Portable Medical Orders and End of Life Measures in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Tracking no: ADV-2021-004775R2

Marissa Locastro (University of Rochester School of Medicine and Dentistry, United States) Andrea Baran (University of Rochester Medical Center, United States) Jane Liesveld (University of Rochester, United States) Michael Becker (University of Rochester, United States) Kristen O'Dwyer (University of Rochester Medical Center, United States) Omar Aljitawi (University of Rochester Medical Center, United States) Megan Baumgart (University of Rochester Medical Center, United States) Eric Snyder (University of Rochester Medical Center, United States) Benzi Kluger (University of Rochester Medical Center, United States) Jason Mendler (University of Rochester Medical Center, United States) Kah Poh Loh (University of Rochester Medical Center, United States)

Abstract:
Patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) experience high rates of hospitalization, intensive care unit (ICU) admissions, and in-hospital deaths at end of life (EOL). Early goals-of-care (GOC) discussions might reduce intensity of care at EOL. Portable Medical Order (POLST) forms, known as Medical Orders for Life Sustaining Treatment (MOLST) forms in New York State, allow patients to translate GOC discussions into specific medical orders that communicate their wishes during a medical emergency. To determine if timing of MOLST form completion might be associated with EOL care in patients with AML and MDS. We conducted a retrospective study of 358 adult patients with AML and MDS treated at a single academic center and/or its affiliated sites and who died over a five year period. One-third of patients completed at least one MOLST form >30 days prior to death. Compared to patients who completed a MOLST form within 30 days of death or never completed a MOLST form, those who completed a MOLST form >30 days prior to death were less likely to receive transfusion [Adjusted Odds ratio (AOR) 0.39, p<0.01], chemotherapy (AOR 0.24, p<0.01), life-sustaining treatments (AOR 0.21, p<0.01), or to be admitted to the ICU (AOR 0.21, p<0.01) at EOL. They were also more likely to utilize hospice (AOR 2.72, p<0.01). Earlier MOLST form completion was associated with lower intensity of care at EOL in patients with MDS and AML.

Conflict of interest: COI declared - see note

COI notes: Dr. Loh has served as a consultant to Pfizer and Seattle Genetics. The remaining authors declare that they have no conflicts of interest. All other authors have no relevant conflicts of interest to report.

Preprint server: No;

Author contributions and disclosures: M.L., K.P.L., and J.H.M conceived and designed the study; A.M.B, performed the analyses; M.L. acquired the data, M.L., K.P.L., and J.H.M. wrote the manuscript; and all authors interpreted the data and critically revised the manuscript.

Non-author contributions and disclosures: Yes; We wish to acknowledge Dr. Susan Rosenthal, MD, for her editorial assistance.

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact jason_mendler@urmc.rochester.edu.

Clinical trial registration information (if any):
Title: Portable Medical Orders and End-of-Life Measures in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Running Title: Portable medical orders & EOL measures in AML/MDS

Marissa LoCastro, BS1  
Andrea M. Baran, MS2  
Jane L. Liesveld, MD2  
Eric Huselton, MD2  
Michael W. Becker, MD2  
Kristen Marie O’Dwyer, MD2  
Omar S. Aljitawi, MD2  
Megan Baumgart, MD2  
Eric Snyder2  
Benzi Kluger, MD, MS3,4  
Kah Poh Loh, MBBCH BAQ2*  
Jason H. Mendler, MD, PhD2*  
marissa_locastro@urmc.rochester.edu  
andrea_baran@urmc.rochester.edu  
jane_liesveld@urmc.rochester.edu  
eric_huselton@urmc.rochester.edu  
michael_becker@urmc.rochester.edu  
kristen_odwyer@urmc.rochester.edu  
omar_aljitawi@urmc.rochester.edu  
megan_baumgart@urmc.rochester.edu  
eric_snyder@urmc.rochester.edu  
benzi_kluger@urmc.rochester.edu  
kahpoh_loh@urmc.rochester.edu  
jason_mendler@urmc.rochester.edu

1School of Medicine and Dentistry, University of Rochester, Rochester, NY  
2Division of Hematology/Oncology, Department of Medicine, James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY  
3Department of Neurology, University of Rochester Medical Center, Rochester, NY  
4Division of Palliative Care, Department of Medicine, University of Rochester Medical Center, Rochester, NY  
*The authors contributed equally

Corresponding Author:  
Jason H. Mendler, MD, PhD  
James P. Wilmot Cancer Center  
University of Rochester School of Medicine and Dentistry  
601 Elmwood Avenue, Box 704  
Rochester, NY 14624  
Phone: 585-276-4354  
Email: jason_mendler@urmc.rochester.edu

Word count: 3,526
Abstract: 240
Keywords: Portable medical orders, end of life measures, hematologic malignancies, AML, MDS, MOLST, POLST
Tables: 4
Figure: 5
Supplemental Table: 0
References: 30
Key Points:

1) AML/MDS patients often receive high intensity care near end of life, including admission to hospital/ICU and life sustaining treatments.
2) Completion of a portable medical order form > 30 days before death was associated with lower intensity care near end of life.
Abstract (max: 237; current: 237)

Patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) experience high rates of hospitalization, intensive care unit (ICU) admissions, and in-hospital deaths at end of life (EOL). Early goals-of-care (GOC) discussions might reduce intensity of care at EOL. Portable Medical Order (POLST) forms, known as Medical Orders for Life Sustaining Treatment (MOLST) forms in New York State, allow patients to translate GOC discussions into specific medical orders that communicate their wishes during a medical emergency. To determine if timing of MOLST form completion might be associated with EOL care in patients with AML and MDS. We conducted a retrospective study of 358 adult patients with AML and MDS treated at a single academic center and/or its affiliated sites and who died over a five year period. One-third of patients completed at least one MOLST form >30 days prior to death. Compared to patients who completed a MOLST form within 30 days of death or never completed a MOLST form, those who completed a MOLST form >30 days prior to death were less likely to receive transfusion [Adjusted Odds ratio (AOR) 0.39, p<0.01], chemotherapy (AOR 0.24, p<0.01), life-sustaining treatments (AOR 0.21, p<0.01), or to be admitted to the ICU (AOR 0.21, p<0.01) at EOL. They were also more likely to utilize hospice (AOR 2.72, p<0.01). Earlier MOLST form completion was associated with lower intensity of care at EOL in patients with MDS and AML.

Introduction
Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are two life threatening hematologic malignancies that often require intensive supportive therapy. Despite many advances in treatment, these diseases prove fatal for a majority of patients. Patients with hematologic malignancies are more likely to receive high intensity care at end of life (EOL) than patients with solid tumors.\(^1\)\(^-\)\(^3\) Studies focused on EOL care in AML have demonstrated high rates of hospitalization within the last 30 days of life, intensive care unit (ICU) admission within the last 30 days of life, and in-hospital death, as well as low utilization of hospice services.\(^1\)\(^-\)\(^5\) In a Surveillance, Epidemiology, and End Results (SEER)-Medicare database study of patients with MDS, 28% of patients were admitted to the ICU within the last 30 days of life and 49% were enrolled in hospice.\(^5\) While in some cases high intensity care leads to remissions and cures, it often does not. High intensity care is associated with worse quality of life near the EOL.\(^6\)\(^,7\) In patients with incurable hematologic malignancies, high intensity EOL care occurs for a variety of reasons including patients’ desire for all available medical interventions, patients’/family members’ difficulty understanding the limitations of life-sustaining treatments,\(^8\)\(^-\)\(^10\) lack of provider training to have GOC conversations,\(^10\) provider concern about taking away hope,\(^11\) unrealistic clinician expectations,\(^11\) and provider uncertainty about prognosis.\(^8\)\(^-\)\(^12\) These issues may contribute to circumstances where patients receive futile or unwanted medical care that ultimately does not improve their outcomes or EOL experience.

Early palliative care referrals and/or early goals-of-care (GOC) discussions may limit the intensity of care near EOL for patients with hematologic malignancies.\(^12\) In a study that included 366 patients with advanced cancer (29 of whom had hematologic
malignancy), palliative care referrals made more than 3 months before death were associated with decreased emergency department (ED) visits/hospitalizations within the last 30 days of life and decreased likelihood of death in the hospital. In a separate study focused on patients with hematologic malignancies using the SEER-Medicare registry, the use of “early” billed palliative care services (initiated >30 days before death) was associated with a lower likelihood of ED visits/hospitalizations/ICU admissions in the last 30 days of life and a lower likelihood of inpatient death. Another study of 383 patients with hematologic malignancies showed that having the first GOC discussion >30 days before death and having a hematologic oncologist present were associated with lower odds of ICU admission within the last 30 days of life and earlier hospice use. More studies are needed to determine the impact of early GOC discussions on EOL measures in specific subsets of hematologic malignancies, such as AML and MDS, which generally have poorer prognoses than other hematologic malignancies such as lymphoma and multiple myeloma.

Portable Medical Order (POLST; polst.org) forms are designed for people who are seriously ill to translate GOC discussions into specific medical orders that communicate patients’ wishes during a medical emergency. These orders usually include patient preferences for several medical interventions including cardiopulmonary resuscitation). In studies conducted primarily in patients with solid tumors, POLST forms were completed in a minority of patients (22-35%) and associated with a decreased likelihood of in-hospital death and increased utilization of hospice. Little is known
about utilization of POLST forms in specific subsets of hematologic malignancies and its association with EOL measures.

The goal of this study was to better understand utilization of POLST forms in patients with AML and MDS and assess its association with EOL measures.

Methods:

Study Design, Setting, and Sample

We conducted a retrospective study of consecutive patients aged 18 years and older with AML and MDS treated at a single academic cancer center and its affiliated practices and who died between January 1, 2014, and December 31, 2019. This research received approval by the University of Rochester Research Subjects Review Board.

Data Collection

A trained investigator (ML) extracted demographic and clinical information from the electronic medical record which contains data from the two largest healthcare systems in Rochester, New York, as well as scanned notes from other healthcare systems. Demographic data included age at diagnosis, gender, race/ethnicity, and zip code (used to categorize urban vs. rural based on the 2010 Rural-Urban Commuting Areas Codes (RUCAs) Categorization C.\textsuperscript{17,18} Clinical data included all comorbidities (without the use of standard comorbidity indices), ECOG, Eastern Cooperative Oncology Group (ECOG) performance, diagnosis (AML and/or MDS), intent of care as stated in the treating oncologist’s note (curative, palliative, or not stated). We also collected dates of palliative
care referral and visit. Any ambiguous cases were discussed with senior authors (KPL and/or JHM).

**POLST form [also known as Medical Orders for Life-Sustaining Treatment (MOLST) in New York State]**

MOLST form data was extracted from the electronic medical record (only data from scanned forms were used). For each patient, the number of MOLST forms completed with the date of each form was recorded. Data collected from each MOLST form included patient preference for cardiac resuscitation, intubation, future hospitalization/transfer, artificially administered fluids and nutrition (i.e., feeding tube and intravenous fluids), and antibiotics. In addition, we also recorded which individual completed the MOLST form (i.e., oncologist vs. other). Throughout the study period, there were no changes in how POLSTs were filled out, entered into the medical record, or displayed in the medical record during the study period.

**EOL Measures**

We collected EOL measures that have been established in published studies and are endorsed by the American Society of Clinical Oncology (ASCO).\(^1\)\(^-\)\(^4\) These EOL measures include: 1) Place of death (hospital, home or other), 2) Transfusion within the last 7 days of life, 3) Utilization of life-sustaining treatment (e.g., mechanical ventilation, vasopressors, tracheostomy, dialysis for acute kidney injury, percutaneous endoscopic gastrostomy, and cardiopulmonary resuscitation)\(^19\), 3) hospital, emergency department
(ED) and intensive care unit (ICU) use within the last 30 days of life, 4) Chemotherapy administration within the last 14 days of life, and 5) Hospice enrollment.

**Statistical Analyses**

Descriptive statistics including medians and interquartile ranges (IQR) for continuous variables and counts and proportions for categorical variables were used to describe the study population as a whole and within AML and MDS cohorts. We summarized time from first hematology visit, MOLST form completion (including who completed the MOLST), palliative care referral, palliative care visit, and hospice enrollment to date of death within the AML and MDS cohorts to understand the timing of these interventions. Among patients that completed a MOLST form, we compared time from MOLST form completion to death between specialty of provider who completed the MOLST using the non-parametric Kruskal-Wallis test.

To better understand the timing of MOLST form completion and palliative care referral/visit relative to first hematology visit, we used cumulative incidence functions to estimate the probability of MOLST form completion and palliative care referral/visit within 12 weeks of the first hematology visit, accounting for the competing risk of death. We chose 12 weeks as ASCO recommends palliative care referral within 8 weeks of the first hematology visit. Because many patients in this study did not have their diagnosis at the time of first visit, we chose to extend the time to 12 weeks to account for the diagnostic time.
To evaluate the association of MOLST form completion with EOL measures, we divided the patients into those who completed a first MOLST form more than 30 days prior to death (early) vs those who never completed or completed a first MOLST form within 30 days of death (delayed). We chose 30 days based on the ASCO Quality Oncology Practice Initiatives and a prior study.\textsuperscript{21} In addition, given many of our EOL measures were defined within 30 days of death, using a cut-off of 30 days rather than defining yes/no for MOLST form completion eliminated cases where MOLST form occurred after the outcome (e.g., hospice enrollment). We did not exclude patients who survived less than 30 days from their AML or MDS diagnosis. Fisher’s exact test was used to identify patient characteristics associated with early MOLST completion. We used multivariate logistic regression to model the association of early MOLST completion on EOL measures, adjusted for age, race, number of comorbidities, diagnosis, disease status at first hematology visit, and geographical location (rural vs. urban). We did not include ECOG and intent of care in the models due to large numbers of missing data. We explored interactions between early MOLST completion and each adjustment variable; significant interactions are highlighted in the Results section.

For sensitivity analyses, we excluded patients who died within the first 30 days of diagnosis and repeat the multivariate logistic regression. All reported p-values are two-sided, with p<0.05 considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

\textit{Data Sharing Statement}
Results:

Demographics

We included 358 patients; 238 had AML and 120 had MDS (Table 1). Among patients with AML, the median age was 67 years (range 20-95) and 84% were white. The median age of patients with MDS was 75 years (range 26-93). Median times from first hematology visit to death in patients with AML and MDS were 9.8 months (IQR 18.3) and 17.9 months (IQR 28.1), respectively.

MOLST Forms

Of 358 patients, 12 had transferred to our institution, so data on MOLST form completion was unavailable. A large proportion (85.8%, 297/346) of patients had completed a MOLST form prior to death. One-third of patients (118/346) completed a first MOLST form more than 30 days prior to death; 51.7% (179/346) completed a first MOLST form within 30 days of death, and 14.2 % (49/346) never completed a MOLST form.

Among those who had a MOLST form completed prior to death, 4.0% (12/297) were completed prior to the initial hematology visit and 96.0% (285/297) were completed on the date of or after the initial hematology visit. Approximately two-thirds (184/297; 61.6%) had one, 29.6% (88/297) had two, and 8.4% (25/297) had three or more MOLST forms completed; 5.1% (15/297) of the first MOLST forms were full code. Do-Not-Resuscitate (DNR) and Do-Not-Intubate (DNI) orders occurred in 72.7% (216/297),

For original data, please contact jason_mendler@urmc.rochester.edu.
DNR only orders occurred in 21.6% (64/297), and DNI only orders occurred in 0.7% (2/297). Preferences for future hospitalization/transfer (19.2%, 57/297), feeding tube (25.9%, 77/297), intravenous fluids (16.5%, 49/297), and antibiotics (26.6%, 79/297) were indicated (Figure 1). The primary oncologist completed the first MOLST form in 19.5% (58/297); the remaining MOLST forms were completed by other oncologists (25.6%, 76/297), hospitalist/medicine providers (9.8%, 29/297), ICU providers (18.5%, 55/297), palliative care providers (8.1%, 24/297), or other (5.1%, 15/297). We were not able to determine the clinician subspecialty (unclear) in 13.5% (40/297), usually because the signature on the MOLST form was unreadable. Time from initial MOLST form completion to death, as a function of clinician subspecialty, is shown in Figure 2; there was a significant difference among the various specialties (p<0.0001). Among patients who had either DNR and/or DNI orders (N=282), 4 patients changed to full code in a subsequent MOLST (Figure 3). Among patients who did not have DNR/DNI orders (15/297) in the first MOLST, 11 patients changed to DNR and/or DNI in a subsequent MOLST.

Compared to those who completed a MOLST form within 30 days of death or never completed a MOLST form, those who completed a MOLST form more than 30 days prior to death were more likely to be older (median 73.5 vs. 67.0 years, p<0.0001), have more comorbidities (median 4 vs. 3, p=0.01), and have palliative intent documented in their medical record (52.5 vs. 38.6%, p=0.03) (Table 2).

EOL Measures
Figure 4 shows the EOL measures for AML and MDS. Life-sustaining treatment was utilized in 36.8% (82/223) and 34.6% (38/110) of patients with AML and MDS, respectively, within the last 30 days of life. Figure 5 demonstrates the utilization of various life-sustaining treatments in patients with AML and MDS. Among patients with AML (N=223), 14.8%, 12.1%, and 9.9% utilized one, two, and three or more types of life-sustaining treatment, respectively. Among patients with MDS (N=110), 17.3%, 7.3%, and 10% utilized one, two, and three or more types of life-sustaining treatment, respectively. In terms of hospice, 46.1% of patients with AML (N=105) and 49.1% of patients with MDS (N=55) were enrolled; 27.2% (N=62) and 28.6% (N=32) of patients with AML and MDS were enrolled for more than 3 days, respectively. For those who were on hospice (N=160), median length of time in hospice was 4.5 days (IQR 8 days).

Table 3 demonstrates the timing from MOLST form completion, palliative care referral, palliative care visit, and hospice enrollment to date of death. The probability of palliative care referral, palliative care visit, and completing a MOLST form within 12 weeks of diagnosis was 16.7%, 16.2% and 23.7%, respectively for AML. The probability of palliative care referral, palliative care visit, and completing a MOLST form within 12 weeks of diagnosis was 7.1%, 6.3% and 12.0%, respectively for MDS.

**Multivariate Analyses**

On multivariate analyses, early MOLST form completion (versus delayed MOLST form completion or MOLST form never completed) was associated with lower utilization of transfusion [Adjusted Odds Ratio (AOR) 0.39, 95% Confidence Interval
(CI) 0.24-0.64, p=0.0002], life-sustaining treatment (AOR 0.21, 95% CI 0.11-0.38, p<0.0001), ICU admission (AOR 0.21, 95% CI 0.11-0.39, p<0.0001), and chemotherapy utilization (AOR 0.24, 95% CI 0.10-0.59, p=0.002) near EOL, as well as higher utilization of hospice (AOR 2.69, 95% CI 1.66-4.38, p<0.0001) as well as hospice for more than 3 days (AOR 2.50, 95% CI 1.49-4.17, p=0.001; Table 4a/b). A significant interaction was found between early MOLST form completion and diagnosis for inpatient death (p=0.01) and hospitalization (p=0.005). Among patients with AML, early MOLST form completion was associated with lower odds of inpatient death (AOR 0.25, 95% CI 0.12-0.51, p=0.0001) and hospitalization (AOR 0.15, 95% CI 0.06-0.37, p<0.0001) near the EOL. Among patients with MDS, early MOLST form completion was not significantly associated with inpatient death (AOR 1.09, 95% CI 0.44-2.69, p=0.85) or hospitalization (AOR 0.99, 95% CI 0.37-2.67, p=0.99) near the EOL.

In our sensitivity analyses, after excluding 29 patients who died within the first 30 days of diagnosis, multivariate logistic regression demonstrated similar results.

Discussion:

It is critical to understand the EOL experience for patients with AML and MDS to ensure patient preferences are accounted for in decision making. We found that a majority of patients died in the hospital and that greater than one third were in the ICU and on life-sustaining treatment near EOL. MOLST form completion, palliative care referrals/visits, and hospice enrollment generally occurred very close to the time of death.
Patients who completed a MOLST form early (versus late or never) were less likely to receive high intensity care near the EOL.

Relatively few studies have explored EOL care in the MDS and AML patient populations.3,22 Our findings confirm those of others, demonstrating that most patients with AML are hospitalized near EOL,23 die in the hospital,23 receive initial palliative care services within the last 2 weeks of life,23 and receive hospice services less than 7 days before death.3,4 Our finding that approximately one-third of patients with AML and MDS are admitted to the ICU within the last 30 days of life is also consistent with other studies.3-5 To our knowledge, our study is the first to investigate how MOLST forms are utilized in the MDS and AML patient populations and their associations with EOL measures. In prior studies of solid tumors, POLST forms were completed in 22-35% of patients, compared to over 80% in our study.15,16 The higher rate of MOLST form completion may be due to a higher frequency of healthcare contacts in AML and MDS and a high proportion of patients being hospitalized near the EOL.3 However, it is important to note that only one-third of patients completed these forms more than 30 days before death. Those who completed MOLST forms early were less likely to be admitted to or die in the hospital (patients with AML only), to be admitted to the ICU, and to receive blood transfusions, chemotherapy, and life-sustaining treatments near EOL, and more likely to enroll in hospice compared to those who completed MOLST forms late or never completed MOLST forms. Our findings suggest that early MOLST completion, reflecting early GOC discussions, may result in lower intensity of care at EOL in patients with AML and MDS. In this regard, our data confirm and extend those of Odejide and
colleagues who found that early GOC discussions were associated with decreased ICU admissions within the last 30 days of life\textsuperscript{14} in patients with hematologic malignancies.

Our study raises the question of why GOC discussions and MOLST form completion do not occur earlier in patients with AML and MDS. Barriers may include unrealistic patient/family member expectations,\textsuperscript{11,24,25} patients’/family members’ difficulty accepting a poor prognosis,\textsuperscript{8-10,24} patients’ desire for aggressive treatment,\textsuperscript{10,24} patients’ incapacity to make GOC decisions,\textsuperscript{8,9} patients’/family members’ difficulty understanding the limitations of life-sustaining treatments,\textsuperscript{8-10} lack of family agreement about GOC,\textsuperscript{8-10} lack of provider training to have GOC conversations,\textsuperscript{10} provider concern about taking away hope,\textsuperscript{11} unrealistic clinician expectations\textsuperscript{11}, and provider uncertainty about prognosis.\textsuperscript{11} In patients with hematologic malignancies, healthcare providers have difficulty identifying the EOL phase as a result of the continuing potential for cure of advanced disease and the often-rapid pace of decline near death. It is often challenging for patients and physicians to not be “aggressive” when there is still a potential for cure. In this regard, “signposts” have been developed to help identify the EOL phase in patients with hematologic malignancies.\textsuperscript{11} Importantly, most studies addressing barriers to discussing EOL care are from the perspective of healthcare providers. Studies from patients’ perspectives are needed to determine their willingness to discuss preferences for EOL care earlier in the disease course.

According to the national POLST program, POLST form completion is appropriate for patients with serious illness or frailty whose health care provider would
not be surprised if they died within a year. We would argue that this definition applies to a large percentage of AML and MDS patients, particularly older patients or younger patients with relapsed/refractory or high-risk disease (e.g., those with complex cytogenetics or TP53 mutations). It is our belief that chemotherapy (even if given with curative intent) and GOC discussions/POLST form completion could occur concurrently in these patient populations so that patients have a realistic view of treatment outcomes and a chance to set limits on the intensiveness of EOL care should they so choose. As a prior study suggested, hematologic oncologist participation in GOC discussions/POLST completion may be important in guiding the use of intensive treatments and hospice care.

Our study has limitations. First, our study included patients who died over a time period (retrospective) rather than patients who were dying (prospective). Since it is impossible to accurately predict death, it raises the utility of using a cut-off point for MOLST completion prior to death. Nonetheless, our study informs the need to investigate utilization of POLST forms in a population that is likely going to die (e.g., poor-risk AML or high-risk MDS, relapsed AML) and prospectively evaluate the association of MOLST form completion with EOL measures. Second, we acknowledge that patients may have engaged in early GOC discussions but not completed a MOLST form because their preference was for no limitations to care. MOLST forms may also have been completed and not scanned into the electronic medical record. Third, while our electronic medical record contains data from the two largest healthcare systems in Rochester, New York, and scanned notes from other healthcare systems, data may be missing among patients who received some of their care outside of our system. Forth, although our study
demonstrates an association between early MOLST form completion and EOL measures, it does not establish causation. Completion of a MOLST form may be a proxy for disease progression, illness severity, or transition from disease- to comfort-oriented care, and these patients may have been less likely to utilize aggressive care due to perceived futility. That said, our findings are consistent with other studies that have demonstrated a benefit of early GOC discussions on EOL measures in patients with cancer.\textsuperscript{6,14,28,29} Moreover, our findings support National Comprehensive Cancer Network (NCCN) palliative care guidelines recommending that GOC discussions begin while patients have a life expectancy of years-to-months and that decisions should be documented in the medical record, including MOLST/POLST.\textsuperscript{30} Fifth, MOLST/POLST forms are specific to the United States, and the content of these forms varies across states. Thus, the generalizability of our findings to other countries and states will need to be determined. Third, the single-center design and lack of racial/ethnic diversity may also limit the generalizability of our findings. Sixth, while we did adjust our analysis for patient comorbidities, we did not adjust for disease related characteristics that may impact EOL measures. Despite these limitations, this study provides important data to justify the development of intervention studies to prospectively evaluate the effects of early POLST/MOLST form completion on EOL care for patients with AML and MDS.

In conclusion, we have found that AML and MDS patients often receive high intensity care near EOL and that early MOLST completion is associated with lower intensity EOL care. Future studies should be aimed at better understanding patients’ wishes regarding care near EOL, their perceptions of what constitutes patient-centered
EOL care, their willingness to engage in earlier GOC conversations, and the impact of early GOC discussions/MOLST form completion on EOL measures.

Acknowledgments:

This research study was supported by LoGerfo Medical Student Fellowship through the University of Rochester Medical Center (to LoCastro). Dr. Loh is supported by the National Cancer Institute at the National Institute of Health (K99CA237744) and the Wilmot Research Fellowship Award. We wish to acknowledge Dr. Susan Rosenthal, MD, for her editorial assistance.

Author Contributions:

Contribution: M.L., K.P.L., and J.H.M conceived and designed the study; A.M.B, performed the analyses; M.L. acquired the data, M.L., K.P.L., and J.H.M. wrote the manuscript; and all authors interpreted the data and critically revised the manuscript.

Conflicts of Interest Disclosure:

Dr. Loh has served as a consultant to Pfizer and Seattle Genetics. The remaining authors declare that they have no conflicts of interest. All other authors have no relevant conflicts of interest to report.
References

1. Verhoef MJ, de Nijs EJM, Ootjers CS, et al. End-of-Life Trajectories of Patients With Hematological Malignancies and Patients With Advanced Solid Tumors Visiting the Emergency Department: The Need for a Proactive Integrated Care Approach. *Am J Hosp Palliat Care.* 2020;37(9):692-700.

2. 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.

3. El-Jawahri AR, Abel GA, Steensma DP, et al. Health care utilization and end-of-life care for older patients with acute myeloid leukemia. *Cancer.* 2015;121(16):2840-2848.

4. Wang R, Zeidan AM, Halene S, et al. Health Care Use by Older Adults With Acute Myeloid Leukemia at the End of Life. *J Clin Oncol.* 2017;35(30):3417-3424.

5. Fletcher SA, Cronin AM, Zeidan AM, et al. Intensity of end-of-life care for patients with myelodysplastic syndromes: Findings from a large national database. *Cancer.* 2016;122(8):1209-1215.

6. Zhang B, Nilsson ME, Prigerson HG. Factors important to patients' quality of life at the end of life. *Arch Intern Med.* 2012;172(15):1133-1142.

7. Hales S, Chiu A, Husain A, et al. The quality of dying and death in cancer and its relationship to palliative care and place of death. *J Pain Symptom Manage.* 2014;48(5):839-851.

8. Piggott KL, Patel A, Wong A, et al. Breaking silence: a survey of barriers to goals of care discussions from the perspective of oncology practitioners. *BMC Cancer.* 2019;19(1):130.

9. You JJ, Downar J, Fowler RA, et al. Barriers to goals of care discussions with seriously ill hospitalized patients and their families: a multicenter survey of clinicians. *JAMA Intern Med.* 2015;175(4):549-556.

10. Maradana S, Kate Y, Pandey D, et al. Barriers to goals of care discussion and early palliative care referral in patients with advanced cancer: A community oncology clinic survey. *Journal of Clinical Oncology.* 2020;38(15_suppl):e19199-e19199.

11. Odejide OO, Salas Coronado DY, Watts CD, Wright AA, Abel GA. End-of-life care for blood cancers: a series of focus groups with hematologic oncologists. *J Oncol Pract.* 2014;10(6):e396-403.

12. Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer.* 2014;120(11):1743-1749.

13. Rao V, Olszewski A, Egan P, LeBlanc T, Belanger E. Billed palliative care services and end-of-life care in patients with hematologic malignancies. *2019 Supportive Care in Oncology Symposium.* 2019.

14. 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.* 2020;126(3):515-522.
15. Nugent SM, Slatore CG, Ganzini L, et al. POLST Registration and Associated Outcomes Among Veterans With Advanced-Stage Lung Cancer. *Am J Hosp Palliat Care*. 2019;36(7):564-570.
16. Pedraza SL, Culp S, Knestrick M, Falkenstine E, Moss AH. Association of Physician Orders for Life-Sustaining Treatment Form Use With End-of-Life Care Quality Metrics in Patients With Cancer. *J Oncol Pract*. 2017;13(10):e881-e888.
17. WWAMI. Rural Health Research Center. Using RUCA Data. [http://depts.washington.edu/uwruca/ruca-uses.php](http://depts.washington.edu/uwruca/ruca-uses.php); 2017. [Accessed May 23, 2021].
18. USDA. Rural-Urban Commuting Area Codes. [https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/](https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/); 2020. [Accessed May 23, 2021].
19. Loh KP, Abdallah M, Shieh MS, et al. Use of Inpatient Palliative Care Services in Patients With Advanced Cancer Receiving Critical Care Therapies. *J Natl Compr Canc Netw*. 2018;16(9):1055-1064.
20. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35(1):96-112.
21. Odejide OO, Cronin AM, Earle CC, Tulsky JA, Abel GA. Why are patients with blood cancers more likely to die without hospice? *Cancer*. 2017;123(17):3377-3384.
22. 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.
23. Foster J, Blonquist TM, El-Jawahri A, et al. The End of Life for Patients with Acute Myeloid Leukemia (AML)- a Single Center Experience. *Blood*. 2015;126(23):3318-3318.
24. Ethier JL, Paramsothy T, You JJ, Fowler R, Gandhi S. Perceived Barriers to Goals of Care Discussions With Patients With Advanced Cancer and Their Families in the Ambulatory Setting: A Multicenter Survey of Oncologists. *J Palliat Care*. 2018;33(3):125-142.
25. Loh KP, Xu H, Back A, et al. Patient-hematologist discordance in perceived chance of cure in hematologic malignancies: A multicenter study. *Cancer*. 2020;126(6):1306-1314.
26. Bach PB, Schrag D, Beg CB. Resurrecting treatment histories of dead patients: a study design that should be laid to rest. *Jama*. 2004;292(22):2765-2770.
27. Duberstein PR, Chen M, Hoerger M, et al. Conceptualizing and Counting Discretionary Utilization in the Final 100 Days of Life: A Scoping Review. *J Pain Symptom Manage*. 2020;59(4):894-915.e814.
28. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *J Clin Oncol*. 2012;30(35):4387-4395.
29. Doll KM, Stine JE, Van Le L, et al. Outpatient end of life discussions shorten hospital admissions in gynecologic oncology patients. *Gynecol Oncol*. 2013;130(1):152-155.
30. Dans M, Smith T, Back A, et al. NCCN Guidelines Insights: Palliative Care, Version 2.2017. *J Natl Compr Canc Netw*. 2017;15(8):989-997.
| Table 1: Characteristics of the study sample | All Patients, N=358 | AML, N=238 | MDS, N=120 |
|---------------------------------------------|---------------------|------------|------------|
| **Age at diagnosis in years, median (IQR)** | 70 (17)             | 67 (17)    | 75 (15)    |
| **Age at diagnosis in years, N (%)**        |                     |            |            |
| ≥70 years                                   | 187 (52.2)          | 104 (43.7) | 83 (69.2)  |
| <70 years                                   | 171 (47.8)          | 134 (56.3) | 37 (30.8)  |
| **Race, N (%)**                             |                     |            |            |
| White                                       | 311 (86.9)          | 199 (83.6) | 112 (93.3) |
| Black                                       | 17 (4.7)            | 16 (6.7)   | 1 (0.8)    |
| Other (Asian, Hispanic, not stated)         | 30 (8.4)            | 23 (9.7)   | 7 (5.8)    |
| **ECOG prior to death, N (%)**              |                     |            |            |
| 0                                           | 8 (4.2)             | 7 (5.5)    | 1 (1.6)    |
| 1                                           | 28 (14.7)           | 21 (16.5)  | 7 (11.1)   |
| ≥2                                          | 154 (81.1)          | 99 (78.0)  | 55 (87.4)  |
| **ECOG at diagnosis, N (%)**                |                     |            |            |
| 0                                           | 42 (20.5)           | 29 (20.4)  | 13 (20.6)  |
| 1                                           | 83 (40.5)           | 63 (44.4)  | 20 (31.8)  |
| ≥2                                          | 80 (39.0)           | 50 (35.2)  | 30 (47.6)  |
| **Number of comorbidities [median (IQR)]**  | 3 (3)               | 3 (3)      | 4 (3)      |
| **Comorbidities, N (%)**                    |                     |            |            |
| Hypertension                                | 192 (53.6)          | 120 (50.4) | 72 (60.0)  |
| Hyperlipidemia                              | 134 (37.4)          | 83 (34.9)  | 51 (42.5)  |
| Diabetes                                    | 77 (21.5)           | 44 (18.5)  | 33 (27.5)  |
| Chronic Obstructive Pulmonary Disease       | 57 (15.9)           | 32 (13.5)  | 25 (20.8)  |
| Coronary Artery Disease                     | 61 (17.0)           | 30 (12.6)  | 31 (25.8)  |
| **Disease status at first hematology visit, N (%)** |               |            |            |
| New diagnosis                               | 226 (63.1)          | 159 (66.8) | 67 (55.8)  |
| Relapsed disease/disease progression        | 31 (8.7)            | 19 (8.0)   | 12 (10.0)  |
| Other                                       | 101 (28.2)          | 60 (25.2)  | 41 (34.2)  |
| **Intent of care at first visit, N (%)**    |                     |            |            |
| Curative                                    | 47 (13.1)           | 37 (15.6)  | 10 (8.3)   |
| Palliative                                  | 156 (43.6)          | 92 (38.7)  | 64 (53.3)  |
| Not stated                                  | 155 (43.3)          | 109 (45.8) | 46 (38.3)  |
| **Geographical location**                   |                     |            |            |
| Urban                                       | 268 (74.9)          | 60 (25.2)  | 30 (25.0)  |
| Rural                                       | 90 (25.1)           | 178 (74.8) | 90 (75.0)  |

*a* 168 patients did not have data for this variable in their medical record

*b* 153 patients did not have data for this variable in their medical record

*c* Included patients who were transferring care, being evaluated for a second opinion, or their diagnosis was greater than 4 weeks after their initial visit
Abbreviations: AML, Acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group performance status; IQR, Interquartile range; MDS, Myelodysplastic syndrome
Table 2: Characteristics of patients who completed Medical Orders for Life-Sustaining Treatment (MOLST) forms greater than 30 days prior to death vs patients who completed MOLST forms within 30 days of death or never

| Characteristic                                      | MOLST completed >30 days prior to death N=118 (%) | MOLST never completed or completed within 30 days of death N=228 (%) | P-value |
|-----------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------|---------|
| Age at diagnosis in years, median (IQR)             | 73.5 (16)                                         | 67 (16.5)                                                           | <0.0001 |
| Age at diagnosis in years, N (%)                    |                                                   |                                                                     | 0.0002  |
| ≥70 years                                           | 78 (66.1)                                         | 101 (44.3)                                                          |         |
| <70 years                                           | 39 (33.9)                                         | 127 (55.7)                                                          |         |
| Race, N (%)                                         |                                                   |                                                                     | 0.18    |
| White                                               | 106 (90.7)                                        | 194 (85.1)                                                          |         |
| Black or other (Asian, Hispanic, other)             | 11 (9.3)                                          | 34 (14.9)                                                           |         |
| ECOG prior to death, N (%)                          |                                                   |                                                                     | 0.25    |
| 0                                                   | 3 (4.3)                                           | 4 (3.5)                                                             |         |
| 1                                                   | 6 (8.6)                                           | 20 (17.5)                                                           |         |
| ≥2                                                  | 61 (87.1)                                         | 90 (79.0)                                                           |         |
| ECOG at diagnosis, N (%)                            |                                                   |                                                                     | 0.21    |
| 0                                                   | 11 (14.3)                                         | 30 (24.6)                                                           |         |
| 1                                                   | 34 (44.2)                                         | 45 (36.9)                                                           |         |
| ≥2                                                  | 32 (41.6)                                         | 47 (38.6)                                                           |         |
| Number of comorbidities [median (IQR)]              | 4 (3)                                             | 3 (2.5)                                                             | 0.01    |
| Comorbidities, N (%)                                |                                                   |                                                                     |         |
| Hypertension                                        | 68 (57.6)                                         | 118 (51.8)                                                          | 0.31    |
| Hyperlipidemia                                      | 45 (38.1)                                         | 86 (37.7)                                                           | 1.00    |
| Diabetes                                            | 27 (22.9)                                         | 48 (21.1)                                                           | 0.68    |
| Chronic obstructive pulmonary disease               | 24 (20.3)                                         | 32 (14.0)                                                           | 0.17    |
| Coronary artery disease                             | 20 (17.0)                                         | 38 (16.7)                                                           | 1.00    |
| Diagnosis                                           |                                                   |                                                                     | 0.12    |
| Acute myeloid leukemia                              | 72 (61.0)                                         | 159 (69.7)                                                          |         |
| Myelodysplastic syndrome                            | 46 (39.0)                                         | 69 (30.3)                                                           |         |
| Disease status at first hematology visit, N (%)     |                                                   |                                                                     | 0.66    |
| New diagnosis                                       | 71 (60.2)                                         | 148 (64.9)                                                          |         |
| Relapsed disease/disease progression                | 11 (9.3)                                          | 18 (7.9)                                                            |         |
| Otherc                                              | 36 (30.5)                                         | 62 (27.2)                                                           |         |
| Intent of care at first visit, N (%)                |                                                   |                                                                     | 0.03    |
| Curative                                             | 10 (8.5)                                          | 35 (15.4)                                                           |         |
| Palliative                                          | 61 (52.5)                                         | 89 (38.6)                                                           |         |
| Not stated                                          | 46 (39.0)                                         | 105 (46.1)                                                          |         |
| Geographical location                               |                                                   |                                                                     | 0.36    |
| Rural                                               | 25 (21.2)                                         | 59 (25.9)                                                           |         |
| Urban                                               | 93 (78.8)                                         | 169 (74.1)                                                          |         |

*162 patients did not have data for this variable in their medical record

b 147 patients did not have data for this variable in their medical record
Included patients who were transferring care, being evaluated for a second opinion, or their diagnosis was greater than 4 weeks after their initial visit.

Abbreviations: AML, Acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group performance status; IQR, Interquartile range; MDS, Myelodysplastic syndrome.
Table 3: Timing of Medical Orders for Life-Sustaining Treatment form completion, palliative care referral, and hospice enrollment to death in patients with acute myeloid leukemia and myelodysplastic syndrome

| Time Event                                      | AML     | MDS     |
|------------------------------------------------|---------|---------|
| Time from MOLST to death, in days [N=294, (IQR)]| 14.5 (47.0) | 37.0 (178.0) |
| Time from palliative care referral to death, in days [N=204, median (IQR)] | 14.0 (46.0) | 12.0 (52.0) |
| Time from palliative care visit to death, in days [N=198, median (IQR)] | 11.0 (42.0) | 12.0 (49.0) |
| Time from hospice enrollment to death, in days [N=160, median (IQR)] | 5.0 (6.0) | 4.0 (10.0) |

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MOLST, Medical Orders for Life-Sustaining Treatment
Table 4a: Multivariate analyses showing the associations of Medical Orders for Life-Sustaining Treatment form completion with end of life measures

|                     | Inpatient death | Transfusion | Life-sustaining treatment | Hospitalization | ED visit |
|---------------------|-----------------|-------------|---------------------------|-----------------|---------|
|                     | OR   | 95% CI | P-value | OR   | 95% CI | P-value | OR   | 95% CI | P-value | OR   | 95% CI | P-value |
| MOLST form completion (early vs late/never) | 0.44 | 0.25-0.77 | p=0.004 | 0.39 | 0.24-0.64 | p=0.0002 | 0.21 | 0.11-0.38 | p<0.0001 | 0.35 | 0.18-0.67 | p=0.002 |
| Age (continuous, per year) | 0.96 | 0.93-0.98 | p=0.001 | 0.97 | 0.95-0.99 | p=0.001 | 0.96 | 0.94-0.98 | p<0.0001 | 0.95 | 0.91-0.98 | p=0.001 |
| Race (Non-white vs. White) | 4.19 | 1.18-14.8 | p=0.03 | 0.80 | 0.39-1.63 | p=0.54 | 1.16 | 0.56-2.43 | p=0.69 | 2.15 | 0.58-7.93 | p=0.25 |
| Number of comorbidities (continuous) | 1.05 | 0.91-1.20 | p=0.54 | 0.97 | 0.86-1.09 | p=0.61 | 1.16 | 1.03-1.32 | p=0.02 | 1.22 | 1.02-1.45 | p=0.03 |
| Diagnosis (MDS vs. AML) | 0.84 | 0.46-1.53 | p=0.56 | 1.05 | 0.62-1.77 | p=0.86 | 1.22 | 0.70-2.14 | p=0.48 | 0.59 | 0.30-1.19 | p=0.14 |
| Geographical location (Rural vs. Urban) | 0.60 | 0.32-1.13 | p=0.11 | 0.66 | 0.38-1.14 | p=0.13 | 1.16 | 0.65-2.07 | p=0.62 | 0.54 | 0.26-1.10; | p=0.09 |
| New diagnosis (vs. relapsed/refractory) | 1.09 | 0.38-3.10 | p=0.87 | 0.97 | 0.41-2.30 | p=0.94 | 1.21 | 0.47-3.09 | p=0.69 | 1.48 | 0.51-4.35 | p=0.47 |

Abbreviations: AML, acute myeloid leukemia; ED, emergency department; ICU, intensive care unit; MDS, myelodysplastic syndrome; MOLST, Medical Orders for Life-Sustaining Treatment; OR, Odds Ratio; CI, Confidence Interval
Table 4b: Multivariate analyses showing the associations of Medical Orders for Life-Sustaining Treatment form completion with end of life measures

|                                | ICU admission | Chemotherapy | Hospice | Hospice for more than 3 days |
|--------------------------------|---------------|--------------|---------|-----------------------------|
|                                | OR 95% CI     | P-value      | OR 95% CI | P-value     | OR 95% CI     | P-value      | OR 95% CI     | P-value      |
| MOLST form completion (early vs late/never) | 0.21 (0.11-0.39) | p<0.0001 | 0.24 (0.10-0.59) | p=0.002 | 2.69 (1.66-4.43) | p<0.0001 | 2.50 (1.49-4.17) | p<0.001 |
| Age (continuous, per year)      | 0.95 (0.93-0.97) | p<0.0001 | 0.98 (0.96-1.00) | p=0.10 | 1.03 (1.02-1.05) | p=0.0006 | 1.04 (1.01-1.06) | p=0.001 |
| Race (Non-white vs. White)      | 1.07 (0.50-2.29) | p=0.85 | 0.52 (0.19-1.40) | p=0.20 | 0.80 (0.39-1.61) | p=0.53 | 1.16 (0.54-2.49) | p=0.71 |
| Number of comorbidities (continuous) | 1.18 (1.04-1.35) | p=0.01 | 0.92 (0.78-1.09) | p=0.35 | 1.00 (0.89-1.12) | p=0.97 | 1.07 (0.94-1.21) | p=0.33 |
| Diagnosis (MDS vs. AML)         | 1.45 (0.82-2.58) | p=0.20 | 0.38 (0.17-0.88) | p=0.02 | 0.81 (0.49-1.36) | p=0.43 | 0.71 (0.40-1.27) | p=0.25 |
| Geographical location (Rural vs. Urban) | 1.03 (0.57-1.87) | p=0.92 | 0.74 (0.35-1.55) | p=0.42 | 0.76 (0.45-1.31) | p=0.33 | 0.83 (0.45-1.54) | p=0.56 |
| New diagnosis (vs. relapsed/refractory) | 0.66 (0.26-1.66) | p=0.38 | 1.04 (0.32-3.39) | p=0.95 | 1.39 (0.59-3.28) | p=0.45 | 1.00 (0.38-2.59) | p=0.99 |

Abbreviations: AML, acute myeloid leukemia; ED, emergency department; ICU, intensive care unit; MDS, myelodysplastic syndrome; MOLST, Medical Orders for Life-Sustaining Treatment; OR, Odds Ratio; CI, Confidence Interval
Figure 1: Flow chart describing patient preferences on the first MOLST form

Abbreviations: IV, intravenous fluids; MOLST, Medical Orders for Life-Sustaining Treatment

Figure 2: Time from initial MOLST form completion to death as a function of clinician subspecialty

“Unclear” subspecialty refers to providers who could not be identified because the signature on the MOLST form was unreadable

Figure 3: Flow chart depicting changes in code status as stated on the MOLST forms

Abbreviations: MOLST, Medical Orders for Life-Sustaining Treatment

Figure 4: End of life measures in patients with acute myeloid leukemia and myelodysplastic syndromes

Abbreviations: AML, acute myeloid leukemia; ED, emergency department; ICU, intensive care unit; MDS, myelodysplastic syndrome; MOLST, Medical Orders for Life-Sustaining Treatment

Figure 5: Utilization of life-sustaining treatments in patients with acute myeloid leukemia and myelodysplastic syndrome
Figure 2

Median (range) by specialty
- ICU Providers: 1 day (0-158)
- Other Oncologist: 14 days (1-366)
- Unclear: 28 days (0-956)
- Primary Oncologist: 38 days (0-505)
- Palliative Care Providers: 64 days (0-905)
- Other: 88 days (0-561)
- Hospitalist/Medicine Providers: 135 days (2-1677)
Figure 3

MOLST form
N=346

Completed
N=297

Did not complete
N=49

DNR/DNI
N=216,
73 with subsequent MOLST (1 missing specifics)

Remained
N=64

Changed
N=9

DNR
N=4

DNI
N=1

Full code
N=4

DNR only
N=64,
27 with subsequent MOLST

Remained
N=3

Changed
N=24

DNR/DNI
N=24

DNI
N=1

DNR
N=8

DNI
N=3

DNI only
N=2,
1 with subsequent MOLST

Changed
N=1

Full code
N=15,
12 with subsequent MOLST

Remained
N=1

Changed
N=11

DNR/DNI
N=8

DNR
N=3
