Original Article

Frontline Treatment Patterns and Outcomes Among Older Adults With Acute Myeloid Leukemia: A Population-Based Analysis in the Modern Era

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BACKGROUND: Traditionally, conventional induction chemotherapy has been the primary frontline treatment for acute myeloid leukemia (AML); however, older adults are often poor chemotherapy candidates. Recently, several nonconventional frontline AML regimens, including hypomethylating agents, the BCL-2 inhibitor venetoclax, and targeted therapies, have emerged, and they may offer new options for older adults. This study was aimed at describing treatment patterns and outcomes of older adult AML in a modern population-based cohort. **METHODS:** This study evaluated patients aged ≥60 years with a first primary diagnosis of AML (2014-2017) in the California Cancer Registry linked to inpatient hospitalizations. Multivariable regression examined factors associated with the frontline treatment regimen and survival. **RESULTS:** In all, 3068 patients were included; 36% received frontline therapy with a conventional chemotherapy backbone, 42% received nonconventional therapy, and 22% received no treatment. The use of nonconventional therapy increased over time from 38% of patients in 2014 to 47% in 2017 ($P < .001$). In multivariable analyses, receipt of treatment was associated with an age younger than 80 years, fewer than 2 comorbidities, and care at a National Cancer Institute–designated cancer center (NCI-CC). Compared with conventional chemotherapy, nonconventional therapy was associated with Black race/ethnicity, public health insurance, fewer hospital admissions, and fewer inpatient days. Receiving frontline therapy at an NCI-CC was independently associated with superior overall survival. **CONCLUSIONS:** Using a population-based approach, this study has demonstrated that patterns of care for frontline AML treatment in older adults are changing, with increasing use of nonconventional therapies. A significant proportion of older adults remain untreated. At the population level, there remain opportunities to increase therapy access for older adults with AML.
***Cancer* 2022;128:139-149**.

KEYWORDS: acute myeloid leukemia, older adults, patterns of care.

INTRODUCTION

Acute myeloid leukemia (AML) is primarily a disease of older adults with a median age at diagnosis of 68 years.[1] Traditionally, frontline AML induction therapy involves intensive cytotoxic chemotherapy using a combination of an anthracycline and standard-dose cytarabine, and it may be followed by allogeneic hematopoietic cell transplantation (HCT). However, because of multiple comorbidities and a reduced performance status, older adults are often poor candidates for these therapies.[2] As recently as a decade ago, nearly half of AML patients 65 years old or older did not receive any treatment.[3,4] Consequently, prior survival estimates of this population have been dismal. For example, between 2000 and 2008, the 2-year overall survival (OS) of AML patients 70 years old or older was only 14%.[5]

Over the past several years, new treatment options for frontline AML therapy have emerged. These nonconventional therapy options include hypomethylating agents (HMAs),[6,7] the BCL-2 inhibitor venetoclax,[8] liposomal anthracycline and cytarabine, and oral targeted agents.[9-11] Compared with conventional chemotherapy, these nonconventional agents may offer less intense side-effect profiles, can often be administered in the outpatient setting, and provide novel treatment options for older adults. The current uptake of these newer therapies is poorly understood. Therefore, using a population-based approach, we evaluated how frontline treatment patterns in older adults with AML are changing in the modern era. We hypothesized that the advent of nonconventional therapies has allowed a greater proportion of older adults with AML to receive frontline treatment and thereby improved survival for this population. Furthermore, we hypothesized that relative to conventional chemotherapy, these nonconventional agents would be associated with fewer hospital admissions

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33873, **Received:** May 12, 2021; **Revised:** July 9, 2021; **Accepted:** July 21, 2021, **Published online** August 26, 2021 in Wiley Online Library (wileyonlinelibrary.com)

and in-hospital days during the first 100 days after the AML diagnosis.

MATERIALS AND METHODS

Data Sources

This study used the California Cancer Registry (CCR) linked with the Patient Discharge Database (PDD) of California's Office of Statewide Health Planning and Development; the methodology of the linkage has been previously described.[12] The CCR is California's population-based cancer surveillance system and is composed of 3 Surveillance, Epidemiology, and End Results registries of the National Cancer Institute. The CCR has been state-mandated to collect reports on cancers diagnosed in California since 1988. The PDD contains longitudinal information for individual patients on all admissions at acute care hospitals in California (excluding 14 federal hospitals).

Data abstracted from the CCR included the following: date of diagnosis, age at diagnosis, sex, race/ethnicity, presence and type of health insurance, neighborhood socioeconomic status (nSES; derived from the 2000 US Census and the 2006-2010 American Community Survey[13]), rural zip code versus urban zip code (derived from the 2000 US Census and the 2010 US Census), and number of comorbidities (adapted from the Charlson Comorbidity Index[14]).

The frontline treatment setting was also obtained from the CCR and was categorized as a National Cancer Institute–designated cancer center (NCI-CC) if either part or all of the first course of treatment occurred at, or the decision not to treat was determined at, 1 of the 8 NCI-CCs in California. The frontline treatment regimen was manually abstracted from unstructured free-text data fields in the CCR (Supporting Table 1) and was subdivided into 3 categories: conventional chemotherapy backbone, nonconventional therapy (defined as an HMA, venetoclax, liposomal anthracycline and cytarabine, or oral targeted agents), and no treatment. Data abstracted from the PDD included the date of receipt of HCT and the number of admissions and in-hospital days during the first 100 days after the AML diagnosis.

Study Population

We identified patients ≥60 years old who received a first primary diagnosis of AML between 2014 and 2017 in the CCR. A diagnosis of AML was defined with *International Classification of Diseases for Oncology, Third Edition* codes (9840, 9461, 9865-9867, 9869, 9871-9874, 9898, 9910-9911, 9920, and 9891).

Statistical Analysis

Descriptive statistics (frequencies, percentages, and χ^2 tests) were used to characterize baseline patient attributes, examine the relationships between patient characteristics and frontline regimen categories, and examine the relationships between the frontline regimen and the number of admissions, number of in-hospital days, and discharge destination. Multivariable logistic regression was used to determine factors associated with the receipt of any treatment (vs none), the receipt of a nontraditional frontline treatment regimen (vs a traditional regimen), and the receipt of HCT (vs none). We also conducted sensitivity analyses combining patients excluded from the primary analyses on account of absent treatment data (n = 1018) with patients receiving no treatment because we hypothesized that these patients were most likely to be untreated. Models included the following: diagnosis year, age, sex, race/ethnicity, nSES, health insurance, rural/urban residence, comorbidity score, and NCI-CC status. Results are presented as adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs).

Kaplan-Meier product limit survival estimates were used to examine OS and leukemia-specific survival (LSS) by frontline regimen type. Multivariable Cox proportional hazards regression was used to examine factors associated with OS and LSS. The survival time was calculated as the days from the date of diagnosis to the date of death from any cause for OS and to the date of death from cancer for LSS, the date of last follow-up, or the study end date (December 31, 2017), whichever occurred first. We assessed proportional hazards assumptions with tests based on Schoenfeld residuals and an inspection of the survival curves (survival function vs survival time and log(−log) of the survival function vs the log of time) for all variables in the models. Models were adjusted for the following: diagnosis year, age, sex, race/ethnicity, nSES, health insurance, rural/urban residence, comorbidity score, initial treatment at an NCI-CC, frontline regimen, and receipt of HCT. Receipt of HCT was analyzed as a time-dependent variable in the survival analyses. Sensitivity analyses assessed the impact of combining patients excluded from the primary analyses on account of absent treatment data (n = 1018) with patients receiving no treatment on survival. Results are presented as adjusted hazard ratios (HRs) and associated 95% CIs. Analyses were conducted with SAS software (version 9.4; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patient and Treatment Characteristics

In all, 4371 patients ≥60 years old who were diagnosed with AML between 2014 and 2017 were identified in the

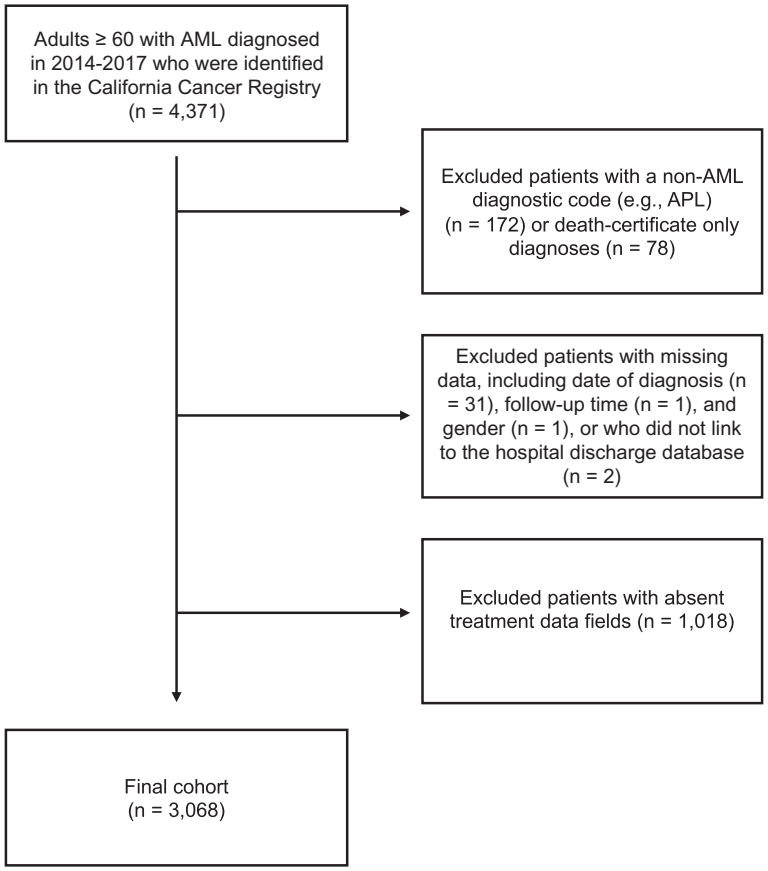

Figure 1. Study cohort diagram. AML indicates acute myeloid leukemia; APL, acute promyelocytic leukemia.

CCR; we excluded 250 patients for having invalid or incomplete diagnostic codes, 35 patients for missing data or nonlinkage to the PDD, and 1018 patients for having their treatment field listed as blank or "unknown" (Fig. 1).

The final study cohort included 3068 adults. The baseline patient characteristics, the setting of frontline treatment, and the receipt of HCT stratified by the type of frontline treatment regimen are described in Table 1. In the full cohort, 34% of the patients were 60 to 69 years old at diagnosis, 39% were 70 to 79 years old, and 27% were 80 years old or older. Thirty-three percent received frontline therapy at an NCI-CC, and 12% underwent HCT.

Across the time period studied, 36% of the patients received induction with a conventional chemotherapy backbone as their frontline treatment regimen, 42% received nonconventional therapy, and 22% received no treatment. Of the patients receiving conventional chemotherapy, 84% received anthracycline plus standard-dose cytarabine ("7 + 3"). Of those receiving conventional therapy, the vast majority (85%) received HMA monotherapy, whereas 8% received HMA plus venetoclax and 3% received liposomal cytarabine plus anthracycline.

Treatment Patterns Over Time

Over time, the use of nonconventional therapy increased, with 38% of patients receiving nontraditional therapy in 2014 versus 47% in 2017 ($P < .0001$). In tandem, the use of conventional therapy declined, with 26% of patients receiving conventional therapy in 2014 versus 23% in 2018 ($P < .0001$). In contrast, the proportion of patients not receiving treatment did not significantly change, with 23% receiving no treatment in 2014 versus 24% in 2017 ($P = .20$; Fig. 2A). Among the patients who received any type of frontline treatment, the receipt of HCT increased over time as well from 14% in 2014 to 18% in 2017 ($P < .0001$; Fig. 2B).

Factors Affecting the Frontline Treatment Regimen

In a multivariable analysis of the entire study cohort (n = 3068), receipt of any treatment was significantly associated with younger age (OR for 70-79 vs 60-69 years, 0.55; 95% CI, 0.42-0.72; OR for ≥80 vs 60-69 years, 0.15; 95% CI, 0.12-0.20) and having fewer than 2 comorbidities (OR, 0.57; 95% CI, 0.43-0.75; Table 2). Patients

TABLE 1. Baseline Characteristics of Adults Aged ≥60 Years Diagnosed With Acute Myeloid Leukemia by Frontline Treatment Regiment, California, 2014-2017

Characteristic	Entire Cohort (n = 3068)	Frontline Induction Therapy		
		Conventional Chemotherapy Backbone (n = 1115 [36.3%])	Nonconventional Therapy (n = 1277 [41.6%])	No Treatment (n = 676 [22.0%])
Year of diagnosis, No. (%)				
2014	717 (23.4)	293 (26.3)	271 (21.2)	153 (22.6)
2015	752 (24.5)	267 (23.9)	303 (23.7)	182 (26.9)
2016	796 (25.9)	297 (26.6)	323 (25.3)	176 (26.0)
2017	803 (26.2)	258 (23.1)	380 (29.8)	165 (24.4)
Age at diagnosis, No. (%)				
60-69 y	1041 (33.9)	740 (66.4)	211 (16.5)	90 (13.3)
70-79 y	1197 (39.0)	334 (30.0)	654 (51.2)	209 (30.9)
≥80 y	830 (27.1)	41 (3.7)	412 (32.3)	377 (55.8)
Sex, No. (%)				
Female	1276 (41.6)	482 (43.2)	507 (39.7)	287 (42.5)
Male	1792 (58.4)	633 (56.8)	770 (60.3)	389 (57.5)
Race/ethnicity, No. (%)				
NH White	2041 (66.5)	724 (64.9)	857 (67.1)	460 (68.0)
NH Black	136 (4.4)	44 (3.9)	62 (4.9)	30 (4.4)
Hispanic	477 (15.5)	196 (17.6)	181 (14.2)	100 (14.8)
Asian/PI	392 (12.8)	142 (12.7)	166 (13.0)	84 (12.4)
Other/unknown	22 (0.7)	9 (0.8)	11 (0.9)	2 (0.3)
Neighborhood SES (tertiles), No. (%)				
Lowest	681 (22.2)	254 (22.8)	273 (21.4)	154 (22.8)
Middle	1082 (35.3)	405 (36.3)	431 (33.8)	246 (36.4)
Highest	1305 (42.5)	456 (40.9)	573 (44.9)	276 (40.8)
Health insurance, No. (%)				
Private/military	1731 (56.4)	709 (63.6)	677 (53.0)	345 (51.0)
Public	1282 (41.8)	394 (35.3)	577 (45.2)	311 (46.0)
Uninsured/self-pay	21 (0.7)	7 (0.6)	9 (0.7)	5 (0.7)
Unknown	34 (1.1)	5 (0.4)	14 (1.1)	15 (2.2)
Patient location, No. (%)				
Urban	2647 (86.3)	957 (85.8)	1096 (85.8)	594 (87.9)
Rural	421 (13.7)	158 (14.2)	181 (14.2)	82 (12.1)
Comorbidities, No. (%)[a]				
None	736 (24.0)	320 (28.7)	297 (23.3)	119 (17.6)
1 comorbidity	506 (16.5)	210 (18.8)	194 (15.2)	102 (15.1)
≥2 comorbidities	859 (28.0)	249 (22.3)	362 (28.3)	248 (36.7)
No admission	967 (31.5)	336 (30.1)	424 (33.2)	207 (30.6)
Frontline treatment at NCI cancer facility, No. (%)				
Yes	1020 (33.2)	526 (47.2)	440 (34.5)	54 (8.0)
No	2048 (66.8)	589 (52.8)	837 (65.5)	622 (92.0)
Transplant, No. (%)				
Yes	358 (11.7)	296 (26.5)	61 (4.8)	1 (0.1)
No	2710 (88.3)	819 (73.5)	1216 (95.2)	675 (99.9)

Abbreviations: NCI, National Cancer Institute; NH, non-Hispanic; PI, Pacific Islander; SES, socioeconomic status.
[a]Defined with the Charlson Comorbidity Index and only determinable in patients with at least 1 hospitalization in California.

receiving any frontline treatment were also significantly more likely to receive their initial care at an NCI-CC (OR, 5.62; 95% CI, 4.16-7.58). Patient sex, race/ethnicity, nSES, location (rural vs urban), and presence or type of health insurance were not associated with whether a patient received AML treatment. Separate sensitivity analyses combining patients with absent treatment with the no-treatment group demonstrated similar results with the exception of increased receipt of treatment over time and increased receipt of treatment in the highest tertile nSES (Supporting Table 2).

In a multivariable analysis of the 2392 patients who received frontline treatment, receipt of nonconventional therapy was significantly associated with older age (OR for 70-79 vs 60-69 years, 6.84; 95% CI, 5.55-8.43; OR for ≥80 vs 60-69 years, 35.11; 95% CI, 24.4-50.5) and having 2 or more comorbidities (OR, 1.50; 95% CI, 1.15-1.96) in comparison with conventional chemotherapy (Table 2). Receipt of nonconventional therapy was also more likely in Black patients relative to non-Hispanic Whites (OR, 1.68; 95% CI, 1.05-2.67) and patients with public health insurance relative to patients with private

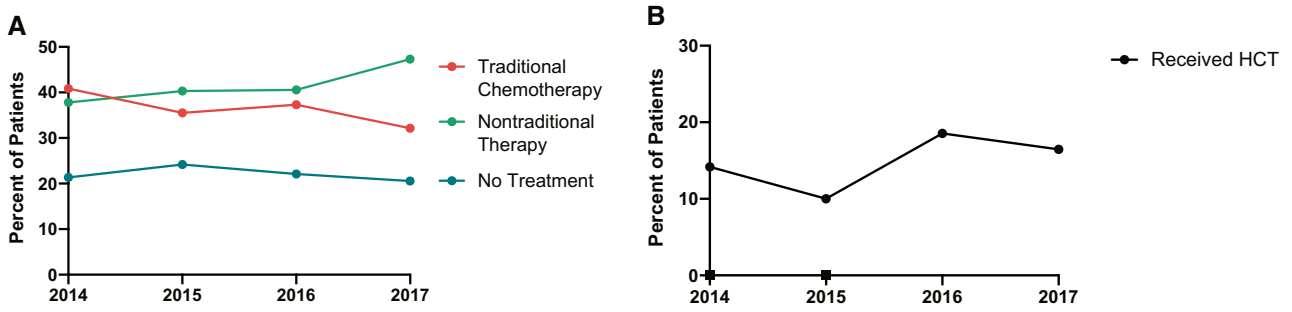

Figure 2. Changes in treatment patterns over time in (A) the frontline treatment regimen and (B) the receipt of HCT for adults aged ≥60 years who were diagnosed with acute myeloid leukemia in 2014-2017 in California. HCT indicates hematopoietic cell transplantation.

insurance (OR, 1.31; 95% CI, 1.08-1.60). The type of frontline therapy was not associated with patient sex, nSES, location (rural vs urban), or whether the frontline treatment was administered at an NCI-CC.

Factors Affecting HCT

Among the 2392 patients who received frontline treatment, receipt of HCT was significantly associated with younger age (OR for 70-79 vs 60-69 years, 0.28; 95% CI, 0.21-0.39; OR for ≥80 vs 60-69 years, 0.01; 95% CI, 0.0-0.09), but there was no relationship between the receipt of HCT and the presence of comorbidities (Table 2). Patients undergoing HCT were more likely to reside in a neighborhood of high socioeconomic status (SES; OR for highest tertile vs lowest tertile, 1.53; 95% CI, 1.01-2.32) and were less likely to have public health insurance (OR for public vs private health insurance, 0.56; 95% CI, 0.41-0.75). Patients undergoing HCT were less likely to have received nonconventional frontline therapy (OR, 0.29; 95% CI, 0.20-0.40) and were more likely to have received frontline treatment at an NCI-CC (OR, 7.82; 95% CI, 5.73-10.70).

Factors Affecting Survival

The 100-day overall mortality of the entire cohort was 40.03%. The 100-day mortality was 26.37% for patients receiving conventional chemotherapy, 30.15% for patients receiving nonconventional chemotherapy, and 81.21% for patients who were not treated ($P < .0001$). The 1-year OS rate of the entire cohort was 25% (95% CI, 23.6%-26.5%). The 1-year OS rate was 44% (95% CI, 40.8%-47.1%) for patients receiving conventional chemotherapy, 31.4% (95% CI, 28.6%-34.3%) for patients receiving nonconventional therapy, and 4.4% (95% CI, 2.7%-6.0%) for patients who were not treated ($P < .001$; Fig. 3). In multivariable models, both receipt of conventional chemotherapy and receipt of nonconventional therapy were associated with superior OS (HR for conventional chemotherapy, 0.22; 95% CI, 0.19-0.25; HR for nonconventional therapy, 0.28; 95% CI, 0.25-0.31) and LSS (HR for conventional chemotherapy, 0.30; 95% CI, 0.25-0.35; HR for nonconventional therapy, 0.32; 95% CI, 0.28-0.37), as was receipt of HCT (HR, 0.75; 95% CI, 0.60-0.95) (Table 3). Multiple variable models also demonstrated that an age ≥ 80 years (HR, 1.19; 95% CI, 1.04-1.36) and 2 or more comorbidities (HR, 1.33; 95% CI, 1.19-1.49) were associated with inferior OS. In contrast, treatment at an NCI-CC (HR, 0.67; 95% CI, 0.61-0.74), high nSES (HR, 0.84; 95% CI, 0.74-0.94), and Asian/Pacific Islander ethnicity (HR, 0.86; 95% CI, 0.75-0.98) were associated with improved OS. In a subset analysis of only patients who received treatment (n = 2392), receipt of HCT remained associated with superior OS (HR, 0.69; 95% CI, 0.56-0.86) and LSS (HR, 0.76; 95% CI, 0.60-0.98).

Multivariable models of LSS paralleled OS, with an age ≥ 80 years (HR, 1.39; 95% CI, 1.18-1.63) and 2 or more comorbidities (HR, 1.27; 95% CI, 1.11-1.44) associated with inferior LSS and with treatment at an NCI-CC (HR, 0.68; 95% CI, 0.60-0.77) associated with improved OS. nSES and race/ethnicity did not affect LSS. When patients with absent treatment data were included in the no-treatment group, findings from survival analyses were similar (Supporting Table 3).

Admissions and In-Hospital Days

Across the full cohort, the median number of in-hospital days during the first 100 days after the diagnosis was 22, and 79.8% of patients had at least 1 hospitalization (Table 4). Compared with patients receiving conventional chemotherapy, patients receiving nonconventional therapy spent less time in the hospital (42 vs 15 days; $P <$ .001). Patients receiving conventional chemotherapy also

TABLE 2. Multivariable-Adjusted ORs and Associated 95% CIs of Factors Associated With the Frontline Treatment Regimen and the Receipt of HCT Among Adults Aged ≥60 Years With Acute Myeloid Leukemia, California, 2014-2017

Characteristic	OR (95% CI)		
	Frontline Treatment: Receipt of Treatment vs No Treatment	Frontline Treatment: Receipt of Nonconventional vs Conventional Therapy	Receipt of HCT vs No HCT
Year of diagnosis			
2014	1.00 (reference)	1.00 (reference)	1.00 (reference)
2015	0.76 (0.58-1.00)	1.34 (1.02-1.76)	0.60 (0.39-0.92)
2016	0.94 (0.71-1.23)	1.18 (0.90-1.55)	1.79 (1.22-2.62)
2017	1.03 (0.72-1.47)	2.05 (1.45-2.92)	1.97 (1.16-3.34)
Age at diagnosis			
60-69 y	1.00 (reference)	1.00 (reference)	1.00 (reference)
70-79 y	0.55 (0.42-0.72)	6.84 (5.55-8.43)	0.28 (0.21-0.39)
≥80 y	0.15 (0.12-0.20)	35.11 (24.4-50.5)	0.01 (0.00-0.09)
Sex			
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	1.06 (0.87-1.28)	1.10 (0.91-1.34)	1.10 (0.83-1.46)
Race/ethnicity			
NH White	1.00 (reference)	1.00 (reference)	1.00 (reference)
NH Black	1.04 (0.65-1.64)	1.68 (1.05-2.67)	0.61 (0.26-1.41)
Hispanic	1.13 (0.85-1.49)	0.84 (0.64-1.11)	0.70 (0.46-1.07)
Asian/PI	1.13 (0.84-1.53)	0.96 (0.72-1.29)	1.01 (0.67-1.53)
Other/unknown	2.56 (0.56-11.80)	0.72 (0.26-1.98)	0.79 (0.15-4.28)
Neighborhood SES (tertile)			
Lowest	1.00 (reference)	1.00 (reference)	1.00 (reference)
Middle	0.97 (0.75-1.26)	1.06 (0.82-1.38)	1.08 (0.72-1.62)
Highest	1.15 (0.88-1.50)	1.07 (0.82-1.40)	1.53 (1.01-2.32)
Health insurance			
Private/military	1.00 (reference)	1.00 (reference)	1.00 (reference)
Public	0.91 (0.75-1.11)	1.31 (1.08-1.60)	0.56 (0.41-0.75)
Uninsured/self-pay	0.57 (0.19-1.68)	1.97 (0.65-5.94)	0.31 (0.03-2.84)
Unknown	0.45 (0.21-0.99)	2.50 (0.80-7.82)	0.68 (0.08-5.56)
Patient location			
Urban	1.00 (reference)	1.00 (reference)	1.00 (reference)
Rural	1.02 (0.76-1.38)	1.31 (0.99-1.74)	0.72 (0.48-1.09)
Comorbidities[a]			
None	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 comorbidity	0.73 (0.53-1.01)	1.16 (0.86-1.55)	0.95 (0.64-1.41)
≥2 comorbidities	0.57 (0.43-0.75)	1.50 (1.15-1.96)	0.68 (0.45-1.02)
No admission	0.67 (0.47-0.95)	0.99 (0.71-1.37)	0.64 (0.39-1.03)
Frontline treatment at NCI cancer facility			
Yes	5.62 (4.16-7.58)	0.89 (0.73-1.08)	7.82 (5.73-10.7)
No	1.00 (reference)	1.00 (reference)	1.00 (reference)
Frontline treatment regimen			
Conventional chemotherapy	—	—	1.00 (reference)
Nonconventional therapy	—	—	0.29 (0.20-0.40)

Abbreviations: CI, confidence interval; HCT, hematopoietic cell transplantation; NCI, National Cancer Institute; NH, non-Hispanic; OR, odds ratio; PI, Pacific Islander; SES, socioeconomic status.
Models were adjusted for all variables in the table.
[a] Defined with the Charlson Comorbidity Index and only determinable in patients with at least 1 hospitalization in California.

had more hospital admissions, with 63.4% having 2 or more admissions versus 46.8% of patients receiving nonconventional therapy ($P < .001$).

DISCUSSION

The past decade has brought forth several new treatment options for older adults with AML. In this population-based study, we demonstrate that the treatment approach for older adults with AML is changing, with an increasing proportion of patients receiving initial treatment in comparison with historical reports[3,15] and with an increase in the use of newer therapies over time. These evolving treatment patterns are reflected in improving survival estimates in this population in comparison with historical reports,[3,16] Despite these advancements, we continue to find that roughly one-quarter of adults aged ≥60 years with AML remain untreated. Although the fraction of untreated patients has improved from the 60% described in

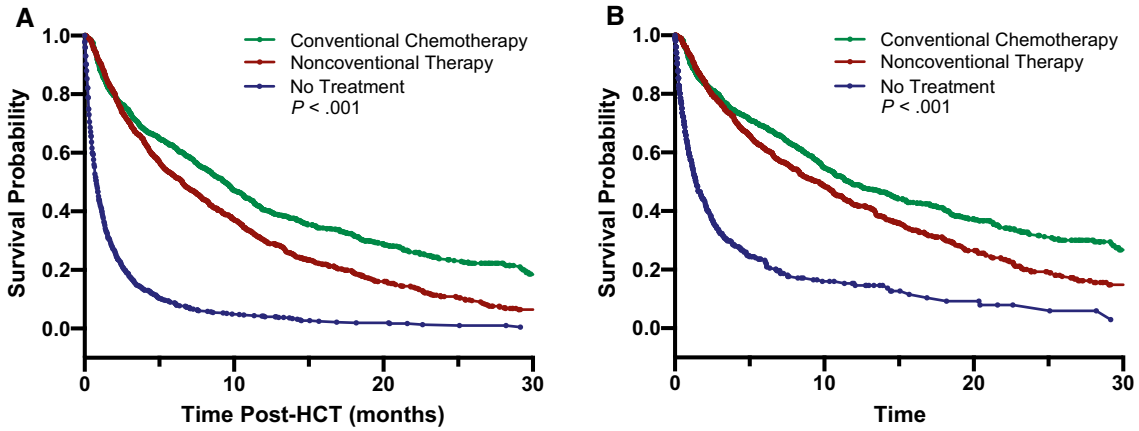

Figure 3. (A) Overall survival stratified by the frontline treatment regimen and (B) leukemia-specific survival stratified by the frontline treatment regimen. HCT indicates hematopoietic cell transplantation.

a Surveillance, Epidemiology, and End Results–Medicare report of older adults with AML treated between 2000 and 2009,[3] a substantial proportion of patients remain untreated in the modern era. In our analysis, receipt of frontline treatment was associated with patient age and comorbidity, as described previously,[3,17,18] whereas a patient's insurance status, SES, and location (rural vs urban) did not affect treatment receipt.

In addition, we found that older adults receiving their care at an NCI-CC were significantly more likely to receive frontline treatment, and this was consistent with prior studies examining the role of the frontline care setting in AML.[17-19] In a study of more than 60,000 patients of all ages with AML treated between 2003 and 2011, patients treated at an academic center were more likely to receive initial chemotherapy, were more likely to receive HCT, and had superior OS.[20] In a separate study by the same authors, it was shown that patients treated at academic centers were 1.5-fold more likely to receive therapy for AML.[18] Untreated patients were also more likely to be female, to be of Black race/ethnicity, to reside in lower SES neighborhoods, and to have public or no health insurance.[18] In our study, we did not observe the receipt of any treatment to be affected by patient sociodemographics, and this suggests that the setting of frontline care may be a prognostic factor independent of patient-specific factors. However, we observed that newer, nonconventional agents were more common among Black patients and patients with public health insurance. Although strategies to mitigate treatment disparities are complex, our data indicate that nontraditional therapies may offer an emerging option to patients who historically have had less access to frontline leukemia care.

We also have demonstrated that the use of nonconventional chemotherapies in older adults with AML is increasing. In our cohort, nonconventional therapies were associated with inferior 100-day mortality, OS, and LSS; this differed slightly from historical reports of older adults with AML that found intensive induction chemotherapy to be associated with inferior 100-day mortality relative to HMA monotherapy.[6] We also found nonconventional therapy to be associated with older age and increased comorbidities relative to conventional chemotherapy; however, unlike the receipt of any treatment, the type of frontline regimen was not associated with the frontline care setting. This suggests that, thus far, there is uptake of nonconventional therapies across leukemia care settings. Because many of these novel therapies are easier to administer in comparison with conventional chemotherapy, our findings are not surprising. Other studies have demonstrated that treatments with HMAs and other oral agents can be safely and effectively administered in the outpatient setting,[15] are associated with decreased costs of care,[21] and may be associated with improved quality of life.[22] Importantly, our analysis also demonstrated that patients who received nonconventional therapies experienced fewer hospital admissions and in-hospital days. Although these are not formal quality-of-life metrics, spending less time in the hospital is particularly relevant to older and frailer patients,[23] and this further supports consideration of nonconventional therapies in this population.

TABLE 3. Multivariable-Adjusted HRs and Associated 95% CIs of Factors Affecting Overall and Leukemia-Specific Survival Among Adults Aged ≥60 Years With Acute Myeloid Leukemia, California, 2014-2017

	Overall Survival		Leukemia-Specific Survival	
	No. of Patients	HR (95% CI)	No. of Patients	HR (95% CI)
Year of diagnosis				
2014	637	1.00 (reference)	458	1.00 (reference)
2015	642	0.92 (0.82-1.03)	460	0.93 (0.82-1.06)
2016	584	0.91 (0.81-1.02)	429	0.93 (0.81-1.07)
2017	363	1.07 (0.91-1.26)	254	0.99 (0.82-1.20)
Age at diagnosis				
60-69 y	649	1.00 (reference)	471	1.00 (reference)
70-79 y	864	1.04 (0.92-1.17)	629	1.14 (1.00-1.31)
≥80 y	713	1.19 (1.04-1.36)	501	1.39 (1.18-1.63)
Sex				
Female	917	1.00 (reference)	664	1.00 (reference)
Male	1309	1.00 (0.92-1.09)	937	0.99 (0.89-1.09)
Race/ethnicity				
NH White	1494	1.00 (reference)	1082	1.00 (reference)
NH Black	103	0.87 (0.71-1.06)	74	0.90 (0.71-1.15)
Hispanic	350	0.93 (0.82-1.05)	242	0.92 (0.79-1.06)
Asian/PI	265	0.86 (0.75-0.98)	194	0.88 (0.76-1.03)
Other/unknown	14	1.02 (0.60-1.73)	9	0.91 (0.47-1.76)
Neighborhood SES (tertile)				
Lowest	515	1.00 (reference)	358	1.00 (reference)
Middle	809	0.95 (0.85-1.07)	578	0.98 (0.85-1.12)
Highest	902	0.84 (0.74-0.94)	665	0.87 (0.76-1.00)
Health insurance				
Private/military	1231	1.00 (reference)	898	Reference
Public	955	1.04 (0.96-1.14)	677	1.02 (0.93-1.14)
Uninsured/self-pay	15	1.40 (0.84-2.33)	13	1.69 (0.98-2.94)
Unknown	25	0.56 (0.38-0.84)	13	0.44 (0.25-0.76)
Patient location				
Rural	320	1.00 (reference)	230	1.00 (reference)
Urban	1906	0.93 (0.82-1.06)	1371	0.92 (0.79-1.06)
Comorbidities[a]				
None	568	1.00 (reference)	419	1.00 (reference)
1 comorbidity	404	1.13 (1.00-1.29)	299	1.15 (0.99-1.33)
≥2 comorbidities	753	1.33 (1.19-1.49)	517	1.27 (1.11-1.44)
No admission	501	0.87 (0.75-1.01)	366	0.93 (0.79-1.10)
Frontline treatment at NCI cancer center				
Yes	605	0.67 (0.61-0.74)	455	0.68 (0.60-0.77)
No	1621	1.00 (reference)	1146	1.00 (reference)
Frontline treatment regimen				
Conventional chemotherapy	676	0.22 (0.19-0.25)	532	0.30 (0.25-0.35)
Nonconventional therapy	916	0.28 (0.25-0.31)	669	0.32 (0.28-0.37)
No treatment	634	1.00 (reference)	400	1.00 (reference)
Transplant[b]				
Yes	107	0.75 (0.60-0.93)	87	0.82 (0.64-1.04)
No	2119	1.00 (reference)	1514	1.00 (reference)

Abbreviations: CI, confidence interval; HR, hazard ratio; NCI, National Cancer Institute; NH, non-Hispanic; PI, Pacific Islander; SES, socioeconomic status.
Models were adjusted for all variables in the table.
[a] Defined with the Charlson Comorbidity Index and only determinable in patients with at least 1 hospitalization in California.
[b] *Transplant* was considered a time-dependent variable.

Historically, one reason that a provider may choose to treat with traditional, intensive chemotherapy is the ability to bridge a patient to potentially curative HCT, a practice that may be changing. In the initial trial of frontline HMAs plus venetoclax in adults ≥65 years old, 14% of patients ultimately underwent HCT.[8,24] More recently, multiple retrospective studies have shown favorable outcomes for older adults undergoing HCT after this combination as well.[25-27] Similarly, oral targeted monotherapies were also shown to provide successful bridges to HCT.[9,28] In our analyses, we demonstrate that the use of HCT in older adults with AML is increasing over time, even as the use of frontline cytotoxic chemotherapy declines. Although the use of HCT remains associated with younger patient age and use of frontline therapy with a conventional chemotherapy backbone, these relationships

TABLE 4. Hospitalizations and In-Hospital Days in the First 100 Days After the Acute Myeloid Leukemia Diagnosis Among Adults Aged ≥60 Years, California, 2014-2017

		Frontline Treatment Regimen		
	Entire Cohort (n = 3068)	Conventional Chemotherapy (n = 1115)	Nonconventional Therapy (n = 1277)	No Treatment (n = 676)
Admissions within first 100 d after diagnosis, No. (%)				
≥2 admissions	1452 (47)	707 (63.4)	597 (46.8)	148 (21.9)
≥3 admissions	722 (23.5)	391 (35.1)	286 (22.4)	45 (6.6)
Total in-hospital days within first 100 d after diagnosis, median (range)	22 (0-256)	42 (1-256)	15 (0-172)	6 (0-251)

may change as the role of HCT after nonconventional therapies becomes increasingly defined.

Between the ability to administer in a community setting, the reduced time spent in the hospital, and the ability to potentially bridge to HCT, we anticipate that the use of nonconventional frontline therapies in older adults with AML will continue to increase. Importantly, since our analysis was conducted, additional treatment options have emerged; these include the 2018 Food and Drug Administration approvals of HMAs plus venetoclax, gilteritinib, and glasdegib and the 2019 approval of isosidenib.[29] More recently, oral HMAs received Food and Drug Administration approval in 2020, and though not yet studied as frontline AML therapy, they may also offer an additional option particularly amenable to the outpatient and/or community setting. Although our data set currently includes data only through 2017, over the next 3 to 5 years, additional analyses will allow for an understanding of how treatment patterns continue to evolve for older adults with newly diagnosed AML. We anticipate that the distribution of frontline treatment modalities highlighted in Supporting Table 1 will likely shift over time to reflect increased use of nonconventional therapies, especially HMAs plus venetoclax, which has shown particularly promising outcomes in older and unfit patients.[8,26,27,30] Given the strong associations of age and comorbidities with treatment, we also anticipate that the proportion of untreated older adults with AML will continue to decline.

As in all population science research, our study is limited by data completeness and the data elements available. Although we were able to abstract treatment data from text fields, many key treatment details such as dosing, the number of cycles, and subsequent treatment lines were not available. Disease-related variables, such as European LeukemiaNet risk stratification and specific pathologic features, were also not available in the study databases. Additionally, although we excluded nearly 25% of the initially identified patients because they had unknown treatment data in the CCR, the findings from our sensitivity analyses suggest that these missing treatment fields likely reflected patients who did not receive AML therapy. These data suggest that the proportion of older adults with AML who continue to not receive treatment is likely much greater than the 22% identified in our primary analysis, up to 47% of older adult patients with AML.

Our data highlight that, at a population level, there remains significant opportunity to increase access to treatment for older adults, especially those who present to non–NCI-CCs. When possible, a timely referral to specialized cancer centers should be considered for diagnostic workup, initial therapy, and consideration for clinical trials. At the same time, however, there remains an opportunity for growth in community-based care, where many older adults remain untreated. This could include increased use of newer, conventional frontline agents as well as new strategies in multidisciplinary, community-based leukemia care. Potential programs include community-academic partnerships, such as those used in acute promyelocytic leukemia,[31] and a hybrid model of initial therapy at an academic center followed by community-based supportive care.[32] As the number of both conventional and nonconventional treatment options for older adults continues to expand, there remain fewer reasons why older adults with AML should remain untreated in the modern era.

FUNDING SUPPORT

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; by the National Cancer Institute's Surveillance, Epidemiology and End Results program under contracts awarded to the Cancer Prevention Institute of California, the University of Southern California, and the Public Health Institute; and by the National Program of Cancer Registries of the Centers for Disease Control and Prevention under an agreement awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the authors, and endorsement by the State

of California Department of Public Health, the National Cancer Institute, the Centers for Disease Control and Prevention, or their contractors and subcontractors is not intended nor should be inferred.

CONFLICT OF INTEREST DISCLOSURES

Vanessa E. Kennedy reports a Hematology Opportunities for the Next Generation of Research Scientists award from the American Society of Hematology. Lori S. Muffly reports grants from Jasper, Servier, and Adaptive and personal fees from Amgen, Astellas, Pfizer, Jazz, UpToDate, and Adaptive. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Vanessa E. Kennedy: Conceptualization, literature search, study design, data curation, data interpretation, figure development, and writing (original draft, revision, and editing). **Theresa H. M. Keegan:** Conceptualization, study design and investigative methodology, data analysis and interpretation, and writing (revision and editing). **Qian Li:** Data collection, data analysis and interpretation, figure development, and writing (revision and editing). **Frances B. Maguire:** Data collection, data analysis and interpretation, figure development, and writing (revision and editing). **Lori S. Muffly:** Conceptualization, study design and investigative methodology, data interpretation, and writing (original draft, revision, and editing).

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