ED (Table 4), hospitalization (Table 4), chemotherapy (Appendix III), and radiation (Appendix IV) claims in the 90 days before death were captured. The institutions associated with these claims were identified using the INST dataset.[120] The following algorithm was created as a way to capture whether a patient had contact with a pediatric institution in the 90 days before death. The algorithm relied on at least one claim being associated with a pediatric institution in INST, or inferring that the care was in a pediatric setting based on the age at death.

    i. **Children's Hospital of Eastern Ontario, The Hospital for Sick Children:** In the INST dataset, Children's Hospital of Eastern Ontario and The Hospital for Sick Children were categorized as exclusively pediatric institutions. Patients with any claims associated with these two institutions were classified as having a pediatric LOC near death.

    ii. **Hamilton Health Sciences Corporation-McMaster:** After April 4, 2011, this institution was classified as an exclusively pediatric institution in the INST dataset, whereas prior to this date it was a mixed pediatric-adult

institution.[120] Patients with any claims from this institution with a service date after April 4, 2011 were classified as having a pediatric LOC near death. For patients with any claims from this institution with service dates before and including April 4, 2011, they were classified as having a pediatric LOC near death if the age at death was **less than 18 years**. If the age at death was **greater or equal to 18 years**, they were classified as having an adult LOC near death.

iii. **London Health Sciences Centre-Victoria Hospital:** In the INST dataset, this institution was classified as a pediatric institution for patients less than 18 years of age.[120] For patients with any claims from this institution whose age at death was **less than 18 years**, they were classified as having a pediatric LOC near death. Otherwise they were classified as having an adult LOC near death.

iv. **Kingston General Hospital:** In the INST dataset, this institution was classified as a mixed pediatric-adult institution.[120] For patients with any claims from this institution whose age at death was **less than 18 years**, they were classified as having a pediatric LOC near death, Otherwise they were classified as having an adult LOC near death.

v. **Patients not captured using claims from the 90 days before death:** For the patients who were not captured using claims from the 90 days before death (no ED visits, hospitalizations, chemotherapy, or radiation), if their age at death was **less than 18 years**, they were classified as having a

pediatric LOC near death. Otherwise, they were classified as having an adult LOC near death.

c. **Alternative algorithm to determine LOC near death for sensitivity analyses:** Using the age at death of less than 18 years to classify patients as having a pediatric LOC near death was a conservative decision to minimize the possibility patients who received EOL care in an adult centre were misclassified as pediatric. However, this young age threshold likely resulted in a few patients with true pediatric LOC near death being misclassified as adult LOC near death. A variation of the above algorithm was created where the age at death threshold for pediatric LOC near death was increased to less than 19 years.

3.6.2. Disease-Related Variables

1. **Cancer Type:** Patients diagnosed with leukemia, Hodgkin lymphoma, and Non-Hodgkin lymphoma were categorized as hematological malignancies, and the remainder were classified as solid tumor malignancies to reflect the disease categorization used in most previous literature.
2. **Relapse Status:** Disease relapse status was obtained from POGONIS and chart-abstracted data and used as a dichotomous predictor variable (relapsed disease/not relapsed disease).

3.6.3. Demographic Variables

1. **Age at Death:** The age (in years) at the time of death was determined using the RPDB and treated as a continuous variable.

2. **Patient Sex:** The sex (male/female) of the patient was determined using the RPDB.

3. **Period of Death:** The year of death was determined using the RPDB. The period of death was used as a dichotomous predictor variable (early period 1992-2004 versus late period 2005-2017).

4. **Rurality:** The patient's rurality was determined using the RPDB rural variable based on the postal code. Rurality was used as a dichotomous predictor variable (rural/urban) and was determined at both the cancer diagnosis and at death time points. Due to concerns of collinearity, only rurality at diagnosis was used as a candidate predictor in logistic regression models. In comparing patients' rurality statuses at diagnosis and death, the majority of patients (463/482, 96.1%) maintained the same classification at diagnosis and death therefore the distinction between the two timepoints was deemed to be negligible.

5. **Neighborhood Income Quintile:** Neighborhood income, divided into quintiles, was used as a proxy for SES and determined using the RPDB postal code. This measure was based on the average income per single-person equivalent (SPE) in a dissemination area (DA) obtained from the 2011 census data as described below.[123] Dissemination blocks cover all areas of Canada and represent the smallest geographical counts for population and dwelling,[124] whereas DAs are geographic units composed of one or more dissemination

blocks (average population 400-700 persons) and represent the geographic unit of census data.[125] Total income for each DA was calculated then divided by the sum of the SPE in the DA to obtain the average income per SPE.[126] The SPE is based on Statistics Canada's low-income cut-offs and is used to determine appropriate multipliers for different household sizes.[123,127] DAs were ranked by SPE from the lowest to highest average income and assigned to five groups containing one-fifth of the population of each area.[126] Within each census metropolitan area, census agglomeration area, or residual area in Ontario, neighborhood income quintiles were constructed.[126,127] The quintile data was pooled across areas to mitigate the effects of differences in income, housing, and other costs of living.[123,126] Neighborhood income quintiles were assigned at the DA level with Q1 corresponding to the poorest neighborhoods Q5 corresponding to the wealthiest.[123,126] This ordinal predictor variable was determined at both cancer diagnosis and at death using the RPDB postal code.[22,128,129] Due to concerns of collinearity, only neighborhood income quintile at diagnosis was used as a candidate predictor in logistic in logistic regression models. In comparing patients' neighborhood income quintiles at diagnosis and death, 73.8% (354/480) maintained the same neighborhood income quintile at both timepoints. Of the 126 patients who had different neighborhood income quintiles at diagnosis and death, 60 increased quintiles and 66 decreased quintiles.

6. **Distance to Treating Centre:** For patients who received their oncology care at a pediatric centre (LOC for cancer therapy = pediatric), the treating centre was defined as the closest tertiary pediatric hospital (Appendix VI) from the patient's postal code at the time of death, which was obtained from the RPDB.[130] The Euclidian distance between the

treating pediatric centre and the postal code at the time of death was calculated. For patients who received their oncology care at an adult centre (LOC for cancer therapy = RCC or community), the treating centre was defined as the institution identified for the LOC for cancer therapy variable. The Euclidian distance between the treating centre and the centre of the postal code area at the time of death was calculated. The distance from the treating centre was dichotomized as short versus long on the basis of the 75th centile.

3.7. Statistical Analysis

All statistical analyses were conducted using SAS software, Version 9.4 of the SAS System for Unix (SAS Institute Inc., Cary, NC, USA).[131]

3.7.1. Analysis of Objective 1: Determining the Prevalence of HI-EOL Care Among AYA with Specific Cancers in Ontario Diagnosed Between 1992-2012

Prevalence was defined as the number of decedents who experienced the outcome of HI-EOL care divided by the total number of deaths. The prevalence of the composite measure of HI-EOL care and the individual measures of HI-EOL care were calculated along with 95% Clopper-Pearson confidence intervals.[132] The crude prevalence rates of the composite outcome of HI-EOL care and the individual measures were calculated over the study period (1992-2016) as well as over three-year periods to describe changes over time. The Cochran-Armitage test for linear trends in proportions was applied to evaluate the change in the prevalence of HI-EOL care over time (two-sided p-values for the asymptotic test were reported).[133]

3.7.2. Analysis of Objective 2: Determining the Prevalence of MI-EOL Care and In-Hospital Death Among AYA with Specific Cancers in Ontario Diagnosed Between 1992-2012

Prevalence was defined as the number of decedents who experienced the measures of MI-EOL care or in-hospital death divided by the total number of deaths. The prevalence of the measures of MI-EOL care and in-hospital death was calculated along with 95% Clopper-Pearson confidence intervals.[132] The crude prevalence rates of the measures of MI-EOL care and in-hospital death were calculated over the study period (1992-2016) as well as over three-year periods to describe changes over time. The Cochran-Armitage test for linear trends in proportions was applied to evaluate the change in the prevalence of MI-EOL care and in-hospital death over time (two-sided p-values for the asymptotic test were reported).[133]

3.7.3. Analysis of Objective 3: Determining the Predictors of HI-EOL Care Among AYA with Specific Cancers in Ontario Diagnosed Between 1992-2012

Logistic regression models were used to analyze the associations between the candidate predictor variables and the composite outcome of HI-EOL care. These analyses were based on patients with complete candidate predictor data (N = 480). Logistic regression models were used to estimate unadjusted ORs for associations between the individual candidate predictor variables and the composite outcome of HI-EOL care. The assumption of linearity was verified in logit for the continuous predictor variable of age at death and the estimates were provided per one year

increase in age at death. The following candidate predictor variables were included *a priori* in the multivariable model regardless of statistical significance in the univariate models based on being key variables of interest (LOC for cancer therapy, LOC near death) or previous literature (cancer type, period of death, age at death). Additional candidate predictors significant at the $P < 0.25$ level were included in the multivariable model. Interactions between LOC for cancer therapy and cancer type, LOC near death and cancer type, LOC for cancer therapy and period of death, LOC near death and period of death, LOC for cancer therapy and age at death, and LOC near death and age at death were evaluated and included in the final model if found to be statistically significant. Alternative ways of model building were explored by including all candidate predictors in the multivariable model without interactions to assess for changes in estimates. A sensitivity analysis was conducted using the alternative LOC near death candidate predictor variable to construct a new multivariable logistic regression model.

3.7.4. Analysis of Objective 4: Determining the Predictors of MI-EOL Care and In-Hospital Death Among AYA with Specific Cancers in Ontario Diagnosed Between 1992-2012

Unadjusted logistic regression models were used to estimate ORs for the associations between the candidate predictor variables and the measures of MI-EOL care (mechanical ventilation in the 14 days before death, death in an ICU) and in-hospital death. These analyses were based on patients with complete candidate predictor data ($N = 480$). The assumption of linearity was verified in logit for the continuous predictor variable of age at death and the estimates were provided per one year increase in age at death. The same candidate predictor variables were

included *a priori* in the multivariable model regardless of statistical significance as noted above. Additional candidate predictors significant at the $P < 0.25$ level were included in the multivariable models. Interactions between LOC for cancer therapy and cancer type, LOC near death and cancer type, LOC for cancer therapy and period of death, LOC near death and period of death, LOC for cancer therapy and age at death, and LOC near death and age at death were evaluated and included in the final models if found to be statistically significant. Alternative ways of model building were explored by including all candidate predictors in each multivariable model without interactions to assess for changes in estimates. Sensitivity analyses were conducted using the alternative LOC near death candidate predictor variable to construct new multivariable logistic regression models for each MI-EOL care outcome.

4. RESULTS

4.1. Cohort Creation

This study identified 651 decedent AYA through POGONIS and OCR who were diagnosed with either leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, bone sarcoma, or testicular cancer between January 1, 1992 and December 31, 2012. Patients were excluded due to missing death dates (<6), dying after December 31, 2017 (risk of incomplete data) (<6), or losing OHIP eligibility at some point during the study period between cancer diagnosis and death (<6). One hundred thirteen patients (N = 113) who died more than five years after their primary cancer diagnosis date were excluded. An additional 39 patients were excluded for dying of external causes or dying less than or equal to 30 days from the primary cancer

diagnosis date (grouped due to small cell sizes). The final cohort included 483 patients. The descriptive statistics were based on the final cohort of 483 patients, however the logistic regression models were based on patients with complete candidate predictor data (N = 480).

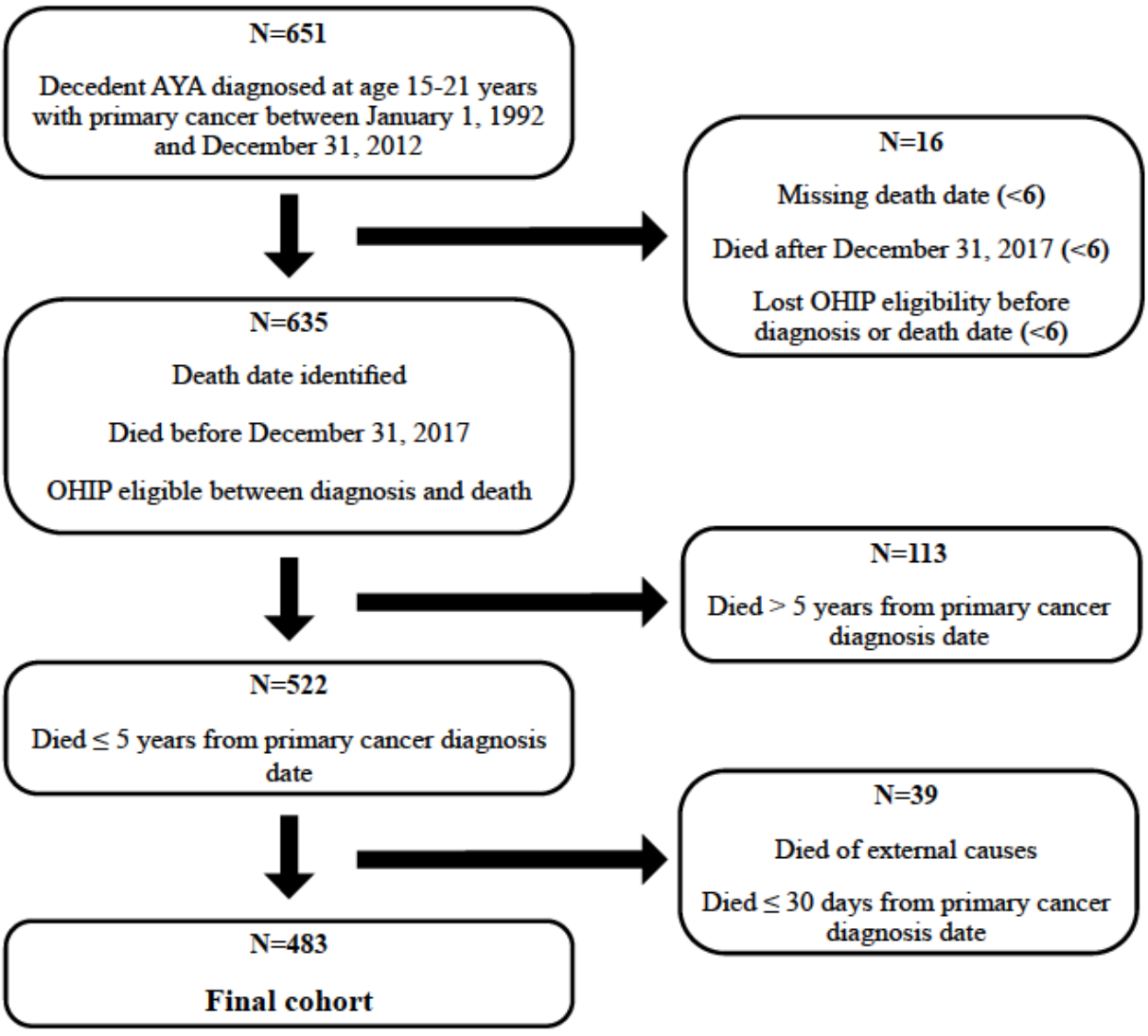

Figure 1. Cohort Creation
OHIP: Ontario Health Insurance Plan

4.2. Descriptive Statistics

The descriptive statistics of the cohort are outlined in Table 6. Among the 483 patients, 245 (50.7%) received their initial cancer therapy in RCCs, 159 (32.9%) in pediatric institutions, and 79 (16.4%) in community institutions. Three-hundred ninety (N = 390, 80.8%) patients had an adult LOC near death compared to 93 (19.2%) with a pediatric LOC near death. AYA were diagnosed with hematological malignancies in 271 (56.1%) cases and with solid tumors in 212 (43.9%) cases. Two-hundred fifty-eight (N = 258, 53.4%) patients had relapsed disease. Three-hundred nineteen (N = 319, 66.1%) patients were male. The median age at death was 20 years (IQR 3 years). The frequencies of the neighborhood income quintiles were evenly distributed at diagnosis and at death. The only variables with missing data were neighborhood income quintile at diagnosis (N = 3, 0.6%), neighborhood income quintile at death (N = 1, 0.2%), and rurality at diagnosis (N = 1, 0.2%). The majority of AYA lived in urban settings both at diagnosis and death. Two-hundred fifty-eight (N = 258, 53.4%) patients died in the early period (1992-2004). Three-hundred sixty-two (N = 362, 75.0%) patients lived a short distance from their cancer treatment centres.

Table 6. Demographic and Disease Characteristics of Cohort (N=483)

Characteristic[1]	Patients, No.	Patients, %
Locus of care for cancer therapy		
Pediatric	159	32.9
RCC	245	50.7
Community	79	16.4
Locus of care near death		
Pediatric	93	19.2
Adult	390	80.8
Locus of care near death (alternative definition for sensitivity analysis)		
Pediatric	104	21.5
Adult	379	78.5

Cancer type		
Hematological	271	56.1
Solid Tumor	212	43.9
Relapsed disease	258	53.4
Sex		
Male	319	66.1
Female	164	33.9
Age at death (years) **Median (IQR)**	20	(18-21)
Income quintile at diagnosis		
Q1 (lowest)	84	17.4
Q2	89	18.4
Q3	92	19.1
Q4	125	25.9
Q5 (highest)	90	18.6
Missing	3	0.6
Income quintile at death		
Q1 (lowest)	91	18.8
Q2	96	19.9
Q3	88	18.2
Q4	107	22.2
Q5 (highest)	100	20.7
Missing	1	0.2
Rurality at diagnosis		
Urban	420	87.0
Rural	62	12.8
Missing	1	0.2
Rurality at death		
Urban	418	86.5
Rural	65	13.5
Year of death **Median (IQR)**	2004	(1999-2009)
Time period of death		
Early (1992-2004)	258	53.4
Late (2005-2016)	225	46.6
Distance from treating centre		
Short	362	75.0
Long	121	25.0

[1]Variable distributions are reported as N (%) unless otherwise specified.
IQR: interquartile range; RCC: Regional Cancer Centre; Q: Quintile

4.3. Prevalence of HI-EOL Care, MI-EOL Care, and In-Hospital Death

4.3.1. Period Prevalence of HI-EOL Care, MI-EOL Care, and In-Hospital Death Between 1992-2016

The prevalence of the composite measure of HI-EOL care, the individual measures of HI-EOL care, the measures of MI-EOL care, and in-hospital death are presented in Table 7 along with the corresponding 95% confidence intervals. Across the study period, 292 patients (60.5%, 95% CI 55.9-64.8) experienced the composite measure of HI-EOL care. Of the individual measures of HI-EOL care, the most frequent was more than one hospitalization within 30 days of death experienced by 135 (28.0%) patients.

Table 7. Numbers and Percentages of Cohort Patients Positive for HI-EOL Care, MI-EOL Care, and In-Hospital Death Measures From 1992-2016 (N=483)

Care Measure[1]	Patients, No.	Patients, %
Composite of below measures (primary measure of HI-EOL care)	292	60.5 (55.9, 64.8)
More than one ED visit within 30 days of death	92	19.1 (15.6, 22.8)
ICU admission within 30 days of death	123	25.5 (21.6, 29.6)
More than one hospitalization within 30 days of death	135	28.0 (24.0, 32.2)
IV chemotherapy within 14 days of death	116	24.0 (20.3, 28.1)
Death in ICU	110	22.8 (19.1, 26.8)
Mechanical ventilation within 14 days of death	98	20.3 (16.8, 24.2)
In-hospital death	333	68.9 (64.6, 73.1)

[1]Percentages are reported with 95% confidence intervals using the Clopper-Pearson exact method

ED: emergency department; EOL: end-of-life; HI: high-intensity; ICU: intensive care unit; IV: intravenous

4.3.2. Prevalence Trend of HI-EOL Care, MI-EOL Care, and In-Hospital Death

The prevalence trend of the composite outcome of HI-EOL care, the individual measures of HI-EOL care, the measures of MI-EOL care, and in-hospital death are presented graphically in Figures 2 and 3 and numerically in Table 8. Over the study period, the prevalence of the

composite measure of HI-EOL care decreased. With the exception of ICU admission within 30 days of death and IV chemotherapy within 14 days of death, the prevalence of the individual measures of HI-EOL care demonstrated a decreased trend over time.

The prevalence of the two measures of MI-EOL care did not change over time. In-hospital death showed a decrease in prevalence over time.

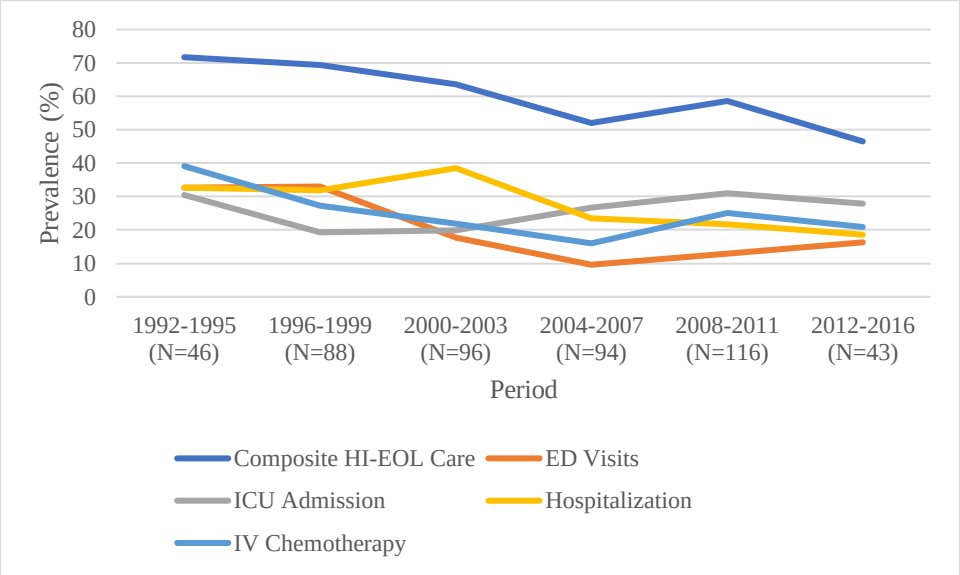

Figure 2. Prevalence Rates of HI-EOL Care (Composite and Individual Measures) Between 1992-2016 (N=483)
ED: emergency department; EOL: end-of-life; HI: high-intensity; ICU: intensive care unit; IV: intravenous

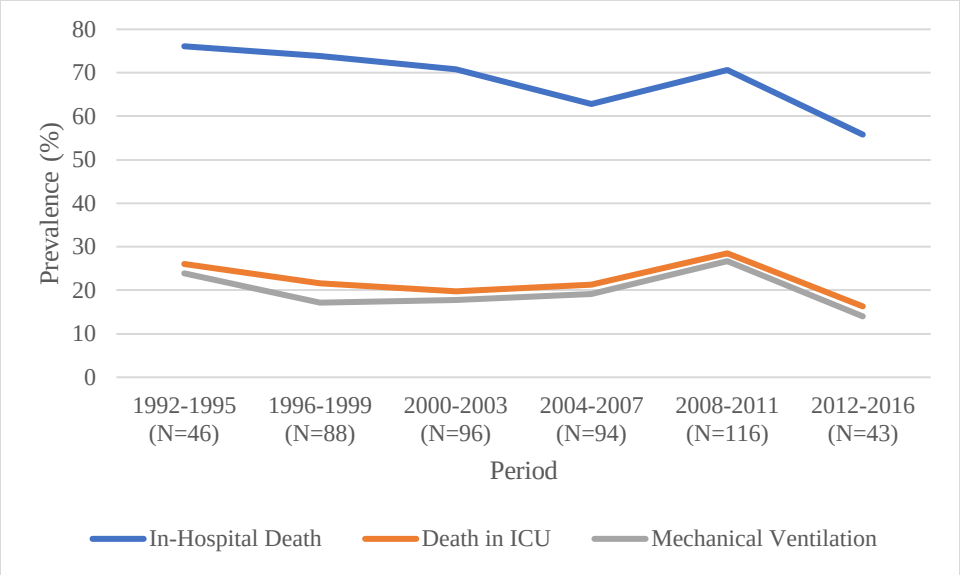

Figure 3. Prevalence Rates of MI-EOL Care Measures and In-Hospital Death Between 1992-2016 (N=483)
EOL: end-of-life; ICU: intensive care unit; MI: most invasive

Table 8. Prevalence Rates of HI-EOL Care, MI-EOL Care, and In-Hospital Death Measures Between 1992-2016 (N=483)

Care Measure[1]	**1992-1995 (N=46)**	**1996-1999 (N=88)**	**2000-2003 (N=96)**	**2004-2007 (N=94)**	**2008-2011 (N=116)**	**2012-2016 (N=43)**	**P value**[2]
Composite of below measures (primary measure of HI-EOL care)	71.7 (56.5, 84.0)	69.3 (58.6, 78.7)	63.5 (53.1, 73.1)	52.1 (41.6, 62.5)	58.6 (49.1, 67.7)	46.5 (31.2, 62.4)	<0.01
More than one ED visit within 30 days of death	32.6 (19.5, 48.0)	33.0 (23.3, 43.8)	17.7 (10.7, 26.8)	9.6 (4.5, 17.4)	12.9 (7.4, 20.4)	16.3 (6.8, 30.7)	<0.01
ICU admission within 30 days of death	30.4 (17.7, 45.8)	19.3 (11.7, 29.1)	19.8 (12.4, 29.2)	26.6 (18.0, 36.7)	31.0 (22.8, 40.3)	27.9 (15.3, 43.7)	0.21
More than one hospitalization within 30 days of death	32.6 (19.5, 48.0)	31.8 (22.3, 42.6)	38.5 (28.8, 49.0)	23.4 (15.3, 33.3)	21.6 (14.5, 30.2)	18.6 (8.4, 33.4)	<0.01
IV chemotherapy within 14 days of death	39.1 (25.1, 54.6)	27.3 (18.3, 37.8)	21.9 (14.1, 31.5)	16.0 (9.2, 25.0)	25.0 (17.4, 33.9)	20.9 (10.0, 36.0)	0.06
Death in ICU	26.1 (14.3, 41.1)	21.6 (13.5, 31.7)	19.8 (12.4, 29.2)	21.3 (13.5, 30.9)	28.5 (20.5, 37.6)	16.3 (6.8, 30.7)	0.92

Mechanical ventilation within 14 days of death	23.9 (12.6, 38.8)	17.1 (9.9, 26.6)	17.7 (10.7, 26.8)	19.2 (11.8, 28.6)	26.7 (18.9, 35.7)	14.0 (5.3, 27.9)	0.69
In-hospital death	76.1 (61.2, 87.4)	73.9 (63.4, 82.7)	70.8 (60.7, 79.7)	62.8 (52.2, 72.5)	70.7 (61.5, 78.8)	55.8 (39.9, 70.9)	0.05

[1]Prevalence rates (%) are reported with 95% confidence intervals using the Clopper-Pearson exact method
[2]P value from Cochran-Armitage test (two-sided, asymptotic)
ED: emergency department; EOL: end-of-life; HI: high-intensity; ICU: intensive care unit; IV: intravenous

4.4. Predictors of HI-EOL Care

Logistic regression models were used to evaluate the associations between the candidate predictor variables and the odds of the composite outcome of HI-EOL care (Table 9). The assumption of linearity was met for the age at death variable and the estimates were provided per year of change. There were no significant interactions between predictors identified. In univariate analysis, there was an increased odds of experiencing HI-EOL for patients with hematological malignancies compared to solid tumors (OR 2.1, 95% CI 1.4-3.0), and decreased odds for relapsed disease (OR 0.5, 95% CI 0.4-0.8), yearly increase in age at death (OR 0.9, 95% CI 0.8-1.0), and dying in the later period compared to the earlier period (OR 0.7, 95% CI 0.5-1.0). Neighborhood income quintile at diagnosis was not included in the multivariable model as it did not meet the statistical significance threshold (P = 0.85). In the multivariable model, after controlling for the other predictors, there remained an increased odds of HI-EOL care for patients with hematological malignancies compared to solid tumors (OR 2.4, 95% CI 1.6-3.5) and decreased odds for those with relapsed disease (OR 0.5, 95% CI 0.3-0.8).

Table 9. Results from Univariate and Multivariate Modeling of the Primary Composite Measure of HI-EOL Care Among Study Cohort Patients (N=480)

		Univariate		Multivariate	
Characteristic	**Number of Cases**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy					
Pediatric	101	1.2 (0.8, 1.9)	0.31	0.9 (0.5, 1.8)	0.83
RCC (ref)	143	-	-	-	-
Community	45	0.9 (0.6, 1.5)	0.77	1.2 (0.7, 2.1)	0.55
LOC near death					
Pediatric	63	1.5 (0.9, 2.4)	0.10	1.3 (0.6, 2.6)	0.51
Adult (ref)	226	-	-	-	-
Cancer type					
Hematological	184	2.1 (1.4, 3.0)	<0.01	2.4 (1.6, 3.5)	<0.01
Solid Tumor (ref)	105	-	-	-	-
Relapsed disease					
Yes	136	0.5 (0.4, 0.8)	<0.01	0.5 (0.3, 0.8)	<0.01
No (ref)	153	-	-	-	-
Sex					
Male (ref)	199	-	-	-	-
Female	90	0.7 (0.5, 1.0)	0.09	0.7 (0.5, 1.0)	0.08
Age at death (years)	Median 19.0, IQR 3.0	0.9 (0.8, 1.0)	<0.01	0.9 (0.8, 1.0)	0.21
Income quintile at diagnosis					
Q1 (lowest)	47	0.7 (0.4, 1.3)	0.25	-	-
Q2	53	0.8 (0.4, 1.5)	0.50	-	-
Q3	55	0.8 (0.5, 1.5)	0.52	-	-
Q4	76	0.9 (0.5, 1.5)	0.59	-	-
Q5 (highest; ref)	58	-	-	-	-
Rurality at diagnosis					
Urban (ref)	247	-	-	-	-
Rural	42	1.5 (0.9, 2.7)	0.14	1.4 (0.7, 2.6)	0.33
Time period of death					
Early (1992-2004; ref)	166	-	-	-	-
Late (2005-2016)	123	0.7 (0.5, 1.0)	0.04	0.8 (0.5, 1.1)	0.16
Distance from treating centre					
Short (ref)	208	-	-	-	-
Long	81	1.5 (1.0, 2.3)	0.06	1.4 (0.8, 2.2)	0.20

-: not applicable; CI: confidence interval; IQR: interquartile range; LOC: locus of care; OR: odds ratio; ref: reference

An alternative multivariable model including all candidate predictors was built (Appendix VII). The estimates of the predictors were unchanged compared to the initial model (Table 9) and the income quintile at diagnosis variable was not found to be statistically significant (P = 0.83).

A sensitivity analysis was conducted using the alternative LOC near death candidate predictor variable and a new multivariable logistic regression model was built (Appendix VIII). The alternative definition of LOC near death categorized patients as pediatric if the age at death was less than 19 years (compared to a threshold of 18 years for the LOC near death variable used for the primary logistic regression analyses). The alternative LOC near death variable categorized 104 (21.5%) patients as pediatric and 379 (78.5%) as adult, compared to the original variable which categorized 93 (19.2%) patients as pediatric and 390 (80.8%) as adult (Table 6). The ORs of the predictor variables in this model were largely unchanged compared to the original multivariable model (Table 9). In this model, an interaction between the LOC near death and age at death variables (interaction term P = 0.06) was explored in two stratified analyses. Among patients who died in a pediatric setting, every one-year increase in age at death was associated with a decreased odds of HI-EOL care (OR 0.6, 95% CI 0.4-0.8, P < 0.01). The association was in the same direction but of a more modest magnitude among patients who died in an adult setting (OR 0.9, 95% CI 0.8-1.0, P = 0.04).

4.5. Predictors of MI-EOL Care

4.5.1. Predictors of Death in the ICU

Table 10 outlines the results of univariate and multivariate modeling of the death in ICU outcome. The assumption of linearity was met for the age at death variable and the estimates were provided per year of change. Care in a pediatric centre near death compared to an adult

centre (OR 2.4, 95% CI 1.4-3.9), hematological malignancies compared with solid tumors (OR 3.4, 95% CI 2.1-5.5), and rural living at diagnosis (OR 1.9, 95% CI 1.1-3.5) were associated with increased odds of ICU death in univariable models. Relapsed disease (OR 0.5, 95% CI 0.3-0.7) and yearly increase in age at death (OR 0.9, 95% CI 0.8-1.0) were associated with decreased odds of dying in an ICU in the univariable models. The LOC for cancer therapy, LOC near death, and age at death candidate predictor variables were *a priori* included in the multivariable model. The sex and neighborhood income quintile variables were not included in the multivariable model as they did not reach statistical significance thresholds in univariate analyses. In the multivariable model, after controlling for the other predictors including LOC for cancer therapy, care in a pediatric centre near death compared to an adult centre (OR 3.1, 95% CI 1.3-7.5), hematological malignancies compared to solid tumors (OR 4.9, 95% CI 2.8-8.4), rural living at diagnosis (OR 2.2, 95% CI 1.1-4.1), and death in the later study period compared to the earlier period (OR 1.7, 95% CI 1.0-2.7) were all associated with an increased odds of death in the ICU; relapsed disease (OR 0.4, 95% CI 0.2-0.6) was associated with a decreased odds of death in the ICU.

Table 10. Results from Univariate and Multivariate Modeling of the Death in ICU Outcome among Study Cohort Patients (N=480)

		Univariate		**Multivariate**	
Characteristic	**Number of Cases**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy					
Pediatric	44	1.5 (1.0, 2.4)	0.08	0.8 (0.3, 1.8)	0.52
RCC (ref)	49	-	-	-	-
Community	17	1.1 (0.6, 2.0)	0.80	1.8 (0.9, 3.6)	0.10
LOC near death					
Pediatric	34	2.4 (1.4, 3.9)	<0.01	3.1 (1.3, 7.5)	0.01
Adult (ref)	76	-	-	-	-
Cancer type					
Hematological	85	3.4 (2.1, 5.5)	<0.01	4.9 (2.8, 8.4)	<0.01
Solid Tumor (ref)	25	-	-	-	-

Relapsed disease					
Yes	42	0.5 (0.3, 0.7)	<0.01	0.4 (0.2, 0.6)	<0.01
No (ref)	68	-	-	-	-
Sex					
Male (ref)	77	-	-	-	-
Female	33	0.8 (0.5, 1.2)	0.29	-	-
Age at death (years)	Median 19.0, IQR 4.0	0.9 (0.8, 1.0)	0.02	1.0 (0.9, 1.1)	1.0
Income quintile at diagnosis					
Q1 (lowest)	17	0.7 (0.3, 1.4)	0.32	-	-
Q2	25	1.1 (0.6, 2.1)	0.83	-	-
Q3	19	0.7 (0.4, 1.4)	0.34	-	-
Q4	25	0.7 (0.4, 1.3)	0.25	-	-
Q5 (highest; ref)	24	-	-	-	-
Rurality at diagnosis					
Urban (ref)	89	-	-	-	-
Rural	21	1.9 (1.1, 3.5)	0.02	2.2 (1.1, 4.1)	0.02
Time period of death (categorized)					
Early (1992-2004; ref)	54	-	-	-	-
Late (2005-2016)	56	1.3 (0.8, 1.9)	0.29	1.7 (1.0, 2.7)	0.03
Distance from treating centre					
Short (ref)	80	-	-	-	-
Long	30	1.2 (0.7, 1.9)	0.53	-	-

-: not applicable; CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; LOC: locus of care; OR: odds ratio; ref: reference

An interaction between the LOC near death and cancer type predictors was explored (interaction term P = 0.05). Among patients with hematological malignancies, care in a pediatric centre near death compared to an adult centre was associated with an increased odds of death in the ICU (OR 3.7, 95% CI 2.0-6.8). This disparity was not seen among patients with solid tumors (OR 0.8, 95% CI 0.3-2.5). Dying of hematological malignancies compared with solid tumors was associated with an increased odds of dying in the ICU across both the pediatric (care near death in pediatric setting with hematological malignancy versus care near death in pediatric setting with solid tumor OR 10.9, 95% CI 3.4-35.1) and adult settings (care near death in adult setting

with hematological malignancy versus care near death in adult setting with solid tumor OR 2.4, 95% CI 1.4-4.2).

An alternative multivariable model was built with all the candidate predictor variables included in the adjusted model without testing for statistical significance (Appendix IX). The estimates were largely unchanged in this model compared to the model which included the candidate predictors of interest and those meeting the statistical significance threshold of $P < 0.25$ (Table 10).

A sensitivity analysis was conducted using the alternative LOC near death candidate predictor variable and a new multivariable logistic regression model was built (Appendix X). The alternative definition of LOC near death categorized patients as pediatric if the age at death was less than 19 years (compared to a threshold of 18 years for the LOC near death variable used for the majority of the logistic regression analyses). In the multivariable model when controlling for the other predictors with the exception of sex, neighborhood income quintile at diagnosis, and distance from treating centre, the alternative LOC near death predictor variable was associated with an increased odds of death in the ICU (OR 2.5, 95% CI 1.0-6.3). The other predictor estimates were unchanged compared to the initial model.

4.5.2. Predictors of Mechanical Ventilation Within 14 Days of Death

Table 11 outlines the results of univariate and multivariate modeling of the mechanical ventilation within 14 days of death outcome. The assumption of linearity was met for the age at

death variable and the estimates were provided per year of change. In univariate models, hematological malignancies compared to solid tumors were associated with an increased odds of mechanical ventilation (OR 3.8, 95% CI 2.2-6.5) as was living in a rural location at diagnosis (OR 1.8, 95% CI 1.0-3.2); relapsed disease was associated with a decreased odds of mechanical ventilation (OR 0.6, 95% CI 0.4-0.9). The LOC for cancer therapy, LOC near death, and age at death candidate predictor variables were *a priori* included in the multivariable model. The sex and distance from treating centre variables were excluded from the multivariable model as they did not meet the statistical significance threshold. In the multivariable model, an increased odds of mechanical ventilation was detected among patients with hematological malignancies compared to solid tumors (OR 5.4, 95% CI 3.0-9.7), rural living at diagnosis compared to urban living (OR 2.0, 95% CI 1.0-3.8), and death in the later period of study compared to the earlier period (OR 1.9, 95% CI 1.1-3.0); a decreased odds was detected among patients with relapsed disease (OR 0.5, 95% CI 0.3-0.8).

Table 11. Results from Univariate and Multivariate Modeling of the Mechanical Ventilation Outcome among Study Cohort Patients (N=480)

		Univariate		**Multivariate**	
Characteristic	**Number of Cases**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy					
Pediatric	34	1.1 (0.7, 1.9)	0.60	0.7 (0.3, 1.6)	0.43
RCC (ref)	47	-	-	-	-
Community	17	1.1 (0.6, 2.1)	0.67	1.9 (0.9, 3.9)	0.07
LOC near death					
Pediatric	24	1.5 (0.9, 2.5)	0.15	1.9 (0.8, 4.6)	0.15
Adult (ref)	74	-	-	-	-
Cancer type					
Hematological	78	3.8 (2.2, 6.5)	<0.01	5.4 (3.0, 9.7)	<0.01
Solid Tumor (ref)	20	-	-	-	-
Relapsed disease					
Yes	42	0.6 (0.4, 0.9)	0.02	0.5 (0.3, 0.8)	<0.01
No (ref)	56	-	-	-	-
Sex					
Male (ref)	67	-	-	-	-

Female	31	0.9 (0.5, 1.4)	0.55	-	-
Age at death (years)	Median 19.0, IQR 4.0	0.9 (0.9, 1.0)	0.16	1.0 (0.8, 1.1)	0.52
Income quintile at diagnosis					
Q1 (lowest)	15	0.6 (0.3, 1.3)	0.22	0.7 (0.3, 1.5)	0.34
Q2	23	1.0 (0.5, 2.0)	0.96	1.2 (0.6, 2.5)	0.64
Q3	18	0.7 (0.4, 1.4)	0.33	0.7 (0.3, 1.5)	0.33
Q4	19	0.5 (0.3, 1.0)	0.06	0.6 (0.3, 1.2)	0.16
Q5 (highest; ref)	23	-	-	-	-
Rurality at diagnosis					
Urban (ref)	80	-	-	-	-
Rural	18	1.8 (1.0, 3.2)	0.06	2.0 (1.0, 3.8)	0.04
Time period of death (categorized)					
Early (1992-2004; ref)	47	-	-	-	-
Late (2005-2016)	51	1.3 (0.8, 2.1)	0.22	1.9 (1.1, 3.0)	0.01
Distance from treating centre					
Short (ref)	76	-	-	-	-
Long	22	0.8 (0.5, 1.4)	0.51	-	-

-: not applicable; CI: confidence interval; IQR: interquartile range; LOC: locus of care; OR: odds ratio; ref: reference

An interaction between the LOC near death and period of death predictors was detected and explored (interaction term P = 0.05). Among patients who died in the early period, LOC near death was not associated with odds of mechanical ventilation (OR 0.8, 95% CI 0.3-1.8). However, among patients who died in the later period, care in a pediatric setting near death compared to an adult setting was associated with an increased odds of mechanical ventilation (OR 2.4, 95% CI 1.2-4.8).

An alternative multivariable model was built with all the candidate predictor variables included in the adjusted model without testing for statistical significance (Appendix XI). In this model, the OR of living in a rural location at diagnosis compared to an urban location increased from 2.0 (95% CI 1.0-3.8) in the original model (Table 11) to 2.5 (95% CI 1.2-5.1) but the other estimates remained unchanged.

A sensitivity analysis was conducted using the alternative LOC near death candidate predictor variable and a new multivariable logistic regression model was built (Appendix XII). The alternative definition of LOC near death categorized patients as pediatric if the age at death was less than 19 years (compared to a threshold of 18 years for the LOC near death variable used for the majority of the logistic regression analyses). The ORs of the predictor variables were unchanged compared to the estimates in the original multivariable model (Table 11).

4.6. Predictors of In-Hospital Death

Table 12 outlines the results of univariate and multivariate modeling of the in-hospital death outcome. The assumption of linearity was met for the age at death variable and the estimates were provided per year of change. In the univariable model, hematological malignancies compared to solid tumors were associated with increased odds of in-hospital death (OR 3.1, 95% CI 2.1-4.7). Neighborhood income quintile at diagnosis was not included in the multivariable model as it did not reach the statistical significance threshold (P = 0.42). The LOC for cancer therapy, LOC near death, and age at death candidate predictor variables were *a priori* included in the multivariable model. In the multivariable model when controlling for the other predictors, hematological malignancies compared to solid tumors were associated with an increased odds of in-hospital death (OR 3.4, 95% CI 2.2-5.3), while relapsed disease (OR 0.6, 95% CI 0.4-1.0), and living a long distance from the oncology treatment centre (OR 0.6, 95% CI 0.3-0.9) were associated with decreased odds of in-hospital death.

Table 12. Results from Univariate and Multivariate Modeling of the Death in Hospital Outcome among Study Cohort Patients (N=480)

		Univariate		Multivariate	
Characteristic	**Number of Cases**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy					
Pediatric	105	0.8 (0.5, 1.2)	0.24	0.6 (0.3, 1.1)	0.09
RCC (ref)	175	-	-	-	-
Community	50	0.7 (0.4, 1.1)	0.14	1.0 (0.6, 1.8)	0.94
LOC near death					
Pediatric	66	1.1 (0.7, 1.9)	0.61	1.4 (0.7, 3.0)	0.33
Adult (ref)	264	-	-	-	-
Cancer type					
Hematological	215	3.1 (2.1, 4.7)	<0.01	3.4 (2.2, 5.3)	<0.01
Solid Tumor (ref)	115	-	-	-	-
Relapsed disease					
Yes	167	0.7 (0.5, 1.0)	0.08	0.6 (0.4, 1.0)	0.04
No (ref)	163	-	-	-	-
Sex					
Male (ref)	223	-	-	-	-
Female	107	0.8 (0.5, 1.2)	0.23	0.8 (0.5, 1.2)	0.20
Age at death (years)	Median 20.0, IQR 3.0	1.0 (0.9, 1.1)	0.54	0.9 (0.8, 1.1)	0.36
Income quintile at diagnosis					
Q1 (lowest)	63	1.2 (0.6, 2.4)	0.56	-	-
Q2	63	1.0 (0.5, 1.9)	0.96	-	-
Q3	58	0.7 (0.4, 1.3)	0.25	-	-
Q4	82	0.8 (0.4, 1.4)	0.39	-	-
Q5 (highest; ref)	64	-	-	-	-
Rurality at diagnosis					
Urban (ref)	284	-	-	-	-
Rural	46	1.5 (0.8, 2.7)	0.23	2.0 (1.0, 3.9)	0.06
Time period of death (categorized)					
Early (1992-2004; ref)	186	-	-	-	-
Late (2005-2016)	144	0.7 (0.5, 1.0)	0.07	0.8 (0.6, 1.3)	0.42
Distance from treating centre					
Short (ref)	254	-	-	-	-
Long	76	0.7 (0.5, 1.1)	0.14	0.6 (0.3, 0.9)	0.02

-: not applicable; CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; LOC: locus of care; OR: odds ratio; ref: reference

An alternative multivariable model was built with all the candidate predictor variables included in the adjusted model without testing for statistical significance (Appendix XIII). The estimates in this model were unchanged compared to the original multivariable model above.

A sensitivity analysis was conducted using the alternative LOC near death candidate predictor variable and a new multivariable logistic regression model was built (Appendix XIV). The estimates were unchanged compared to the initial model (Table 12).

5. DISCUSSION

5.1 Summary of Key Findings

In this population-based cohort of 483 AYA cancer decedents, 60.5% received at least one measure of HI-EOL care. Over time, the composite measure of HI-EOL care as well as the individual measures of ED visits and hospitalizations in the last month of life decreased. The individual measures of ICU admission in the last month of life and IV chemotherapy in the two weeks before death did not change over time. The receipt of HI-EOL care was associated with hematological malignancies compared to solid tumors (increased odds) and relapsed disease (decreased odds).

For the measures of the MI-EOL care, 22.8% died in the ICU and 20.3% were mechanically ventilated in the last two weeks of life. These measures did not decrease over time. Similar to the HI-EOL care outcome, these measures were associated with hematological malignancies

(increased odds) and relapsed disease (decreased odds). We also identified predictors that were unique to the MI-EOL care measures. Receiving care in a pediatric setting near death was associated with an increased odds of dying in an ICU; exploratory analyses suggested this association may be unique to patients with hematological malignancies. Rural living at diagnosis and dying in the later period of study were both associated with increased odds of the MI-EOL care measures.

The majority of the cohort (68.9%) died in an hospital setting. This measure was close to the statistical significance threshold suggesting a decrease over time. The predictors of this outcome were similar to the HI-EOL care measure (hematological malignancies, relapsed disease). Unique to this measure was that living a long distance to the treating centre, compared to a short distance, was associated with decreased odds of dying in hospital.

5.2. Prevalence of HI-EOL Care

Few population-based EOL studies of AYA cancer decedents exist. Table 13 compares the results of our study with the published population-based studies of HI-EOL care in AYA with cancer. The main methodological differences are also highlighted.

Table 13. Study Comparisons of Percentage of Cohort Positive for Each HI-EOL Care Measure and Methodological Differences in AYA Cohorts

	Current Study (%)	**Johnston 2017[80] (%)**	**Mack 2015[81] (%)**	**Mack 2015[82] (%)**
Composite measure	60.5	59.0	68.0	75.0
>1 ED visit	19.1	-	22.0	44.0
ICU admission	25.5	18.7	22.0	21.0

>1 hospitalization	28.8	20.3	62.0	64.0
IV chemotherapy	24.0	3.1	11.0	38.0
Study differences	-	Broader HI-EOL care definition Outcomes assessed for last inpatient admission Did not capture ED use Only inpatient chemotherapy captured ICU proxy codes used	Only AYA with relapsed or metastatic cancer All chemotherapy and hospitalizations included	Medicaid recipients All chemotherapy included

AYA: adolescents and young adults; ED: emergency department; ICU: intensive care unit; IV: intravenous

The published studies of AYA decedent populations have reported prevalence rates of HI-EOL care over 50%[80-82,105] and our study findings were in keeping with these estimates. Variations in outcome definitions and study inclusion criteria may have contributed to estimate differences. For example, Johnston et al. used a broader definition of HI-EOL care, ED use was not captured, and only patients who were hospitalized in the last six months of life were included.[80] The results of other published AYA studies may be less comparable to our study population since their inclusion criteria relied upon medical insurance status.[81,82] The above study design differences likely contributed to estimate discrepancies.

Prevalence trend analyses of HI-EOL care among decedent AYA with cancer have shown either stable or decreasing rates over time. In our study, the composite outcome of HI-EOL care decreased over the study period. Decreased rates over time were observed for the individual

measures of HI-EOL care except for ICU admissions in the 30 days before death and IV chemotherapy in the two weeks before death which remained unchanged. Other studies have reported that later deaths were not associated with HI-EOL care outcomes, suggesting stability over time.[80-82]

It may be difficult to compare the reported prevalence rates in these studies based on a number of methodological and health system differences. One challenge lies in the inconsistency of the definition of HI-EOL care between studies. Another limitation relates to the divergent data sources from which these studies are based. Population-based studies from the United States have relied upon databases with unique coding systems and captured variables which may not exist in Ontario databases, such as measures of hospice care for pediatric patients.[42] HI-EOL care rates may be higher in the United States due to hospital and practitioner financial incentives for the provision of aggressive EOL care (for example, chemotherapy overuse) even when not clinically indicated, which do not exist to the same extent in Canada.[42,134] Despite these differences, similar estimates were observed between studies.

Population-based decedent cohorts of AYA with cancer have shown higher rates of HI-EOL care compared to pediatric and adult cohorts. Trend analyses of these outcomes have suggested that rates may be stable or decreasing among children and AYA. The adult literature has suggested a trend toward increase of the receipt of HI-EOL care.

The prevalence rates of HI-EOL care in population-based pediatric cohorts have been generally lower than rates in AYA. The published estimates have ranged from 40-60% [61,63,64,70,71] with

trends toward stability or decrease. As in the case of the AYA literature, pediatric studies have used different HI-EOL care definitions, cohort inclusion criteria, and reflected different cultural practices. In the Ontario pediatric study, death in the later periods of study was not associated with receipt of the composite outcome of HI-EOL care.[63] Children who die of cancer may be less likely to experience HI-EOL care compared to AYA though prevalence trends over time have been comparable.

In general, prevalence rates of HI-EOL care among adult cancer decedents have been lower than the rates observed in our AYA population but have demonstrated trends towards increasing prevalence.[42,135] Ho et al. examined the trends and prevalence rates of HI-EOL care among 227,161 adults in Ontario who died between 1993 and 2004. In this study, 22.4% experienced the composite outcome of HI-EOL care which was defined in a similar way to our study.[42] Between 1993 and 2004, most measures increased slightly: ED visits from 8.6% to 10.3%; ICU admissions from 3.1% to 5.4%; and chemotherapy from 2.0 to 2.9%.[42] The prevalence of repeat hospitalizations decreased from 8.5% to 7.5%[42] which may have been partially explained by the reduction in the number of acute care beds across Canada beginning in the mid-1980s.[136] The study found that patients had a 1% increased odds of experiencing HI-EOL care with each successive year.[42]

The utility of comparing crude prevalence rates between AYA and adult cohorts may be limited by the varying distributions of malignancy types. For example, approximately 50% of our AYA cohort had hematological malignancies, whereas in older adult cohorts from Ontario and the United States only 9.7% and 10.1% of the patients suffered from hematologic malignancies.[39,42]

5.3. Prevalence of MI-EOL care

Table 14 compares the results of MI-EOL care of our study with the published population-based studies of AYA and children with cancer. In this study, 22.8% of patients died in the ICU and 20.3% were mechanically ventilated in the last two weeks of life. Neither of these trends changed over the study period. One possibility is the small cohort size was not powered to detect a statistical change in these two measures over time. In adjusted logistic regression models, however, dying in the later period of study (2005-2016) compared to the earlier period (1992-2004) was associated with an increased odds of dying in the ICU (OR 1.7, 95% CI 1.0-2.7) and being mechanically ventilated in the two weeks before death (OR 1.9, 95% CI 1.1-3.0), suggesting that these measures may be increasing over time.

Table 14. Study Comparisons of Percentage of Cohort Positive for MI-EOL Care Measures in AYA and Pediatric Cohorts

	Current Study (%)	**Revon-Rivière 2019[70] (%) French Children, AYA**	**Johnston 2017[61] (%) Californian Children, AYA**	**Kassam 2017[63] (%) Ontario Children**	**Hung 2016[66] (%) Taiwanese Children**	**Park 2014[71] (%) Korean Children**
Death in ICU	22.8	-	-	-	-	-
Mechanical ventilation within 14 days from death	20.3	22.9	19.9	16.7	46.5	8.8
Trend	Stable, possibly increasing	-	Possibly increasing	Possibly increasing	Stable	Stable
Study differences	-	Outcomes measured in last month of life	-	-	Outcomes measured in last month of life	Outcome of more than one intubation

						in last month of life

AYA: adolescents and young adults; ICU: intensive care unit

Similar prevalence rates and trends towards stability or increase of MI-EOL care measures have been previously described in pediatric and AYA population-based cohorts. Cultural and religious differences between countries may influence prevalence rates of MI-EOL care. For example, prevalence rates were higher among decedent Taiwanese and Korean children and the authors hypothesized these findings may have been related to the lack of palliative care integration into pediatric oncology.[66,71] Few adult studies have reported prevalence rates and trends of MI-EOL care measures.

5.4. Prevalence of In-Hospital Death

Table 15 compares the prevalence rates of in-hospital death of our study with selected published population-based studies of children, AYA, and adults with cancer.

Table 15. Study Comparisons of Percentage of Cohort Positive for In-Hospital Death in AYA, Pediatric, and Adult Cohorts

	Current Study (%)	**Johnston 2017[80] (%) Californian AYA**	**Rajeshuni[79] 2017 (%) Californian AYA**	**Mack 2015[82] (%) New York AYA**	**Gao 2016[67] (%) British Children, AYA**	**Kassam 2017[63] (%) Ontario Children**	**Huang 2002[136] (%) Ontario Adults**	**Barbera 2010[137] (%) Ontario Adults**
In-hospital death	68.9	52.9	50.0	65.0	48.9	43.4	~70.0	55.0
Trend	Decrease	Stable	Stable, possible decrease	Stable	Decrease	Possible increase	Decrease	Decrease

AYA: adolescents and young adults

In this study, 68.9% of patients died in hospital and the rate decreased over the study period. The rates of hospital deaths among AYA with cancer have been examined previously in population-based studies, with rates ranging from 57-65%.[79,80,82] Overall, studies have not shown dramatic changes over time.

Rates of in-hospital deaths among pediatric cohorts have ranged from 44.1% to 78.8%.[61,64,94] Trends have predominantly shown stability or decrease over time. A trend towards decreased prevalence of in-hospital deaths has been described in the adult oncology literature.[135,136,138]

5.5. Predictors of HI-EOL Care, MI-EOL Care, and In-Hospital Death

5.5.1. LOC near Death

This study was the first to describe disparities among AYA decedents of cancer based on the LOC near death (pediatric versus adult setting). The patterns of HI- and MI-EOL care differed according to whether patients were cared for in a pediatric or adult setting at the time of death. A pediatric LOC near death was not associated with the HI-EOL care composite outcome nor the death in hospital outcome. However, the study demonstrated that patients who died in a pediatric setting experienced significantly increased odds of dying in an ICU. Due to small patient numbers, any interaction between the LOC near death and cancer type predictor variables could not be adequately addressed. However, our preliminary exploration of this interaction suggested

that patients with hematological malignancies treated under pediatric care had disproportionately higher odds of dying in an ICU. These analyses could only be interpreted as preliminary explorations because the estimates were limited by small frequencies and wide confidence intervals.

An exploration of the interaction between the LOC near death and the period of death for the mechanical ventilation outcome suggested that disparity for pediatric patients may be worsening over time. In the early period of study, patients who died in a pediatric setting had similar odds of mechanical ventilation compared to adult patients. When restricting the analysis to the later period, pediatric patients had a 2.4 times greater odds of being mechanically ventilated compared to adult patients. Again, the interpretation of this association needed to be within the context of an unadjusted model with low event frequencies.

Due to methodological difficulties in assigning the LOC near death in this study, we were unable to determine which adult patients received care at an RCC versus a community institution at death. It was possible we overlooked an association between the type of adult centre and the receipt of HI-EOL care. Among adult hematologists, there have been different practice patterns described between community and academic practitioners; academic providers may be more likely to pursue aggressive care at the EOL for their patients compared to providers in a community setting.[138] Population-based studies in the United States and Taiwan have reported that care by an oncologist at the EOL compared to other types of physicians resulted in higher odds of HI-EOL care measures such as treatment with chemotherapy close to death, longer hospital stays, in-hospital deaths, and late referral to palliative care.[39,139] Other studies have

examined the association between care at a specialized oncology centre with HI-EOL care among AYA but have not distinguished between pediatric and adult centres.[61,70,80] Mixed pediatric-AYA decedent cohort studies have depicted conflicting associations between care at specialty centres and the receipt of HI-EOL.[61,70] The potential association of nonspecialty centres with HI-EOL care have brought into question whether a lack of experience working with younger AYA at the EOL may have led to higher rates of HI-EOL care. However, the results of these studies may have been limited by misclassification bias. For example, Johnston et al. determined in their study that National Cancer Institute-designated centres were not considered to be specialized centres for patients who died at less than 18 years of age because "pediatric patients have improved outcomes when treated at pediatric centres (ie, COG centres)."[80] This assumption is not always true and brings into the question the validity of this predictor variable because it does not account for the realistic care of these patients.[80]

In previous AYA oncology work, younger age at death has been associated with higher rates of HI-EOL care,[61,80] hospital deaths,[79] greater time spent in hospital in the last year of life[78], and greater inpatient costs in the last year of life.[78] In our study, after controlling for demographic, health system, and disease-related factors, age at death was not associated with increased odds of experiencing HI- or MI-EOL care. One hypothesis that could have explained this finding was that our inclusion of LOC near death as a candidate predictor variable may have accounted for the effect of age at death that has been demonstrated in previous studies.[79] The narrow age range of inclusion may also have limited our ability to detect an association.

The association of care by pediatric providers, compared to adult providers, with higher odds of receiving the MI-EOL care has been previously suggested. A Taiwanese population-based pediatric decedent cohort study of 1603 patients identified a potential association between care by pediatric practitioners with measures of MI-EOL care.[66] However, given the cohort was largely pediatric patients, the study may not have been powered to detect a true difference between pediatric and adult care since so few patients would have been cared for by adult physicians.[66] In our study, the association between pediatric care and the receipt of MI-EOL care may have been explained by several factors. Adult providers likely had more experience initiating prognosis discussions and transitioning the focus of care from curative intent to palliation in considering the relatively lower survival rates among adult cancer patients and greater patient volume. The perspectives of adult oncologist regarding the use of HI- and MI-EOL care measures may ultimately have been different from those of pediatric oncologists.[81] Compared to adults, younger patients undergoing cancer treatment may be better able to tolerate intensive anticancer therapies and overcome treatment-related complications due to a lower incidence of coexisting morbidities and better organ function.[140] Therefore pediatric providers may have been more likely to continue life-sustaining therapy and intensive treatment despite treatment-related toxicities and/or advanced disease;[24,25] this continuation of intensive therapy possibly translated into higher rates of care in the ICU including mechanical ventilation. AYA treated at pediatric centres were more likely to be registered on a clinical trial,[24] received more cytotoxic treatment, and experienced more hospitalizations during therapy than if treated in an adult centre.[25] Other philosophical differences between the care received in pediatric versus adult centres likely extended to higher thresholds for admission to hospital and admission to the ICU in the adult environment due to more limited resources as a result of higher patient numbers.[25]

Whether financial factors contributed to this disparity is relevant but undetermined, and prior work has demonstrated high costs of EOL care for both pediatric and adult hospitals.[25] Whether adult providers were more cognisant of healthcare utilization costs and therefore limited costly interventions such as admission to an ICU for patients with fatal disease was unknown.

We did not observe that the LOC for initial oncology therapy predicted the receipt of HI- or MI-EOL care. One possible explanation for this finding was there may have been nondifferential misclassification among adult patients treated at RCCs or community institutions. We classified the LOC of adult patients based on the codes in the year before death and not in the year following diagnosis. Therefore it was possible that some patients may have been initially treated at an RCC but categorized as having an LOC for initial oncology therapy as community, or vice versa. It was therefore possible that we did not capture an association between the LOC for initial cancer therapy with the receipt of HI-EOL care when in fact one existed.[141] In this cohort, 50.7% of patients received their initial cancer therapy at an RCC and 16.4% at a community centre. This distribution was in keeping with other publications[22,24,142] examining this cohort which minimized the likelihood of a significantly biased candidate predictor variable.

It was also possible that in assigning the LOC near death categories, some patients who should have been classified as having a pediatric LOC near death may have been nondifferentially misclassified as having an adult LOC near death. For patients who did not have any treatment claims in the 90 days before death, or were cared for in hospitals where pediatric versus adult care could not be differentiated, patients were classified as having a pediatric LOC near death if their age at death was less than 18 years. Sensitivity analyses were conducted using an

alternative LOC near death candidate predictor variable where the age at death threshold for pediatric LOC was increased to less than 19 years. The estimates derived from the sensitivity analyses were not further from the null compared to the estimates from the original analyses, which suggested minimal nondifferential misclassification of this exposure, if at all.[141]

5.5.2. Hematological Malignancies

Across the pediatric, AYA, and adult oncology literature, patients with hematological malignancies have demonstrated the strongest associations with the receipt of HI-EOL care as well as measures of the MI-EOL care. The results of this study were in keeping with previous work. AYA who died of hematological malignancies, compared to solid tumors, had increased odds of experiencing HI-EOL care, MI-EOL care (dying in the ICU, being mechanically ventilated in the last 14 days of life), and dying in hospital.

In the AYA literature, patients with hematological malignancies have had the strongest associations with in-hospital deaths[79] and the receipt of HI-EOL care compared to patients with solid tumors.[80,81] AYA with hematological malignancies compared to solid tumors have also shown higher odds of spending more time admitted to hospital in the last year of life.[78] Pediatric population-based studies have also reported increased odds of HI- and MI-EOL care, in-hospital deaths, and decreased likelihood of accessing specialized pediatric palliative care among patients with hematological malignancies.[63,65-67,70,94] Mixed cohorts of adults with hematological malignancies and solid tumors have consistently demonstrated higher rates of HI- and MI-EOL care among patients with hematological cancers.[39,42,135,139,143]

There were limitations to comparing the clinical courses of children and AYA with hematological malignancies with the trajectories of adults. Among younger patients, acute leukemias and aggressive lymphomas were the most prevalent cancers, whereas adults suffered from a wider spectrum of diseases which included indolent cancers with distinct, less aggressive clinical courses and varying degrees of curability.[144] The intensive therapies needed to treat the pediatric-type malignancies predisposed to longer, more frequent, and unplanned hospital stays due to acute complications.[79,139]

Table 16 outlines potential barriers to quality EOL care for patients with hematological malignancies.[138]

Table 16. Potential Barriers to Quality EOL Care for Patients with Hematological Malignancies

Disease Characteristics	**Treatment Approaches**	**Prognoses**	**EOL Course**	**Care Providers**
Pancytopenia predisposing to hemorrhage, infection, transfusion dependence	Higher likelihood of in-hospital care for antibiotics, transfusions, etc.	Can be uncertain which may predispose to HI-EOL care, especially if receiving experimental therapies	Often progress rapidly following relapse which may lead to inadequate EOL care planning	Hematologists may be less likely to refer to palliative care
High rates of acute complications in context of curable disease, when HI-EOL care would be appropriate	Availability of novel agents may lead to unclear transition to EOL and higher rates of HI-EOL care			Lower rates of symptoms (chronic pain) that would normally prompt palliative care consultation

HI: high-intensity; EOL: end-of-life

There exists a number of disease, treatment, EOL course, outcome, and care provider characteristics that may predispose patients with hematological malignancies to receive HI-EOL care and subsequently, poorer quality EOL care. These patients have profoundly low blood counts, placing them at risk of severe hemorrhage, infection, and transfusion dependence; these factors increase the likelihood of receiving care in a hospital setting even for palliative intent.[81,138,145] The high likelihood of requiring these supportive measures also translates into patients with curable disease receiving measures of HI- and MI- care, when it would be appropriate. From a treatment perspective, the management of hematological malignancies for all ages has evolved to include immunotherapies and targeted agents which have resulted in sustained cure rates even for patients with relapsed or refractory disease.[146-149] While the success of these novel agents must be celebrated, patients with aggressive cancers are now more likely to pursue active anticancer therapy for longer periods; the availability of salvage therapies has made it increasingly difficult to determine prognosis as well as the time when a patient starts to transition into the EOL phase of their journey.[78,138,150] For patients with advanced solid tumors, the poor prognoses are often understood at diagnosis[81,82] whereas for patients with hematological diseases the outcomes or timelines to death may be uncertain.[138] The uncertain prognoses likely contribute to the tendency towards HI-EOL care preferences for both providers and patients.[81] High rates of acute complications from aggressive cancer compounded with adverse events from experimental therapies means these patients are likely to receive HI- and MI-EOL care despite low survival rates.[143] Another difference between malignancy types is that patients with leukemia and lymphoma may progress more rapidly following relapse compared to patients with solid tumors.[81] The risk of sudden deterioration in the context of disease with an unclear prognosis may hinder planning for the EOL journey.[151] The acute nature of the EOL for patients

with hematological malignancies may leave little time for discussions of goals of care, or transfer to home or hospice from the hospital after an admission.[151] Lastly, hematologists may be less likely to refer to palliative care compared to oncologists caring for patients with solid tumors.[152] Current guidelines[153] recommend early referral to palliative care for patients with advanced cancer, so this practice difference may have contributed further to EOL care disparities for patients with hematological malignancies.

Patients with hematological malignancies may also have different needs at the EOL compared to patients with solid tumors, where the EOL course may be longer and less acute.[138] Patients with hematological malignancies are less likely to experience chronic, debilitating pain which often triggers referral to a palliative service, especially in adult centres and therefore may be less likely to receive care from specialist palliative care or hospice teams compared to other malignancy groups.[144,150] The ability to capture the involvement of specialist palliative care teams in our study would shed light on the relationship between cancer type and the receipt of HI-EOL care while accounting for this potential predictor.

Patients with hematological malignancies have unique needs and experiences both during cancer treatment and at the EOL, all of which likely contribute to the highest odds of receiving HI- and MI-EOL care as estimated in this study and others.

5.5.3. Relapsed Disease

In this study, relapsed disease was associated with decreased odds of experiencing HI-EOL care, MI-EOL care (dying in an ICU, mechanical ventilation), and dying in hospital. As a general oncological principle, relapsed cancer is a poor prognostic indicator and often carries decreased chances of cure. Our study included relapse status as a candidate predictor of HI- and MI-EOL because death from progressive or incurable cancer would be more anticipated in this cohort. A higher likelihood of death might prompt discussions about goals of care and treatment limitations between physicians and patients; influence referrals to palliative care; or lead to decisions by the medical team to not offer care felt to be unhelpful, such as MI-EOL care. Our study was unique in our inclusion of relapse status as a candidate predictor variable for the receipt of HI- or MI-EOL care. Most population-based cancer registries did not contain relapse data and therefore this important variable has not been included in most of the published literature for all age groups. Some studies have included survival time post diagnosis as candidate predictor variables of HI-EOL care.[154] Other studies have inferred relapsed disease based on registry codes of new metastases or receipt of more than one chemotherapy regimen[81,105] or used metastatic disease as a surrogate for higher risk disease, a characteristic which may not be useful in the cases of hematological malignancies.[66,71] The inclusion of relapse status allowed us to isolate its impact to better understand the relationship with our outcomes.

5.5.4. Rurality and Distance from Treating Centre

The influence of healthcare resources on practice patterns, even when disease and demographic characteristics were accounted for, has been suggested in previous work.[154] This study described an increased odds of death in the ICU and mechanical ventilation in the last 14 days of life

among patients living in rural areas at the time of their cancer diagnosis. Patients who lived a long distance from the oncology treating centre had decreased odds of dying in hospital compared to patients who lived a shorter distance.

The association between geographical factors and the receipt of HI- and MI-EOL care may not be simple to understand or dissect. The comparison of our results to other decedent AYA oncology studies was also limited based on different predictor variable definitions and varying outcomes. Some studies have reported that living close to a hospital centre was associated with increased odds of HI-EOL care and in-hospital death.[79,80] Rurality has been inconsistently associated with HI-EOL care.[70,80] The type of hospital (specialty versus nonspecialty) may partially account for the relationship between rurality and the type of EOL care received, since rural patients may be more likely to receive care a nonspecialty centres.[80] We were not able to include the type of centre at the EOL (speciality versus nonspecialty) as a candidate predictor variable so we could not further dissect these complex associations.

The association of rural living at diagnosis with death in an ICU and mechanical ventilation in the last two weeks of life may have been explained by differential palliative care resources across the province, with fewer resources in more rural settings.[42,129] Though not measured in our study, the receipt of home care in the last 6 months of life (compared to no home care) and receipt of a physician house call in the last 2 weeks of life (compared to no house call) were both associated with decreased odds of death in an acute care bed in a decedent cohort of older adults.[137] Based on these findings, it was therefore conceivable that AYA living in rural areas with decreased physician support may have been at increased risk of disproportionate levels of

HI-, MI-EOL care, and in-hospital death. However, we were limited in our interpretation of these associations. We did not know if these patients died in rural settings closer to home or in an urban environment. It was possible that as patients neared death there was a preference to be cared for at community hospitals closer to home, where providers may have had less experience caring for AYA with cancer at the EOL or were less familiar with the patients compared to their primary oncologists.

One possible explanation for these findings is that traveling long distances between the treating centre and home may have incentivized patients to receive EOL care at home or at a hospice closer to home. We were limited in our ability to interpret the association of the distance from treating centre predictor variable based on how this variable was defined. For patients who received their cancer therapy in a pediatric centre, the distance to oncology treating centre was calculated from the closest tertiary pediatric hospital to the postal code at the time of death. For adult patients, the distance was calculated from the hospital which had the most codes in the year before death to the postal code at the time of death. Over the course of their illnesses and especially in the case of younger AYA, the hospital used to define the distance variable may not have been the hospital in which they received care at the EOL. Therefore, the distance between home and the treating centre at diagnosis may not have reflected the distance between home and the treating centre at the EOL. Future work should examine the association between the distance between home and the centre providing care at the EOL as this relationship would be more clinically useful.

The associations of rurality and distance to oncology treating centre with the receipt of HI- and MI-EOL care measures have been difficult to ascertain. These unclear and conflicting patterns may have stemmed from predictor variable definitions that were based on geographical circumstances at cancer diagnosis and not at the EOL. In addition, differing predictor variable definitions between studies limited the comparisons of results between studies.

5.5.5. Income Quintile

In this study, neighborhood income quintile at diagnosis did not predict the receipt of HI-EOL care, MI-EOL care, nor death in hospital. The relationships between income levels and the receipt of HI-EOL care measures among decedent AYA with cancer have been inconsistent.[80,81] Mack et al.'s population-based study of decedent AYA on Medicaid plans reported overall higher odds of HI-EOL care compared to our study and others as well as significantly higher odds of patients who were continuously enrolled on Medicaid compared to patients with intermittent Medicaid; these findings suggested a relationship between lower socioeconomic status, disability, and minority status with the receipt of HI-EOL care.[82] This association has been reported in pediatric studies.[67,70]

These findings may be explained by the model of healthcare delivery in the United States where socioeconomic status and health insurance are closely linked; the lack of universal healthcare may have been a barrier to care.[82,142] AYA in the United States are at increased risk of being uninsured, and this risk only increases following a cancer diagnosis when they may not be able to work.[82] Non health maintenance organization insurance has been associated with the receipt of

HI-EOL care measures,[80,155] greater time spent in hospital in the last year of life among decedent AYA with cancer.[78] Patients who are uninsured may be unable to obtain pain medication and other supportive care supplies for home, which may in turn result in higher rates of care in acute settings such as the ED and readmissions to hospital.[39]

Among decedent population-based cohort studies, socioeconomic disadvantage has predicted higher likelihood of in-hospital deaths across a number of publications.[65,79,137,154] One hypothesis was that families from lower socioeconomic backgrounds may have been unable to take time off work to care for their loved ones at home at the EOL, therefore contributing to an increased likelihood of dying in hospital.[68]

5.6. Themes and Clinical Implications

AYA with cancer represent a unique population, distinct from children and older adults with cancer. The AYA population spans different life stages and circumstances, all of which may influence the EOL trajectory.[81] While population-based studies of HI-EOL care cannot account for the unmeasured experiences of individual patients and families, they have provided insight into patterns and predictors of HI-EOL care and the impact on the healthcare system at large.[81]

The study of the patterns of HI- and MI-EOL care for Ontario AYA who died of cancer demonstrated prevalence rates that exceeded estimates in comparable pediatric and older adult decedent cohort studies. These disparities likely reflect the unique challenges of caring for AYA at the EOL experienced by both pediatric and adult providers; caring for AYA falls outside the

comfort zone of practitioners in both spheres of care.[98] It was especially concerning that these inequalities may be worsening over time and disproportionally affecting AYA receiving care in pediatric settings, where parents may be more likely to drive EOL care decisions and may not involve their AYA children. Our study raised the question of whether oncologists in general, though particularly pediatric oncologists, receive adequate training in working with AYA at the EOL.[20,109] Compared to adult oncologists, pediatric oncologists may have less experience with transitioning from cancer-directed care to EOL care and, when this transition occurs, may more often communicate with the parents of their patients. On the other hand, adult oncologists more often manage malignancies with poor outcomes but may be less comfortable working with younger patients who, prior to their diagnoses, had high quality of life and perceived long life expectancies. The care of AYA with cancer at the EOL is routine for neither pediatric nor adult oncologists.[156] Caring for AYA with cancer at the EOL has been described as stressful, emotionally draining, and subject to a high risk of countertransference.[157] These factors likely translate into delayed discussions of advance care planning and palliative care consultation, and a continuation of anticancer therapy despite lack of clinical benefit. As described by Earle and others, these practices of pursuing aggressive anticancer therapy despite limited benefit may be physician-driven in an attempt to maintain hope and avoid distressing conversations about refocusing therapy efforts to primarily supportive care; "it is often easier to recommend another line of chemotherapy."[39] Caring for AYA with cancer at the EOL is difficult for both pediatric and adult providers but may translate into poorer quality EOL care for those AYA cared for in pediatric settings.

While the prevalence trends of HI-EOL care differed in the AYA population compared to pediatric and adult groups, the predictors that were identified have been consistent across all ages. Patients with hematologic malignancies have experienced the highest odds of receiving HI- and MI-EOL care and dying in hospital compared to other disease groups. Patients with relapsed cancers may be protected from these EOL outcomes as demonstrated in the decreased odds of experiencing HI- and MI-EOL measures. This finding was reassuring because as an aggregate, it may not be appropriate for this population to receive intensive EOL care. This predictor variable has not been included in most health services cohort studies due to the difficulty in capturing relapse status in cancer registries. Patients living in rural settings may experience disproportionately higher odds of the MI-EOL care which may be related to disparities in supportive care resources in rural settings.

The findings of this study did not pertain to modifiable factors but represented the initial steps to determining why these disparities existed and understanding why the prevalence rates of the MI-EOL care measures may be increasing. Only once we have defined what ideal EOL care for AYA with cancer is, though, can we begin to understand why these trends are unfolding.[109] Just as prior work has outlined appropriate EOL care benchmarks for adult patients with cancer based on literature review, focus groups, and expert panel review,[36] the same processes should be undertaken to establish meaningful benchmarks of quality care for AYA.[78]

Importantly, AYA may value different quality EOL care indicators than older adult patients.[36] Older adults with terminal cancer have favoured comfort care over life-extending therapies and home deaths, though not unanimously.[158-160] It is possible that for AYA with cancer at the EOL

the previously established measures of poor-quality care may not be applicable; they may wish to receive all possible interventions in order to live as long as possible while also requesting comfort care to maximize quality of life.[82,105] Elevated rates of HI-EOL care may not represent a failure of communication regarding prognosis, realistic benefits of chemotherapy, and introducing palliative care late or not at all.[39] But rather an indication of a different value system compared to older adults[81,161]: "it is possible that young patients are more willing to accept invasive measures at the EOL than their older counterparts out of a desire to live as long as possible, and in an effort to support and protect loved ones from the pain of their loss."[82] It is possible that for AYA pursuing life-prolonging therapies while optimizing symptom control may represent the desired EOL care, and previously outlined HI-EOL care measures may not necessarily represent poor quality care for AYA with cancer.

It is also possible that the high prevalence of HI-EOL care reflects unmet needs for this unique population.[162] Patients with intractable symptoms at the EOL may be better managed in a hospital setting.[160] In-hospital death for AYA with cancer may not necessarily represent poor-quality care, especially in the presence of difficult to control symptoms or poor coping at home.[151] It is yet to be determined whether the receipt of HI- and MI-EOL care among this cohort of AYA with cancer is preventable though improved symptom control, better communication around EOL trajectory and prognosis, or easier access to home or hospice services.[78] The outcome of death in hospital may not be an appropriate measure of poor-quality care and perhaps a shift towards time spent in hospital as an outcome should be pursued among AYA with cancer. Perhaps targeting the most harmful EOL care measures such as ICU admission, death in the ICU, and mechanical ventilation, for example, should become the focus

of future work and used to establish measures of poor quality EOL care.[63,94] Whether these disparities exist as a result of systemic inequalities, distinct values held by AYA, or a combination of other factors can only partially be answered by administrative health linkage studies.

Several patient, disease, and health systems predictors of HI- and MI-EOL care were identified. Clinicians who care for AYA with cancer should have a heightened awareness of these associations. These disparities are critical for oncologists to be cognisant of in light of the above findings that AYA may have unique values and wishes at the EOL. From a resource planning perspective, targeted interventions for these patients should be undertaken. For example, in a pediatric study, there was a significant association between specialized pediatric palliative care teams and a reduced likelihood of receiving HI- and MI-EOL care, while no such association existed with generalized palliative care. [94] It is possible that the AYA population may similarly benefit from the creation of oncology and palliative care teams specializing in the care of AYA with cancer.

The harm of HI-EOL care may extend past the experience of the individual patient to the healthcare system at large; HI-EOL care is costly. Previous work outlining the elevated cost of HI-EOL care among AYA with cancer has been based in the United States.[78] Canadian data for this population is limited. In Ontario, care in the last year of life for all residents cost approximately $4.7 billion annually and represented 10% of the provinces health care budget; inpatient care accounted for over 40% of these costs and predominantly in the last 120 days of life.[163] Among all healthcare sectors, an admission to hospital with an ICU stay represented the

highest cost and was experienced by 21.3% of the population.[163] In a population-based cost analysis of all phases of care among AYA with cancer in Ontario, the terminal phase (last 360 days of life) was the costliest.[25] One population-based study analysed EOL care costs for all Ontario children up to age 19 years who died over a 3-year period (2010-2013) but did not report cancer-specific costs.[164] Among the children with chronic diseases (including cancer diagnoses), those who were admitted to an ICU at least once in the last year of life represented the highest mean hospital costs (mean cost of $116,630 CAD).[164]

5.7. Strengths and Limitations of Study

5.7.1. Strengths of Study

Our study has addressed many of the limitations of previous work of HI-EOL care among AYA with cancer. Unlike much of the published literature, our patient cohort contained complete and accurate diagnostic, clinical, and outcome data in order to better identify predictors of HI-EOL care.[22] This was the first study to examine LOC-based disparities at the EOL among decedent AYA with cancer. The data sources of the published literature did not contain the granularity of the IMPACT cohort in order to determine the LOC at the onset of treatment and at the EOL. Many population-based registries did not contain the patient age at diagnosis.[80] Another clinically relevant variable which was not captured in most cancer registries was disease relapse status.[36,78,80] We have determined that these variables were associated with the type of EOL care received by AYA with cancer. Not all studies have included frequent ED use as a measure of HI-EOL care, which has been routinely identified as potential indicator of poor quality EOL

care.[36,80] By capturing the receipt of care in all acute care settings (ED, ICU, and inpatient unit), this study provided a complete description of HI-EOL care among AYA with cancer, and could be more easily compared with other studies that have defined HI-EOL care in the same way.[22] This completeness contrasted with some studies which only captured patients who received inpatient care.[78] While most studies have reported the prevalence of in-hospital death, our study has also captured death in the ICU as a measure of MI-EOL care, which has not been reported previously as a separate outcome from in-hospital death. This distinction between in-hospital death versus death in ICU is clinically relevant. Many AYA with cancer chose to die in hospital,[104] but this choice implies dying on the inpatient unit (not in the ICU); in the pediatric literature in-hospital death is not always considered to be an undesirable outcome.[63,165-168] In contrast, death in the ICU is largely considered to be inappropriate for patients with progressive or incurable cancer and was therefore treated as a distinct outcome of MI-EOL care.[98] Another strength was the length of time during which the outcomes were observed; this study included patients diagnosed over a 20-year period but may have died up until 2016.

5.7.2. Limitations of Study

The IMPACT cohort was limited to AYA ages 15 to 21 years at the time of cancer diagnosis. This age definition of AYA did not reflect the currently accepted age definition of 15 to 39 years.[8] Despite the narrow age range for inclusion of our study based on the age at diagnosis, the age at death of the patients in this cohort ranged from 15 to 26 years of age. In the current body of population-based AYA oncology literature, patients were included based their age at death of 15 to 39 years, with one study[82] including patients ages 15 to 29 years at the time of death.[78-81,105]

The distribution of the loci of care for our cohort also reflected what would be expected of a larger age range where the majority of patients would be cared for in an adult setting; 67.1% of our cohort received their initial cancer therapy in a non-pediatric setting (RCC or community hospital) and 80.8% of our cohort received care in an adult setting around the time of death.

In our study, 113 patients who died more than five years from their primary diagnosis date were excluded from the analysis. In doing so, we excluded patients who may have died following later relapses of their primary cancers or died from subsequent malignant neoplasms resulting from the initial therapy or cancer predisposition. In our study, relapsed disease was well represented as approximately half of the cohort had relapsed cancer. Relapsed disease was a strong predictor for lower odds of experiencing the composite measure of HI-EOL care, MI-EOL care measures, as well as in-hospital death. The patients who died more than five years following their initial diagnoses may have received EOL care that differed from patients who died closer to diagnosis. However, this group may also have been more likely to have developed subsequent neoplasms which would have been treated as new primary malignancies, with EOL courses similar to our study cohort. Considering these possibilities, it was unlikely that the exclusion of these patients resulted in selection bias or skewed estimates of the prevalence rates of HI-EOL care.

Other limitations were inherent to the use of administrative health data, which were not collected for the purpose of answering clinical questions and therefore may not include important covariates.[38,39,42,169] For example, we did not measure comorbidity indices[78,170,171] which have been associated with higher rates of ED visits, ICU admissions, hospitalizations, and hospital deaths in adult,[39,42,135,139,172] pediatric,[70] and combined[67,155] oncology cohorts. Comorbidity

indices have been used as proxies for care complexity and measures of healthcare utilization.[67,135] Some authors have excluded ED visits, hospitalizations, and ICU admissions as outcomes of interest in logistic regression analyses because they may be so strongly influenced by comorbidity status in adults and therefore "appear less useful as measures of aggressive cancer care."[39] We were also unable to capture minority race/ethnicity. In prior studies, minority status has been associated with the receipt of HI-EOL care measures,[61,80-82,135,173] longer inpatient stays in the last year of life,[78] increased hospitalization rates near the EOL,[174] hospital deaths,[61,65,68,79,154] and receiving EOL care at nonspecialty centres.[80] Disability and functional status was not assessed but has been associated with decreased odds of HI-EOL care in one decedent older adult cohort.[135]

Another limitation of our study was the inability to capture the involvement of palliative care providers, both general or specialist, which would have shed light on a modifiable predictor in the EOL care of AYA. Palliative care consultations, and hospice admissions and discharges, have been difficult to accurately capture in administrative health databases and in this study the involvement of palliative care was not included as a candidate predictor variable.[70,71,164,175] Unfortunately, it is difficult to comprehensively study the trends of HI-EOL care without capturing the impact of palliative care teams. In adult populations, benchmarking standards of at least 55% of patients receiving hospice services before death from cancer, and less than 8% admission rate to hospice within three days of death have been established as measures of quality EOL care.[37] The association between palliative care and the receipt of HI-EOL care, as well as understanding the barriers to AYA accessing palliative care services were important to discern but data was lacking.

The impact of palliative care on the receipt of HI-EOL and MI-EOL care has been well described. [70,94,98,138,151] Specialist palliative care teams focus on intensive symptom control, psychosocial support, organizing complex discharges, and transitions to EOL care.[143] For some patients, an admission to a palliative care service could be a reasonable alternative to an ICU admission.[143] The likelihood of accessing specialized palliative care services may be increasing in pediatric centres,[94] yet it is unclear how frequently AYA have accessed these resources in either the pediatric, RCC, or community settings.[129]

Conceptually, quality EOL care is related to but distinct from quality living at the EOL.[143] A limitation inherent to health services research was the inability to determine whether the administrative indicators of quality EOL care were in line with goal-concordant care of patients and their families; the intent of care could not be ascertained.[81,105,138] For example, a patient dying in their preferred place of death was considered a marker of quality EOL care that could not be captured in administrative health databases.[151] Measuring this outcome would require detailed chart abstraction which is time consuming, costly, and subject to bias as patients with missing records would be excluded.[105,151] The process of hand searching is also challenging as medical documentation may not always be accurate or complete and can easily be misinterpretation by the abstractor. This is especially true when inferring patient and family preferences for EOL care which can be complex and difficult to categorize for analysis.[105] When electronic medical records were readily available within healthcare delivery systems, however, the process of manually abstracting data was feasible and valuable to understand how patient preferences affect intensity of care at the EOL.[105]

There are strengths and limitations to using retrospective population-based cohorts for the study of EOL care. Compared to prospective designs, retrospective cohort studies are cost-effective[176] and efficient for identifying cohorts of relevant patients, identifying cases, and maximizing follow-up rates considering the challenges of interviewing patients in the last months of life.[41,177-179] Retrospective studies can help mitigate potential selection biases inherent to prospective cohorts of dying patients which require a diagnosis or event to take place for the patient to be recognized as dying.[177,178] In the case of EOL care, identifying when a patient has entered the EOL phase of their cancer journey is especially challenging clinically and cannot be achieved with health services databases.[178] Physicians are generally unable to prognosticate when a malignancy will stop responding to therapy and when a patient has entered the last month or weeks of life, when HI-EOL care would be considered inappropriate; there are also rare cases of patients recovering when they were expected to die.[81,177,180-182] Population-based studies using health services resources allow for consistency in the way data is collected and avoid "sampling variability" by examining the healthcare utilization of all patients.[41] Some authors have heavily criticized the extrapolation of findings from decedent cohorts to be used in the care of patients who are actively dying.[81,183] Some have argued that cohort studies require there to be a clear temporal relationship between eligibility and the events of interest, with eligibility preceding the events.[183] In keeping with this logic, Bach et al. maintain that decedent cohort studies should instead be called case series since the events of interest (EOL care) occurred prior to the patient becoming eligible for inclusion (death).[183] By including all decedent patients with certain diagnoses instead of restricting to patients who would be "expected to die," Bach et al. argue that biased estimates may result since the clinical characteristics of these patients may be inherently

different; patients with early stage cancers who died of treatment-related effects likely would have experienced different EOL care than patients initially diagnosed with metastatic disease.[183] Our study design had somewhat accounted for these biases in excluding patients who died within the first month and after five years from the initial diagnosis, though the inability to exclude patients who died of treatment-related causes could not fully counter the potential for biased results. Despite these potential methodological limitations, decedent population-based studies have provided an overarching assessment of the burden of HI-EOL care measures and have highlighted disparities in patterns of care. These assessments may play an important role in cost analyses and resource allocation at the provincial and national levels.

Logistic regression models were used to determine the association between predetermined clinical, demographic, and health systems factors and the odds of experiencing the outcome of HI-EOL care, which was common. As a result of this outcome being common (over 10%), the estimated odds ratio likely overestimated the risk ratio of experiencing this outcome.[184-187] Another limitation of this analytic strategy was that the non-collapsible property of the odds ratio limited the ability to assess for confounding.[184-187] Despite this limitation of being unable to ascertain risk, logistic regression was used as the primary statistical method for comparisons with the majority of EOL population-based decedent cohort studies. Future analyses could use log-binomial regression or Poisson regression with robust variance estimation to estimate risk ratios.[188,189]

6. CONCLUSION

In this population-based decedent cohort study of AYA with cancer, we identified important trends and predictors of HI-EOL care, MI-EOL care, and in-hospital deaths. AYA experienced disproportionately elevated rates of all outcomes compared to Ontario cohorts of children and older adults. There was evidence that the prevalence of the MI-EOL care measures, death in ICU and mechanical ventilation in the last two weeks of life, may be worsening over time. This is the first study to describe unique disparities for the MI-EOL care outcomes for AYA treated in pediatric centres near the EOL, namely that patients who were cared for in pediatric settings, who died of hematological malignancies, and who lived in rural settings experienced the highest odds of these outcomes.

7. FUTURE DIRECTIONS

This is the first study to describe the association between a pediatric LOC near death and the potential for higher odds of the MI-EOL care among decedent AYA with cancer. We have additionally identified important demographic and disease characteristics of patients associated with the highest odds of HI- and MI-EOL care, namely patients with hematological malignancies, patients living in rural settings, and patients who died in later years of the study period.

Future work should leverage health service databases to understand why AYA receive HI-EOL care; possible etiologies include poor symptom management, lack of planning for the EOL, or

lack of palliative care services. As a first step, future work should aim to better characterize patient needs at the EOL. Knowledge of patient needs may allow for the modification of administrative indicators of quality EOL care.[138] Furthermore, understanding the clinical needs of patients will inform targeted interventions to optimize care. Authors have used claims-based indicators of "high palliative needs" such as the use of opioids, transfusions, and determining the number of days with physician visits.[138] Others have established claims-based algorithms for determining disability status at the EOL.[190] Understanding which clinical factors contribute to the receipt of HI- and MI-EOL care would help to define interventions aimed at improving the quality of EOL care.[138]

Additional understanding of resource distribution and healthcare provider skillset will help target interventions to support providers who care for AYA with cancer at the EOL. Previous work has demonstrated that the majority of AYA admissions at the EOL have occurred at nonspecialty centres.[78] Access to specialist palliative care teams with AYA experience is not uniform across the province. Future work should shed light on the impact of specialist palliative care involvement on the receipt of HI- and MI-EOL care measures in this population, and work towards defining appropriate benchmarks of quality EOL care for AYA with cancer.

HI-EOL care is costly to the medical system[78] and may be mitigated to some extent by the involvement of palliative care teams.[138] In the adult literature, patients who engaged in formal EOL discussions with their providers received EOL care in the last week of life (ICU and hospital stays, hospice care, life-sustaining procedures such as mechanical ventilator use and resuscitation) that was significantly less costly than for patients who did not have such

discussions; these patients also had improved quality of death compared to patients with higher care costs.[191] Interventions targeting communication skills specific for providers who care for AYA may have important financial benefits.

One important area of future work is to describe the prevalence and predictors of HI-EOL care for AYA with CNS tumors. The poor prognosis of many CNS tumors is often known at diagnosis; the trajectory of these patients would lend well towards early integration of palliative care. However, many patients with brain tumours experience severe symptoms at the EOL such as intractable pain, impaired consciousness, seizures, nausea and vomiting, ataxia, cranial nerve paralysis, and tetraparesis which may lead to higher rates of inpatient care for symptom control.[192] The identification of LOC-based disparities in this population is important given the poor survival rates for many types of brain and spinal cord tumors and the potential for impactful interventions to improve care at the EOL.

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9. APPENDICES

Appendix I: OHIP Fee Codes Used to Derive Outcome Measures

Diagnostic Code	Associated Diagnosis
Intensive Care Unit Admission	
G400	CRIT.INTENS.CARE EXCL.VENTIL.SUPPORT-PHYS.IN CHARGE 1ST DAY
G401	CRIT.INTENS.CARE EXCL.VENTIL.SUP-PHYS.IN CHGE.2ND-10TH DAY
G402	CRIT.INTENS.CARE EXCL.VENTIL.SUP-PHYS.IN CHGE.11TH DAY ONWAR
G405	CRIT.CARE VENTIL.SUPPORT-INTENS.CARE-PHYS.IN CHGE-1ST DAY
G406	CRIT.CARE VENT.SUPPORT INTENS.CARE PHYS IN CHGE 2ND TO 10DAY
G407	CRIT CARE VENT.SUPPORT INTENS CARE PHYS IN CHGE 11TH DAY ON
G557	D/T PROC.COMPREHEN.INTENS.CRIT.VENT.SUP.PHYS.IN CHGE-1STDAY
G558	D/T PROC.COMP.INTENS.CRIT.VENT.PHYS.IN CHGE 2NDTO10THDAY
G559	COMPR.INTENS.CARE CRIT.&VENT.SUP.PHYS.IN CHGE.11TH DAY ONWAR
Intravenous Chemotherapy	
G281	D./T. PROC.INJ/INF-INTRAVEN-CHEMOTHERAPY-EA.ADD.INJ.TO G381
G339	CHEMOTHERAPY - SINGLE AGENT INTRAVENOUS CHEMOTHERAPY I.E. DOXORUBICIN, DAUNORUBICIN, EPIRUBICIN, MITOXINTRONE, CISPLATIN OR BLEOMYCIN (GREATER THAN 10 UNITS PER METRE SQUARE)
G345	D&T MULT.AGENTS CHEMOTHER.GREATER THAN 10 UNITS PER MET.SQ.
G359	D&T SING.AGENT CHEMOTHER.(GREATER THAN 2G/M2 OR 1G/M2.)
G381	D./T. PROC. INJECT/INFUS. INTRAVENOUS CHEMOTHERAPY-1ST INJ
G390	SUPV'N CHEMO. - AC. LEUKE/MYELOABLATIVE THER. PRE BM. TRANSP
H530	CHEMOTHERAPY (OUTPT)
Mechanical Ventilation	
G405	CRIT.CARE VENTIL.SUPPORT-INTENS.CARE-PHYS.IN CHGE-1ST DAY
G406	CRIT.CARE VENT.SUPPORT INTENS.CARE PHYS IN CHGE 2ND TO 10DAY

G407	CRIT CARE VENT.SUPPORT INTENS CARE PHYS IN CHGE 11TH DAY ON
G557	D/T PROC.COMPREHEN.INTENS.CRIT.VENT.SUP.PHYS.IN CHGE-1STDAY
G558	D/T PROC.COMP.INTENS.CRIT.VENT.PHYS.IN CHGE 2NDTO10THDAY
G559	COMPR.INTENS.CARE CRIT.&VENT.SUP.PHYS.IN CHGE.11TH DAY ONWAR

OHIP: Ontario Health Insurance Plan

Appendix II: DAD Procedure and Intervention Codes Used to Derive Outcome Measures

Procedure/Intervention Code	Associated Procedure/Intervention
Intravenous Chemotherapy	
1355	INJECTION OR INFUSION OF CANCER CHEMOTHE
1ZZ35HAM0	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous needle approach [intramuscular, intravenous, subcutaneous, intradermal] antineoplastic agent NOS
1ZZ35HAM1	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] alkylating agent
1ZZ35HAM2	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] antimetabolite
1ZZ35HAM3	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] plant alkaloid and other natural product
1ZZ35HAM4	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] cytotoxic antibiotic and related substance
1ZZ35HAM5	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] other antineoplastic
1ZZ35HAM9	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] Combination [multiple] antineoplastic agents

DAD: Discharge Abstract Database

Appendix III: Chemotherapy Administration Codes Used to Classify Oncology Locus of Care

Administrative Code	Associated Diagnosis, Procedure, or Intervention
OHIP Fee Code	
G281	D./T. PROC.INJ/INF-INTRAVEN-CHEMOTHERAPY-EA.ADD.INJ.TO G381
G339	CHEMOTHERAPY - SINGLE AGENT INTRAVENOUS CHEMOTHERAPY I.E. DOXORUBICIN, DAUNORUBICIN, EPIRUBICIN, MITOXINTRONE, CISPLATIN OR BLEOMYCIN (GREATER THAN 10 UNITS PER METRE SQUARE)
G345	D&T MULT.AGENTS CHEMOTHER.GREATER THAN 10 UNITS PER MET.SQ.
G359	D&T SING.AGENT CHEMOTHER.(GREATER THAN 2G/M2 OR 1G/M2.)
G381	D./T. PROC. INJECT/INFUS. INTRAVENOUS CHEMOTHERAPY-1ST INJ
G390	SUPV'N CHEMO. - AC. LEUKE/MYELOABLATIVE THER. PRE BM. TRANSP
H530	CHEMOTHERAPY (OUTPT)
DAD/NACRS Procedure Code (Before 2002)	
1355	INJECTION OR INFUSION OF CANCER CHEMOTHE
DAD/NACRS Diagnosis Code (Before 2002)	
V581	Chemotherapy
DAD/NACRS Diagnosis Code (2002 and Later)	
Z511	Chemotherapy session for neoplasm
Z512	Other chemotherapy
DAD/NACRS Intervention Code (2002 and Later)	
1ZZ35HAM0	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous needle approach [intramuscular, intravenous, subcutaneous, intradermal] antineoplastic agent NOS
1ZZ35HAM1	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] alkylating agent
1ZZ35HAM2	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] antimetabolite
1ZZ35HAM3	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] plant alkaloid and other natural product
1ZZ35HAM4	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] cytotoxic antibiotic and related substance
1ZZ35HAM5	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] other antineoplastic

1ZZ35HAM9	Pharmacotherapy, total body antineoplastic and immunomodulating agents percutaneous approach [intramuscular, intravenous, subcutaneous, intradermal] Combination [multiple] antineoplastic agents

DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; OHIP: Ontario Health Insurance Plan

Appendix IV: Radiation Administration Codes Used to Classify Oncology Locus of Care

Administrative Code	Associated Diagnosis, Procedure, or Intervention
OHIP Fee Code	
X310	TREATMENT PLANNING LEVEL 1
X311	TREATMENT PLANNING LEVEL 2
X312	TREATMENT PLANNING LEVEL 3
X313	TREATMENT PLANNING LEVEL 4
DAD/NACRS Procedure Code (Before 2002)	
0631	SUPERFICIAL RADIATION
0632	ORTHOVOLTAGE RADIATION
DAD/NACRS Diagnosis Code (2002 and Later)	
Z510	Radiotherapy session
DAD/NACRS Intervention Code (2002 and Later)	
1--27	Any code that fits the following pattern: 1--27 (1 in the first character position, 2 in the fourth character position, 7 in the fifth character position). Example: 1ZZ27 (Radiation, total body)

DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; OHIP: Ontario Health Insurance Plan

Appendix V: List of Regional Cancer Centres[122]

Regional Cancer Centre	**Host Hospital**	**Year RCC Established**	**Postal Code (as of 2014)**
Windsor Regional Cancer Centre	Windsor Regional Hospital	1935	N8W 2X3
London Regional Cancer Program	London Health Sciences Centre	1932	N6A 4L6
Grand River Regional Cancer Centre	Grand River Hospital	2003	N2G 1G3
Juravinski Cancer Centre	Hamilton Health Sciences	1960	L8V 5C2
Carlo Fidani Regional Cancer Centre	Trillium Health Partners-Credit Valley Site	2005	L5M 2N1
Odette Cancer Centre	Sunnybrook Health Sciences Centre	1981	M4N 3M5
Princess Margaret Cancer Centre	University Health Network	1932	M5G 2M9
Stronach Regional Cancer Centre at Southlake	Southlake Regional Health Centre	2010	L3Y 2P9
R.S. McLaughlin Durham Regional Cancer Centre	Lakeridge Health	2007	L1G 2B9
Cancer Centre of Southeastern Ontario	Kingston General Hospital	1932	K7L 5P9
The Ottawa Hospital Cancer Centre	The Ottawa Hospital	1943	K1H 8L6
Simcoe Muskoka Regional Cancer Centre	Royal Victoria Hospital	2010	L4M 6M2
Northeast Cancer Centre	Health Sciences North/Horizon Santé-Nord	1990	P3E 5J1
Regional Cancer Care Northwest	Thunder Bay Regional Health Sciences Centre	1947	P7B 6V4
Algoma District Cancer Program	Sault Area Hospital	2011	
Walker Family Cancer Centre	Niagara Health System	2013	

Appendix VI: List of Tertiary Pediatric Cancer Centres[130]

Pediatric Cancer Centre	**Postal Code**
Children's Hospital (London Health Sciences Centre)	N6C 2V5
CHEO	K1H 8L1
Kingston Health Sciences Centre (Kingston General Hospital Site)	K7L 2V7
McMaster Children's Hospital	L8N 3Z5
The Hospital for Sick Children	M5G 1X8

Appendix VII: Results from Univariate and Multivariate Modeling of the Primary Composite Measure of HI-EOL Care Among Study Cohort Patients (All Predictors Included) (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.2 (0.8, 1.9)	0.31	0.9 (0.5, 1.7)	0.79
RCC (ref)	-	-	-	-
Community	0.9 (0.6, 1.5)	0.77	1.2 (0.7, 2.1)	0.58
LOC near death				
Pediatric	1.5 (0.9, 2.4)	0.10	1.3 (0.6, 2.6)	0.49
Adult (ref)	-	-	-	-
Cancer type				
Hematological	2.1 (1.4, 3.0)	<0.01	2.3 (1.5, 3.5)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.5 (0.4, 0.8)	<0.01	0.5 (0.3, 0.8)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.7 (0.5, 1.0)	0.09	0.7 (0.5, 1.0)	0.07
Age at death (years)	0.9 (0.8, 1.0)	<0.01	0.9 (0.8, 1.0)	0.21
Income quintile at diagnosis				
Q1 (lowest)	0.7 (0.4, 1.3)	0.25	0.7 (0.4, 1.3)	0.27
Q2	0.8 (0.4, 1.5)	0.50	0.9 (0.5, 1.7)	0.77
Q3	0.8 (0.5, 1.5)	0.52	0.9 (0.5, 1.7)	0.68
Q4	0.9 (0.5, 1.5)	0.59	1.0 (0.5, 1.7)	0.88
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.5 (0.9, 2.7)	0.14	1.4 (0.7, 2.7)	0.30
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	0.7 (0.5, 1.0)	0.04	0.8 (0.5, 1.1)	0.16
Distance from treating centre				
Short (ref)	-	-	-	-
Long	1.5 (1.0, 2.3)	0.06	1.4 (0.9, 2.2)	0.19

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix VIII: Results from Univariate and Multivariate Modeling of the Primary Composite Measure of HI-EOL Care Among Study Cohort Patients Using Alternative Locus of Care at Death Variable (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.2 (0.8, 1.9)	0.31	1.2 (0.6, 2.3)	0.64
RCC (ref)	-	-	-	-
Community	0.9 (0.6, 1.5)	0.77	1.2 (0.7, 2.1)	0.56
LOC near death (alternative definition)				
Pediatric	1.2 (0.8, 1.9)	0.44	0.8 (0.4, 1.7)	0.53
Adult (ref)	-	-	-	-
Cancer type				
Hematological	2.1 (1.4, 3.0)	<0.01	2.4 (1.6, 3.5)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.5 (0.4, 0.8)	<0.01	0.5 (0.3, 0.8)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.7 (0.5, 1.0)	0.09	0.7 (0.5, 1.0)	0.08
Age at death (years)	0.9 (0.8, 1.0)	<0.01	0.9 (0.8, 1.0)	0.11
Income quintile at diagnosis				
Q1 (lowest)	0.7 (0.4, 1.3)	0.25	-	-
Q2	0.8 (0.4, 1.5)	0.50	-	-
Q3	0.8 (0.5, 1.5)	0.52	-	-
Q4	0.9 (0.5, 1.5)	0.59	-	-
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.5 (0.9, 2.7)	0.14	1.4 (0.7, 2.6)	0.31
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	0.7 (0.5, 1.0)	0.04	0.8 (0.5, 1.1)	0.18
Distance from treating centre				
Short (ref)	-	-	-	-
Long	1.5 (1.0, 2.3)	0.06	1.4 (0.8, 2.2)	0.21

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix IX. Results from Univariate and Multivariate Modeling of the Death in ICU Outcome Among Study Cohort Patients With All Variables Included (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.5 (1.0, 2.4)	0.08	0.7 (0.3, 1.7)	0.45
RCC (ref)	-	-	-	-
Community	1.1 (0.6, 2.0)	0.80	1.7 (0.8, 3.4)	0.14
LOC near death				
Pediatric	2.4 (1.4, 3.9)	<0.01	3.5 (1.4, 8.7)	<0.01
Adult (ref)	-	-	-	-
Cancer type				
Hematological	3.4 (2.1, 5.5)	<0.01	4.9 (2.8, 8.5)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.5 (0.3, 0.7)	<0.01	0.4 (0.2, 0.6)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.8 (0.5, 1.2)	0.29	0.7 (0.4, 1.2)	0.22
Age at death (years)	0.9 (0.8, 1.0)	0.02	1.0 (0.9, 1.2)	0.84
Income quintile at diagnosis				
Q1 (lowest)	0.7 (0.3, 1.4)	0.32	0.7 (0.3, 1.6)	0.41
Q2	1.1 (0.6, 2.1)	0.83	1.3 (0.6, 2.7)	0.51
Q3	0.7 (0.4, 1.4)	0.34	0.6 (0.3, 1.4)	0.25
Q4	0.7 (0.4, 1.3)	0.25	0.8 (0.4, 1.6)	0.49
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.9 (1.1, 3.5)	0.02	2.3 (1.1, 4.7)	0.02
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	1.3 (0.8, 1.9)	0.29	1.7 (1.1, 2.8)	0.03
Distance from treating centre				
Short (ref)	-	-	-	-
Long	1.2 (0.7, 1.9)	0.53	0.9 (0.5, 1.7)	0.80

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix X. Results from Univariate and Multivariate Modeling of the Death in ICU Outcome Among Study Cohort Patients Using the Alternative Locus of Care at Death Variable (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.5 (1.0, 2.4)	0.08	0.8 (0.3, 1.9)	0.61
RCC (ref)	-	-	-	-
Community	1.1 (0.6, 2.0)	0.80	1.8 (0.9, 3.6)	0.10
LOC near death (alternative definition)				
Pediatric	2.0 (1.3, 3.3)	<0.01	2.5 (1.0, 6.3)	0.04
Adult (ref)	-	-	-	-
Cancer type				
Hematological	3.4 (2.1, 5.5)	<0.01	4.9 (2.8, 8.5)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.5 (0.3, 0.7)	<0.01	0.4 (0.2, 0.6)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.8 (0.5, 1.2)	0.29	-	-
Age at death (years)	0.9 (0.8, 1.0)	0.02	1.0 (0.9, 1.1)	0.86
Income quintile at diagnosis				
Q1 (lowest)	0.7 (0.3, 1.4)	0.32	-	-
Q2	1.1 (0.6, 2.1)	0.83	-	-
Q3	0.7 (0.4, 1.4)	0.34	-	-
Q4	0.7 (0.4, 1.3)	0.25	-	-
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.9 (1.1, 3.5)	0.02	2.2 (1.1, 4.1)	0.02
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	1.3 (0.8, 1.9)	0.29	1.7 (1.0, 2.7)	0.03
Distance from treating centre				
Short (ref)	-	-	-	-
Long	1.2 (0.7, 1.9)	0.53	-	-

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference
An interaction between the alternative LOC near death and time period of death predictors was explored (interaction term P = 0.06). Among patients who died in the early period of the study, death in a pediatric setting compared to an adult setting was associated with an increased odds of

death in an ICU (OR 2.8, 95% CI 1.4-5.5); the estimate was not as pronounced among those who died in the later period of study (death in pediatric versus adult setting OR 1.5, 95% CI 0.7-2.9).

Appendix XI. Results from Univariate and Multivariate Modeling of the Mechanical Ventilation Outcome Among Study Cohort Patients With All Variables Included (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.1 (0.7, 1.9)	0.60	0.7 (0.3, 1.7)	0.45
RCC (ref)	-	-	-	-
Community	1.1 (0.6, 2.1)	0.67	1.9 (0.9, 3.9)	0.07
LOC near death				
Pediatric	1.5 (0.9, 2.5)	0.15	1.9 (0.8, 4.5)	0.17
Adult (ref)	-	-	-	-
Cancer type				
Hematological	3.8 (2.2, 6.5)	<0.01	5.5 (3.1, 9.9)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.6 (0.4, 0.9)	0.02	0.5 (0.3, 0.8)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.9 (0.5, 1.4)	0.55	0.8 (0.5, 1.4)	0.49
Age at death (years)	0.9 (0.9, 1.0)	0.16	0.9 (0.8, 1.1)	0.47
Income quintile at diagnosis				
Q1 (lowest)	0.6 (0.3, 1.3)	0.22	0.7 (0.3, 1.5)	0.35
Q2	1.0 (0.5, 2.0)	0.96	1.2 (0.6, 2.4)	0.70
Q3	0.7 (0.4, 1.4)	0.33	0.7 (0.3, 1.5)	0.34
Q4	0.5 (0.3, 1.0)	0.06	0.6 (0.3, 1.2)	0.17
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.8 (1.0, 3.2)	0.06	2.5 (1.2, 5.1)	0.01
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	1.3 (0.8, 2.1)	0.22	1.9 (1.2, 3.1)	0.01
Distance from treating centre				
Short (ref)	-	-	-	-
Long	0.8 (0.5, 1.4)	0.51	0.6 (0.3, 1.1)	0.12

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix XII. Results from Univariate and Multivariate Modeling of the Mechanical Ventilation Outcome Among Study Cohort Patients Using the Alternative Using Alternative Locus of Care at Death Variable (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	1.1 (0.7, 1.9)	0.60	0.8 (0.3, 1.8)	0.56
RCC (ref)	-	-	-	-
Community	1.1 (0.6, 2.1)	0.67	1.9 (0.9, 3.9)	0.07
LOC near death (alternative definition)				
Pediatric	1.3 (0.8, 2.2)	0.30	1.6 (0.6, 4.0)	0.31
Adult (ref)	-	-	-	-
Cancer type				
Hematological	3.8 (2.2, 6.5)	<0.01	5.4 (3.0, 9.7)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.6 (0.4, 0.9)	0.02	0.5 (0.3, 0.8)	<0.01
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.9 (0.5, 1.4)	0.55	-	-
Age at death (years)	0.9 (0.9, 1.0)	0.16	0.9 (0.8, 1.1)	0.45
Income quintile at diagnosis				
Q1 (lowest)	0.6 (0.3, 1.3)	0.22	0.7 (0.3, 1.5)	0.36
Q2	1.0 (0.5, 2.0)	0.96	1.2 (0.6, 2.4)	0.65
Q3	0.7 (0.4, 1.4)	0.33	0.7 (0.3, 1.5)	0.35
Q4	0.5 (0.3, 1.0)	0.06	0.6 (0.3, 1.2)	0.16
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.8 (1.0, 3.2)	0.06	2.0 (1.0, 3.8)	0.04
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	1.3 (0.8, 2.1)	0.22	1.9 (1.1, 3.0)	0.01
Distance from treating centre				
Short (ref)	-	-	-	-
Long	0.8 (0.5, 1.4)	0.51	-	-

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix XIII. Results from Univariate and Multivariate Modeling of the Death in Hospital Outcome Among Study Cohort Patients With All Variables Included (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	0.8 (0.5, 1.2)	0.24	0.6 (0.3, 1.1)	0.09
RCC (ref)	-	-	-	-
Community	0.7 (0.4, 1.1)	0.14	1.1 (0.6, 1.9)	0.84
LOC near death				
Pediatric	1.1 (0.7, 1.9)	0.61	1.5 (0.7, 3.1)	0.28
Adult (ref)	-	-	-	-
Cancer type				
Hematological	3.1 (2.1, 4.7)	<0.01	3.5 (2.2, 5.4)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.7 (0.5, 1.0)	0.08	0.6 (0.4, 1.0)	0.03
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.8 (0.5, 1.2)	0.23	0.8 (0.5, 1.2)	0.20
Age at death (years)	1.0 (0.9, 1.1)	0.54	1.0 (0.8, 1.1)	0.44
Income quintile at diagnosis				
Q1 (lowest)	1.2 (0.6, 2.4)	0.56	1.4 (0.7, 2.7)	0.41
Q2	1.0 (0.5, 1.9)	0.96	1.2 (0.6, 2.3)	0.67
Q3	0.7 (0.4, 1.3)	0.25	0.8 (0.4, 1.5)	0.42
Q4	0.8 (0.4, 1.4)	0.39	0.9 (0.5, 1.8)	0.85
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.5 (0.8, 2.7)	0.23	2.0 (1.0, 3.9)	0.05
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	0.7 (0.5, 1.0)	0.07	0.9 (0.6, 1.3)	0.49
Distance from treating centre				
Short (ref)	-	-	-	-
Long	0.7 (0.5, 1.1)	0.14	0.6 (0.3, 0.9)	0.03

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference

Appendix XIV. Results from Univariate and Multivariate Modeling of the Death in Hospital Outcome Among Study Cohort Patients Using the Alternative Locus of Care at Death Variable (N=480)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
LOC for cancer therapy				
Pediatric	0.8 (0.5, 1.2)	0.24	0.6 (0.3, 1.2)	0.17
RCC (ref)	-	-	-	-
Community	0.7 (0.4, 1.1)	0.14	1.0 (0.6, 1.8)	0.95
LOC near death (alternative definition)	1.0 (0.6, 1.6)	0.90	1.1 (0.5, 2.4)	0.72
Pediatric	-	-	-	-
Adult (ref)				
Cancer type				
Hematological	3.1 (2.1, 4.7)	<0.01	3.4 (2.2, 5.3)	<0.01
Solid Tumor (ref)	-	-	-	-
Relapsed disease				
Yes	0.7 (0.5, 1.0)	0.08	0.6 (0.4, 1.0)	0.04
No (ref)	-	-	-	-
Sex				
Male (ref)	-	-	-	-
Female	0.8 (0.5, 1.2)	0.23	0.8 (0.5, 1.2)	0.20
Age at death (years)	1.0 (0.9, 1.1)	0.54	0.9 (0.8, 1.1)	0.28
Income quintile at diagnosis				
Q1 (lowest)	1.2 (0.6, 2.4)	0.56	-	-
Q2	1.0 (0.5, 1.9)	0.96	-	-
Q3	0.7 (0.4, 1.3)	0.25	-	-
Q4	0.8 (0.4, 1.4)	0.39	-	-
Q5 (highest; ref)	-	-	-	-
Rurality at diagnosis				
Urban (ref)	-	-	-	-
Rural	1.5 (0.8, 2.7)	0.23	2.0 (1.0, 3.9)	0.05
Time period of death (categorized)				
Early (1992-2004; ref)	-	-	-	-
Late (2005-2016)	0.7 (0.5, 1.0)	0.07	0.9 (0.6, 1.3)	0.44
Distance from treating centre				
Short (ref)	-	-	-	-
Long	0.7 (0.5, 1.1)	0.14	0.6 (0.3, 0.9)	0.02

-: not applicable; CI: confidence interval; LOC: locus of care; OR: odds ratio; ref: reference