Boston University

OpenBU **http://open.bu.edu**

Boston University Theses & Dissertations Boston University Theses & Dissertations

2020

Factors associated with intensity of end-of-life care for patients with acute myeloid leukemia

https://hdl.handle.net/2144/41738

"Downloaded from OpenBU. Boston University's institutional repository."

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

FACTORS ASSOCIATED WITH INTENSITY OF END-OF-LIFE CARE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA

by

DAGNY VAUGHN

B.A., University of Chicago, 2018

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2020

© 2020 by
DAGNY VAUGHN
All rights reserved

Approved by

First Reader ____

Mina Moussavi, Ph.D.
Assistant Professor of Physiology & Biophysics

Second Reader ____

Areej El-Jawahri, M.D.
Assistant Professor of Medicine
Harvard Medical School

ACKNOWLEDGMENTS

Thank you to Areej El-Jawahri for being the most brilliant, supportive mentor and for allowing me to complete this thesis. Additional thanks to Jennifer Temel, Joseph Greer, Lara Traeger, Vicki Jackson, and all members of the Cancer Outcomes Research Program for giving me a year of invaluable growth and experience. You have all taught me how to be a better researcher, clinician, team member, and friend.

A special thanks to Alyssa, Annemarie, Carlisle, Bailey, and Matt for all the times I made you turn off your music or stop talking so I could work on this thesis. You all are the best heme team I could hope for!

FACTORS ASSOCIATED WITH INTENSITY OF END-OF-LIFE CARE FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA

DAGNY VAUGHN

ABSTRACT

INTRODUCTION: Older patients with AML ($\geq$60 years) often receive intensive EOL care including hospitalizations and chemotherapy close to death. Intensive EOL care has been shown to increase emotional and financial burdens for patients and families, while often not aligning with patients' preferences. However, factors associated with the intensity of EOL care in this population are unknown.

OBJECTIVES: There is a need to better understand the factors associated with intense EOL care, in hopes of providing more informed, high-quality EOL care in line with patient preferences and decreasing burdens associated with unnecessary healthcare. We aim to describe the associations between the intensity of EOL care, patient demographics, and baseline psychological distress in older patients with AML.

METHODS: We conducted a secondary analysis of two supportive care studies including 168 deceased older patients with AML. We assessed patients' demographics, quality of life (QOL) [Functional Assessment Cancer Therapy-Leukemia], and anxiety and depression symptoms [Hospital Anxiety and Depression Scale (HADS); Patient Health Questionnaire (PHQ-9)] at the time of diagnosis. We used multivariate logistic regression models to examine the association among demographic factors, patient-

reported outcomes, and the following EOL care outcomes abstracted from the electronic health record: 1) hospitalizations in the last 7 days of life; 2) receipt of chemotherapy in the last 30 days of life; and 3) hospice utilization.

RESULTS: The median age of the cohort was 69 (range 20-100), and the majority were males (63.7% 107/168). Overall, 66.7% (110/165) of patients were hospitalized in the last 7 days of life, 51.8% (71/137) received chemotherapy in the last 30 days of life, and 40.7% (70/168) utilized hospice services. In multivariate models, higher education (OR = 1.54, SE=0.24, P=0.006), and elevated depression symptoms [PHQ-9: OR=1.09, SE=0.04, P=0.028] at the time of diagnosis were associated with higher odds of being hospitalized in the last 7 days of life. In contrast, higher QOL at diagnosis [OR=0.98, SE=0.01, P=0.009] was associated with lower odds of being hospitalized in the last 7 days of life. Depression symptoms at the time of diagnosis as measured by the HADS was the only factor associated with the receipt of chemotherapy in the last 30 days of life [HADS-Depression: OR=1.10, SE=0.05, P=0.042]. Patients factors were not associated with hospice utilization.

CONCLUSIONS: Older patients with AML who are more educated and report elevated depression symptoms and lower QOL at the time of diagnosis were more likely to receive intensive EOL care. These findings identify a population at the time of diagnosis of AML who are at higher risk for hospitalizations and chemotherapy use at the EOL and who may benefit from targeted supportive care interventions.

TABLE OF CONTENTS

ACKNOWLEDGMENTS iv

ABSTRACT v

TABLE OF CONTENTS vii

LIST OF TABLES ix

LIST OF FIGURES xi

LIST OF ABBREVIATIONS xii

INTRODUCTION 1

  Defining Intense EOL Care 1

  Healthcare Utilization and EOL Care Among Cancer Patients 5

  Healthcare Utilization and EOL Care in Hematologic Malignancies 6

  Acute Myeloid Leukemia 9

  Healthcare Utilization and EOL Care in AML 16

  Factors Associated with Intensity of EOL Care 17

  Specific Aims of the Present Study 18

METHODS 20

  Study Procedures 20

  Measures of Patient Report Outcomes 20

  Retrospective Medical Chart Review 22

  Statistical Analysis 23

RESULTS 25

Patient Characteristics.. 25

Healthcare Utilization in Patients with AML 26

Associations with Intense EOL Care 28

DISCUSSION 35

Patients with AML are Likely to Experience Intense EOL Care................................. 36

Education Levels and EOL Care.. 37

QOL and EOL Care 38

Psychological Distress and EOL Care 39

The Importance of Palliative Care and Hospice Care Utilization................................ 39

Limitations 41

CONCLUSION.. 43

APPENDIX I: Demographics Questionnaire.. 45

APPENDIX II: FACT- Leu Questionnaire.. 46

APPENDIX III: HADS Questionnaire 49

APPENDIX IV: PHQ-9 Questionnaire.. 50

REFERENCES 51

CURRICULUM VITAE 59

LIST OF TABLES

Table	Title	Page
1	Quality of EOL Care Indicators, Solid Tumors vs. Hematologic Malignancies.	8
2	Research Studies Used to Select Patients.	24
3	Patient Characteristics.	25
4	Healthcare Utilization in Patients with AML.	27
5	Univariate Analysis of Factors Associated with Death in the Hospital.	29
6	Multivariate Analysis of Factors Associated with Death in the Hospital.	30
7	Univariate Analysis of Factors Associated with Hospice Use.	30
8	Multivariate Analysis of Factors Associated with Hospice Use.	30
9	Univariate Analysis of Factors Associated with Hospice LOS	31
10	Multivariate Analysis of Factors Associated with Hospice LOS	31

11	Univariate Analysis of Factors Associated with Total Hospitalizations	31
12	Multivariate Analysis of Factors Associated with Total Hospitalizations	32
13	Univariate Analysis of Factors Associated with ICU Stays	32
14	Multivariate Analysis of Factors Associated with ICU Stays	32
15	Univariate Analysis of Factors Associated with Chemotherapy Use in the Last 30 Days of Life	32
16	Multivariate Analysis of Factors Associated with Chemotherapy Use in the Last 30 Days of Life	33
17	Univariate Analysis of Factors Associated with Hospitalization in the Last 7 Days of Life	33
18	Multivariate Analysis of Factors Associated with Hospitalization in the Last 7 Days of Life	34

LIST OF FIGURES

Figure	Title	Page
1	Hematopoiesis	10
2	Peripheral Blood Smear of a Patient with AML	12
3	Longitudinal QOL During Chemotherapy for AML	14
4	Longitudinal Anxiety and Depression Symptoms During Chemotherapy for AML	15

LIST OF ABBREVIATIONS

AML .... Acute Myeloid Leukemia

DFCI .... Dana Farber Cancer Institute

ED .... Emergency Department

EMR .... Electronic Medical Record

EOL .... End-of-Life

FACT-Leu .... Functional Assessment of Cancer Therapy- Leukemia

GI .... Gastrointestinal

HADS .... Hospital Anxiety and Depression Scale

HSC .... Hematopoietic Stem Cell

HSCT .... Hematopoietic Stem Cell Transplant

ICU .... Intensive Care Unit

LOS .... Length of Stay

MGH .... Massachusetts General Hospital

OR .... Odds Ratio

PHQ-9 .... Patient Health Questionnaire-9

QOL .... Quality-of-Life

SE .... Standard Error

INTRODUCTION

Until recently, the majority of patients in the US died in the hospital, despite most expressing a preference to die at home.[1-3] Even though home has now become the most common place of death in the US, nearly 30% of patient deaths still occur in hospital settings.[2] In addition to spending the last moments of life in the hospital, many patients experience frequent interactions with healthcare settings for much of their time before death.[4] This high amount of healthcare utilization at the end-of-life (EOL) is particularly common in patients suffering from cancer, with over half of these patients being admitted to the hospital in the last month of life.[5, 6] For cancers such as Acute Myeloid Leukemia (AML), a life-threatening hematologic malignancy, high rates of intense care and death in hospital settings are even more frequent.[7, 8] Given the established discrepancy between patient preferences and outcomes at the EOL, there is a need to better understand the factors that are associated with intense EOL care, in hopes of providing more informed, high-quality EOL care in line with patient preferences and decreasing burdens associated with unnecessary healthcare.

Defining Intense EOL Care

The EOL for an ill individual can be a time marked by emotional burden,[9] high healthcare costs and utilization,[4] and difficult decision-making.[10, 11] A major factor that impacts these experiences is the quality of care received and the goals of that care. Generally, care at the EOL is described as "aggressive" or not, meaning "care that

focuses mostly or exclusively on disease-modifying treatments at the expense of good symptom management and/or advance care planning".[12] Because determining the best course of care for a patient is highly individual and influenced by many factors, the "aggressiveness" of care will be discussed as "intensity" of care in this study, as not to imply that such care is negative in every situation. However, intense EOL care has been broadly shown to negatively impact patients' quality-of-life (QOL),[13] perceptions of quality-of-care,[14] and families' experiences,[13-15] while not always providing better health outcomes.[15-16] Additionally, more intense EOL care is associated with higher financial burdens, especially for older patients with multiple comorbidities.[4]

Six "poor quality" EOL care indicators were identified in a pioneering study utilizing literature review, focus groups with cancer patients and family members, and an expert panel.[17] These indicators have since been widely used to study the type of EOL care delivered across countries and disease types.[5, 15, 18] Similar indicators have also been used to describe healthcare utilization in non-cancer patient populations.[4] These indicators were defined as measures of a healthcare system's ability to provide high quality EOL care, but not as measures to analyze the care of an individual patient.[17] These indicators include: the use of chemotherapy in the last month of life, a high number of emergency department (ED) visits, hospital admissions, or intensive care unit (ICU) stays at the EOL, lack of hospice use, and death in the hospital.[17]. Importantly, these indicators have now been accepted by professional societies including The American Society of Clinical Oncology (ASCO) and the American Academy of Hospice and Palliative Medicine (AAHPM) as well as the Institute of Medicine as indicators of poor-

quality of care at the EOL.[19] A summary of the rationale behind each group of indicators, as explained by Earle et al., is included below:

- *Chemotherapy Usage at the EOL*

  In the defining paper by Earle et al., the continued, late usage of anticancer therapies was described as potentially leading to greater toxicity than clinical benefit. Continued conversations regarding new anticancer therapies despite successive therapeutic failures was noted to be potentially distracting from conversations about prognosis with providers. In focus groups conducted by this study team, patients and families both felt that they should be given the option to try treatments regardless of effectiveness, however they also endorsed the concept of discontinuing therapy at an appropriate time before death. Failure to do so was said to give the family an inaccurate idea of how advanced the disease had become, leading to greater shock at the time of death. Typically, chemotherapy usage at the EOL is measured as new therapies or doses occurring within the last 30 days of life.[7, 15, 17,]

- *Emergency Department (ED) Visits, Hospital Admissions, Intensive Care Unit (ICU) stays at the EOL*

  High numbers of ED visits, unplanned hospital admissions, and stays in the ICU are thought to be indicative of intense care, a lack of symptom management, and insufficient use of home services or hospice care. Additionally, it is thought that many of these visits and admissions could be prevented with high-quality EOL care including home-care support, education, and symptom care, as provided by

specialty palliative care and hospice services. This would allow the patient to spend more time at home through the EOL, which is known to be preferred amongst most patients. Typically, rates of admissions, ED visits, and ICU stays are measured in the last 30 days of life and/or the last 7 days of life.[7, 15, 17]

- *Lack of Hospice Use and Death in the Hospital*

  Given the well-established fact that most patients prefer to die at home, it is thought that a higher proportion of patients dying outside of the hospital setting is a sign of high quality EOL care.[1, 17, 20] Along that line, hospice care at the EOL specifically is thought of as a sign of high quality care because of its focus on symptom relief and QOL rather than active intervention.[21, 22] Hospice care is associated with less aggressive and costly care at the EOL,[23-26] and has been shown to be related to better patient QOL and lower caregiver depression and complicated bereavement.[26-30] However, studies have shown that patients only derive these benefits if they receive hospice care at a minimum of 7 days before death,[26, 29, 30] so referral very close to death is not considered beneficial.[17, 26]

According to these indicators, the quality of EOL care is defined overall by how frequently a patient interacts with acute healthcare settings and how much focus is given to symptom-reduction, QOL improvement, and patient preferences. Palliative and hospice care is known to specialize in symptom management and QOL improvement, and it can also be provided in the home setting. [21, 22] Thus, its usage is commonly associated with high quality EOL care.[31] On the other hand, large amounts of time spent in hospital

settings or in pursuit of treatment with curative intent at the EOL is indicative of poor quality EOL care, as defined by Earle et al. Thus, intensity of care at the EOL, defined by the above indicators, is thought of as inversely related to quality of care at the EOL.

Healthcare Utilization and EOL Care Among Cancer Patients

Patients with cancer are known to have high healthcare utilization throughout the course of disease, with many experiencing intense EOL care.[5, 18, 32] In a study of patients with solid tumors, thirty percent had at least one indicator of intense EOL care, with more than half of that group having multiple indicators.[5] In another study of cancer patients, 22.4% experienced at least one indicator of intense EOL care.[18] Additionally, rates of intense EOL care have increased in recent decades, specifically in frequencies of ED visits, hospitalizations, ICU stays, and late chemotherapy usage.[5, 18] Concurrently, the rates of cancer patients admitted to hospice has also increased, which is thought to be inversely correlated with indicators of intense care.[5] However, high numbers of patients were found to be admitted to hospice closer to death, which is not considered favorable and rather a result of delayed referral.[17]

High healthcare utilization is expected for the cancer patient population due to the high symptom burden and complications many patients face. Patients are often hospitalized for symptoms such as pain,[6, 33] fever,[34] dyspnea,[33] neurological symptoms,[33] and fatigue,[6, 31] with specific symptoms varying largely by cancer type. In a study of patients with gastrointestinal (GI) cancer, 53% of their hospitalizations were due to cancer symptoms and 28% were due to complications of treatment.[34] However, 19% of

these hospitalizations were determined to be unnecessary,[34] pointing to the possibility of reducing the amount of healthcare utilization the cancer patient population experiences.

Healthcare Utilization and EOL Care in Hematologic Malignancies

Hematologic malignancies, including leukemias, myelomas, and lymphomas, are known to be associated with especially high rates of healthcare utilization and intense EOL care, compared with other cancer types.[7, 15, 18, 31, 35-37] In one study, patients with hematologic malignancies had nearly double the odds of experiencing intense EOL care as other cancer types studied.[18] Results of another study (presented in Table 1) show that 54% of patients with hematologic malignancies experienced ED visits in the last month of life, 81% experienced hospital admissions, 39% were admitted to the ICU, and 47% died in the hospital.[7] Furthermore, patients with hematologic malignancies are less likely to be admitted to a palliative care unit or receive palliative care consultation in the last month of life, compared to other cancer types.[7, 31, 37, 38]

Many factors contribute to high health care utilization and intense EOL care for patients with hematologic malignancies including 1) the curable potential of these illnesses; 2) prognostic uncertainty regarding the illness trajectory; and 3) hematologists-oncologists' desire to give more aggressive treatment for patients with hematologic malignancies.[31] These qualities especially impact the low rates of timely referral to hospice care and/or involvement of specialty palliative care services.[31] The curable potential of these malignancies, along with the difficulty defining a transition point

between curative and palliative phases of treatment, lead to many patients receiving supportive care interventions very close to death or not at all.[31]

These malignancies are also associated with very high physical symptom burden and need for intervention to manage the disease, both of which contribute to levels of healthcare utilization.[31, 35] In addition to symptoms such as fatigue, pain, dyspnea, and neuropathy experienced across many cancer types, patients with hematologic malignancies also commonly experience cytopenias, infections, and coagulopathies, which lead to frequent hospitalizations and acute care visits for management.[7] Notably, higher rates of clinically significant fatigue and drowsiness are reported among patients with hematological malignancies, with fatigue affecting 80-90% of patients with acute leukemia, myelodysplastic syndrome, and multiple myeloma.[31, 39] Higher psychological distress scores are also common for patients with hematologic malignancies, which compounds the number of symptoms this population faces.[35] A recent analysis even suggests that patients with hematological malignancies are more distressed than patients of any other cancer type.[31, 40]

Patients with hematologic malignancies are more likely to experience every category of intense EOL care, including the use of chemotherapy near the EOL, frequent hospital admissions, a lack of palliative care or hospice care utilization, and a higher risk of dying in an acute care setting.[7, 15, 31, 36. 37, 41] In line with what is known about the effects of intense EOL care on patient QOL, patients with hematologic malignancies who die in the ICU or hospital have greater distress and worse QOL, along with higher risk of prolonged grief for caregivers.[7, 42]

The present study will specifically focus on AML, a hematologic malignancy. The pathology, diagnosis, and treatment of AML, patients' experiences, and healthcare utilization patterns will be discussed in detail below.

Table 1: Quality of EOL Care Indicators, rates in solid tumors vs. hematologic malignancies. Taken from Hui et al., "Quality of End-of-Life Care in Patients with Hematologic Malignancies", 2014.[7]

Patient Characteristics	Solid Tumors N=703 (%)	Hematologic Malignancies N=113 (%)	P-value
Within last 30 days of life:			
Any ED visit………………....	300 (43)	61 (54)	0.03
2 or more ED visits…………..	83 (12)	17 (15)	0.35
Any hospital admission……...	333 (47)	91 (81)	< 0.001
2 or more hospital admissions.	73 (10)	26 (23)	<0.001
Hospital death………………..	110 (16)	53 (47)	< 0.001
ICU admission……………….	55 (8)	44 (39)	<0.001
ICU death…………………….	30 (4)	37 (33)	<0.001
Chemotherapy use…………...	98 (14)	49 (43)	<0.001
Palliative care unit admission..	116 (17)	9 (8)	0.020
Composite score for aggressive EOL care:			
0……………………………....	457 (65)	25 (22)	<0.001
1……………………………....	119 (17)	26 (23)	
2……………………………....	58 (8)	14 (12)	
3……………………………....	44 (6)	21 (19)	
Median Score (IQR)...................	0 (0-1)	2 (1-3)	<0.001
Any palliative care consultation...	329 (47)	37 (33)	0.006

Acute Myeloid Leukemia

Prevalence and Prognosis

There are approximately 21,000 new cases of AML diagnosed in the United States each year, which represents 30% of all new cases of leukemia.[43, 44] Despite being the most common type of leukemia, an individual's chance of being diagnosed with AML is relatively rare, with a prevalence of <5 per 10,000.[43, 45] However, the disease is characterized by a poor prognosis, with only about 28% of diagnosed adults surviving 5 years or more.[43] AML is more common in older patients, with the median age at diagnosis being 68 and over 50% of cases being diagnosed in people over the age of 65.[43] This heavily contributes to the poor survival rate of the disease, as a person is more likely to have unfavorable cytogenetics, poorer performance status, and multidrug resistance with advanced age.[46] For people over the age of 59, the median survival time is just 8 to 10 months.[46]

Pathophysiology

In a healthy adult, bone marrow produces red blood cells, platelets, and a variety of white blood cells through a process called hematopoiesis. Hematopoiesis occurs when self-renewing hematopoietic stem cells (HSCs) divide into more specialized types of cells, eventually giving rise to all cellular components of blood. An HSC first divides into either a lymphoid progenitor cell or a myeloid progenitor cell, creating two specific cell lineages as shown in Figure 1.[47-49] When working correctly, this process should give rise to appropriate amounts of each cell type depending on the needs of the body. However, problems such as AML occur when this process does not proceed normally.

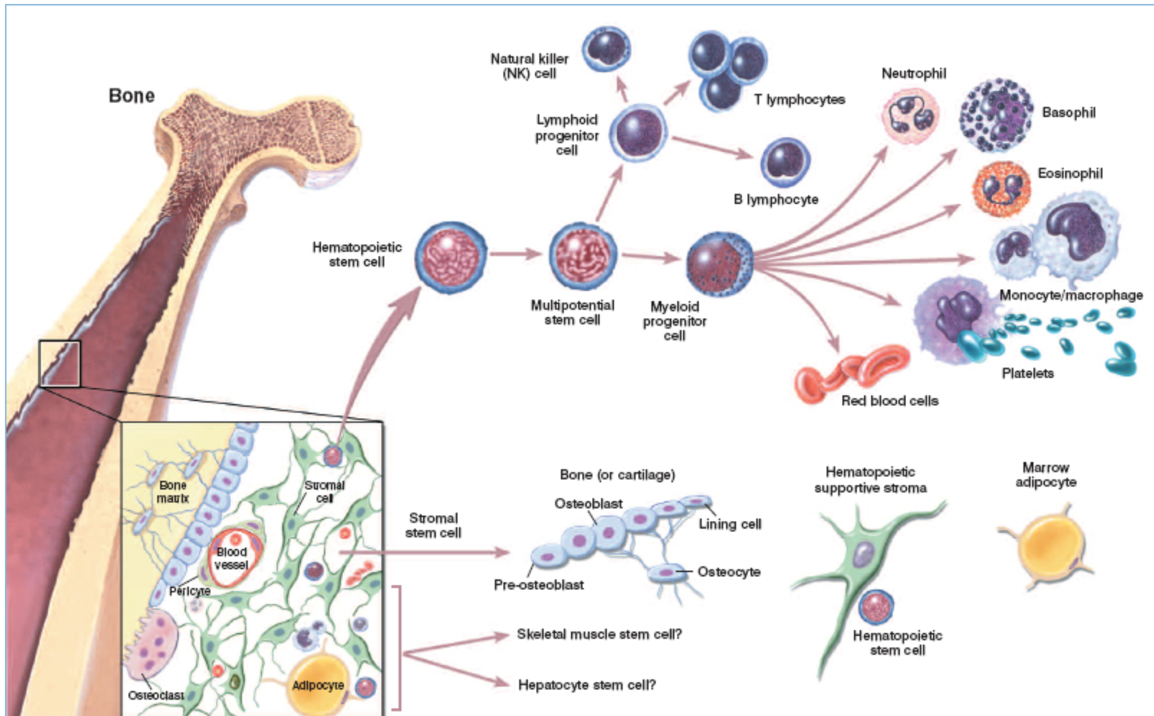


Figure 1: Hematopoiesis. Adapted from Terese Winslow (assisted by Lydia Kibiuk), February 22, 2020.[48]

AML occurs when abnormal myeloid progenitor cells (myeloblasts) accumulate in the bone marrow and fail to divide into their normal specialized cell types.[45] This accumulation interferes with the production of red blood cells, platelets, and white blood cells, causing neutropenia (a low concentration of neutrophils), anemia (a low number of red blood cells), and thrombocytopenia (a low number of platelets).[45, 47] As a result, symptoms of AML commonly include fevers and infections due to a deficiency of infection-fighting immune cells, fatigue due to the reduction of oxygen-carrying red blood cells, and bleeding or bruising due to the reduction of clot-promoting platelets.[45, 47]

Diagnosis and Treatment Options

AML is most often diagnosed by observation of abnormal blood counts and confirmation by bone marrow aspirate. Diagnosis is typically followed by various analyses to detect the patient's specific cytogenetic profile and molecular abnormalities.[50] Treatment goals and therapy selections are determined based on the patient's age, medical fitness, and specific cytogenetic profile, and usually fall into one of the following categories:

- **Intensive Induction Chemotherapy**: Also known as "7+3" therapy, this selection of chemotherapy is chosen for younger patients or those who are determined to be medically fit and able to withstand its toxicity. Administration is done in a hospital setting during a long-term admission. This treatment is pursued with curative intent and is often followed by a hematopoietic stem-cell transplant (HSCT) if remission is reached.[51]
- **Low-Intensity Chemotherapy**: This type of chemotherapy is usually pursued for patients who are not medically fit enough to withstand induction therapy. It may be administered in the inpatient or outpatient setting. Low-intensity therapy helps manage AML, but typically does not lead to a cure.[51]
- **Supportive Care Only:** Supportive care only may be determined to be the most appropriate for a patient, given their fitness, age, and goals of care. With this option, symptoms of AML are controlled by frequent blood transfusions, antibiotic use for infections, and other symptom management techniques.[51]

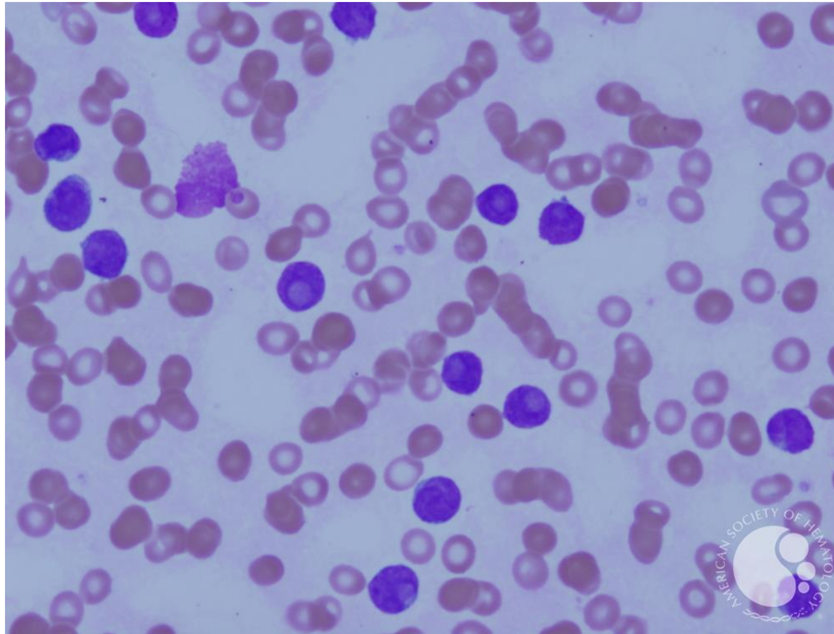


Figure 2: Peripheral blood smear of a patient with AML. Taken from Samip Master, MD; Nebu Koshy, MD via the American Society of Hematology Image Bank.[52]

Experience of Diagnosis and Symptom Burden

Diagnosis of acute leukemia can be particularly traumatic as it is often characterized by abrupt onset and an immediate threat to life without urgent treatment.[53-55] Often, patients are diagnosed after mild to non-existent symptoms, causing the diagnosis to feel extremely unexpected and shocking.[55] It is common for patients to present to their primary care physician who detects abnormal blood counts and quickly refers them to the ED. Patients who are able to withstand intensive chemotherapy face a sudden 4 to 6 week long hospitalization, which quickly removes them from all aspects of their normal life and routine. Those who require low-intensity therapy face a likely terminal diagnosis.[55]

> "You're kind of in shock. I mean I went into the emergency unit, they were trying to find out what was wrong with me. I didn't pack a bag or anything like that. And I wound up staying there overnight, and being shipped to this hospital. Didn't see my apartment for months. I had no idea I wasn't even going to see my apartment for months. Like, they just picked me up and took me, took my life away." (Participant #5014) [55]

After the shock of diagnosis, patients face the significant toxicity, symptom burden, and distress of undergoing chemotherapy.[54, 56] A course of intensive chemotherapy commonly causes significant pain and discomfort, with the most frequent distressing physical symptoms being fever, oral mucositis, loss of appetite, nausea and vomiting, taste and smell changes, weight and hair loss.[56]

The experience of AML diagnosis and treatment also heavily impacts patients psychologically. Beyond the initial shock of diagnosis, the early phase of treatment can be marked by an overwhelming sense of loss, fear, and uncertainty.[54] Baseline health-related QOL is reportedly lower for patients with AML than for other cancer patients or the general population.[45] For patients receiving intensive therapy, QOL has been shown to decline 2 weeks into intensive treatment before improving.[57, 58] A longitudinal study by El-Jawahri et al. found that approximately a third of patients report clinically significant depression and anxiety symptoms shortly after initiation of either intensive or low-intensity chemotherapy.[58] Much like QOL improves over time, patients' anxiety symptoms also improved over time, though depression symptoms did not significantly change.[44] In fact, psychosocial wellbeing of patients who survive treatment has been shown to be impacted even 6 months after diagnosis.[54]

Symptom burden, QOL, and psychological distress experienced by AML patients significantly worsens with proximity to death.[44] The most severe symptoms experienced at the EOL were fatigue, inability to engage in hard word or activity, and anxiety.[32] Additionally, many patients rely on blood transfusions at the EOL.[32] Because of this, several studies have specifically called for increased integration of palliative care services into the EOL care of AML patients.[44, 31, 58]

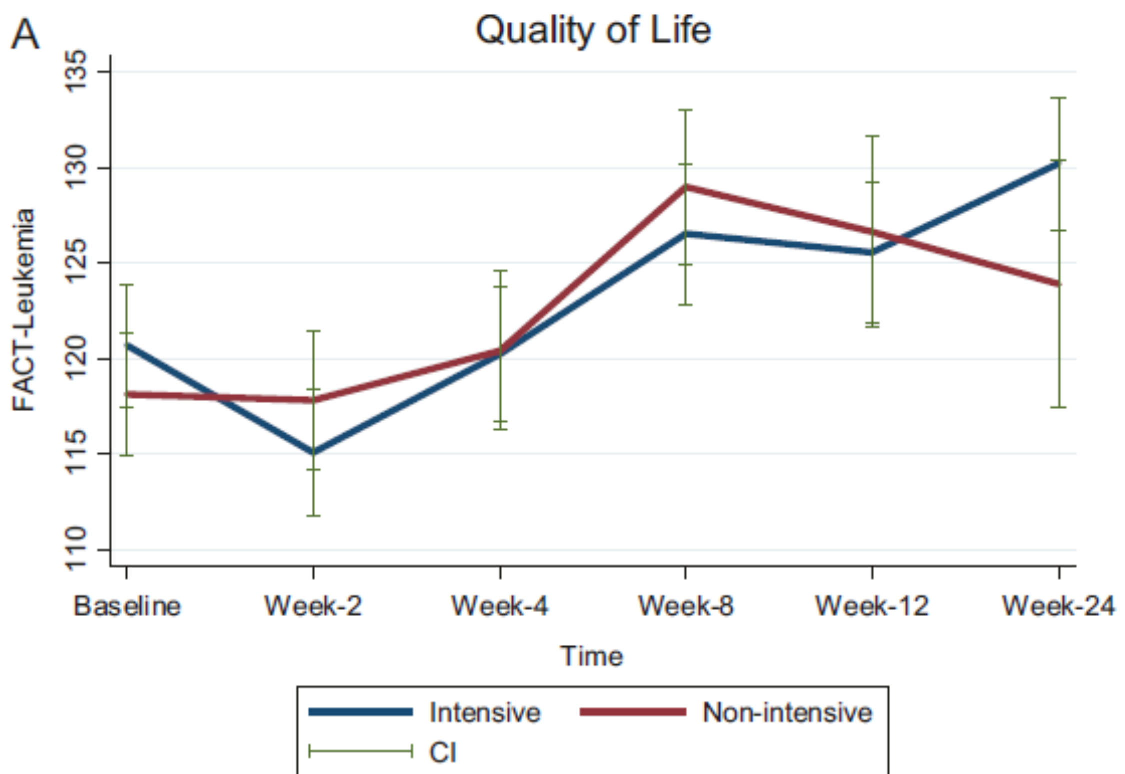


Figure 3: Longitudinal patient QOL during initial chemotherapy treatment for AML as measured by El-Jawahri et al. using the FACT-Leu. CI = 95% Confidence Interval. QOL improved over course of treatment (β= 0.32, 95%CI [0.07, 0.57], p= 0.013), with no significant differences between treatment intensity (β= -1.22, 95%CI [-8.67, 6.23], p=0.748) or in the slope of QOL change over time (β= -0.25, 95%CI [-0.75, 0.25], p=0.324). Taken from El-Jawahri et al, March 29, 2019.[58]

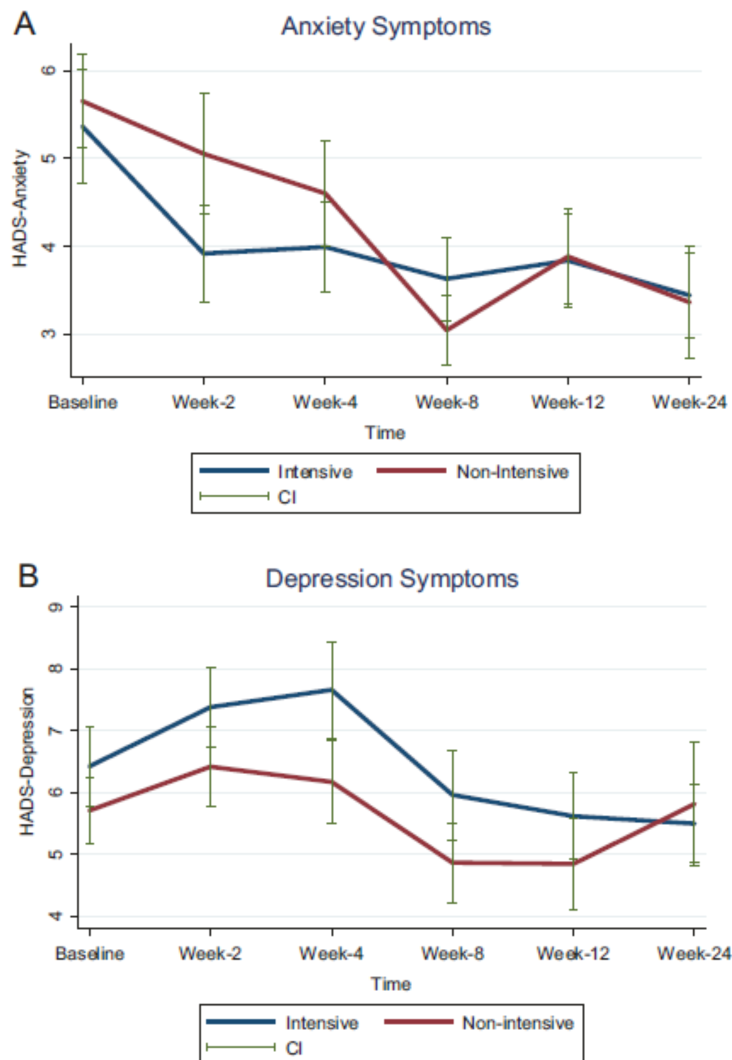


Figure 4: Longitudinal patient anxiety and depression symptoms during chemotherapy for AML as measured by El-Jawahri et al. using the HADS. CI = 95% Confidence Interval. Depression symptoms did not change significantly over time (β= -0.03, 95%CI= [-0.07, 0.01]. p= 0.132), while anxiety symptoms decreased (β= -0.08, 95%CI [-0.11, -0.04], p= <0.001). There were no significant differences between treatment intensity or slope of change over time. Taken from El-Jawahri et al., March 29, 2019.[58]

Healthcare Utilization and EOL Care in AML

Patients diagnosed with AML experience some of the highest rates of healthcare utilization and intense EOL care, as described across hematologic malignancies.[7, 8, 15, 18, 31, 35-37] However, only a few studies have specifically observed healthcare utilization and EOL outcomes in this population.[8, 44] In one study of healthcare utilization among 330 older AML patients, a median number of 4.2 hospitalizations (range, 0-18) was found, with nearly 30% of patient being admitted to the ICU. Almost 90% of this cohort died within 2 years of follow-up, with 61% dying in the hospital. Patients that died were found to have spent a mean of 42.1% of their life after diagnosis in the hospital or attending outpatient clinic visits.[8] Lowe et al. observed equally high rates of healthcare utilization at the EOL among AML patients, with 24 out of 26 patients hospitalized in the last month of life, spending a median of 14 days in the hospital. Of those, 13 were admitted to the ICU and 7 died there.[44]

As shown across hematologic malignancies in general, palliative care services are rarely utilized for patients with AML.[8, 31, 44] In the first study described above, only 14.2% of patients received a palliative care consultation, and for those who died, the median time from palliative care consultation to death was only 7 days.[8] Hospice services were also under-utilized, with only 22.1% of patients receiving hospice services before death and of those, only about half had a hospice length of stay (LOS) greater than 7 days.[8, 26, 31]

Factors Associated with Intensity of EOL Care

In order to provide the most appropriate and highest quality care at the EOL, it is important to identify factors that may be associated with high healthcare utilization and intense care at the EOL, but few studies have done this.[5, 18] As discussed previously, cancer type is related to rates of healthcare utilization and intense EOL care, with hematologic cancers experiencing the highest rates.[18] Female sex [5, 18] and increased age [5, 18] are associated with decreased odds of intensive EOL care [5], while comorbidity is predictive of intensive care.[5, 18] Interestingly, location also impacts risk of receiving intense EOL care. Patients receiving care in a teaching hospital or in a region with more teaching hospitals per capital have a higher likelihood of receiving intense EOL care (Earle). On the other hand, a higher density of hospices is associated with a decrease in the likelihood of experiencing intense EOL care indicators.[5] In a study taking place in Canada, rurality was also predictive of intense EOL care.[18]

In line with the argument for higher utilization and earlier integration of palliative care services, one study found that EOL discussions lower the likelihood of acute or intensive care at the EOL and promote greater use of hospice care.[13] This effect was found to be even greater when EOL discussed occur more than 30 days before death.[13]

Overall, studies examining the factors associated with the intensity of EOL care in patients with cancer are lacking. There is an even greater deficiency of studies examining these factors in patients with hematological malignancies and in those with AML specifically. Better understanding of these factors can help inform and improve EOL care

in these populations, which are known to experience high rate of intense EOL care compared to patients with other types of cancer.

Specific Aims of the Present Study

Patients diagnosed with AML are known to have high healthcare utilization and to undergo intense care towards the EOL.[7, 8, 18, 44] Previous research has described these outcomes and efforts have been proposed to improve care at the EOL through models such as early integrated palliative care.[8, 44] However, factors that are associated with high healthcare utilization and intense care at the EOL have not been well-described for the AML patient population specifically. In fact, few studies to date have examined such factors and those that have focused on the general cancer population. Identification of associated factors may allow for earlier intervention, more informed approaches to EOL care, and greater respect of patient preferences. Additionally, approaching EOL care from this informed standpoint can help reduce unnecessary or unwanted care at the EOL, improving QOL for patients and families, while also reducing unnecessary burdens for patients, families, and healthcare systems.

This study is a retrospective analysis of medical record information and patient-reported outcomes collected from two randomized control trials run by Dr. Areej El-Jawahri at MGH. The specific aims of this study are to:

1. Further describe healthcare utilization and intensity of EOL care received by patients with AML.

2. Describe the associations between patient-reported demographics and intensity of EOL care.
3. Describe the associations between patient-reported outcomes, including anxiety and depression scores, and intensity of EOL care.

METHODS

Study Procedures

We retrospectively analyzed the electronic medical records (EMRs) of 260 patients at five major academic medical centers (Massachusetts General Hospital [MGH], Dana Farber Cancer Institute [DFCI], Duke University Hospital [Duke], the Hospital of the University of Pennsylvania [UPenn], and Ohio State University Hospital [OSU]). All patients had been consented to one of two supportive care research studies led by Dr. Areej El-Jawahri at the MGH. All patients enrolled in these studies had a diagnosis of AML and met all eligibility and exclusion criteria, which are outlined in Table 2. All patients enrolled on these studies completed questionnaires regarding their demographics, QOL, and psychological distress. At the time of informed consent for both studies, patients agreed to have their medical records reviewed for data collection. Both studies included in this analysis were approved by the Dana Farber Harvard Cancer Center Institutional Review Board. Of the 260 EMRs reviewed, 168 deceased patients were ultimately selected for inclusion in this analysis. 92 patients were excluded due to transferring care or if they were not deceased.

Measures of Patient Report Outcomes

As part of both research studies included in this analysis, patients completed baseline questionnaires designed to assess their self-reported demographics, baseline QOL, baseline levels of depression and anxiety, symptom burden, and prognostic understanding. For participants in both included studies, baseline surveys were completed

by patients in the inpatient or outpatient setting and within the first five days of treatment for AML. Baseline patient-reported outcomes questionnaires included the following:

1) **Patient demographics**: This included age, sex, race, relationship status, religion, education level, and average household income. (Appendix I)
2) **Patient-reported QOL**: We used the Functional Assessment of Cancer Therapy [FACT-Leu], a highly-vetted and widely-used instrument comprised of 17 items that measure leukemia-specific health-related QOL.[68] The FACT-Leu consists of four general subscales assessing physical, functional, emotional, and social wellbeing, as well as a fifth leukemia-specific subscale. Higher scores on this assessment indicate better QOL. (Appendix II)
3) **Anxiety and depression symptoms**: We used the Hospital Anxiety and Depression Scale [HADS] to assess depression and anxiety symptoms. This highly vetted and widely used instrument consists of two subscales which assess anxiety and depression symptoms occurring in the past week.[69] Higher scores on this measure indicate worse distress. Possible scores range from 0 (no distress) to 21 (maximal distress), with scores over 7 on the subscales representing clinically significant anxiety or depression. (Appendix III) We also used the Patient Health Questionnaire

[PHQ-9] to additionally measure depression severity in the past 2 weeks. This highly-vetted and widely-used instrument is a set of 9 questions that targets the frequency of different depression symptoms, including suicidal ideation.[70] Higher scores on this measure indicate more frequent depression symptoms, with possible scores ranging from 0 (no depression) to 27 (severe depression).

Retrospective Medical Chart Review

EMRs were analyzed for healthcare utilization and EOL outcomes from the point of diagnosis to the time of death for all deceased patients, or up to one-year post-diagnosis for patients who were still living. EMR notes were reviewed for the following information: date of AML diagnosis, total number of ED visits, total number of hospitalizations, total number of ICU stays, total number of hospitalizations, date of last chemotherapy dose received before death, date of death, place of death, and date of transition to hospice. The number of days between last chemotherapy dose, last hospitalization, hospice admission and death were calculated. All patients included in this study were confirmed to be deceased either by EMR status or online obituary. Place of death was documented using information provided in obituaries or notes from providers in the patients' medical chart.

Statistical Analysis

We performed statistical analyses using STATA (v. 14.2). We calculated descriptive statistics to assess the distribution of demographic factors, healthcare utilization frequencies, and EOL care measures. All variables collected during retrospective medical chart review were included except for the number of ED visits and route of chemotherapy administration. Number of ED visits was excluded as a variable due to discrepancies in the definition of an ED visit between the two studies—data from one study included only ED visits that did not result in admission, while the other included ED visits that also resulted in admission.

We ran unadjusted, univariate logistic regressions to examine the association between patient demographic factors, baseline patient-reported outcomes, and binary EOL outcomes of interest (hospital death, hospice use, any ICU stay, chemotherapy within 30 days of death, hospitalization in the last 7 days of life). We ran unadjusted, univariate linear regressions to examine the association between demographics, patient-reported outcomes, and two continuous outcomes (hospice LOS, total hospitalizations). Predictors of interests were defined a priori based on prior literature and included the following variables (patient-reported demographics, baseline QOL scores, baseline depression scores, baseline anxiety scores). Factors that were associated with outcomes of interest with a $P < 0.15$ were then included in a multivariate logistic regression model (hospital death, hospice use, any ICU stay, chemotherapy within 30 days of death, hospitalization in the last 7 days of life) and multivariate linear regression model (hospice LOS, total hospitalizations). For all multivariate models, we considered a p-value of

<0.05 to be statistically significant. All models adjusted for receipt of intervention on these supportive care studies. Models were also adjusted for intensity of chemotherapy, as receipt of intense chemotherapy vs. low-intensity chemotherapy may impact patient experiences and outcomes. Given collinearity between QOL and psychological distress, they were included in separate models when examining their association with intensity of EOL care. Results were reported as odds ratios (ORs) with 95% confidence intervals.

Table 2: Research Studies Used to Select Patients.

Study	Locations	Eligibility Criteria	Exclusion Criteria	Baseline Survey Timepoint
PROPEL: Patient Reported Outcomes, Prognostic Understanding, and End-of-Life Outcomes in Older Patients with AML (n=100)	MGH DFCI	-Newly diagnosed AML patients who are ≥ 60 years old -Ability to read questions in English or willing to complete questionnaires with an interpreter	-APML diagnosis -Bilineage leukemia -Supportive Care Only -Significant uncontrolled psychiatric disorders or other co-morbid disease -Failure to complete baseline questionnaire for the study	Enrollment and baseline surveys were completed within 72 hours of initiating therapy for AML.
LEAP: Randomized Trial of Collaborative Palliative and Oncology Care Model for Patients with AML (n=160)	MGH Duke OSU UPenn	Hospitalized patients with -Newly diagnosed AML ≥ 60 years -Newly diagnosed AML with antecedent hematologic disorder -Newly diagnosed therapy-related AML -Relapsed AML -Primary refractory AML	-Major psychiatric illness or co-morbid conditions prohibiting compliance with study procedures. -A diagnosis of APML. -Already receiving palliative care -Not receiving intensive treatment	Patients were enrolled within 72 hours of initiating therapy for AML. Baseline surveys were complete within 48 hours of enrollment.

RESULTS

Patient Characteristics

Out of 168 included patients, the average age was 67.35 with a range of 20.11 to 100.31. 88.10% of patients identified as white and 36.31% were female. The majority of patients were married (75%) and described themselves as being of the Catholic (35.12%) or Christian (non-Catholic) faith (35.71%). Most patients had completed degrees after high school, with 26.79% listing high school as their highest degree achieved. Income levels were widely distributed. The majority of included patients were receiving intensive induction therapy for AML (72.62%). 40.48% of included patients were participating at the Massachusetts General Hospital (MGH), which was the primary study site for both research protocols. Complete patient characteristics are listed in Table 3.

Table 3: Patient Characteristics.

Variable	All patients (n=168)
Age, median (range)	67.35 [20.11, 100.31]
Female sex	61 (36.31%)
White race	148 (88.10%)
Relationship Status	
Married	126 (75.00%)
Single	12 (7.14%)
Divorced	15 (8.93%)
Widowed	12 (7.14%)
Missing	3 (1.79%)
Religion	
Catholic	59 (35.12%)
Christin (non-Catholic)	60 (35.71%)
Jewish	12 (7.14%)
Muslim	2 (1.19%)
None	25 (14.88%)

Other	6 (2.57%)
Missing	4 (2.38%)
Education	
High school	45 (26.79%)
College	76 (45.24%)
Post-graduate degree	44 (26.19%)
Missing	3 (1.79%)
Income	
< 25K	24 (14.29%)
25-50K	41 (24.40%)
50-100K	49 (29.17%)
100-150K	14 (8.33%)
>150K	22 (13.10%)
Missing	18 (10.71%)
Treatment intensity	
Intensive induction	122 (72.62%)
Non-intensive therapy	46 (27.38%)
Study Site	
MGH	68 (40.48%)
DFCI	45 (26.79%)
Duke	35 (20.83%)
Penn	16 (9.52%)
OSU	4 (2.38%)

Healthcare Utilization in Patients with AML

The median number of hospitalizations from the time of diagnosis to the time of death was 3 (range, 0-12 hospitalizations) for this deceased patient cohort. 78.18% of patients had at least one hospitalization within the last month of life, while 66.67% were hospitalized within the last week of life. 60 out of 168 patients (35.71%) were admitted to the ICU at least once during their hospitalizations. The majority of these patients died in a hospital setting (59.52%), while only 30.95% of patients died outside of the hospital. Of those that died outside of the hospital, 20.96% died at home. Place of death information

was unknown for 16 patients (9.52%). 70 out of 168 patients utilized hospice services (40.67%), which was defined as either home hospice care, a hospice facility stay, or admission to an inpatient hospice service. The median number of days patients spent in hospice care until death was 8 days (range, 0-97 days). The median time of patients' last chemotherapy dose was 28 days before death (range, 0-236 days), but 51.82% of patients received chemotherapy in the last month of life. Healthcare utilization data is depicted in Table 4.

Table 4: Healthcare Utilization in Patients with AML.

Variable	**All patients (n=168)**
No. hospitalizations, median [range]	3 [0-12]
ICU admissions: n (%)	60 (35.71%)
Hospital death: n (%) Yes No Missing	 100 (59.52%) 52 (30.95%) 16 (9.52%)
Home death: n (%) Yes No Missing	 35 (20.96%) 132 (79.04%) 1
Hospice utilized: n (%)	70 (40.67%)
Time from last chemotherapy does to death, median [range]	28 [0-236]
Time from last hospitalization to death, median [range]	0 [0-441]
Hospice LOS, median [range]	8 [0-97]
Percentage receiving chemotherapy within last 30 days of life	51.82%
Percentage hospitalized within the last 30 days of life	78.18%
Percentage hospitalized within the last 7 days of life	66.67% (110)

Associations with Intense EOL Care

In multivariate analyses, we found several patient-reported baseline characteristics that were associated with high healthcare utilization and intense care at the EOL. Due to collinearity between QOL and psychological distress, these factors were included in separate models for any analyses in which both appeared to be related through univariate analyses (Associations with Hospital Death, Associations with Hospitalization in the Last 7 Days of Life).

Associations with Chemotherapy Use in the Last 30 Days of Life

Tables 15 and 16 depict the associations between patient-reported outcomes and chemotherapy use in the last 30 days of life. Higher depression scores at baseline were significantly associated with receipt of chemotherapy in the last 30 days of life ([HADS] OR=1.102, SE=0.053, P=0.042). There were no significant associations with baseline QOL, baseline anxiety, or demographic factors.

Associations with Hospitalization in the Last 7 Days of Life

Tables 17 and 18 depict the associations between patient-reported outcomes and hospitalization in the last 7 days of life. All three of our outcomes of interest were associated with this facet of intense EOL care. Patients who report higher levels of education (OR=1.538, SE=0.240, P=0.006) and higher baseline depression scores ([PHQ-9] OR=1.089, SE=0.042, P=0.028) had higher odds of being hospitalized in the last 7 days of life. On the other hand, patients who had higher baseline QOL scores had lower odds of being hospitalized in the last 7 days of life (OR=0.976, SE=0.009, P=0.009).

Associations with Hospice Use

Tables 7 and 8 depict the associations between patient-reported outcomes and hospice use. Patients who had higher levels of education had lower odds of using hospice at the EOL (OR=0.356, SE=0.163, P=0.024). Age, baseline QOL, and baseline anxiety symptoms were associated with hospice use in univariate analyses, but they were not statistically significant in multivariate analyses.

Associations with Death in the Hospital

Tables 5 and 6 depict the associations between patient-reported outcomes and death in the hospital. Patients who reported higher levels of education had higher odds of dying in the hospital (OR=1.479, SE=0.234, P=0.013). Additionally, higher baseline anxiety symptoms were associated with increased odds of dying in a hospital setting, though this was not significant (OR=1.090, SE=0.054, P=0.082).

Table 5: Univariate Analysis of Factors Associated with Death in the Hospital.

Variable	OR	SE	P
Hospital Death			
Age	0.94	0.02	0.001
Female sex	1.20	0.42	0.596
Married	0.98	0.41	0.975
Non-intensive chemo	0.34	0.13	0.004
Education			
High School	Ref		
College	1.65	0.67	0.215
Graduate	3.56	1.79	0.012
Baseline QOL	0.98	0.01	0.023
Baseline anxiety	1.11	0.049	0.020
Baseline depression	1.04	0.046	0.399
PHQ-9	1.03	0.035	0.320

Table 6: Multivariate Analysis of Factors Associated with Death in the Hospital.

Hospital Death:							
Model 1- QOL				**Model 2- Mood**			
Variable	**OR**	**SE**	**P**	**Variable**	**OR**	**SE**	**P**
Age	0.955	0.024	0.071	Age	0.957	0.024	0.083
Chemotherapy	0.723	0.368	0.524	Chemotherapy	0.681	0.343	0.445
Palliative Care Arm	1.940	1.010	0.203	Palliative Care Arm	1.943	1.004	0.199
Education	**1.479**	**0.234**	**0.013**	**Education**	**1.498**	**0.236**	**0.010**
Baseline QOL	0.985	0.009	0.110	Baseline anxiety	1.090	0.054	0.082

Table 7: Univariate Analysis of Factors Associated with Hospice Use.

Variable	OR	SE	P
Hospice Use			
Age	1.03	0.014	0.050
Female sex	0.69	0.22	0.262
Married	0.70	0.26	0.338
Non-intensive chemo	1.83	0.65	0.086
Education			
High school			
College	0.77	0.29	0.491
Graduate	0.46	0.19	0.072
Baseline QOL	1.00	0.01	0.227
Baseline anxiety	0.95	0.03	0.186
Baseline depression	0.97	0.04	0.527
PHQ-9	0.99	0.03	0.895

Table 8: Multivariate Analysis of Factors Associated with Hospice Use.

Hospice Use:			
Variable	**OR**	**SE**	**P**
Age	1.021	0.017	0.204
Chemotherapy Intensity	1.229	0.528	0.631
Palliative Care Arm	0.620	0.250	0.235
Education			
1	**1**	**(base)**	
2	**0.605**	**0.246**	**0.217**
3	**0.356**	**0.163**	**0.024**

Table 9: Univariate Analysis of Factors Associated with Hospice LOS.

Variable	OR	SE	P
Hospice LOS			
Age	0.02	0.01	0.051
Female sex	-0.09	0.30	0.769
Married	0.48	0.28	0.084
Non-intensive chemo	0.25	0.28	0.366
Education			
High school			
College	0.02	0.33	0.942
Graduate	-0.16	0.46	0.720
Baseline QOL	-0.003	0.005	0.575
Baseline anxiety	0.035	0.031	0.264
Baseline depression	0.007	0.030	0.856
PHQ-9	-0.009	0.026	0.723

Table 10: Multivariate Analysis of Factors Associated with Hospice LOS.

Hospice LOS: Variable	Coef.	SE	P
Age	0.014	0.011	0.230
Palliative Care Arm	-1.066	0.456	0.019
Relationship status: Married	0.546	0.282	0.053

Table 11: Univariate Analysis of Factors Associated with Total Hospitalizations.

Variable	OR	SE	P
Total Hospitalizations			
Age	-0.001	0.004	0.666
Female sex	-0.025	0.117	0.826
Married	-0.169	0.140	0.227
Non-intensive chemo	0.05	0.128	0.671
Education			
High school			
College	-0.01	0.14	0.930
Graduate	-0.09	0.14	0.477
Baseline QOL	0.0006	0.002	0.807
Baseline anxiety	-0.017	0.010	0.181
Baseline depression	-0.006	0.014	0.667
PHQ-9	0.0037	0.010	0.710

Table 12: Multivariate Analysis of Factors Associated with Total Hospitalizations.

Total Hospitalizations:			
Variable	**Coef.**	**SE**	**P**
Age	-0.005	0.011	0.192
Palliative Care Arm	-0.183	0.123	0.137
Baseline anxiety	-0.020	0.013	0.116

Table 13: Univariate Analysis of Factors Associated with ICU Stays.

Variable	OR	SE	P
ICU Usage			
Age	0.98	0.01	0.207
Female sex	1.09	0.37	0.793
Married	0.99	0.38	0.983
Non-intensive chemo	0.40	0.16	0.023
Education			
High school			
College	1.44	0.57	0.356
Graduate	1.14	0.52	0.764
Baseline QOL	0.99	0.007	0.282
Baseline anxiety	1.008	0.04	0.817
Baseline depression	0.969	0.04	0.460
PHQ-9	1.08	0.03	0.791

Table 14: Multivariate Analysis of Factors Associated with ICU Stays.

ICU Stays:			
Variable	**OR**	**SE**	**P**
Palliative Care Arm	1.058	0.407	0.884
Chemotherapy Intensity	0.408	0.156	0.093

Table 15: Univariate Analysis of Factors Associated with Chemotherapy Use in the Last 30 Days of Life.

Variable	OR	SE	P
Chemo Use in Last 30 Days			
Age	0.99	0.014	0.956
Female sex	1.19	0.43	0.625
Married	1.56	0.64	0.272
Non-intensive chemo	1.03	0.38	0.931
Education			
High school			

College	1.53	0.66	0.329
Graduate	2.14	1.02	0.109
Baseline QOL	0.99	0.007	0.381
Baseline anxiety	1.07	0.043	0.109
Baseline depression	1.08	0.049	0.087
PHQ-9	1.04	0.03	0.197

Table 16: Multivariate Analysis of Factors Associated with Chemotherapy Use in the Last 30 Days of Life.

Chemo Use in Last 30 Days:			
Variable	**OR**	**SE**	**P**
Age	1.011	0.016	0.478
Palliative Care Arm	2.350	1.051	0.056
Baseline depression	**1.102**	**0.053**	**0.042**

Table 17: Univariate Analysis of Factors Associated with Hospitalization in the Last 7 Days of Life.

Variable	**OR**	**SE**	**P**
Hospitalization in Last 7 Days			
Age	0.96	0.01	0.022
Female sex			
Married	1.55	0.59	0.244
Non-intensive chemo	0.39	0.14	0.011
Education			
High school			
College	1.09	0.41	
Graduate	4.38	2.34	
Baseline QOL	0.976	0.012	0.057
Baseline anxiety	1.04	0.04	0.269
Baseline depression	1.07	0.048	0.110
PHQ-9	1.07	0.037	0.054

Table 18: Multivariate Analysis of Factors Associated with Hospitalization in the Last 7 days of Life.

Hospitalization in the last 7 days:							
Model 1- QOL				**Model 2- Mood**			
Variable	**OR**	**SE**	**P**	**Variable**	**OR**	**SE**	**P**
Age	0.972	0.020	0.157	Age	0.969	0.020	0.117
Education	**1.538**	**0.240**	**0.006**	**Education**	**1.577**	**0.251**	**0.004**
Baseline QOL	**0.976**	**0.009**	**0.009**	**Baseline depression**	**1.089**	**0.042**	**0.028**
Palliative Care Arm	2.055	1.015	0.145	Palliative Care Arm	2.126	1.039	0.123
Chemotherapy Intensity	0.622	0.296	0.318	Chemotherapy Intensity	0.667	0.314	0.390

DISCUSSION

In this retrospective analysis, we examined the rates of healthcare utilization of 168 deceased patients with AML in order to determine the intensity of their EOL care. We then examined the relationships between patient factors, baseline QOL and mood, with intensity of EOL care. We demonstrate that patients with AML experience high rates of healthcare utilization and thus often experienced intense EOL care, as expected from past studies of patients with hematologic malignancies. We observed that patients with AML experience a median of 3 hospitalizations from diagnosis to death (range, 0-12), 66.7% were hospitalized within the last 7 days of life, and over 50% received chemotherapy in the last 30 days of life. Additionally, around 36% staying in the ICU at some point, nearly 60% died in the hospital, and only 40.67% utilized hospice services.

Patients' education levels, baseline QOL scores, and baseline depression scores were found to be associated with EOL care outcomes. Specifically, higher education, lower baseline QOL, and higher depression scores were found to be significantly associated with more intense EOL care indicators. Patients with higher education had higher odds of dying in the hospital and being hospitalized in the last week of life, while they also had lower odds of using hospice. Patients reporting higher baseline depression symptoms had a higher likelihood of receiving chemotherapy in the last 30 days of life and of being hospitalized in the last 7 days of life. Higher baseline QOL scores were associated with lower odds of being hospitalized in the last 7 days of life. These findings highlight a relationship between patient characteristics and later care outcomes and

suggest the possibility of streamlining EOL care improvement interventions by focusing on the experiences of patients highest at risk.

Patients with AML are Likely to Experience Intense EOL Care

This is the largest study to date examining factors associated with intensity of EOL care for patients with AML. Our findings are consistent with prior, smaller investigations, underscoring the high intensity of EOL care in this population. This study, along with others, demonstrates that patients with AML experience high rates of chemotherapy use in the last month of life, frequent hospitalizations and ICU admissions in the last month of life, high likelihood of dying in the hospital, and low hospice utilization.[8, 44]

Patients with AML experience high symptom burden and toxicities from treatment, which likely leads to the high frequencies of hospitalizes and ICU stays in this population. The AML disease trajectory is often unpredictable, so patients are often receiving more intense, highly toxic treatments later in life.[31] Additionally, patients with AML often require blood products and intravenous antibiotics at the EOL, which leads to higher amounts of healthcare utilization and lower rates of hospice referral as many hospice facilities cannot meet these needs.[31, 44] Supporting this, previous studies have also shown that transfusion dependent patients are more likely to die in the ICU and less likely to die in hospice.[44] Lower rates of hospice utilization in this population could also be due to difficulty identifying a specific "EOL phase" in the AML trajectory, as a decent number of AML patients may have an abrupt decline close to the EOL.[59]

Finally, studies have shown that patients with hematologic malignancies, including AML, have prognostic understanding as an important challenge in dealing with their treatment, and that these patients have misperceptions about their treatment risks and benefits.[31, 55] Specifically, patients have been shown to overestimate their prognosis with AML, which is correlated with preference for intense medical care at the EOL.[31, 57.]

Education Levels and EOL Care

To our knowledge, this is the first study to examine the relationship between patient-reported education level and intensity of EOL care in the AML patient population. We observed an association between patients' education levels and their likelihood for dying in the hospital, being hospitalized in the last week of life, and using hospice care. It is possible that this relationship could be mediated by proximity to academic medical centers. As Earle et al. found, patients receiving care at teaching hospitals or in regions with higher densities of teaching hospitals are more likely to experience intense EOL care.[5] It is possible that more highly educated patients reside nearer to these centers, who or choose to receive care in these hospitals. There could also be a bias in the number of intensive treatment options presented to patients with higher health literacy levels, or in the way options are understood during goals-of-care conversations. Future studies are needed to explore the possible discrepancies in AML treatment and EOL care for patients of varying health literacy levels or demographic backgrounds in order to better understand the possible factors involved.

QOL and EOL Care

Our results demonstrate that higher baseline QOL scores are associated with a lower likelihood of experiencing intensive EOL care indicators. This is in line with one systematic review study which reported that low baseline health-related QOL scores in AML patients were predictive of poorer outcomes.[45] It is logical that poor outcomes would likely lead to more interactions with acute healthcare settings, and thus more intense care.

Additionally, a large aspect of QOL is symptom burden, with patients experiencing high symptom burden having lower QOL scores. Patients with high symptom burden or poorly controlled symptoms are also more likely to present to an acute healthcare setting. Nipp et al. observed that in solid tumor populations, higher symptom burdens were significantly associated with longer hospital LOS, unplanned hospital readmissions within 90-days, and death or readmission within 90 days.[6]

Another study by Oliva et al. found that QOL scores at diagnosis were related to eventual survival. Patients with lower QOL scores had shorter survival compared to those with higher QOL scores. In this study, the predictive value of these scores on survival was mainly observed for patients over 70, which is in line with the cohort examined in this study (median age 67.35).[60] Finally, QOL has been shown to worsen with proximity to death in AML patients.[44] Thus, it is logical that a lower baseline QOL may become even lower towards the EOL, which could have an effect on overall survival and intensity of EOL care experienced.

Psychological Distress and EOL Care

This study indicated a relationship between psychological distress at baseline and later intense EOL care. Specifically, higher depression scores at baseline were associated with higher odds of being hospitalized in the last week of life and higher odds of receiving chemotherapy in the last month of life. Higher anxiety scores at baseline were associated with higher risk of dying in the hospital, though this was not significant. Prior studies have suggested that depression is associated with poor overall survival and increased healthcare utilization in patients with chronic illness.[61-64] In a study of solid tumor patients, Nipp et al. also found a relationship between patient-reported depression scores, longer hospital LOS, and death or readmission within 90 days.[6] Similarly, in a study of 5055 cancer patients, patients suffering from depression were more likely to have healthcare visits, ED visits, hospitalizations, and 30-day hospital readmission.[61] Additionally, elevated depression symptoms may be predictive of higher mortality among cancer patients.[63, 64] Given these suggested relationships, it is logical that elevated psychological distress, with a particular emphasis on depression symptoms, would lead to more intense EOL care in patients with AML.

The Importance of Palliative Care and Hospice Care Utilization

The findings of this study reiterate the exceptional need for improved access to, utilization of, and early integration of palliative care and hospice for the AML population facing the EOL. There are many barriers to implementing the most beneficial use of these services in the care of AML patients.[31] As discussed above, AML itself can be

unpredictable, which leads to late use of intense treatments such as chemotherapy, a lack of prognostic understanding on the part of the patient, and late referral to hospice.[31] Culturally, providers caring for these patients have reported unrealistic expectations in terms of prognosis,[65] discomfort discussing death and hospice referral with patients, and a higher likelihood to continue prescribing cancer therapy rather than comfort care.[66] Finally, AML patients face unique barriers to hospice care, including a need for blood product support, which is not always available outside of the hospital setting.[31, 44] Despite these barriers, patients with AML have a substantial need for supportive care intervention through palliative care and hospice care at the EOL.[31]

Palliative care services have been shown to reduce symptom burden, improve QOL, and reduce psychological distress. In a study of 160 AML patients receiving usual leukemia care or integrated palliative care, those receiving palliative care reported better QOL and lower depression and anxiety. Additionally, patients in this study were more likely to discuss EOL care preferences with providers and were less likely to receive chemotherapy near the EOL.[67] Thus, integration of palliative care can lead to less intense EOL care, better QOL, and lower psychological distress, which this study showed to be associated with intense EOL care.

Knowledge of patient characteristics that may be associated with later intense EOL care can help identify patients that may be especially at need for these services. Early use of these services can help direct care plans that are in line with the patient's needs and desires, as well as help reduce the symptom burden of these patients. This study shows that factors present early in the care of a patient can have implications later

on, which supports the use of QOL-improving health interventions early in AML care. This study shows that QOL and psychological distress and related to EOL outcomes, which underlines the need for attention to these aspects of patient's lives.

Limitations

This study had several important limitations to consider. First, patients included in this analysis were drawn from two studies at large academic medical centers. Thus, this analysis only captures patients receiving care at such institutions and does not include patients who either have limited access to academic centers, or who choose to receive care elsewhere. These medical centers were located in several different parts of the US, which helps the generalizability of this study, but the sample is still limited to a subset of patients. In terms of generalizability, this cohort of patients was also lacking in some subsets of diversity. The majority of patients were white (88.10%) and married (75%). It is unknown how many patients were ethnically Hispanic or non-Hispanic. Over a quarter of included patients held a post-graduate degree (26.19%). Because of these factors, findings may not be generalizable to all AML patients.

Second, we were unable to ascertain the EOL outcomes of patients who transferred care and did not receive EOL care at our institution, or at one of the institutions participating in the included studies. Because of this limitation, it is likely that healthcare utilization was even higher than observed by this study, as further interactions with healthcare systems likely occurs for patients after transferring care.

Third, this analysis did not include information on the number of ED visits patients experienced. Though this information was collected, it was not included due to a discrepancy in the definition of an ED visit between the two studies included. Though ED visit rates are only one of multiple intense EOL care indicators, having this information would further the knowledge about what kind of healthcare interactions patients with AML experience at the EOL.

Finally, our study examined the associations between the intensity of EOL care, patient demographics, and baseline psychological distress. Through our analysis, we did observe significant relationships, however we are unable to determine the causality of these findings due to the correlational nature of this study. Additional causal research is needed to determine the possible causality of these relationships.

CONCLUSION

In conclusion, this study reiterated that patients with AML have high healthcare utilization and are likely to experience intense EOL care. Despite this, the usage of hospice care services remains subpar, with less than half of patients observed to utilize these services at the EOL. Furthermore, the median hospice LOS was 8 days before death, indicating that if hospice care is initiated, it does not occur until close to death. Given the established benefit of symptom management and comfort-focused care as hospice provides, this may mean that patients with AML could further benefit from earlier integrated hospice care.

There are several factors that may be predictive of a higher risk of intense EOL care. Specifically, this study shows that patients with high education levels may have higher risk of being hospitalized at the EOL and dying in the hospital, as well as lower likelihood of utilizing hospice care. Patients' QOL and psychological distress levels may also be important indicators of later intense EOL care, as higher baseline QOL is associated with lower risk of hospitalization at the EOL, while higher depression symptoms at baseline are associated with higher risk of hospitalization at the EOL. Higher depression scores may also be associated with increased risk of late chemotherapy usage.

These findings suggest that there are multiple patient characteristics that may be useful for identifying patients at higher risk for later intense EOL care. Earlier identification of these patients may aid in planning for the most appropriate EOL care, earlier patient education, and more informed conversations about goals-of-care and EOL

preferences. Identifying those at high risk earlier and planning for the most appropriate care may also help decrease the amount of unnecessary hospitalizations and healthcare interactions near the EOL, reducing the financial burden on patients, families, and healthcare systems.

Moving forward, studies are needed to further explore potential factors that may be associated with increased risk of intense EOL care, as well as studies to examine the benefits and outcomes of earlier identification. Specifically, studies are needed to demonstrate the impact of earlier identification on later healthcare utilization and EOL care, as well as financial outcomes and patient and caregiver QOL outcomes at the EOL.

APPENDIX I: Demographics Questionnaire

Please check the appropriate box or boxes.

1. Gender
- ☐ Man
- ☐ Woman
- ☐ Other

2. Ethnicity
- ☐ Hispanic or Latino
- ☐ Not Hispanic or Latino

3. Race (please check all that apply)
- ☐ American Indian or Alaskan native
- ☐ Asian
- ☐ African American or Black
- ☐ Native Hawaiian or other Pacific Islander
- ☐ White
- ☐ Other (please specify) ______________

4. Religion
- ☐ Catholic Christian
- ☐ Other Christian (such as Protestant, Orthodox, etc.)
- ☐ Jewish
- ☐ Muslim
- ☐ Atheist
- ☐ None
- ☐ Other (please specify)________________

5. <u>Current</u> relationship status
- ☐ Married or living with someone as if married
- ☐ Non-cohabiting relationship
- ☐ Single, never married
- ☐ Divorced/Separated
- ☐ Loss of long term partner/ Widowed

6. Please indicate your highest or current education level
- ☐ 12th grade or less
- ☐ High school graduate or GED
- ☐ 2 years of college/AA degree/Technical school training
- ☐ College graduate (BA or BS)
- ☐ Masters degree
- ☐ Doctorate/Medical degree/Law degree

7. What is your annual combined household income?
- ☐ Less than $25,000
- ☐ $25,000 – 50,000
- ☐ $50,000 -100,000
- ☐ $100,000 – 150,000
- ☐ Greater than $150,000

8. Please indicate who you live with (you may check more than one box)
- ☐ By myself
- ☐ Partner/Spouse
- ☐ Roommate/Friend
- ☐ Children under 18
- ☐ Children over 18
- ☐ Group home/assisted living/nursing home
- ☐ Parent
- ☐ Other (please specify) ______________

9. <u>Current</u> employment status (please check all that apply):
- ☐ Employed (full-time or part-time)
- ☐ Caring for home or family (not currently working and not looking for paid work)
- ☐ Unemployed and looking for work
- ☐ Unable to work due to illness or disability
- ☐ Retired
- ☐ Student
- ☐ Other (please specify) ______________

APPENDIX II: FACT- Leu Questionnaire

	PHYSICAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	Not at all	A little bit	Some- what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4

	ADDITIONAL CONCERNS (continued)	Not at all	A little bit	Some-what	Quite a bit	Very much
Leu1	I am bothered by lumps or swelling in certain parts of my body (e.g. neck, armpits, or groin)…………	0	1	2	3	4
TH1	I bleed easily……………………………………	0	1	2	3	4
TH2	I bruise easily……………………………………	0	1	2	3	4
HI12	I feel weak all over…………………………………	0	1	2	3	4
BMT6	I get tired easily…………………………………	0	1	2	3	4
C2	I am losing weight…………………………………	0	1	2	3	4
C6	I have a good appetite………………………………	0	1	2	3	4
An7	I am able to do my usual activities…………………	0	1	2	3	4
N3	I worry about getting infections …………………	0	1	2	3	4
Leu5	I feel uncertain about my future health……………	0	1	2	3	4
Leu6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs……………………	0	1	2	3	4
Leu7	I feel isolated from others because of my illness or treatment……………………………………	0	1	2	3	4

APPENDIX III: HADS Questionnaire

Read each item and please select the answer which comes closest to how you have been feeling, on the average, IN THE PAST WEEK.

1. I feel tense or "wound up."
   a. Most of the time
   b. A lot of the time
   c. From time to time, occasionally
   d. Not at all

2. I still enjoy the things I used to enjoy.
   a. Definitely as much
   b. Not quite as much
   c. Only a little
   d. Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen.
   a. Very definitely and quite badly
   b. Yes, but not too badly
   c. A little, but it doesn't worry me
   d. Not at all

4. I can laugh and see the funny side of things.
   a. As much as I always could
   b. Not quite so much now
   c. Definitely not so much now
   d. Not at all

5. Worrying thoughts go through my mind.
   a. A great deal of the time
   b. A lot of the time
   c. From time to time but not too often
   d. Only occasionally

6. I feel cheerful.
   a. Not at all
   b. Not often
   c. Sometimes
   d. Most of the time

7. I can sit at ease and feel relaxed.
   a. Definitely
   b. Usually
   c. Not often
   d. Not at all

8. I feel as if I am slowed down.
   a. Nearly all the time
   b. Very often
   c. Sometimes
   d. Not at all

9. I get a sort of frightened feeling like "butterflies" in the stomach.
   a. Not at all
   b. Occasionally
   c. Quite often
   d. Very often

10. I have lost interest in my appearance.
    a. Definitely
    b. I don't take so much care as I should
    c. I may not take quite as much care
    d. I take just as much care as ever

11. I feel restless as if I have to be on the move.
    a. Very much indeed
    b. Quite a lot
    c. Not very much
    d. Not at all

12. I look forward with enjoyment to things.
    a. As much as I ever did
    b. Rather less than I used to
    c. Definitely less than I used to
    d. Hardly at all

13. I get sudden feelings of panic.
    a. Very often indeed
    b. Quite often
    c. Not very often
    d. Not at all

14. I can enjoy a good book or radio or TV program.
    a. Often
    b. Sometimes
    c. Not often
    d. Very seldom

APPENDIX IV: PHQ-9 Questionnaire

Over the **last two weeks** have you been bothered by the following problems?
(Please answer by circling **one** answer for each problem.)

	Not at all	Several Days	More than half the days	Nearly everyday
Little interest or pleasure in doing things.	1	2	3	4
Feeling down, depressed, or hopeless.	1	2	3	4
Trouble falling or staying asleep, or sleeping too much.	1	2	3	4
Feeling tired or having little energy.	1	2	3	4
Poor appetite or overeating.	1	2	3	4
Feeling bad about yourself, or that you are a failure, or have let your family down.	1	2	3	4
Trouble concentrating on things such as reading.	1	2	3	4
Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual.	1	2	3	4
Thoughts that you would be better off dead.	1	2	3	4

REFERENCES

1. Pritchard RS, Fisher ES, Teno JM, et al. Influence of Patient Preferences and Local Health System Characteristics on the Place of Death. Journal of the American Geriatrics Society. 1998;46(10):1242-1250. doi:10.1111/j.1532-5415.1998.tb04540.x.

2. Cross SH, Warraich HJ. Changes in the Place of Death in the United States. New England Journal of Medicine. 2019;381(24):2369-2370. doi:10.1056/nejmc1911892.

3. Gomes, B., Calanzani, N., Gysels, M., Hall, S., & Higginson, I. (2013). Heterogeneity and changes in preferences for dying at home: A systematic review. BMC Palliative Care, 12(1).

4. Greenle MM, Hirschman KB, Coburn K, et al. End-of-life Health-Care Utilization Patterns Among Chronically Ill Older Adults. American Journal of Hospice and Palliative Medicine. 2019;36(6):507-512. doi:10.1177/1049909118824962.

5. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the Aggressiveness of Cancer Care Near the End of Life. Journal of Clinical Oncology. 2004;22(2):315-321. doi:10.1200/jco.2004.08.136.

6. Nipp RD, El-Jawahri A, Moran SM, et al. The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer. 2017;123(23):4720-4727. doi:10.1002/cncr.30912.

7. Hui D, Didwaniya N, Vidal M, et al. Quality of end-of-life care in patients with hematologic malignancies: A retrospective cohort study. Cancer. 2014;120(10):1572-1578. doi:10.1002/cncr.28614.

8. El-Jawahri A, Heavey SF, Leblanc TW, et al. Health Care Utilization and End of Life Care for Older Patients with Acute Myeloid Leukemia Receiving Supportive Care Alone. Blood. 2015;126(23):2126-2126. doi:10.1182/blood.v126.23.2126.2126.

9. Soto-Rubio A, Perez-Marin M, Miguel JT, Martin PB. Emotional Distress of Patients at End-of-Life and Their Caregivers: Interrelation and Predictors. Frontiers in Psychology. 2018;9. doi:10.3389/fpsyg.2018.02199.

10. Verkissen MN, Houttekier D, Cohen J, Schots R, Chambaere K, Deliens L. End-of-life decision-making across cancer types: results from a nationwide

retrospective survey among treating physicians. British Journal of Cancer. 2018;118(10):1369-1376. doi:10.1038/s41416-018-0070-5.

11. Myers J. Improving the quality of end-of-life discussions. Current Opinion in Supportive and Palliative Care. 2015;9(1):72-76. doi:10.1097/spc.0000000000000108.

12. Henson LA, Gomes B, Koffman J, Daveson BA, Higginson IJ, Gao W. Factors associated with aggressive end of life cancer care. Supportive Care in Cancer. 2015;24(3):1079-1089. doi:10.1007/s00520-015-2885-4.

13. Starr LT, Ulrich CM, Corey KL, Meghani SH. Associations Among End-of-Life Discussions, Health-Care Utilization, and Costs in Persons With Advanced Cancer: A Systematic Review. American Journal of Hospice and Palliative Medicine. 2019;36(10):913-926. doi:10.1177/1049909119848148.

14. Teno JM, Mor V, Ward N, et al. Bereaved Family Member Perceptions of Quality of End-of-Life Care in U.S. Regions with High and Low Usage of Intensive Care Unit Care. Journal of the American Geriatrics Society. 2005;53(11):1905-1911. doi:10.1111/j.1532-5415.2005.53563.x.

15. Tang ST, Wu S-C, Hung Y-N, Chen J-S, Huang E-W, Liu T-W. Determinants of Aggressive End-of-Life Care for Taiwanese Cancer Decedents, 2001 to 2006. Journal of Clinical Oncology. 2009;27(27):4613-4618. doi:10.1200/jco.2008.20.5096.

16. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder ÉL. The Implications of Regional Variations in Medicare Spending. Part 2: Health Outcomes and Satisfaction with Care. Annals of Internal Medicine. 2003;138(4):288. doi:10.7326/0003-4819-138-4-200302180-00007.

17. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying Potential Indicators of the Quality of End-of-Life Cancer Care From Administrative Data. Journal of Clinical Oncology. 2003;21(6):1133-1138. doi:10.1200/jco.2003.03.059.

18. Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC. Trends in the Aggressiveness of End-of-Life Cancer Care in the Universal Health Care System of Ontario, Canada. Journal of Clinical Oncology. 2011;29(12):1587-1591. doi:10.1200/jco.2010.31.9897.

19. Institution of Medicine. Dying in America: improving quality and honoring individual preferences near the end of life. Washington, DC: National Academies

Press; 2014. Committee on Approaching Death: Addressing Key End of Life Issues.

20. Beccaro M. Actual and preferred place of death of cancer patients. Results from the Italian survey of the dying of cancer (ISDOC). Journal of Epidemiology & Community Health. 2006;60(5):412-416. doi:10.1136/jech.2005.043646.

21. Smith TJ, Schnipper LJ: The American Society of Clinical Oncology Program to Improve End-of-Life Care. Journal of Palliative Medicine. 1998;1:221.

22. Peppercorn JM, Smith TJ, Helft PR, et al. American Society of Clinical Oncology statement: Toward individualized care for patients with advanced cancer. Journal of Clinical Oncology. 2011;29:755–760

23. Obermeyer Z, Makar M, Abujaber S, Dominici F, Block S, Cutler DM. Association between the Medicare hospice benefit and health care utilization and costs for patients with poor-prognosis cancer. JAMA. 2014;312: 1888-1896.

24. Pyenson B, Connor S, Fitch K, Kinzbrunner B. Medicare cost in matched hospice and non-hospice cohorts. Journal of Pain and Symptom Management. 2004;28: 200-210.

25. Kelley AS, Deb P, Du Q, Aldridge Carlson MD, Morrison RS. Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay. Health Affairs (Millwood). 2013;32: 552-561.

26. El-Jawahri A, Vanbenschoten O, Bhatt SM, et al. Randomized trial of a hospice video decision aid for patients with advanced cancer and their caregivers. Journal of Clinical Oncology. 2019;37(31_suppl):42-42. doi:10.1200/jco.2019.37.31_suppl.42

27. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA: The Journal of the American Medical Association. 2008;300: 1665-1673.

28. Kumar P, Wright AA, Hatfield LA, Temel JS, Keating NL. Family Perspectives on Hospice Care Experiences of Patients with Cancer. Journal of Clinical Oncology. 2017;35: 432-439.

29. Bradley EH, Prigerson H, Carlson MD, Cherlin E, Johnson-Hurzeler R, Kasl SV. Depression among surviving caregivers: does length of hospice enrollment matter? American Journal of Psychiatry. 2004;161: 2257-2262.

30. Kris AE, Cherlin EJ, Prigerson H, et al. Length of hospice enrollment and subsequent depression in family caregivers: 13-month follow-up study. American Journal of Geriatric Psychiatry. 2006;14: 264-269.

31. El-Jawahri A, Nelson AM, Gray TF, Lee SJ, LeBlanc TW. Palliative and End-of-Life Care for Patients With Hematologic Malignancies. Journal of Clinical Oncology. February 2020. doi:10.1200/JCO.18.02386

32. Barbera L, Paszat L, Charter C. Indicators of Poor Quality End-of-Life Cancer Care in Ontario. Journal of Palliative Care. 2006;22(1):12-17. doi:10.1177/082585970602200103.

33. Numico G, Cristofano A, Mozzicafreddo A, et al. Hospital Admission of Cancer Patients: Avoidable Practice or Necessary Care? PLoS One. 2015;10(3). doi:10.1371/journal.pone.0120827.

34. Brooks GA, Abrams TA, Meyerhardt JA, et al. Identification of Potentially Avoidable Hospitalizations in Patients With GI Cancer. Journal of Clinical Oncology. 2014;32(6):496-503. doi:10.1200/jco.2013.52.4330.

35. Manitta V, Zordan R, Cole-Sinclair M, Nandurkar H, Philip J. The Symptom Burden of Patients with Hematological Malignancy: A Cross-Sectional Observational Study. Journal of Pain and Symptom Management. 2011;42(3):432-442. doi:10.1016/j.jpainsymman.2010.12.008.

36. Howell DA, Roman E, Cox H, et al. Destined to die in hospital? Systematic review and meta-analysis of place of death in haematological malignancy. BMC Palliative Care. 2010;9(1). doi:10.1186/1472-684x-9-9.

37. Soares LGL, Gomes RV, Japiassu AM. Trends in Health-Care Utilization at the End of Life Among Patients With Hematologic Malignancies in a Middle-Income Country: Challenges and Opportunities in Brazil. American Journal of Hospice and Palliative Medicine. 2019;36(9):775-779. doi:10.1177/1049909119828086.

38. Moreno-Alonso D, Porta-Sales J, Monforte-Royo C, Trelis-Navarro J, Sureda-Balarí A, Sevilla-Ribosa AFD. Palliative care in patients with haematological neoplasms: An integrative systematic review. Palliative Medicine. 2017;32(1):79-105. doi:10.1177/0269216317735246.

39. Hochman MJ, Yu Y, Wolf SP, Samsa GP, Kamal AH, Leblanc TW. Comparing the Palliative Care Needs of Patients With Hematologic and Solid Malignancies. Journal of Pain and Symptom Management. 2018;55(1). doi:10.1016/j.jpainsymman.2017.08.030

40. Batty GD, Russ TC, Stamatakis E, Kivimäki M. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. BMJ: British Medical Journal. 2017. doi:10.1136/bmj.j108

41. Chino F, Kamal AH, Chino J, Leblanc TW. Disparities in place of death for patients with hematological malignancies, 1999 to 2015. Blood Advances. 2019;3(3):333-338. doi:10.1182/bloodadvances.2018023051.

42. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG. Place of Death: Correlations With Quality of Life of Patients With Cancer and Predictors of Bereaved Caregivers Mental Health. Journal of Clinical Oncology. 2010;28(29):4457-4464. doi:10.1200/jco.2009.26.3863.

43. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.

44. Lowe JR, Yu Y, Wolf S, Samsa G, Leblanc TW. A Cohort Study of Patient-Reported Outcomes and Healthcare Utilization in Acute Myeloid Leukemia Patients Receiving Active Cancer Therapy in the Last Six Months of Life. Journal of Palliative Medicine. 2018;21(5):592-597. doi:10.1089/jpm.2017.0463.

45. Bosshard R, Oreilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treatment Reviews. 2018;69:224-232. doi:10.1016/j.ctrv.2018.07.005.

46. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107(9):3481-3485. doi:10.1182/blood-2005-09-3724.

47. Kouchkovsky ID, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update.' Blood Cancer Journal. 2016;6(7). doi:10.1038/bcj.2016.50.

48. Winslow T, Kibiuk L. *Stem Cell Information: Bone Marrow (Hematopoietic) Stem Cells*. National Institutes of Health; 2001. https://stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter2.htm. Accessed February 22, 2020.

49. Bone Marrow (Hematopoietic) Stem Cells. National Institutes of Health. https://stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter2.htm. Accessed March 1, 2020.

50. Döhner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115(3):453-474. doi:10.1182/blood-2009-07-235358.

51. Larson RA. Acute myeloid leukemia: Treatment and outcomes in older adults. In: *UpToDate*. Waltham, MA: UpToDate; 2020.

52. Master S, Koshy N. *ASH Image Bank.* American Society of Hematology; 2018. https://imagebank.hematology.org/image/61241/figure-1-peripheral-blood-smear-at-50-x-magnification. Accessed February 22, 2020.

53. Rodin G, Yuen D, Mischitelle A, et al. Traumatic stress in acute leukemia. Psycho-Oncology. 2011. doi:10.1002/pon.2092.

54. Ghodraty-Jabloo V, Alibhai SMH, Breunis H, Puts MTE. Keep your mind off negative things: coping with long-term effects of acute myeloid leukemia (AML). Supportive Care in Cancer.
2015;24(5):2035-2045. doi:10.1007/s00520-015-3002-4.

55. Nissim R, Zimmermann C, Minden M, et al. Abducted by the illness: A qualitative study of traumatic stress in individuals with acute leukemia. Leukemia Research. 2013;37(5):496-502. doi:10.1016/j.leukres.2012.12.007.

56. Zittoun R, Achard S, Ruszniewski M. Assessment of quality of life during intensive chemotherapy or bone marrow transplantation. Psycho-Oncology. 1999;8(1):64-73. doi:10.1002/(sici)1099-1611(199901/02)8:1<64::aid-pon337>3.0.co;2-r.

57. Sekeres MA, Stone RM, Zahrieh D, et al. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. Leukemia. 2004;18(4):809-816. doi:10.1038/sj.leu.2403289.

58. El-Jawahri A, Abel GA, Traeger L, et al. Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy. Leukemia. 2019;33(10):2393-2402. doi:10.1038/s41375-019-0449-1

59. Wang R, Zeidan AM, Halene S, et al. Health Care Use by Older Adults With Acute Myeloid Leukemia at the End of Life. Journal of Clinical Oncology. 2017;35(30):3417-3424. doi:10.1200/jco.2017.72.7149

60. Oliva EN, Nobile F, Alimena G, et al. Quality of life in elderly patients with acute myeloid leukemia: patients may be more accurate than physicians. Haematologica. 2011;96(5):696-702. doi:10.3324/haematol.2010.036715

61. Mausbach BT, Irwin SA. Depression and healthcare service utilization in patients with cancer. Psycho-Oncology. 2016;26(8):1133-1139. doi:10.1002/pon.4133

62. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychological Medicine. 2010;40(11):1797-1810. doi:10.1017/s0033291709992285

63. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients. Cancer. 2009;115(22):5349-5361. doi:10.1002/cncr.24561

64. Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. International Review of Psychiatry. 2014;26(1):16-30. doi:10.3109/09540261.2013.875891

65. Odejide OO, Uno H, Murillo A, Tulsky JA, Abel GA. Goals of care discussions for patients with blood cancers: Association of person, place, and time with end-of-life care utilization. Cancer. 2019;126(3):515-522. doi:10.1002/cncr.32549

66. Hui D, Bansal S, Park M, et al. Differences in attitudes and beliefs toward end-of-life care between hematologic and solid tumor oncology specialists. Annals of Oncology. 2015;26(7):1440-1446. doi:10.1093/annonc/mdv028

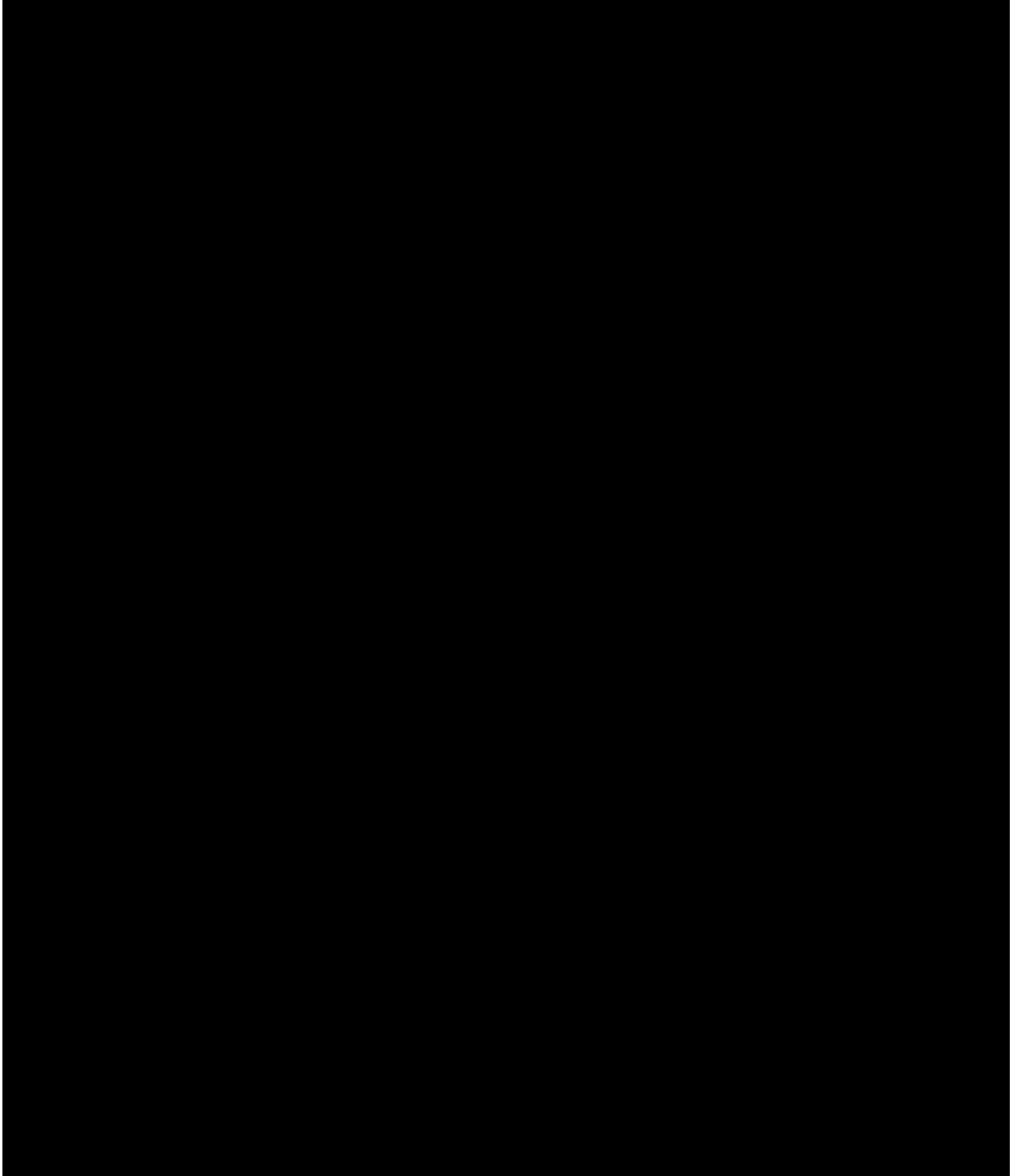
67. El-Jawahri A, LeBlanc TW, Kavanaugh A, et al. Multi-Site randomized trial of integrated palliative and oncology care for patients with acute myeloid leukemia (AML). Unpublished data, February 2020.

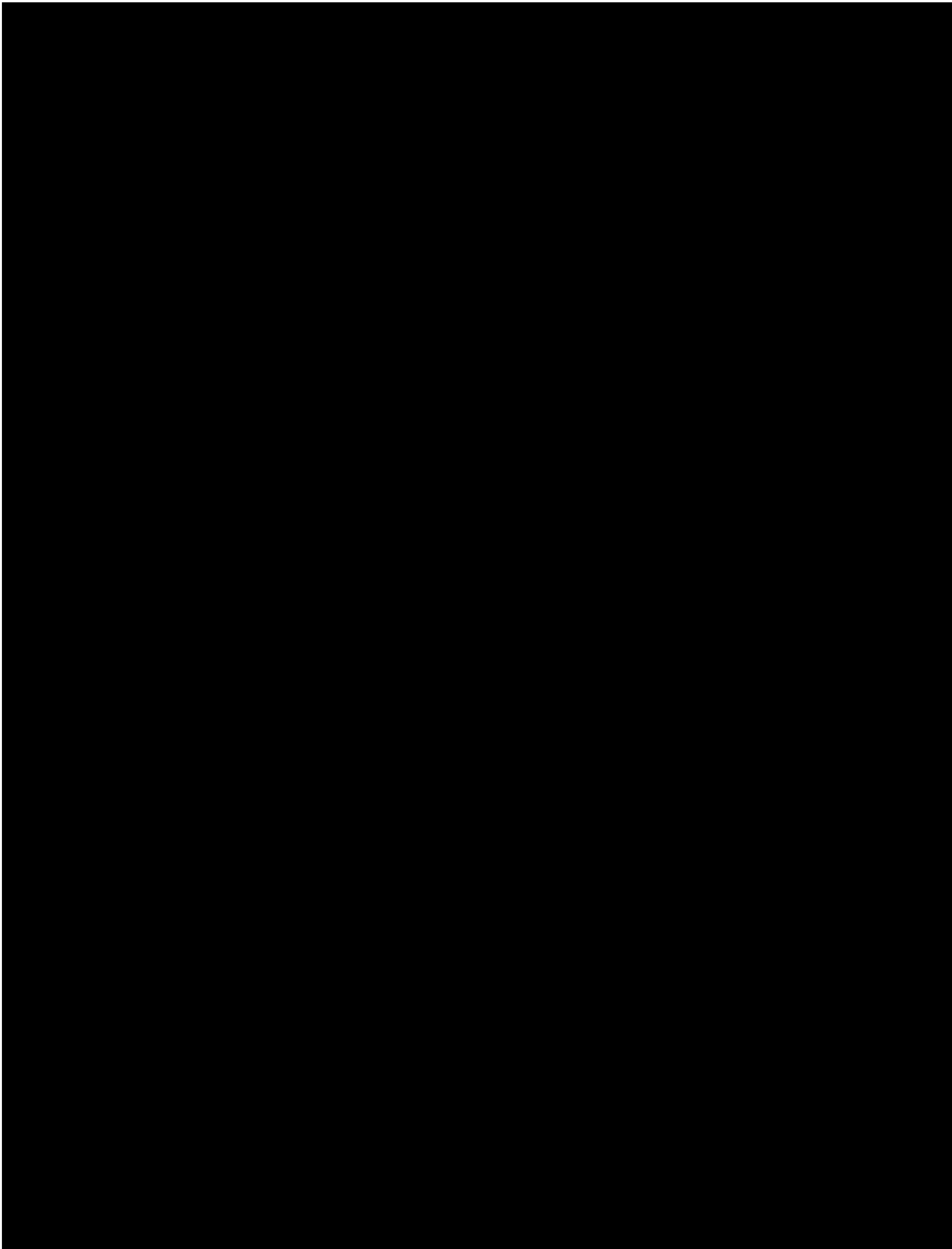
68. Cella D, Jensen SE, Webster K, et al. Measuring Health-Related Quality of Life in Leukemia: The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) Questionnaire. Value in Health. 2012;15(8):1051-1058. doi:10.1016/j.jval.2012.08.2210

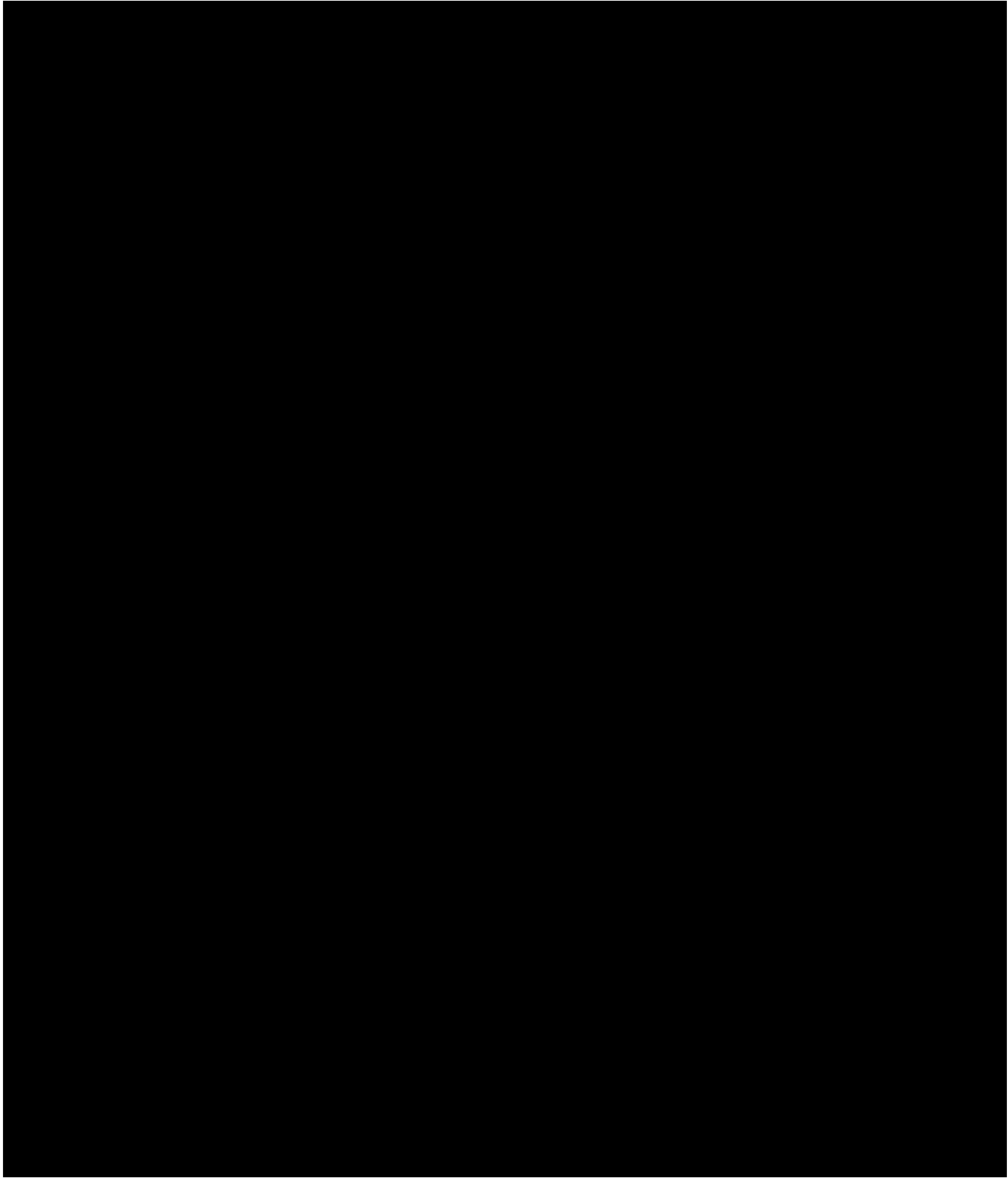
69. Zigmond AS, Snaith RP. Hospital Anxiety and Depression Scale. PsycTESTS Dataset. 1983. doi:10.1037/t03589-000

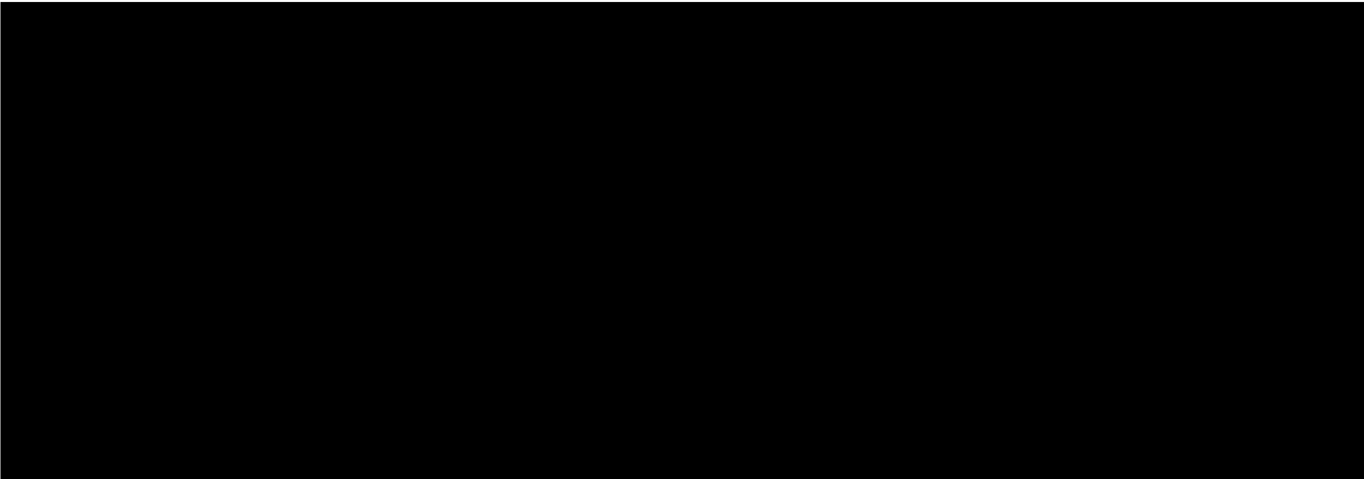
70. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. Journal of General Internal Medicine. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

CURRICULUM VITAE









62