Original Study

A Retrospective Study of Comorbidities and Complications in Elderly Acute Myeloid Leukemia Patients in the United States

Neil Dhopeshwarkar,[1,2] Shahed Iqbal,[1] Xuehong Wang,[1,3] Maribel Salas[1,4]

Abstract

There is limited information on the comorbidities and complications in elderly acute myeloid leukemia (AML) patients. In a sample of 3911 AML patients aged ≥ 65 years identified from the Surveillance, Epidemiology, and End Results–Medicare database, AML patients had more comorbidities, higher rates of complications, and a higher risk of developing cardiovascular disease, type 2 diabetes mellitus, and stroke compared to matched noncancer controls.

Background: Comorbidities in acute myeloid leukemia (AML) patients have been shown to increase with age. However, few studies have described the disease burden in elderly AML patients, a population generally underrepresented in clinical trials. We aimed to characterize the comorbidities and complications in elderly AML patients. **Patients and Methods:** Patients aged ≥ 65 years with a primary diagnosis of AML were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (2000-2013) and were followed until the end of 2014. AML patients were matched 1:1 to noncancer patients by age, sex, geographic region, and race. A subset of patients with relapsed and/or refractory (R/R) AML was identified by modifying a previously validated algorithm. Baseline comorbidities and complications (eg, infectious, hematologic, cardiovascular) during follow-up were assessed using ICD-9 codes. Cox proportional hazards models were used to determine associations between AML and developing select complications. **Results:** Compared to matched noncancer controls, AML patients (n = 3911) had higher baseline National Cancer Institute comorbidity index scores (1.81 vs. 1.63, $P < .01$), higher incidence rates (per 100 person-years) for all events of interest, and a higher risk of developing cardiovascular disease (hazard ratio = 4.61; 95% confidence interval, 4.07-5.21), type 2 diabetes mellitus (hazard ratio = 3.85; 95% confidence interval, 3.35-4.42), and stroke (hazard ratio = 2.60; 95% confidence interval, 2.32-2.92). R/R AML patients were younger, had lower National Cancer Institute comorbidity scores, lower incidence rates of events of interest, and a longer follow-up time compared to non-R/R AML patients. **Conclusion:** Elderly AML patients had more comorbidities and higher rates of complications compared to noncancer controls. Considering comorbidities and complications in elderly AML patients may improve clinical decision making.

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[1]Clinical Safety and Pharmacovigilance and Epidemiology, Daiichi Sankyo Inc, Basking Ridge, NJ
[2]College of Pharmacy and Health Sciences, St John's University, Queens, NY
[3]PRO Unlimited, Burlingame, CA
[4]Center of Clinical Epidemiology and Biostatistics (CCEB) and Center for Pharmacoepidemiology Research and Training (CPeRT), University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA

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Address for correspondence: Maribel Salas, MD, DSc, MSc, FISPE, Daiichi Sankyo Inc, 211 Mt Airy Road, Basking Ridge, NJ 07920
E-mail contact: msalas@dsi.com

Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults and accounts for the largest number of annual deaths from leukemia in the United States, with an estimated 10,670 deaths from AML expected in 2018.[1,2] AML is common in elderly patients; with a median age at diagnosis of 68 years, and with 57.4% of AML patients aged ≥ 65 years (with about a third of patients ≥ 75 years old).[2] The incidence of AML increases with age; older patients are typically more challenging to

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treat, as they have higher rates of relapsed and/or refractory (R/R) disease[3-6] and have a lower prognosis for survival compared to younger patients.[3,7-9] These poor outcomes have been attributed to numerous risk factors for poor-risk leukemia, which appear more frequently in elderly patients, including evolution from preexisting myelodysplastic syndrome or previous malignancy, presence of an adverse karyotype (eg, full or partial losses of chromosomes 5 and 7), absence of favorable karyotype (eg, t(8;21), inv(16), and t(15;17)), and expression of the chemoresistant phenotype glycoprotein MDR1.[10-12]

High comorbidity burden and vulnerability to treatment toxicities are also contributing factors to poor outcomes in elderly AML patients.[3] The assessment of comorbidity burden in elderly patients can help determine eligibility for intensive chemotherapy and guide supportive care.[13,14] However, the baseline comorbidities, complications of disease, treatment, and other factors in this population are not well characterized. Most population-based studies on AML have focused on survival and cost outcomes rather than reporting specific comorbidities and complications.[15-18] A few studies have investigated the effect of comorbidities on survival but did not report other specific outcomes,[7,19] and although clinical trials generally report adverse events, data on this population are sparse as a result of low enrollment of elderly patients.[20-22]

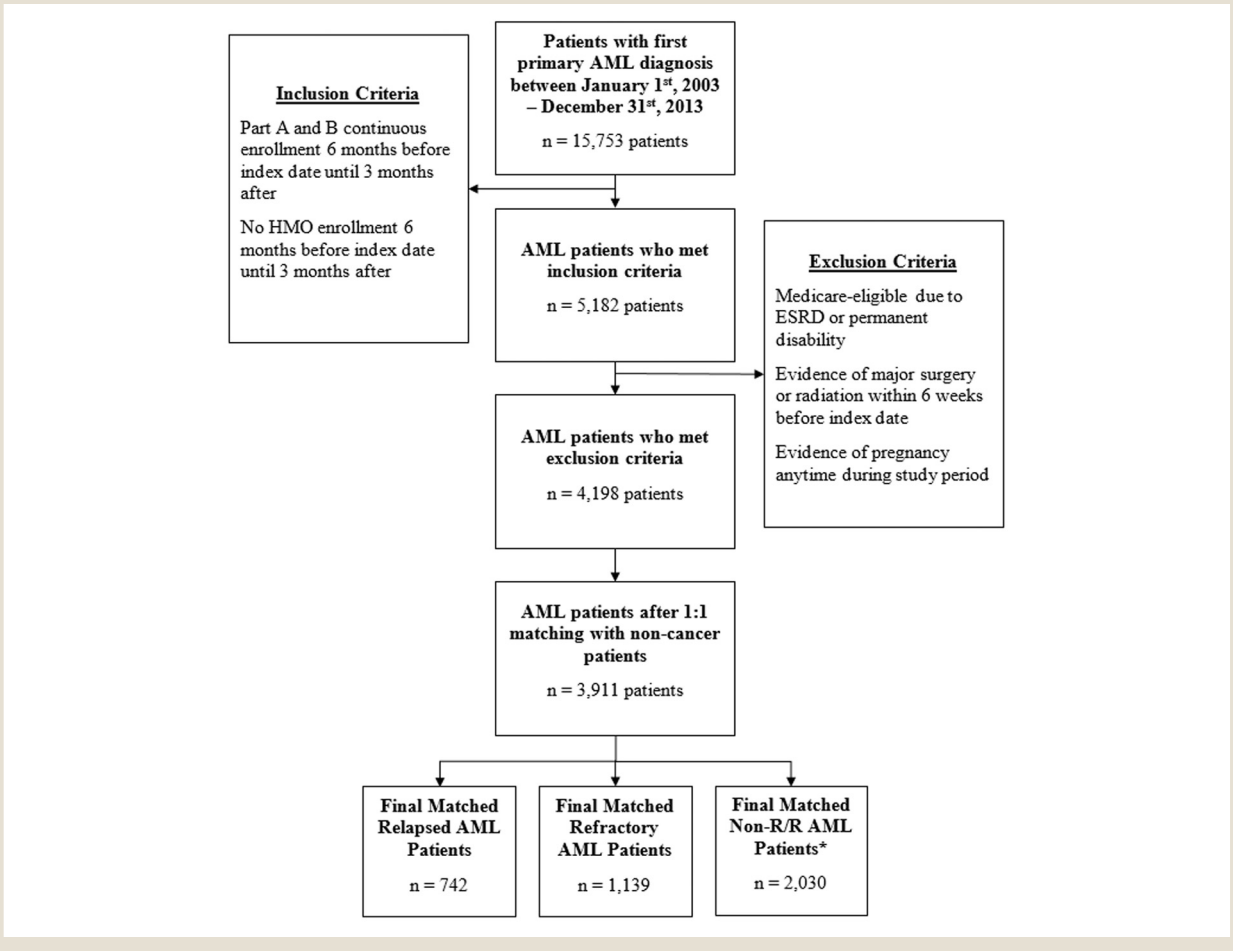
We aimed to describe the baseline comorbidities and complications after AML diagnosis in a representative sample of elderly patients compared to noncancer controls utilizing a large real-world population-based data set.

Patients and Methods

Data Source

Patients were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database provided by the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services.[23] This data set, which links patients in SEER cancer registries with Medicare claims (using a validated algorithm described elsewhere[24]) provides detailed information on cancer

Figure 1 Study Population Flowchart. After Applying Inclusion and Exclusion Criteria and 1:1 Matching to Initial Sample of 15,753 AML Patients, 3911 Matched Pairs of AML Patients and Noncancer Controls Remained. Within This Final Cohort Were 742 Cases of Relapsed AML, 1139 Refractory AML, and 2030 Non-R/R AML Patients. *AML Patients Who did Not Meet Definition for Relapsed or Refractory Were Included in Non-R/R AML Cohort



Abbreviations: AML = acute myeloid leukemia; ESRD = end-stage renal disease; HMO = health maintenance organization; R/R = relapsed/refractory.

Table 1 Demographics of All AML Patients by Disease Type

Characteristic	AML N = 3911	Relapsed AML N = 742	Refractory AML N = 1139	Non-R/R AML N = 2030
Age (Years)				
Mean	77.26	74.37	74.61	79.81
SD	6.96	5.94	6.05	6.82
Age Category				
65-74 years	1530 (39.1)	421 (56.7)	630 (55.3)	479 (23.6)
75-84 years	1730 (44.2)	237 (36.8)	420 (36.9)	1037 (51.1)
85+ years	651 (16.6)	48 (6.5)	89 (7.8)	514 (25.3)
Gender				
Male	2104 (53.8)	419 (56.5)	644 (56.5)	1041 (51.3)
Female	1807 (46.2)	323 (43.5)	495 (43.5)	989 (48.7)
Region				
Midwest	520 (13.3)	99 (13.3)	137 (12.0)	284 (14.0)
Northeast	755 (19.3)	160 (21.6)	208 (18.3)	387 (19.1)
South	940 (24.0)	134 (18.1)	310 (27.2)	496 (24.4)
West	1696 (43.4)	349 (47.0)	484 (42.5)	863 (42.5)

Data are presented as n (%). All AML groups had exact same demographics as their matched noncancer control groups, the result of exact 1:1 matching.
Abbreviations: AML = acute myeloid leukemia; SD = standard deviation; R/R = relapsed/refractory.

patients who are Medicare beneficiaries. The SEER program collects data on cancer cases from 19 US geographic areas that cover about 34% of the US population and are demographically representative of the entire United States,[25] while Medicare, a federal health insurance program, is the primary insurer for 97% of the US elderly (≥65 years of age) population. The majority (93%) of patients ≥ 65 years of age in the SEER data are successfully linked to Medicare data.[23]

The SEER data file contains information on patient demographics, cancer diagnosis, cause of death, and other clinical characteristics; Medicare files contain claims data on the covered health care services from the beginning of a patient's Medicare eligibility until death. The study data set included SEER data from 2003 to 2013, and Medicare data from 2000 to 2014. Also included with the data set is a data file containing Medicare claims of a 5% random sample of patients with no evidence of cancer residing in SEER geographic areas. This study was approved by the New England institutional review board.

Cohort Selection

Patients were included in the study if they had a first primary cancer diagnosis of AML between January 1, 2003, and December 31, 2013. AML diagnosis was identified in SEER using International Classification of Diseases for Oncology, 3rd edition/World Health Organization (ICD-O-3/WHO) 2008 Site Recode 35021. Index date was defined as the earliest AML diagnosis using ICD-O-3/WHO recode 35021 from the SEER file or International Classification of Diseases, 9th Revision (ICD-9), diagnosis code 205.0x from Medicare claims. Patients who were enrolled in Medicare Part A and Part B with no health maintenance organization enrollment were included. Patients who were Medicare eligible as a result of end-stage renal disease or permanent disability any time before the index date were excluded. Patients who had evidence of pregnancy any time during the study period were also excluded. Last, patients who had major surgery or who received radiation within 6 weeks before the index date were excluded in order to prevent capture of surgery-related complications during follow-up and to ensure inclusion of only first primary AML patients (Supplemental Table 1 in the online version). The same inclusion and exclusion criteria were applied to noncancer patients when applicable; these subjects served as noncancer controls. In order to obtain patients with the most complete claims data, continuous enrollment was required from 6 months before the index date until 3 months after the index date. AML patients were 1:1 exact matched to noncancer controls by year of birth, sex, ethnicity, and geographic region (state). Each noncancer control was assigned the same index date as that of their matched AML patient. Patients were followed from AML diagnosis through occurrence of prespecified events, loss to follow-up, death, or end of data period, whichever occurred first.

Defining R/R AML

A subset of relapsed AML patients was defined by modifying a previously published treatment-based and data-driven algorithm.[26] Patients were considered to have evidence of relapsed disease if they had an ICD-9 diagnosis code of relapsed AML (205.02), if they received chemotherapy (Supplemental Table 2 in the online version) after a > 60 day period with no chemotherapy claims, or if they had diagnosis/procedure codes indicating repeated stem-cell/bone marrow transplantation (Supplemental Table 3 in the online version). Patients were considered to have evidence of refractory AML if they had > 2 cycles of chemotherapy.[27,28] A new cycle was defined as a chemotherapy code appearing on day 14 through day 60 since previous chemotherapy. (Chemotherapy within < 14 days of the previous cycle was defined as being part of the same cycle.) Patients with evidence of both relapsed and refractory AML were designated as having whichever occurred earlier. Patients who did

Table 2 Baseline Clinical Characteristics of AML Patients and Matched Noncancer Controls

Characteristic	AML			R/R AML			Non-R/R AML		
	Cancer (N = 3911)	Control (N = 3911)	*P*	Cancer (N = 1881)	Control (N = 1881)	*P*	Cancer (N = 2030)	Control (N = 2030)	*P*
Myelodysplastic syndrome	708 (18.1)	< 11 (<0.3)	< .01	398 (21.2)	< 11 (<0.6)	< .01	310 (15.3)	< 11 (<0.6)	< .01
NCI comorbidities									
Congestive heart failure	842 (21.5)	642 (16.4)	< .01	296 (15.7)	240 (12.8)	0.02	546 (26.9)	402 (19.8)	< .01
COPD	1102 (28.2)	928 (23.7)	0.01	446 (23.7)	425 (22.6)	0.67	656 (32.3)	503 (24.8)	< .01
Cerebrovascular disease	713 (18.2)	740 (18.9)	0.23	292 (15.5)	299 (15.9)	0.53	421 (20.7)	441 (21.7)	0.31
Dementia	157 (4.0)	274 (7.0)	< .01	31 (1.6)	85 (4.5)	< .01	126 (6.2)	189 (9.3)	< .01
Diabetes without chronic complications	1226 (31.3)	1138 (29.1)	0.11	575 (30.6)	518 (27.5)	0.11	651 (32.1)	620 (30.5)	0.47
Diabetes with chronic complications	393 (10.0)	372 (9.5)	0.60	170 (9.0)	153 (8.1)	0.44	223 (11.0)	219 (10.8)	0.97
HIV/AIDS	< 11 (<0.3)	0 (0.0)	0.32	< 11 (<0.6)	0 (0.0)	0.32	0 (0.0)	0 (0.0)	n/a
Moderate/severe liver disease	17 (0.4)	< 11 (<0.3)	0.08	< 11 (<0.6)	< 11 (<0.6)	0.18	< 11 (<0.6)	< 11 (<0.6)	0.26
Mild liver disease	47 (1.2)	30 (0.8)	0.06	22 (1.2)	16 (0.9)	0.36	25 (1.2)	14 (0.7)	0.08
Myocardial infarction	409 (10.5)	315 (8.1)	< .01	170 (9.0)	138 (7.3)	0.09	239 (11.8)	177 (8.7)	< .01
Acute myocardial infarction	182 (4.7)	156 (4.0)	0.21	76 (4.0)	62 (3.3)	0.28	106 (5.2)	94 (4.6)	0.45
History of myocardial infarction	321 (8.2)	249 (6.4)	< .01	136 (7.2)	112 (6.0)	0.17	185 (9.1)	137 (6.7)	< .01
Paralysis	73 (1.9)	98 (2.5)	0.04	31 (1.6)	46 (2.4)	0.07	42 (2.1)	52 (2.6)	0.26
Peripheral vascular disease	757 (19.4)	720 (18.4)	0.51	284 (15.1)	264 (14.0)	0.53	473 (23.3)	456 (22.5)	0.71
Renal disease	420 (10.7)	315 (8.1)	< .01	175 (9.3)	124 (6.6)	< .01	245 (12.1)	191 (9.4)	0.01
Rheumatologic disease	226 (5.8)	201 (5.1)	0.30	93 (4.9)	81 (4.3)	0.44	133 (6.6)	120 (5.9)	0.47
Peptic ulcer disease	174 (4.4)	148 (3.8)	0.19	56 (3.0)	47 (2.5)	0.44	118 (5.8)	101 (5.0)	0.29

not have evidence of either relapsed or refractory AML were assigned to the non-R/R AML subgroup.

Study Measures

During the baseline period (at least 6 months before the index date), demographic characteristics (age, sex, geographic region) were obtained from the SEER file, and clinical characteristics (NCI comorbidity index scores and individual comorbidities)[29] were obtained using ICD-9 codes from Medicare files (Supplemental Table 4 in the online version). During the follow-up period, events of interest (including infectious, hematologic, hemorrhagic, cardiovascular, cerebrovascular, hepatic, and renal events) were obtained using ICD-9 codes from Medicare files (Supplemental Table 5 in the online version). Other hemorrhages included all hemorrhages other than gastrointestinal hemorrhages, intracranial hemorrhage, and epistaxis. With the exception of myocardial infarction (MI) and stroke (ischemic stroke, hemorrhagic stroke, or transient ischemic attack), only incident cases of the events were captured and required no evidence of the event at baseline. Patients with relapsed or refractory disease were collapsed into a single subgroup for the analysis of baseline comorbidities and events of interest.

Statistical Analysis

Frequencies (%) were calculated for comorbidities included in the NCI comorbidity index and events of interest. Incidence rates per 100 person-years (PY) were also calculated for events of interest. Bivariate analyses of categorical variables were conducted by chi-square tests, and *t* tests or Poisson tests were used for continuous variables. $P < .05$ was considered statistically significant. Cell counts and frequencies that contained data of < 11 patients were suppressed in compliance with the SEER-Medicare data use agreement.

Multivariate cox proportional hazards models (adjusting for age, geographic region, sex, baseline myelodysplastic syndrome, and NCI comorbidity index score) and Kaplan-Meier curves were used to evaluate the associations between having AML and developing the following complications, selected because of clinical relevance: cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) with or without complications, and stroke.[30-33] The CVD outcome included heart failure, MI, atrial fibrillation, ventricular tachyarrhythmia, and ischemic heart disease/coronary artery disease (CAD). Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for the listed outcomes. All statistical analyses were performed by SAS 9.3 software (SAS Institute, Cary, NC).

Results

Study Cohort

After applying the inclusion/exclusion criteria and 1:1 matching to noncancer controls, the final cohort included 3911 AML patients from an initial sample of 15,753 AML patients identified from SEER (Figure 1). Of the total cohort, 1811 patients (46.3%) had R/R AML (742 [19.0%] relapsed patients and 1139 [29.1%] refractory patients), and 2030 patients (51.9%) were in the non-R/R AML group.

Baseline Characteristics and Comorbidities

Because AML and noncancer controls were matched, demographic characteristics were similar between groups: mean ±

Table 2 Continued

Characteristic	AML			R/R AML			Non-R/R AML		
	Cancer (N = 3911)	Control (N = 3911)	*P*	Cancer (N = 1881)	Control (N = 1881)	*P*	Cancer (N = 2030)	Control (N = 2030)	*P*
NCI Comorbidity Index Score									
Mean	1.81	1.63	< .01	1.53	1.39	0.01	2.07	1.85	< .01
SD	1.97	1.97		1.82	1.82		2.07	2.08	
0 (%)	1253 (32.0)	1519 (38.8)	< .01	690 (36.7)	821 (43.6)	< .01	563 (29.9)	698 (37.1)	< .01
1 (%)	889 (22.7)	862 (22.0)		485 (25.8)	427 (22.7)		404 (21.5)	435 (23.1)	
2+ (%)	1769 (45.2)	1530 (39.1)		706 (37.5)	633 (33.7)		1063 (56.5)	897 (47.7)	

Abbreviations: AML = acute myeloid leukemia; COPD = chronic obstructive pulmonary disease; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; NCI = National Cancer Institute; R/R = relapsed/refractory; SD = standard deviation.

Table 3 Duration of Follow-Up of AML Patients and Matched Noncancer Controls

Characteristic	All AML (N = 3911)	Noncancer (N = 3911)	R/R AML (N = 1881)	Non-R/R AML (n = 2030)
Follow-up (Months)				
Mean (SD)	14.8 (20.6)	63.0 (37.0)	22.3 (23.7)	7.9 (14.2)
Median	7.4	58.5	14.5	3.6
Death, n (%)	3508 (89.7)	1012 (25.9)	1554 (82.6)	1954 (96.3)
Time to Death (Months)				
Mean (SD)	10.9 (13.5)	48.8 (33.0)	16.5 (15.4)	6.4 (9.7)
Median	6.3	42.6	12.2	3.5

Abbreviations: AML = acute myeloid leukemia; R/R = relapsed/refractory; SD = standard deviation.

standard deviation age was 77.3 ± 7.0 years, and 46.2% of the population was female (Table 1). In both cohorts, most patients resided in the West region of the United States (43.4%), followed by the South (24.0%), Northeast (19.3%), and Midwest (13.3%). Demographics were similar across relapsed, refractory, and non-R/R AML groups. The non-R/R AML patients were older (mean ± standard deviation age, 79.8 ± 6.8 years) compared to relapsed AML patients (age 74.4 ± 5.9 years) and refractory AML patients (age 74.6 ± 6.0 years).

AML patients had more comorbidities (67.9% vs. 61.2% with ≥ 1 comorbidity) and also had higher mean NCI comorbidity index scores (1.81 vs. 1.63, $P < .01$) compared to matched noncancer controls (Table 2). The non-R/R (2.07 vs. 1.85, $P < .01$) and R/R (1.53 vs. 1.39, $P = .01$) subgroups also had significantly higher mean NCI comorbidity index scores compared to noncancer controls. The most common comorbidities among the overall AML cohort included T2DM without complications (31.3%), chronic obstructive pulmonary disease (COPD) (28.2%), and congestive heart failure (CHF) (21.5%). Four comorbidities were significantly higher in the AML group compared to noncancer controls: COPD (28.2% vs. 23.7%, $P < .01$), CHF (21.5% vs. 16.4%, $P < .01$), renal disease (10.7% vs. 8.1%, $P < .01$), and MI (10.5% vs. 8.1%, $P < .01$). Compared to the R/R AML group, the non-R/R AML group had higher percentages of most comorbidities and also had higher NCI comorbidity index scores (NCI comorbidity index score of ≥ 2: 56.5% in non-R/R AML vs. 37.5% in R/R AML).

Duration of Follow-up

All AML groups had a significantly shorter mean follow-up time compared to their noncancer controls. In the entire AML cohort, the mean follow-up time was 14.8 months, versus 63.0 months in noncancer controls ($P < .01$) (Table 3). The non-R/R AML group had a shorter mean follow-up time (7.9 months vs. 64.7 months in noncancer controls, $P < .01$) compared to the R/R AML group (22.3 months vs. 61.2 months in noncancer controls, $P < .01$).

More patients died during follow-up in the overall AML group (n = 3508, 89.7%) than did the noncancer controls (n = 1012, 25.9%), and the overall AML group also had a shorter mean time to death (10.9 ± 13.5 months in overall AML vs. 48.8 ± 33.0 months in noncancer). The non-R/R AML group had a higher percentage of death (96.3%) compared to the R/R AML group (82.6%), as well as a shorter mean time to death (6.4 ± 9.7 months in non-R/R AML and 16.5 ± 15.4 months in R/R AML).

Frequency Percentages of Events of Interest

Most events of interest had significantly higher percentages among overall AML patients compared to noncancer controls with the exception of stroke (18.3% vs. 25.3%, $P < .01$), ischemic heart disease/CAD (23.5% vs. 29.3%, $P < .001$), and herpes zoster (4.2% vs. 7.1%, $P < .01$) (Table 4). The most frequent complications among AML patients included neutropenia (63.6% vs. 1.7%, $P < .01$), pneumonia (53.4% vs. 21.9%, $P < .01$), and other hemorrhages (40.3% vs. 32.0%, $P < .01$). Along with neutropenia and pneumonia, other infection outcomes were also significantly higher in AML patients, including systemic fungal infection (23.5% vs. 7.2%, $P < .01$), respiratory fungal infection (5.0% vs. < 0.3%, $P < .01$), and central nervous system infections (1.7% vs. 0.5%, $P < .01$). Other frequent events of interest included heart failure (33.2% vs. 23.1%, $P < .01$), T2DM (25.1% vs. 22.6%, $P = .047$), and renal failure (acute/chronic) (30.8% vs. 23.8%, $P < .01$).

The R/R AML subgroup also had significantly higher percentages of most events of interest compared to noncancer controls, and also had higher percentages compared to the non-R/R AML group (neutropenia: 85.7% in R/R AML vs. 44.6% in non-R/R AML; pneumonia: 64.4% vs. 42.3%; other hemorrhages: 50.5% vs. 30.2%). The non-R/R AML group, however, had lower percentages for 11 of the events of interest compared to noncancer controls, including other hemorrhages (30.2% vs. 34.6%, $P = .02$), ischemic heart disease/CAD (16.2% vs. 32.8%, $P < .01$), and stroke (13.3% vs. 27.6%, $P < .01$).

Incidence Rates of Events of Interest

Incidence rates of all events of interest were significantly higher in overall AML, R/R AML, and non-R/R AML patients compared to noncancer controls (Table 4). In overall AML, the highest incidence rates of events were neutropenia/febrile neutropenia (151.3 vs. 0.3 per 100 PY in overall AML and in noncancer controls, $P < .01$), other neoplasms (61.3 vs. 4.4 per 100 PY, $P < .01$), and pneumonia (59.3 vs. 4.4 per 100 PY, $P < .01$).

Many cardiovascular/cerebrovascular events had high incidence rates in the AML group, including heart failure (31.8 vs. 4.7 per 100 PY in overall AML vs. noncancer, $P < .01$) and ischemic heart disease/CAD (20.8 vs. 6.2 per 100 PY, $P < .01$). Stroke also had a higher incidence rate in overall AML patients (17.0 vs. 5.7 per 100 PY, $P < .01$). The category of "other hemorrhages" (40.3 vs. 7.1 per 100 PY, $P < .01$) was the most common bleeding event in the AML cohort.

Table 4 Events of Interest During Follow-Up for AML Patients and Matched Noncancer Controls

	AML		R/R AML		Non-R/R AML	
Event	**Cancer**	**Control**	**Cancer**	**Control**	**Cancer**	**Control**
Cardio/Cerebrovascular						
Heart failure	31.8 (33.2)	4.7 (23.1)	25.5 (37.5)	3.7 (17.8)	50.1 (28.4)	5.7 (28.7)
Myocardial infarction	9.4 (10.8)	2.1 (10.5)	7.9 (13.5)	1.7 (8.5)	13.2 (8.3)	2.4 (12.4)
Atrial fibrillation	19.6 (21.4)	4.0 (19.9)	16.8 (26.5)	3.2 (15.5)	27.1 (16.2)	4.8 (24.3)
Ventricular tachyarrhythmia	3.4 (4.1)	0.9 (4.6)	3.1 (5.5)	0.7 (3.7)	4.1 (2.7)	1.0 (5.5)
Ischemic heart disease/CAD	20.8 (23.5)	6.2 (29.3)	19.3 (30.2)	5.6 (26.0)	24.8 (16.2)	6.8 (32.8)
Stroke (ischemic stroke, hemorrhagic stroke, transient ischemic attack)	17.0 (18.3)	5.7 (25.3)	15.0 (23.7)	5.2 (22.8)	22.1 (13.3)	6.1 (27.6)
Hemorrhagic						
GI hemorrhage	17.3 (19.8)	3.7 (17.8)	13.9 (23.3)	3.7 (16.9)	26.0 (16.4)	3.7 (18.6)
Intracranial hemorrhage	6.3 (7.6)	0.7 (3.5)	5.5 (9.9)	0.6 (2.9)	8.3 (5.5)	0.7 (4.0)
Other hemorrhage	40.3 (40.3)	7.1 (32.0)	35.2 (50.5)	6.7 (29.4)	53.2 (30.2)	7.5 (34.6)
Epistaxis	9.8 (11.3)	0.8 (4.1)	8.9 (15.2)	0.7 (3.6)	12.0 (7.6)	0.9 (4.6)
Hematologic						
Neutropenia/febrile neutropenia	151.3 (63.6)	0.3 (1.7)	210.3 (85.7)	0.3 (1.7)	103.4 (44.6)	0.3 (1.8)
Hepatic						
Hepatic failure	1.1 (1.4)	0.1 (0.6)	1.0 (1.8)	0.1 (0.7)	1.6 (1.0)	0.01 (<0.6)
Renal						
Renal failure (acute/chronic)	28.7 (30.8)	4.8 (23.8)	24.4 (38.5)	4.0 (19.6)	39.0 (23.5)	5.4 (27.8)
Infectious						
Hepatitis (A/B/C) infection	0.8 (0.9)	0.2 (0.8)	0.8 (1.5)	0.2 (0.9)	0.7 (<0.6)	0.1 (0.7)
Systemic fungal infection	23.4 (23.5)	1.4 (7.2)	22.5 (32.6)	1.3 (6.3)	25.4 (15.1)	1.5 (8.1)
Respiratory fungal infection	4.2 (5.0)	0.0 (<0.3)	4.6 (8.0)	0.02 (<0.6)	3.3 (2.2)	0.03 (<0.6)
CNS infection	1.4 (1.7)	0.1 (0.5)	1.3 (2.4)	0.05 (<0.6)	1.7 (1.1)	0.1 (0.8)
Pneumonia	59.3 (53.4)	4.4 (21.9)	51.1 (64.4)	3.3 (16.3)	78.7 (42.3)	5.4 (27.5)
Sepsis	35.5 (34.6)	1.9 (9.8)	34.9 (48.1)	1.6 (8.2)	36.7 (22.1)	2.1 (11.3)
Septic shock	8.4 (10.0)	0.6 (3.0)	7.7 (13.6)	0.5 (2.6)	10.2 (6.6)	0.6 (3.4)
Herpes zoster	3.5 (4.2)	1.4 (7.1)	3.8 (6.6)	1.5 (7.1)	2.8 (1.9)	1.4 (7.1)
Other Events						
Other neoplasms	61.3 (32.9)	4.4 (19.1)	58.1 (47.6)	4.4 (18.3)	70.9 (18.7)	4.5 (19.8)
Type 2 diabetes mellitus	25.4 (25.1)	4.8 (22.6)	24.7 (35.3)	4.6 (20.9)	27.2 (15.6)	5.0 (24.3)
Deep-vein thrombosis	5.9 (6.9)	1.0 (5.2)	6.1 (10.7)	1.0 (4.8)	5.3 (3.4)	1.1 (5.7)
Pulmonary embolism	3.7 (4.4)	0.5 (2.7)	3.4 (6.0)	0.5 (2.4)	4.5 (2.9)	0.5 (2.9)

Data are shown as incidence rate per 100 person-years (%). Patients with events of interest during baseline were excluded from these calculations except myocardial infarction and stroke. Incidence rates and frequencies (%) were calculated for full follow-up period. All incidence rates were significantly higher in AML groups compared to noncancer controls ($P < .01$).
Abbreviations: AML = acute myeloid leukemia; CAD = coronary artery disease; CNS = central nervous system; GI = gastrointestinal; R/R = relapsed/refractory.

Hepatic failure was less common compared to other events (1.1 vs. 0.1 per 100 PY in overall AML vs. noncancer, $P < .01$), but renal failure had a higher incidence in AML patients (28.7 vs. 4.8 per 100 PY, $P < .01$).

Along with pneumonia, other infectious events had increased incidence in overall AML patients, including sepsis (35.5 vs. 1.9 per 100 PY in overall AML vs. noncancer, $P < .01$) and systemic fungal infection (23.4 vs. 1.4 per 100 PY, $P < .01$). T2DM also had increased incidence in AML patients (25.4 vs. 4.8 per 100 PY, $P < .01$).

The non-R/R AML group had higher incidence rates compared to the R/R AML group for all events except for neutropenia/febrile neutropenia (103.4 vs. 210.3 per 100 PY in non-R/R AML vs. R/R AML), hepatitis (A/B/C) infections (0.7 vs. 0.8 per 100 PY), respiratory fungal infection (3.3 vs. 4.6 per 100 PY), herpes zoster (2.8 vs. 3.8 per 100 PY), and deep-vein thrombosis (5.3 vs. 6.1 per 100 PY).

Despite neutropenia/febrile neutropenia having a lower incidence rate in non-R/R AML compared to R/R AML, the incidence of many infectious events was higher in non-R/R AML, including pneumonia (78.7 vs. 51.1 per 100 PY in non-R/R AML vs. R/R AML), sepsis (36.7 vs. 34.9 per 100 PY), and systemic fungal infection (25.4 vs. 22.5 per 100 PY).

Cox Proportional Hazard Models

After adjusting for age, geographic region, sex, baseline myelodysplastic syndrome, and NCI comorbidity index score, AML patients had a higher risk of developing CVD, T2DM, and stroke

Table 5 Cox Proportional Hazard Models for Selected Outcomes

Variable	Adjusted HR[a] (95% CI)			Unadjusted HR (95% CI)		
	CVD[b]	T2DM[b]	Stroke	CVD[b]	T2DM[b]	Stroke
AML status, Yes versus no	4.61 (4.07-5.21)*	3.85 (3.35-4.42)*	2.60 (2.32-2.92)*	4.51 (4.02-5.05)*	3.86 (3.39-4.40)*	2.58 (2.32-2.87)*
Age category, 75-84 years versus 65-74 years	1.35 (1.20-1.51)*	0.99 (0.87-1.14)	1.26 (1.13-1.40)*	1.19 (1.07-1.34)*	0.92 (0.81-1.05)	1.17 (1.05-1.30)*
Age category, 85 + years versus 65-74 years	1.22 (1.04-1.42)*	0.97 (0.81-1.15)	1.30 (1.13-1.49)*	1.13 (0.97-1.31)	0.88 (0.75-1.04)	1.17 (1.03-1.34)*
Female versus male	0.83 (0.75-0.92)*	0.95 (0.84-1.07)	0.98 (0.89-1.08)	0.90 (0.82-1.00)	0.96 (0.85-1.08)	0.99 (0.90-1.09)

CVD includes congestive heart failure, myocardial infarction, atrial fibrillation, ventricular tachyarrhythmia, and ischemic heart disease/CAD.
Abbreviations: AML = acute myeloid leukemia; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; T2DM = type 2 diabetes mellitus.
[a]HRs adjusted for geographic region, baseline myelodysplastic syndromes, and National Cancer Institute index score.
[b]Patients with events of interest during baseline were excluded from these calculations except myocardial infarction and stroke.
*Statistically significant ($P < .05$).

compared to noncancer controls at any point during follow-up (Table 5). CVD had the highest risk of development any time during follow-up (HR = 4.61; 95% CI, 4.07-5.21), followed by T2DM (HR = 3.85; 95% CI, 3.35-4.42) and stroke (HR = 2.60; 95% CI, 2.32-2.92).

Chemotherapy and Treatments

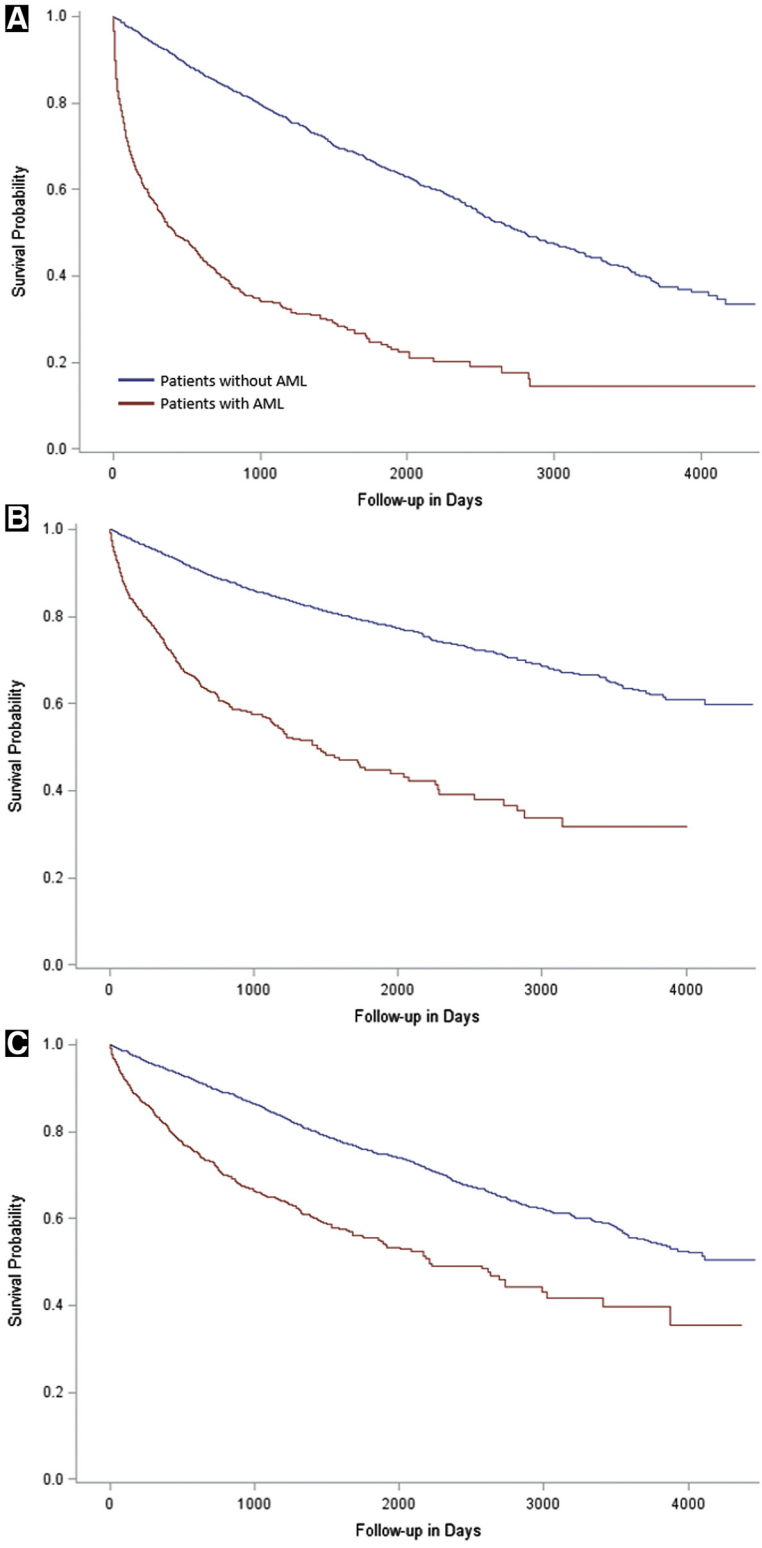
Among the total AML cohort, 66.2% of patients had received chemotherapy (Supplemental Table 6 in the online version). As expected because the R/R AML definition consisted of receipt of chemotherapy, the refractory AML group had the highest rate of chemotherapy (100.0%) compared to the relapsed group (94.7%) and the non-R/R AML group (36.8%). The refractory AML group also had the highest mean ± standard deviation number of chemotherapy cycles per patient (8.6 ± 7.5 cycles), and the non-R/R AML group had the lowest (0.5 ± 0.7 cycles). Rates of bone marrow and stem-cell transplantation, respectively, were lowest in the non-R/R AML group (both < 0.6%) compared to the relapsed AML group (10.6% and 10.1%) and the refractory AML group (9.5% and 8.7%).

Discussion

Using a large AML patient population, we found that AML patients had more comorbidities and experienced more complications compared to noncancer controls. AML patients had higher NCI comorbidity scores and higher rates of COPD, CHF, renal disease, and MI at baseline, and also had higher incidence rates of all events of interest during follow-up. After adjusting for covariates, AML patients were found to have a higher risk of developing CVD, T2DM, and stroke at any point during follow-up (Figure 2). Over the course of the study period, AML patients had lower survival and a shorter mean follow-up time compared to noncancer controls. The non-R/R AML group had higher incidence rates of events of interest, shorter mean follow-up time, and lower receipt of chemotherapy compared to the R/R AML group.

Studies have reported that a significant number of elderly AML patients have comorbid conditions.[13,19,34] Commonly reported comorbidities include CVD, T2DM, cerebrovascular disease, and chronic pulmonary disease.[34] However, these studies did not include a noncancer comparison group. Having a control group allowed us to assess the magnitude of increased burden of comorbidities in elderly AML patients. We found that the AML group had a higher comorbidity burden before diagnosis compared to noncancer controls. Diabetes (diabetes without chronic complications, 31.3%; diabetes with chronic complications, 10.0%), cardiovascular conditions (CHF, 21.5%; MI, 10.5%), and COPD (28.2%) were commonly present at baseline in our AML population. Ferrara et al[35] constructed a consensus-based definition of unfitness for intensive or nonintensive chemotherapy in AML that comprised several factors, including severe comorbidities. Although the severity of the condition was unattainable in our data, the presence of some comorbidities was consistent with those included in the Ferrara criteria (eg, cardiac, pulmonary, hepatic, and renal comorbidity). CHF and COPD were among the most frequent comorbidities in our population, and renal and hepatic comorbidities were present to a lesser extent. The consistency of our results with the Ferrara definition suggests that a large proportion of elderly

Figure 2 Kaplan-Meier Curves for Developing (A) CVD, (B) T2DM, and (C) Stroke During Follow-Up. Patients With AML Had Significantly Higher Risk of Developing All 3 Diseases Compared to Patients Without AML (Log-Rank Test, $P < .01$ For All Outcomes)



Abbreviations: AML = acute myeloid leukemia; CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus.

AML patients may be at risk for poor outcomes with standard chemotherapy. While frequencies of CHF, COPD, and MI were significantly higher in AML patients compared to noncancer controls, diabetes without chronic complications was not. Rates of other comorbidities were also similar between groups, including cerebrovascular disease and peripheral vascular disease. In general, patients are expected to have more comorbidities as they age.[36] This differs from our prior findings in a younger AML population, which had significantly higher rates of almost all NCI comorbidities compared to matched noncancer controls.[30] The differences in some of the comorbidity frequencies between AML patients and noncancer controls seemed to narrow with increasing age.

AML patients experienced higher incidence rates of all events of interest during follow-up. However, the actual frequencies and proportions of the events of interest varied and were not all significantly increased in AML patients compared to noncancer controls. This may be a function of higher mortality and shorter follow-up time among AML patients compared to noncancer controls, thus reducing the probability of AML patients developing certain chronic conditions.

Our findings regarding treatment and disease-related outcomes were similar to what has been reported in the literature. Neutropenia and infectious events were among the most common events during follow-up. It has been well established that myelosuppression is especially common in AML, given the association with both the chemotherapeutic treatment of AML as well as the pathophysiology and progression of the disease itself,[37] with reported rates of grade 3 or 4 neutropenia of about 90% after induction therapy.[38] This high rate of neutropenia predisposes AML patients to bacterial and fungal infections,[39-41] as was observed for infectious events in our AML cohort as well. Like other studies, we found pneumonia to be the most common type of infection.[38,39,42] Bleeding outcomes were also common during follow-up in our study. Hemorrhage has been reported as a common complication after stem-cell transplantation or induction therapy,[43-45] and is an important cause of mortality in AML patients.[46]

The higher rate of comorbidities, incidence rates of events of interest, and higher mortality in the non-R/R AML group compared to R/R AML needs further exploration because patients with R/R disease are expected to have a worse prognosis.[47,48] In a previous study among a younger AML cohort (mean age, 54 years) assessing similar comorbidities and complications in AML subgroups identified by the same R/R AML algorithm, we found quite the opposite compared to the current findings among R/R AML and non-R/R AML patients.[30] The previous study, utilizing a younger and commercially insured population, found the non-R/R AML subgroup to have lower rates of comorbidities and complications as well as lower mortality compared to the R/R subgroup. However, age and comorbidity burden are important factors in the decision to treat AML, with about 30% to 60% of elderly patients not receiving standard induction chemotherapy.[49-53] In the current study, because the R/R subgroup was defined using a treatment-based algorithm (ie, patients were considered to have R/R disease on the basis of their receipt of chemotherapy and stem-cell/bone marrow transplantation),[26] almost all (98%) R/R AML patients received chemotherapy, compared to only 37% of non-R/R AML patients. It is possible that the non-R/R AML group mostly represents a frail patient population unfit to receive chemotherapy as a result of old age and heavy comorbidity burden. This is supported by the non-R/R AML subgroup being older (mean age of 79.8 years, compared to mean age of 74.5 years in the R/R group), with higher proportions of several comorbidities used in assessing fitness of AML patients (CHF: 26.9% in non-R/R AML vs. 15.7% in R/R AML; COPD: 32.3% in non-R/R AML vs. 23.7% in R/R AML).[35] These contradicting results further emphasize the challenges of treating an elderly AML population and the role of age and comorbidities in overall treatment decisions and patient management.

AML patients had increased risk of developing CVD, T2DM, and stroke compared to patients without AML at any time during follow-up after adjusting for covariates. CVD, which had the highest risk of all 3 outcomes, may be a complication of some AML treatments, which have been known to have cardiac adverse effects, including anthracyclines and cytarabine.[33,54-56] Age has been stated as a risk factor for developing anthracycline cardiotoxicity,[54] making this study population especially prone. Though AML patients are known to be at an increased risk for hemorrhage and thrombosis,[57,58] there is limited information on the association between AML and developing stroke. One population-based study using the 2012 National Inpatient Sample, however, did find a 50-fold increase in the risk of stroke in AML patients admitted to the hospital compared to all admitted patients.[31] The overall incidence of stroke was low among the study population, but AML patients who experienced a stroke were found to have a 3.5-fold increase in mortality compared to AML patients with no stroke. Considering the severity of this complication and the increased incidence in AML patients, clinicians should be aware of this risk when caring for these patients.

Literature on the development of T2DM in AML patients is also lacking, as only one other population-based study assessed this association. Similar to our findings, a Taiwanese study reported a higher risk of developing T2DM (HR = 2.27; 95% CI 1.48-3.48) in 3356 AML patients compared to the normal population from the Taiwanese National Health Insurance Research Database.[18] This study, however, did not explore further the possible causes of T2DM in AML patients. A prior meta-analysis of studies linking T2DM to hematologic malignancies did pose a possible biological link between the two conditions, as T2DM is associated with immunosuppression, chronic inflammation, and B- and T-cell dysfunction.[32] The increased incidence of T2DM may also be explained by adverse effects of treating AML and its complications, such as the hyperglycemic effect of glucocorticoids used to treat differentiation syndrome.[59,60] Future studies should assess these different potential explanations to determine the cause of T2DM in AML patients.

To our knowledge, this is the largest nationally represented population-based study describing an elderly AML population—a population that is not well described in either real-world studies or clinical trials. The results of this study fill this information gap by providing valuable insight into the common comorbidities and complications that these patients experience during the course of their disease. Also, this study uses a clinical data source (SEER registries) linked with an administrative claims data source (Medicare), thus providing high-quality cancer diagnosis data.

This study has several limitations that must be considered. The use of SEER-Medicare data restricts the study population to US population, so findings might not be generalizable to AML patients outside the United States. The algorithm used to define the R/R AML group is largely based on chemotherapy administration claims, as clinical diagnosis is not routinely available in this data set. This algorithm does not detect patients with R/R disease but were not treated during the reoccurrence. Also, the algorithm for identifying patients with refractory AML has not yet been validated but was based on prior findings that patients can experience remission after one or two cycles of chemotherapy.[27,28] However, patients who have experienced remission may receive additional cycles as post-remission consolidation therapy.[61] Our refractory AML group may include patients who experienced remission within two cycles but who received additional postremission therapy soon after. Not all ICD-9 codes from Medicare administrative claims used to capture comorbidities and events of interest have been validated and may have varied and unknown predictive values. Certain complications that are driven by laboratory values (such as neutropenia) may be underestimated as a result of the inability to assess laboratory results in this data source. Last, the cause of the events of interest assessed in this study cannot be determined, as they may be complications of AML disease, treatments, or other factors.

Conclusion

This large population-based study demonstrated that elderly AML patients had a greater number of comorbidities at diagnosis and developed more complications after diagnosis compared to their matched noncancer controls. High rates of certain complications in AML patients were expected; however, increased rates of others, including T2DM and stroke, warrant further investigation into causal factors and biological pathways. In view of the comorbidity burden being an important predictor of treatment outcomes in the elderly AML population, awareness of these common comorbidities and complications can help clinicians assess the appropriateness of available treatment options.

Clinical Practice Points

- AML is common in elderly adults, with a median age at diagnosis of 68 years.
- Elderly patients generally have poorer outcomes compared to younger patients, in part as a result of higher comorbidity burden and treatment toxicities. However, the comorbidities and complications in elderly AML patients have not been well described.
- Our study found that AML patients had higher NCI comorbidity index scores and higher incidence rates (per 100 PY) of all events of interest (eg, infectious, hematologic, cardiovascular, cerebrovascular) compared to noncancer controls.
- AML patients also had a higher risk of developing CVD, T2DM, and stroke at any point during follow-up.
- Our results provide valuable information about common comorbidities and complications that can potentially influence treatment outcomes experienced by older AML patients. Awareness of these results may help in future treatment decisions.

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Disclosure

N.D. was a St John's University postdoctoral fellow with Daiichi Sankyo Inc at the time the study was conducted. S.I. and M.S. were employees of Daiichi Sankyo Inc at the time the study was conducted. of the study. X.W. was a contracted employee of Daiichi Sankyo Inc. The other authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2019.04.012.

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Supplemental Data

Supplemental Table 1 Codes for Major Surgery, Radiation, and Pregnancy

Condition/Event	ICD-9 Diagnosis or Procedure Code	Description	HCPCS Code
Major Surgery			
Spine surgeries	03.xx	Operations on spinal cord and spinal canal structures	
	77.29	Wedge osteotomy, vertebra	
	77.39	Other division of bone, vertebra	
	80.5x	Excision, destruction and other repair of intervertebral disc	
	81.0x	Spinal fusion	
	81.3x	Refusion of spine	
	81.6x	Other procedures on spine	
	84.6x	Replacement of spinal disc	
	84.8x	Insertion, replacement and revision of posterior spinal motion preservation device(s)	
	84.51	Insertion of interbody spinal fusion device	
	84.59	Insertion of other spinal devices	
Colon surgeries	17.3x	Laparoscopic partial excision of large intestine	
	45.4x	Local excision or destruction of lesion or tissue of large intestine	
	45.7x	Open and other partial excision of large intestine	
	45.8x	Total intra-abdominal colectomy	
	45.9x	Intestinal anastomosis	
	46.03	Exteriorization of large intestine	
	46.04	Resection of exteriorized segment of large intestine	
	46.1x	Colostomy	
	48.xx	Operations on rectum, rectosigmoid and perirectal tissue	
Gall bladder removal	51.2x	Cholecystectomy	
Urologic surgeries	55.xx	Operations on kidney	
	56.xx	Operations on ureter	
	57.xx	Operations on urinary bladder	
	58.xx	Operations on urethra	
	59.xx	Other operations on urinary tract	
Abdominal surgeries	43.xx	Incision and excision of stomach	
	44.xx	Other operations on stomach	
	45.xx	Incision, excision, and anastomosis of intestine	
	46.xx	Other operations on intestine	
	47.xx	Operations on appendix	
	48.xx	Operations on rectum, rectosigmoid and perirectal tissue	
	50.xx	Operations on liver	
	51.xx	Operations on gallbladder and biliary tract	
	52.xx	Operations on pancreas	
	53.xx	Repair of hernia	
	54.xx	Other operations on abdominal region	
Orthopedic surgeries	76.xx	Operations on facial bones and joints	
	77.xx	Incision, excision, and division of other bones	
	78.xx	Other operations on bones, except facial bones	
	79.xx	Reduction of fracture and dislocation	
	80.xx	Incision and excision of joint structures	
	81.xx	Repair and plastic operations on joint structures	

Supplemental Table 1 Continued

Condition/Event	ICD-9 Diagnosis or Procedure Code	Description	HCPCS Code
	84.xx (excl. 84.51, 84.59, 84.6, 84.8)	Other procedures on musculoskeletal system	
Cardiac and vascular surgeries	35.xx	Operations on valves and septa of heart	
	36.xx	Operations on vessels of heart	
	37.xx	Other operations on heart and pericardium	
	38.xx	Incision, excision, and occlusion of vessels	
	39.xx	Other operations on vessels	
Breast surgeries	85.xx	Operations on the breast	
Respiratory surgeries	30.xx	Excision of larynx	
	31.xx	Other operations on larynx and trachea	
	32.xx	Excision of lung and bronchus	
	33.xx	Other operations on lung and bronchus	
	34.xx	Operations on chest wall, pleura, mediastinum, and diaphragm	
Brain surgery	01.xx	Incision and excision of skull, brain, and cerebral meninges	
	02.xx	Other operations on skull, brain, and cerebral meninges	
Gynecologic surgery (excluding sterilization)	65.xx	Operations on ovary	
	66.xx (excl. 66.3x, 66.63)	Operations on fallopian tubes (excluding sterilization)	
	67.xx	Operations on cervix	
	68.xx	Other incision and excision of uterus	
	69.xx	Other operations on uterus and supporting structures	
	70.xx	Operations on vagina and cul-de-sac	
	71.xx	Operations on vulva and perineum	
Major trauma (proxy for major surgery)	800.xx-829.xx	Fracture	
	850.xx-854.xx	Intracranial injury, excluding those with skull fractures	
	860.xx-869.xx	Internal injury of thorax, abdomen, and pelvis	
	870.xx-897.xx	Open wound	
	925.xx-929.xx	Crushing injury	
	940.xx-949.xx	Burns	
	950.xx-957.xx	Injury to nerves and spinal cord	
	958.xx	Certain early complications of trauma	
Radiotherapy			
Radiotherapy	92.2x	Therapeutic radiology and nuclear medicine	77401-77499, 77520, 77523, 77750-77799, G0256, G0261
	92.3x	Stereotactic radiosurgery	
	92.4x	Intraoperative radiation procedures	
Pregnancy			
Evidence of pregnancy	V22.xx	Normal pregnancy	
	V23.xx	Supervision of high-risk pregnancy	
	V27.xx	Outcome of delivery	
	630.xx-679.xx	Complications of pregnancy, childbirth, and the puerperium	

Note: "x" denotes any character, including blank.
Abbreviations: HCPCS = Healthcare Common Procedure Coding System; ICD-9 = International Classification of Diseases, 9th Revision.

Supplemental Table 2 Codes for Chemotherapy Administration

Code Set	Code	Description
Chemotherapy Administration		
ICD-9 Diagnosis	V58.11	Encounter for antineoplastic chemotherapy
ICD-9 Procedure	99.25	Injection or infusion of cancer chemotherapeutic substance
HCPCS	Q0083	Chemotherapy by intravenous push
	Q0084, Q0085	Chemotherapy by infusion alone or with another technique
	J7150, J8999, and J9000 to J9999	Chemotherapy
CPT-4	96400	Subcutaneous or intramuscular chemotherapy administration
	96408, 96410, 96412, 96414	Intravenous chemotherapy
	96545	Provision of chemotherapy
Specific Chemotherapeutic Agents		
HCPCS	C9422, J9098, J9100, J9110	Cytarabine
	C9218, J9025, S0168	Azacitidine
	C9231, J0894	Decitabine
	C9429, J9211	Idarubicin
	C9424, J9150, J9151	Daunorubicin
	C9415, J9000, J9001	Doxorubicin
	C9419, J9065	Cladribine
	J9293	Mitoxantrone
	S0117	Clindamycin phosphate and tretinoin, tretinoin
	J9017	Arsenic trioxide

Abbreviations: CPT = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD-9 = International Classification of Diseases, 9th Revision.

Supplemental Table 3 Codes for Stem-Cell and Bone Marrow Transplantation

Code Set	Code	Description
Bone Marrow Transplantation		
ICD-9 diagnosis	V42.81	Bone marrow replaced by transplant
	996.85	Complications of transplanted bone marrow
ICD-9 procedure	41.00	Bone marrow transplantation, not otherwise specified
	41.01	Autologous bone marrow transplantation without purging
	41.02	Allogenic bone marrow transplantation with purging
	41.03	Allogenic bone marrow transplantation without purging
	41.09	Autologous bone marrow transplantation with purging
CPT	38240	Hematopoietic progenitor cell; allogenic transplantation per donor
	38241	Hematopoietic progenitor cell; autologous transplantation
	38242	Allogenic lymphocyte infusions
Stem-Cell Transplantation		
ICD-9 diagnosis	V42.82	Peripheral stem cells replaced by transplantation
	996.88	Complications of transplanted organ, stem cell
ICD-9 procedure	41.04	Autologous hematopoietic stem-cell transplant without purging
	41.05	Allogenic hematopoietic stem-cell transplant without purging
	41.06	Cord blood stem-cell transplant
	41.07	Autologous hematopoietic stem-cell transplant with purging
	41.08	Allogenic hematopoietic stem-cell transplant with purging

Abbreviations: CPT = Current Procedural Terminology; ICD-9 = International Classification of Diseases, 9th Revision.

Supplemental Table 4 Codes for National Cancer Institute Index Baseline Comorbidities

Comorbidity	ICD-9 Diagnosis Code	ICD-9 Procedure Code
Acute myocardial infarction	410.xx with inpatient length of stay > 2 days	
History of myocardial infarction	412.bb	
Congestive heart failure	398.91, 425.4x-425.5x, 425.7x-425.9x, 428.xx	
Peripheral vascular disease	093.0x, 440.xx-441.xx, 442.0x-442.8x, 443.1x-443.9x, 447.70-447.73, 785.4x, V43.4x	00.60, 38.13, 38.14, 38.15, 38.16, 38.18, 38.33, 38.34, 38.36, 38.38, 38.43, 38.44, 38.46, 38.48, 38.68, 39.25, 39.29
Cerebrovascular disease	430.xx- 438.xx	00.61, 00.62, 00.63, 00.65, 38.12, 38.32, 38.42, 39.22, 39.28, 39.74
Chronic obstructive pulmonary disease	416.8x-416.9x, 490.xx-496.xx, 500.xx-505.xx, 506.4x, 519.1x	
Dementia	290.xx, 291.0x-291.2x, 292.82, 294.1x, 331.0x-331.2x, 331.82	
Paralysis (hemiplegia or paraplegia)	342.xx, 344.0x-344.6x, 344.9x	
Diabetes without chronic complications	250.bb, 250.0x-250.3x	
Diabetes with chronic complications	250.4x-250.9x, 362.0x	
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.xx-583.xx, 585.xx-586.xx, 588.xx, V42.0x, V45.1x, V56.xx	39.27, 39.42, 39.95, 54.98, 55.69
Mild liver disease	070.32-070.33, 070.54, 571.2x, 571.4x-571.6x	
Moderate/severe liver disease	070.22-070.23, 070.44, 456.0x-456.2x, 572.2x-572.8x, V42.7x	39.1b, 42.91, 50.5x
Peptic ulcer disease	531.xx-534.xx	
Rheumatologic disease	710.0x, 710.1x, 710.4x, 714.0x-714.2x, 714.81, 725.bb	
AIDS	042.xx-044.x, V08.bb, 795.71	

Note: "b" denotes blank; "x" denotes any character, including blank.
Abbreviation: ICD-9 = International Classification of Diseases, 9th Revision.

Supplemental Table 5 Codes for Events of Interest During Follow-Up

Condition/Event	ICD-9 Diagnosis	Description
Heart failure	428.xx	Heart failure
	428.0x	Congestive heart failure, unspecified
	428.1x	Left heart failure
	428.2x	Systolic heart failure
	428.3x	Diastolic heart failure
	428.4x	Combined systolic and diastolic heart failure
	428.9x	Heart failure, unspecified
Myocardial infarction	410.xx	Acute myocardial infarction
Atrial fibrillation	427.3x	Atrial fibrillation
Ventricular tachyarrhythmia	427.1x	Paroxysmal ventricular tachycardia
Ischemic heart disease/coronary artery disease	410.xx	Acute myocardial infarction
	411.xx	Other acute and subacute forms of ischemic heart disease
	412.xx	Old myocardial infarction
	413.xx	Angina pectoris
	414.xx	Other forms of chronic ischemic heart disease
Hepatic failure	570.xx	Acute and subacute necrosis of liver
Hepatitis (A/B/C) infections	070.xx	Viral hepatitis
	070.0x	Viral hepatitis A with hepatic coma
	070.1x	Viral hepatitis A without mention of hepatic coma
	070.2x	Viral hepatitis B with hepatic coma
	070.3x	Viral hepatitis B without mention of hepatic coma
	070.41	Acute hepatitis C with hepatic coma
	070.44	Chronic hepatitis C with hepatic coma
	070.7x	Unspecified viral hepatitis C
Renal failure (acute/chronic)	586.xx	Renal failure, unspecified
	585.9x	Chronic kidney disease, unspecified
	584.xx	Acute renal failure
End-stage renal disease/dialysis	585.6	End stage renal disease
Systemic fungal infection	114.xx	Coccidioidomycosis
	115.xx	Histoplasmosis
	116.xx	Blastomycotic infection
	117.xx	Other mycoses
	118.xx	Opportunistic mycoses
	136.3x	Pneumocystosis
Respiratory fungal infection	112.4x	Candidal pneumonia
	114.0x	Primary coccidioidomycosis (pulmonary)
	115.5x	Histoplasmosis pneumonia
	117.3x	Aspergillosis
	117.5x	Cryptococcosis
Central nervous system infections	320.xx	Bacterial meningitis
	321.xx	Meningitis due to other organisms
	322.xx	Meningitis of unspecified cause
	323.xx	Encephalitis, myelitis, and encephalomyelitis
	324.xx	Intracranial and intraspinal abscess
	326.xx	Late effects of intracranial abscess or pyogenic infection
Pneumonia	480.xx	Viral pneumonia
	481.xx	Pneumococcal pneumonia; Streptococcus pneumoniae (pneumococcal disease)
	482.xx	Other bacterial pneumonia
	483.xx	Pneumonia due to other specified organism
	484.xx	Pneumonia in infectious diseases classified elsewhere
	486.xx	Pneumonia, organism unspecified
Herpes zoster	053.xx	Herpes zoster

Supplemental Table 5 Continued

Condition/Event	ICD-9 Diagnosis	Description
	053.11	Ramsey hunt syndrome
Neoplasms (other primary or secondary cancer)	200.xx-203.xx	Malignant neoplasm of lymphatic and hematopoietic tissue
	140.xx-149.xx	Malignant neoplasm of lip, oral cavity, and pharynx
	150.xx-159.xx	Malignant neoplasm of digestive organs and peritoneum
	160.xx-165.xx	Malignant neoplasm of respiratory and intrathoracic organs
	170.xx, 171.xx, 174.xx-176.xx	Malignant neoplasm of bone, connective tissue, skin, and breast
	179.xx-189.xx	Malignant neoplasm of genitourinary organs
	190.xx-196.xx	Malignant neoplasm of other and unspecified sites
	209.xx	Neuroendocrine tumors
	197.0x	Secondary malignant neoplasm of the lung
	197.1x	Secondary malignant neoplasm of the mediastinum
	197.2x	Secondary malignant neoplasm of the pleura
	197.3x	Secondary malignant neoplasm of other respiratory organs
	197.4x	Secondary malignant neoplasm of the small intestine, including duodenum
	197.5x	Secondary malignant neoplasm of the large intestine and rectum
	197.6x	Secondary malignant neoplasm of the retroperitoneum
	197.7x	Secondary malignant neoplasm of the liver
	197.8x	Secondary malignant neoplasm of the other digestive organs and spleen
	198.0x	Secondary malignant neoplasm of the kidney
	198.1x	Secondary malignant neoplasm of other urinary organs
	198.3x	Secondary malignant neoplasm of the brain and spinal cord
	198.4x	Secondary malignant neoplasm of the other parts of the nervous system
	198.6x	Secondary malignant neoplasm of the ovary
	198.7x	Secondary malignant neoplasm of the adrenal gland
	209.1x-209.3x	Neuroendocrine tumors
	172.xx	Malignant melanoma of skin
	v10.82	Malignant melanoma of skin
	173.xx	Other malignant neoplasm of skin (excluding malignant melanoma of skin)
DVT	453.4x	Venous embolism and thrombosis of unspecified deep vessels of lower extremity
PE	415.1x	Pulmonary embolism and infarction
T2DM	250.02, 250.00	Diabetes mellitus without mention of complication
	250.12, 250.10	Diabetes with ketoacidosis
	250.22, 250.20	Diabetes with hyperosmolarity
	250.32, 250.30	Diabetes with other coma
	250.42, 250.40	Diabetes with renal manifestations
	250.52, 250.50	Diabetes with ophthalmic manifestations
	250.62, 250.60	Diabetes with neurological manifestations
	250.72, 250.70	Diabetes with peripheral circulatory disorders
	250.82, 250.80	Diabetes with other specified manifestations
	250.92, 250.90	Diabetes with unspecified complication
Neutropenia/febrile neutropenia	288.0x	Neutropenia
	780.61	Fever presenting with conditions classified elsewhere
Sepsis	995.91	Sepsis
	995.92	Severe sepsis
Septic shock	785.52	Septic shock
Ischemic stroke	433.xx	Occlusion and stenosis of precerebral arteries
	434.xx	Occlusion of cerebral arteries
	436	Acute, but ill-defined, cerebrovascular disease
Hemorrhagic stroke	430.xx	Subarachnoid hemorrhage
	431.xx	Intracerebral hemorrhage
	432.xx	Other and unspecified intracranial hemorrhage
Transient ischemic attack	435.9	Unspecified transient cerebral ischemia

Supplemental Table 5 Continued

Condition/Event	ICD-9 Diagnosis	Description
	V12.54	Transient ischemic attack, and cerebral infarction without residual deficits
	362.34	Amaurosis fugax
Epistaxis	784.7x	Epistaxis
Gastrointestinal hemorrhage	455.2x	Internal hemorrhoids with other complication
	455.5x	External hemorrhoids with other complication
	455.8x	Unspecified hemorrhoids with other complication
	456.0x	Esophageal varices with bleeding
	456.2x	Esophageal varices with bleed diseases classified elsewhere
	530.21	Ulcer of esophagus with bleeding
	530.7x	Gastroesophageal laceration-hemorrhage syndrome
	530.82	Esophageal hemorrhage
	531.0x	Acute gastric ulcer with hemorrhage
	531.2x	Acute gastric ulcer with hemorrhage and perforation
	531.4x	Chronic or unspecified gastric ulcer with hemorrhage
	531.6x	Chronic or unspecified gastric ulcer with hemorrhage and perforation
	532.0x	Acute duodenal ulcer with hemorrhage
	532.2x	Acute duodenal ulcer with hemorrhage and perforation
	532.4x	Chronic/unspecified duodenal ulcer with hemorrhage
	532.6x	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
	533.0x	Acute peptic ulcer unspecified site hemorrhage
	533.2x	Acute peptic ulcer unspecified site with hemorrhage and perforation
	533.4x	Chronic/unspecific peptic ulcer unspecified site with hemorrhage
	533.6x	Chronic/unspecific peptic ulcer with hemorrhage and perforation
	534.0x	Acute gastrojejunal ulcer with hemorrhage
	534.2x	Acute gastrojejunal ulcer with hemorrhage and perforation
	534.4x	Chronic/unspecific gastrojejunal ulcer with hemorrhage
	534.6x	Chronic/unspecific gastrojejunal ulcer with hemorrhage and perforation
	535.01	Acute gastritis with hemorrhage
	535.11	Atrophic gastritis with hemorrhage
	535.21	Gastric mucosal hypertrophy with hemorrhage
	535.31	Alcoholic gastritis with hemorrhage
	535.41	Other specified gastritis with hemorrhage
	535.51	Unspecified gastritis and gastroduodenitis with hemorrhage
	535.61	Duodenitis with hemorrhage
	535.71	Eosinophilic gastritis with hemorrhage
	537.83	Angiodysplasia of stomach and duodenum with hemorrhage
	537.84	Dieulafoy lesion (hemorrhagic) of stomach and duodenum
	562.02	Diverticulosis of small intestine with hemorrhage
	562.03	Diverticulitis of small intestine with hemorrhage
	562.12	Diverticulosis of colon with hemorrhage
	562.13	Diverticulitis of colon with hemorrhage
	569.3x	Hemorrhage of rectum and anus
	569.85	Angiodysplasia of intestine with hemorrhage
	578.xx	Gastrointestinal hemorrhage
Pulmonary hemorrhage	770.3x	Pulmonary hemorrhage
Intracranial hemorrhage	430.xx	Subarachnoid hemorrhage
	431.xx	Intracerebral hemorrhage
	432.xx	Other and unspecified intracranial hemorrhage
	852.xx	Subarachnoid, subdural, and extradural hemorrhage, following injury
	853.xx	Other and unspecified intracranial hemorrhage following injury
	800.2x	Closed with subarachnoid, subdural, and extradural hemorrhage
	800.3x	Closed with other and unspecified intracranial hemorrhage

Supplemental Table 5 Continued

Condition/Event	ICD-9 Diagnosis	Description
	800.7x	Open with subarachnoid, subdural, and extradural hemorrhage
	800.8x	Open with other and unspecified intracranial hemorrhage
	801.2x	Closed with subarachnoid, subdural, and extradural hemorrhage
	801.3x	Closed with other and unspecified intracranial hemorrhage
	801.7x	Open with subarachnoid, subdural, and extradural hemorrhage
	801.8x	Open with other and unspecified intracranial hemorrhage
	803.2x	Closed with subarachnoid, subdural, and extradural hemorrhage
	803.3x	Closed with other and unspecified intracranial hemorrhage
	803.7x	Open with subarachnoid, subdural, and extradural hemorrhage
	803.8x	Open with other and unspecified intracranial hemorrhage
	804.2x	Closed with subarachnoid, subdural, and extradural hemorrhage
	804.3x	Closed with other and unspecified intracranial hemorrhage
	804.5x	Open without mention of intracranial injury
	804.7x	Open with subarachnoid, subdural, and extradural hemorrhage
	804.8x	Open with other and unspecified intracranial hemorrhage
Other hemorrhages	246.3x	Hemorrhage and infarction of thyroid
	255.41	Adrenal hemorrhage/glucocorticoid deficiency
	286.5x	Hemorrhagic disorder due to intrinsic circulating anticoagulants
	336.1x	Vascular myelopathies
	362.81	Retinal hemorrhage
	363.6x	Choroidal hemorrhage and rupture
	372.72	Conjunctival hemorrhage
	374.81	Hemorrhage of eyelid
	376.32	Orbital hemorrhage
	377.42	Hemorrhage in optic nerve sheaths
	379.23	Vitreous hemorrhage
	388.69	Other otorrhea
	423.xx	Hemopericardium
	459.0x	Hemorrhage, unspecified (circulatory system)
	568.81	Hemoperitoneum
	569.69	Stomal bleeding
	569.7x	Hemorrhage into bladder wall
	577.8x	Pancreatic hemorrhage
	578.1x	Blood in stool
	580.9x	Acute benign hemorrhagic glomerulonephritis
	596.7x	Hemorrhage into bladder wall
	596.8x	Bladder hemorrhage
	599.7x	Hematuria
	602.1x	Congestion or hemorrhage of prostate
	620.1x	Corpus luteum cyst or hematoma
	622.8x	Other specified noninflammatory disorders of cervix
	623.8x	Other specified noninflammatory disorders of vagina
	719.1x	Hemarthrosis, site unspecified
	782.7x	Spontaneous ecchymoses
	785.59	Shock, hemorrhagic
	784.8x	Hemorrhage from throat
	786.3x	Hemoptysis
	998.1x	Hemorrhage or hematoma or seroma

Note: "x" denotes any character, including blank.
Abbreviations: DVT = deep-vein thrombosis; ICD-9 = International Classification of Diseases, 9th Revision; PE = Pulmonary embolism; T2DM = type 2 diabetes mellitus.

Supplemental Table 6 Chemotherapy Receipt Among AML Patients

Characteristic	All AML (N = 3911)	Relapsed (N = 742)	Refractory (N = 1139)	Non–Relapsed/Refractory (N = 2030)
Bone marrow transplantation	194 (5.0)	79 (10.6)	108 (9.5)	<11 (<0.6)
Stem-cell transplantation	176 (4.5)	75 (10.1)	99 (8.7)	<11 (<0.6)
Chemotherapy	2590 (66.2)	703 (94.7)	1139 (100.0)	748 (36.8)
Chemotherapy Cycles				
Mean (standard deviation)	3.8 (6.0)	5.1 (6.0)	8.6 (7.5)	0.5 (0.7)
Median	2	4	6	0

Data are presented as n (%).
Abbreviation: AML = acute myeloid leukemia.