# Home time among older adults with acute myeloid leukemia by therapy intensity

This study quantified home time (HT) among older adults (age ≥60 years) with acute myeloid leukemia (AML) following diagnosis. The approval of venetoclax for AML introduced clinical equipoise into treatment decision-making for many older adults between high-intensity regimens *versus* venetoclax with a hypomethylating agent. Published remission rates with these regimens are similar,[1] although survival for older adults with AML remains poor, with fewer than 40% living for a year following diagnosis.[2] Our findings show that high-intensity, anthracycline-based treatment is associated with greater mean HT compared to less intensive treatment in this cohort.

We conducted a retrospective, observational study of adults aged ≥60 years diagnosed with AML from 2015 to 2020 utilizing medical records from University of North Carolina (UNC) Health. Data from 12 other regional health systems were available via electronic health record exchanges. Individuals were included if they received first-line therapy with a hypomethylating agent (deemed low-intensity therapy), hypomethylating agent plus venetoclax (intermediate-intensity), or anthracycline-based therapy (high-intensity). Individuals who received any leukemia care not reflected in the available records were excluded. The UNC institutional review board approved the study.

The primary outcome was cumulative HT following diagnosis. A day was counted toward HT if an individual was not hospitalized and did not utilize emergency department or ambulatory oncology services. Days on which a patient was hospitalized, seen in an emergency department, or seen in an oncology clinic were considered "contact days." HT was summed for each individual and quantified in terms of months.

Secondary outcomes included overall survival, treatment response, quality-adjusted HT, and the proportion of days at home and not engaged in care. Overall survival was calculated as days from diagnosis to death or last follow-up alive. Individuals achieving a best response of morphological complete remission, complete remission with incomplete hematologic recovery, or a morphological leukemia-free state were considered to have achieved remission.[3] To calculate quality-adjusted HT, we applied published utility values for treatment-related health states in AML.[4] Disease risk was assessed according to European LeukemiaNet 2017 criteria.[3]

Descriptive statistics are provided as medians with interquartile ranges (IQR) or frequencies. Associations between categorical variables and therapy regimens were evaluated via Monte Carlo simulated Fisher exact tests. Total HT and quality-adjusted HT are presented as means and medians for the overall cohort and stratified by first-line treatment. Comparisons among treatment groups were made via Poisson regression models, considering HT as a count, with robust variance estimation and a log link function. Models were adjusted for age at diagnosis. We conducted sensitivity analyses restricted to 2 and 4 years of follow-up to assess the impact of the small number of long-term survivors. The Kaplan-Meier method and Cox proportional hazards models were used to evaluate associations between overall survival and other variables.

The full cohort included 197 individuals. Their median age was 71 years (range, 60-95), with a plurality in the 60- to 69-year-old age band (43.7%) (Table 1). The majority of the cohort was white (79.4%) and there was a predominance of males (58.4%), mirroring national AML incidence data.[2] The majority had adverse-risk AML (59.0%), followed by intermediate-risk (28.2%) and favorable-risk disease (12.8%). Seventy-five individuals (38.1%) received anthracycline-based treatment, 58 (29.4%) received venetoclax-containing regimens, and 64 (32.5%) received monotherapy with a hypomethylating agent. The median age of patients was lowest in the high-intensity group (65 years *vs*. 72.5 years in the low-intensity group and 75 years in the intermediate-intensity group; $P<0.0001$). Other demographics and European LeukemiaNet risk were similar across groups ($P>0.05$ for all associations).

The median survival of the full cohort was 9.8 months (95% confidence interval [95% CI]: 7.6-12.5). Increasing age was associated with increased mortality risk, with the hazard ratio for mortality being 1.36 (1.10-1.69) per 10 years of age. Race, sex, and European LeukemiaNet risk were not significantly associated with mortality. The high-intensity treatment group had a longer median overall survival at 19.9 months (9.1-30.4) *versus* 7.4 months (2.8-11.9) for the low-intensity group or 7.7 months (3.3-11.0) for the intermediate-intensity group ($P=0.0003$) (Table 2). After adjustment for age, the survival advantage associated with high-intensity therapy remained statistically significant (adjusted hazard ratio=0.50 [0.32-0.79]; $P=0.003$). The median overall survival did not differ significantly between the low- and intermediate-intensity treatment groups.

Individuals receiving high-intensity therapy had a greater initial burden of care days (Figure 1), related to receipt of inpatient chemotherapy. During the first 30 days, mean days at home were 4, 14, and 12 for the high-intensity, intermediate-intensity, and low-intensity treatment groups, respectively. Over the full study period, mean HT for the cohort was 9.1 months (95% CI: 7.4-10.7), with a median of 4.4 (IQR: 1.1-12.5) (Table 2). Mean HT was longest in the

high-intensity group at 13.1 months (95% CI: 9.9-16.4) *versus* 7.6 months (95% CI: 4.8-10.4) in the low-intensity group and 5.5 months (95% CI: 4.0-7.1) in the intermediate-intensity group. The proportion of days at home during each month following diagnosis rose over time in each group (*Online Supplementary Table S1*).

In the age-adjusted model, average total HT for those receiving high-intensity treatment was estimated to be 1.76

**Table 1.** Demographic and disease characteristics of older adults with acute myeloid leukemia.

| Variable | All patients N=197 | Low-intensity group N=64 | Intermediate-intensity group N=58 | High-intensity group N=75 | *P** |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age group, N (%) | | | | | <0.0001 |
| 60-69 years | 86 (43.7) | 15 (23.4) | 12 (20.7) | 59 (78.7) | - |
| 70-79 years | 81 (41.1) | 37 (57.8) | 28 (48.3) | 16 (21.3) | - |
| 80-89 years | 25 (12.7) | 8 (12.5) | 17 (29.3) | 0 (0.0) | - |
| ≥90 years | 5 (2.5) | 4 (6.3) | 1 (1.7) | 0 (0.0) | - |
| Race, N (%) | | | | | 0.390 |
| White | 154 (79.4) | 48 (77.4) | 47 (81.0) | 59 (79.7) | - |
| Black or African-American | 31 (16.0) | 12 (19.4) | 10 (17.2) | 9 (12.2) | - |
| Other | 9 (4.6) | 2 (3.2) | 1 (1.7) | 6 (8.1) | - |
| Sex, N (%) | | | | | 0.827 |
| Female | 82 (41.6) | 25 (39.1) | 26 (44.8) | 31 (41.3) | - |
| Male | 115 (58.4) | 39 (60.9) | 32 (55.2) | 44 (58.7) | - |
| **Disease and treatment** | | | | | |
| First-line treatment, N (%) | | | | | - |
| HMA | 64 (32.5) | 64 (32.5) | - | - | - |
| HMA + venetoclax | 58 (29.4) | - | 58 (29.4) | - | - |
| Anthracycline-based | 75 (38.1) | - | - | 75 (38.1) | - |
| ELN 2017 risk, N (%) | | | | | 0.805 |
| Favorable | 25 (12.8) | 7 (11.3) | 6 (10.3) | 12 (16.0) | - |
| Intermediate | 55 (28.2) | 17 (27.4) | 19 (32.8) | 19 (25.3) | - |
| Adverse | 115 (59.0) | 38 (61.3) | 33 (56.9) | 44 (58.7) | - |

High intensity indicates anthracycline-based therapy, intermediate intensity indicates treatment with venetoclax and a hypomethylating agent and low intensity indicates hypomethylating agent monotherapy. Missing data not available in records: race (3 subjects), employment status (30 subjects), marital status (3 subjects), rurality (3 subjects), household income (3 subjects), and European LeukemiaNet risk (2 subjects). *Comparison between categorical variables assessed via Monte Carlo simulated Fisher exact test. HMA: hypomethylating agent; ELN: European LeukemiaNet.

**Table 2.** Months of survival and home time by therapy intensity.

| Variable | All patients | Low-intensity group | Intermediate-intensity group | High-Intensity group |
|---|---|---|---|---|
| Overall survival in months, median (95% CI) | 9.9 (7.7-12.7) | 7.4 (2.8-11.9) | 7.7 (3.3-11.9) | 19.9 (9.1-30.4)* |
| Total HT in months, mean (95% CI) | 9.1 (7.4-10.7) | 7.6 (4.8-10.4) | 5.5 (4.0-7.1) | 13.1 (9.9-16.4)* |
| Total HT in months, median (IQR) | 4.4 (1.1-12.5) | 3.8 (0.6-9.3) | 3.3 (1.1-7.7) | 5.9 (2.4-21.4) |
| Quality-adjusted HT in months, mean (95% CI) | 5.6 (4.4-6.9) | 3.3 (1.7-4.8) | 3.3 (2.1-4.4) | 9.4 (6.7-12.1)* |
| Quality-adjusted HT in months, median (IQR) | 2.0 (0.3-6.2) | 1.0 (0.2-3.8) | 1.3 (0.3-5.4) | 3.7 (0.9-15.0) |

High intensity indicates anthracycline-based therapy, intermediate intensity indicates treatment with venetoclax and a hypomethylating agent and low intensity indicates hypomethylating agent monotherapy. *Statistically significant difference in models adjusted for age. CI: confidence interval; HT: home time; IQR: interquartile range.

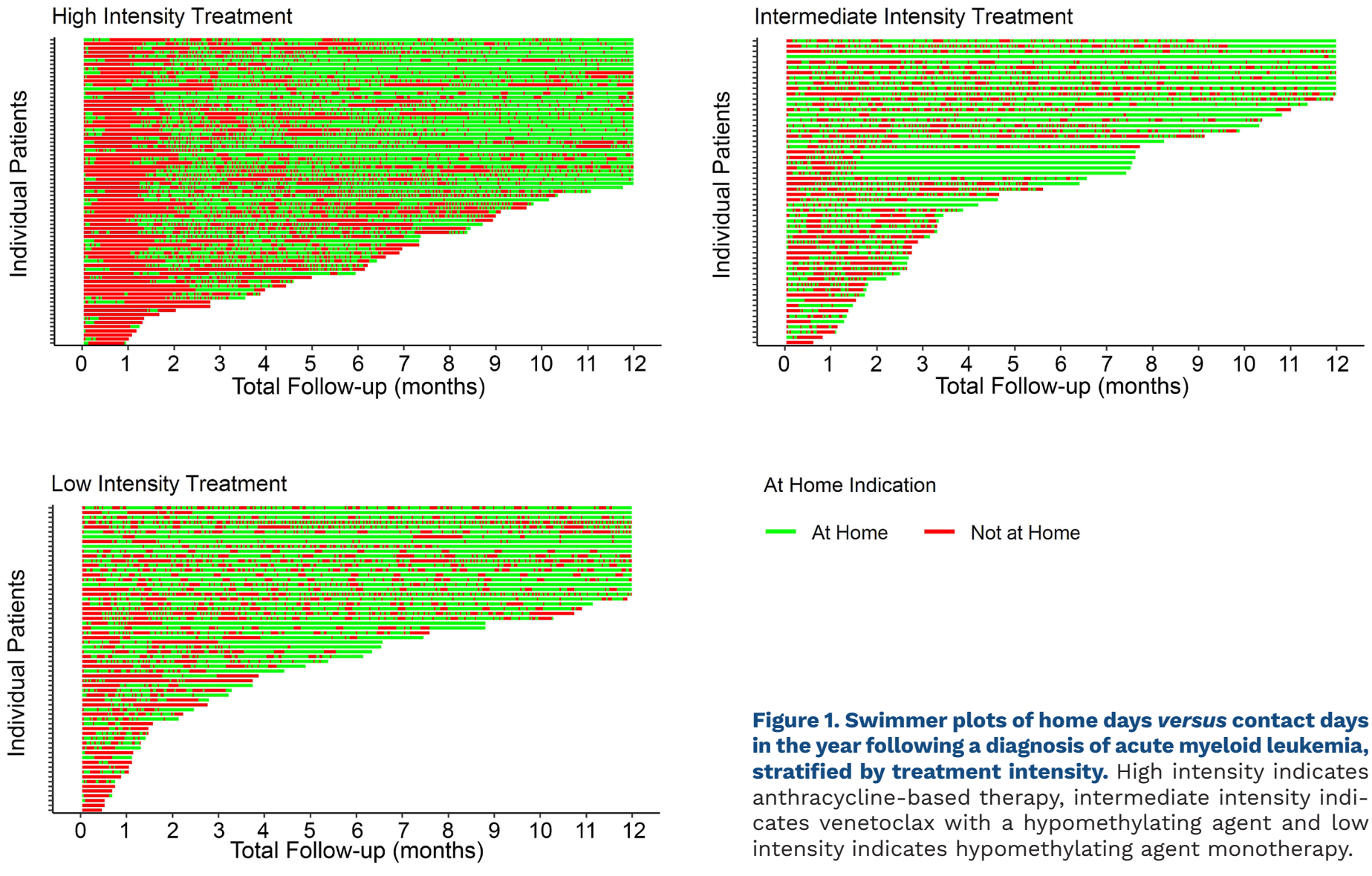


**Figure 1. Swimmer plots of home days *versus* contact days in the year following a diagnosis of acute myeloid leukemia, stratified by treatment intensity.** High intensity indicates anthracycline-based therapy, intermediate intensity indicates venetoclax with a hypomethylating agent and low intensity indicates hypomethylating agent monotherapy.

times (1.10-2.82) that of the low-intensity group (*P*=0.018) and 2.43 times (1.57-3.75) that of the intermediate-intensity group (*P*<0.0001). Intermediate-intensity treatment was not associated with a significant difference in HT compared to low-intensity treatment (*P*=0.166). The advantage for the high-intensity group persisted in sensitivity analyses restricted to 2 or 4 years.

The nature of contact days differed between treatment groups. Inpatient hospitalization accounted for most contact days among the high-intensity group (62% [57-67%]). Among the low- and intermediate-intensity groups, outpatient clinic or infusion visits accounted for the greatest number of contact days (50% [41-59%] and 57% [49-65%], respectively).

Remission rates were higher among the high-intensity (57.3%) and intermediate-intensity (56.1%) groups than in the low-intensity group (19.7%). Survival was longer for individuals achieving remission. Among the 87 patients who achieved remission with first-line therapy, the median overall survival was 19.9 months (11.0-41.0) compared to 3.8 months (2.7-8.3) among the 106 who did not enter remission. Remission status could not be confirmed for four individuals. Among individuals who achieved remission, the proportion of days spent at home was 0.35 (0.31-0.39) prior to achieving remission *versus* 0.71 (0.67-0.75) following remission.

We adjusted HT for quality to reflect variable quality of life experienced at different points in treatment.[4] Mean quality-adjusted HT was greatest in the high-intensity group at 9.4 months (6.7-12.1) *versus* 3.3 months (1.7-4.8) in the low-intensity group and 3.3 months (2.1-4.4) in the intermediate-intensity group. In a model adjusted for age, the average total quality-adjusted HT for those receiving high-intensity treatment was estimated to be 2.61 times (1.41-4.82) that of those with low-intensity treatment (*P*=0.0022) and 2.58 times (1.58-4.22) that of those given intermediate-intensity treatment (*P*=0.0002). Intermediate-intensity treatment was not associated with a significant difference in quality-adjusted HT compared to low-intensity treatment (*P*=0.97).

Overall, high-intensity treatment was associated with a greater initial burden of care days; however, the high-intensity group had significantly greater mean HT and quality-adjusted HT compared to the low-intensity and intermediate-intensity groups. In the long-run, high-intensity treatment may yield more HT for patients despite upfront hospitalization.

We have previously published data regarding HT among older adults with AML receiving azacitidine or venetoclax-containing treatment regimens.[5] We found that HT was similar between patients treated with either regimen. A separate analysis of SEER-Medicare data among older adults with

AML suggested that higher intensity treatment regimens were associated with fewer days at home compared to lower intensity regimens after accounting for frailty.[6] In the current study, we evaluated HT among older adults treated with a broader array of therapy intensities.

HT is a topic increasingly recognized in recent literature. Recent analyses have shown that women with newly diagnosed metastatic breast cancer or adults with newly diagnosed metastatic pancreatic cancer spend approximately 10% of their days engaged in care.[7,8] In this context, the time commitment faced by patients in the current study is striking. Older adults with AML spend over 4 times as many days engaged in oncology care compared to these patients with advanced solid tumors. HT for patients with hematologic malignancies has otherwise not been routinely reported outside of the context of hospice care,[9] although Gupta and colleagues recently described home days *versus* contact days among participants in an international clinical trial for relapsed/refractory non-Hodgkin lymphomas.[10]

Our study has limitations. First, it was conducted at a single center with a relatively small sample, which may limit its generalizability. Second, our study was retrospective, and we were unable to control for potential confounders that influence treatment selection and HT. Importantly, we did not collect data on patients' comorbidities or psychosocial support, which may impact both HT and treatment selection. While Eastern Cooperative Oncology Group performance status was abstracted, extensive missingness in this variable precluded its use in analyses. Our study also equates inpatient and outpatient contact days in the primary outcome. Finally, our study did not account for patients' preferences and values, which are critical factors in shared decision-making.

Older adults with AML spend a tremendous amount of time - roughly 40% of days - engaged in care. The current study provides new data on HT among this population. Our findings suggest that high-intensity treatment may be associated with greater HT and quality-adjusted HT, despite the initial burden of care with high-intensity therapy. Future research should focus on identifying factors that influence treatment selection and HT in this population and developing interventions to optimize this outcome.

## Authors

Christopher E. Jensen,[1,2] Allison M. Deal,[3] Alexis C. Wardell,[3] Hillary M. Heiling,[2,3] Konan E. Beke[1] and Daniel R. Richardson[1,3]

[1]University of North Carolina School of Medicine; [2]University of North Carolina Gillings School of Global Public Health and [3]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

Correspondence:
C.E. JENSEN - christopher.jensen@unchealth.unc.edu

https://doi.org/10.3324/haematol.2023.284133

Received: October 18, 2023.
Accepted: December 12, 2023.
Early view: December 21, 2023.



**Disclosures**

None of the authors has a relevant conflict of interest. CEJ reports research funding (from Conquer Cancer and AbbVie) outside the submitted work. DRR reports research funding (from Conquer Cancer and the Palliative Care Research Cooperative Group) outside the submitted work.

**Contributions**

CEJ and DRR conceptualized the study and identified the study cohort. CEJ and KEB extracted data from charts. CEJ, AMD, ACW, HMH, and DRR designed the data analysis. AMD and ACW performed the data analysis. All authors contributed to interpretation of the results. CEJ drafted the manuscript. All authors reviewed the final manuscript.

**Funding**

The project described was supported by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) through grant award number UL1TR002489 and by a National Research Service Award Post-Doctoral Traineeship from the Agency for Healthcare Research and Quality sponsored by The Cecil G. Sheps Center for Health Services Research at The University of North Carolina at Chapel Hill through grant award number T32-HS000032. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

**Data-sharing statement**

Due to the inclusion of specific dates, the underlying data for the study consists largely of protected health information, which the authors are not authorized to share outside their institution. Aggregate, de-identified data can be made available upon request to the corresponding author.

## References

1. Jaramillo S, Schlenk RF. Update on current treatments for adult acute myeloid leukemia: to treat acute myeloid leukemia intensively or non-intensively? That is the question. Haematologica. 2023;108(2):342-352.
2. Acute myeloid leukemia: SEER stat fact sheets: 2019. Surveillance, Epidemiology, and End Results Program (SEER).

Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML). 2023. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed October 2023.
3. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
4. Stein EM, Yang M, Guerin A, et al. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1):193.
5. Jensen CE, Heiling HM, Beke KE, et al. Time spent at home among older adults with acute myeloid leukemia receiving azacitidine- or venetoclax-based regimens. Haematologica. 2023;108(4):1006-1014.
6. Richardson DR, Zhou X, Jensen CE, et al. Time at home among older adults with acute myeloid leukemia based on treatment intensity: a SEER-Medicare analysis. J Clin Oncol. 2022;40(16_suppl):6586.
7. Rocque GB, Williams CP, Ingram SA, et al. Health care-related time costs in patients with metastatic breast cancer. Cancer Med. 2020;9(22):8423-8431.
8. Bange EM, Doucette A, Gabriel PE, et al. Opportunity costs of receiving palliative chemotherapy for metastatic pancreatic ductal adenocarcinoma. JCO Oncol Pract. 2020;16(8):e678-e687.
9. Cheung MC, Croxford R, Earle CC, Singh S. Days spent at home in the last 6 months of life: a quality indicator of end of life care in patients with hematologic malignancies. Leuk Lymphoma. 2020;61(1):146-155.
10. Gupta A, Hay AE, Crump M, et al. Contact days associated with cancer treatments in the CCTG LY 12 trial. Oncologist. 2023;28(9):799-803.