Economic and Clinical Burden of Acute Myeloid Leukemia Episodes of Care in the United States: A Retrospective Analysis of a Commercial Payer Database

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ABSTRACT

BACKGROUND: In the United States, the incidence of acute myeloid leukemia (AML) has steadily increased over the last decade; in 2019, it was estimated that AML would affect 21,450 new patients and lead to 10,920 deaths. Detailed real-world cost estimates and comparisons of key AML treatment episodes, such as in high-intensity chemotherapy (HIC), low-intensity chemotherapy (LIC), hematopoietic stem cell transplantation (HSCT), and relapsed/refractory (R/R), are scarce in the commercially insured U.S. population.

OBJECTIVE: To examine health resource utilization (HRU), clinical burden, and direct health care costs across various AML treatment episodes in a large sample of commercially insured U.S. patients.

METHODS: A retrospective cohort analysis was conducted. Patients with newly diagnosed AML were followed to identify the key active treatment episodes across the course of their disease. Data were obtained from 2 sources: IQVIA's Real-World Data (RWD) Adjudicated Claims Database—U.S. (formerly known as PharMetrics Plus), which comprises adjudicated claims for more than 150 million unique enrollees across the United States, and IQVIA Charge Detail Master Hospital Database, which has detailed data regarding services received in an inpatient setting. Calculation of all-cause HRU was based on physician office visits, nonphysician office visits, emergency department visits, inpatient visits, and outpatient pharmacy utilization. Calculation of all-cause health care costs was based on total allowed costs and reported by the following cost components: physician office visits, nonphysician office visits, emergency department visits, inpatient visits, and outpatient pharmacy utilization. Symptom and toxicity events were estimated via proxies such as diagnosis codes, procedures, and treatments administered.

RESULTS: The final study sample consisted of 1,542 HIC-induction (HIC-I), 591 HIC-consolidation (HIC-C), 628 LIC, 1,000 patients with HSCT, and 707 patients with R/R AML. Total mean episode costs were highest in R/R episodes (\$439,104), followed by HSCT (\$329,621), HIC-I (\$198,657), HIC-C (\$73,428), and LIC (\$53,081) episodes. Across all treatment episodes, hospitalization was the largest contributor to cost with mean hospitalization costs ranging from \$308,978 in the R/R setting to \$49,580 for patients receiving LIC; of these, costs related to intensive care unit admission were a noteworthy contributor. In patients with R/R AML and HSCT, expenditures related to pharmacy utilization averaged \$24,640 and \$12,203, respectively, and expenditures related to physician office visits averaged \$10,926 and \$6,090, respectively; these expenditures were much lower across other episodes. Across all categories of symptom and toxicity events, cardiovascular events was the only category of event that was a significant predictor of higher cost across all episodes. Symptom and toxicity events commonly associated with AML were associated with significantly increased costs, especially in R/R episodes.

CONCLUSIONS: This resource utilization and direct health care cost analysis highlights the substantial economic burden associated with key AML treatment episodes in the United States, specifically during HIC-I, HSCT, and R/R episodes.

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What is already known about this subject

- In the United States, the incidence of acute myeloid leukemia (AML) has steadily increased over the past decade.
- Analyses examining the costs associated with different AML treatment episodes in the commercially insured U.S. population are rare and difficult to assemble.

What this study adds

- Total mean episode costs were highest in relapsed/refractory episodes (\$439,104), followed by hematopoietic stem cell transplantation (\$329,621), high-intensity induction chemotherapy (\$198,657), high-intensity consolidation chemotherapy (\$73,428), and low-intensity chemotherapy (\$53,081) episodes; inpatient hospitalization was the largest contributor to cost, accounting for roughly 70% of cost across all treatment groups.
- This resource utilization and direct health care cost analysis demonstrate the substantial economic burden associated with various AML treatment episodes, especially during high-intensity induction chemotherapy, hematopoietic stem cell transplantation, and relapsed/refractory episodes.
- Hospitalization is a major cost driver across all episodes.

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults in the United States and its incidence has steadily increased over the last decade. In 2019, it was estimated that AML would affect 21,450 new patients and lead to 10,920 deaths.¹ Outcomes for patients with AML remain unsatisfactory, with a 5-year overall survival of only 28%.²

While the National Comprehensive Cancer Network guidelines for AML treatment often include chemotherapy with

cytarabine and anthracyclines and/or hematopoietic stem cell transplantation (HSCT), additional regimens are available, including targeted therapy and immunotherapy. Despite improvements in available treatment options, most patients with AML will relapse, at which point 5-year survival plummets to 5%-11%.^{3,4}

Detailed real-world cost estimates are important for understanding the economic and physical resources necessary to help facilitate higher standards of care. To date, detailed real-world cost estimates of key AML treatment episodes, such as high-intensity chemotherapy (HIC), low-intensity chemotherapy (LIC), HSCT, and relapsed/refractory (R/R) AML, are scarce and difficult to assemble. To the extent AML-related cost estimates exist,⁵⁻⁸ discrepancies in study methodology, therapeutic approaches, and treatment costs make studies hard to interpret and/or not widely applicable. Also, there is limited data regarding the economic and clinical burden associated with the journey from diagnosis to death of a patient with AML, and no studies have used single datasets to understand the continuum of care in AML. As such, this analysis examined health resource utilization (HRU) and direct health care costs, as well as their relationship with clinical outcomes of patients who progress from newly diagnosed to transplant, to relapsed and refractory, and/or to death—all within a single dataset.

Methods

Study Design

This retrospective cohort study of health care claims data used IQVIA's Real-World Data (RWD) Adjudicated Claims Database-U.S. (formerly known as PharMetrics Plus) as the primary data source and IQVIA's Charge Detail Master (CDM) as the secondary data source. The study period ran from July 2007 to June 2016; all patients were indexed between January 2008 and March 2016 (Appendix A, available in online article). Index date was defined as the date of the first observed claim with an AML diagnosis. All enrolled patients were newly diagnosed using a 6-month washout period and were required to be continuously enrolled in their health plan for ≥ 6 months before and ≥ 3 months after the index date.

Data Sources

Data from 2 databases were combined and analyzed to achieve study objectives. The primary data source, IQVIA RWD Adjudicated Claims Database, is one of the largest U.S. health plan claims databases, comprising adjudicated claims from more than 150 million unique enrollees. This database has a diverse representation of geography, employers, payers, providers, and therapy areas and is considered representative of the national, commercially insured population in terms of age and gender. As IQVIA owns this database, permission for its use was not necessary. All data are de-identified and fully compliant with the patient confidentiality requirements of the Health

Insurance Portability and Accountability Act (HIPAA). As such, no institutional review board approval was required.

The IQVIA CDM hospital database, the secondary data source, has detailed data on all services received in inpatient settings. Anonymized patient-level data are sourced from hospital charge detail masters within > 350 short-term, acute-care, and nonfederal hospitals.

The RWD and CDM databases were linked using IQVIA's patented deterministic linking methodology. The RWD database was the primary source used to assess AML burden of illness. Once linked to the RWD, the CDM provided additional details on inpatient use of AML therapies to aid in the identification of patients who received HIC or LIC, as these therapies are frequently administered in the inpatient setting.

Patient Selection

Patients were required to have a diagnosis of AML in the RWD Adjudicated Claims Database during the sample selection window (January 1, 2008, to March 31, 2016), evidenced by ≥ 2 nonancillary outpatient claims with an AML diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 205.00) > 30 days apart or ≥ 1 inpatient claim with an AML diagnosis. Ancillary services include laboratory tests, radiology procedures, and other services provided to support the work of the primary physician. Patients were also required to have continuous health plan enrollment in the RWD Adjudicated Claims Database ≥ 6 months before and ≥ 3 months after the initial AML diagnosis date. Patients must have had HIC, LIC, or HSCT after the initial AML diagnosis and no observed AML diagnoses ≥ 6 months before the initial AML diagnosis date to capture patients during the initial diagnosis of AML.

In order to increase the specificity of the study's AML population, patients were excluded if they had a diagnosis of acute lymphoblastic leukemia or a diagnosis of other primary or secondary malignancies (except for myelodysplastic syndrome, chronic myelogenous leukemia, and secondary AML) during the 6-month period before the initial AML diagnosis date. Patients who received primary or secondary best supportive care after the initial AML diagnosis date were included in the original patient pool but excluded from this analysis due to a high degree of heterogeneity (precluding the ability to make valid inferences).

Treatment Definitions

High-intensity induction chemotherapy (HIC-I) was defined as evidence of inpatient high-dose cytarabine plus anthracycline use within 3 months of diagnosis. The HIC-I episodes began with the first observed HIC (inpatient or outpatient) and ended with initiation of another active treatment (e.g., postremission chemotherapy or HSCT), including consolidation. In patients without a subsequent treatment regimen, the HIC-I episode ended 30 days after HIC-I treatment or at the end of observed follow-up (whichever occurred first).

High-intensity consolidation chemotherapy (HIC-C) was defined as evidence of cytarabine plus anthracycline use during the 2 months following HIC. The HIC-C episodes began with the first of up to 4 cycles of cytarabine (administered in the outpatient setting or inpatient setting if the length of stay was ≤ 7 days) given after HIC induction and ended with initiation of another active treatment. In patients without a subsequent treatment regimen, the HIC consolidation episode ended 30 days after completion of consolidation treatment (up to 4 cycles) or at the end of observed follow-up (whichever occurred first).

LIC was defined as evidence of low-intensity cytarabine, anthracycline, 5-azacytidine, decitabine, clofarabine, or gemtuzumab ozogamicin in the outpatient setting within 3 months of the initial AML diagnosis. Episodes began with receipt of the first LIC agent (within 90 days postindex) and ended with the initiation of another active treatment. In patients without a subsequent treatment regimen, LIC episodes ended 30 days after LIC completion, with a diagnosis code indicative of relapsed disease, the initiation of supportive care, or end of follow-up (whichever occurred first). The HIC and LIC cohorts were mutually exclusive.

The HSCT episodes were defined by a transplant-specific diagnosis or procedure code. The HSCT episodes were defined starting 60 days before the observed transplant procedure date and ending with the initiation of another active treatment, with a diagnosis code indicative of relapsed disease, initiation of secondary supportive care, or end of follow-up (whichever occurred first). In this study, HSCT procedures were not divided into autologous or allogeneic procedures.

The R/R subgroup was defined by either an ICD-9/10-CM diagnosis code for relapsed AML (205.02) or the observation of a new line of therapy (LOT) after the initial therapy, implying failure of the first LOT. A new LOT was defined as initiation of treatment following a 90-day chemotherapy-free period after last observed chemotherapy of interest (representing relapsed AML) or upon initiation of treatment with any new chemotherapy agent following completion of the first 60 days of HIC or LIC treatment (representing primary refractory AML).

In cases where both the diagnosis code and a second LOT were observed, disease was considered R/R, and the earlier event defined the R/R episode start date. The R/R episode was validated by a detailed examination of observed LOTs (i.e., specific chemotherapy drugs received, temporal relationship between LOTs [onset/offset timing and the criteria used to determine each], HSCT, and relapsed ICD codes) guided by expert clinical oncologists. Patients indexed to the relapsed disease code were required to have evidence of treatment (chemotherapy or HSCT) within 30 days after the R/R episode start date to validate occurrence of relapsed disease. It is important to note that in the current study, an emergency department (ED) visit that led to subsequent inpatient care was categorized as part of that inpatient visit.

Endpoints

Demographic characteristics were measured at the time of the initial AML diagnosis and included age, sex, U.S. geographic region, and payer type. Disease characteristics were measured over the 6 months before the initial AML diagnosis date. Diagnosis codes were used to identify general comorbid conditions of interest including cardiovascular, metabolic, renal, hepatic, pulmonary, musculoskeletal, and nervous system illnesses. Charlson Comorbidity Index (CCI) scores were calculated excluding AML diagnoses.

All-cause HRU was reported for the following resource categories: physician office visits, nonphysician office visits (e.g., laboratory claim, ancillary care visit), ED visits, inpatient visits, and pharmacy utilization (outpatient). All-cause health care costs were reported as total health plan allowed costs incurred (i.e., all claims observed during episodes that included, but were not limited to, the above resource categories), in addition to the following cost components: physician office visits, nonphysician office visits, ED visits, inpatient visits, and outpatient pharmacy utilization.

Health care resource utilization and costs were reported for each episode of care, per episode start and end definitions. Category costs were reported for the total cohort (i.e., mean inpatient costs were reported for the total R/R episode, regardless of whether every patient with R/R incurred inpatient costs). Costs were adjusted to 2016 U.S. dollars using the medical care component of the Consumer Price Index for All Urban Consumers.

Symptom and toxicity events (SxTox) measured during episodes were identified via diagnostic/treatment codes and reported as frequencies for blood and lymphatic system disorders, gastrointestinal (GI) disorders, bleeding events, infections and infestations, nervous system disorders, skin and subcutaneous tissue disorders, vascular disorders, renal disorders, liver disorders, and cardiovascular disorders (Appendix B, available in online article).

Statistical Analyses

All analyses used SAS version 9.3 (SAS Institute, Cary, NC). Descriptive analyses were conducted, and generalized linear models (GLMs) with a gamma distribution and log link function (selected based on the tendency for skewness of health care cost data) were used to assess the contribution of SxTox to total episode costs while controlling for age, gender, and CCI score. The dependent variable was total episode cost, and the independent variables included age, gender, CCI, and the binary SxTox categories (blood and lymphatic system disorders, GI disorders, bleeding events, infections and infestations, nervous system disorders, skin and subcutaneous tissue disorders, vascular disorders, renal disorders, liver disorders, and cardiovascular disorders) where the reference groups were patients without a given disorder.

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TABLE 1 Baseline Patient Characteristics

	HIC		LIC	HSCT	R/R
	Induction	Consolidation			
	(n=1,542)	(n= 591)			
Age (years)					
Mean	47.0	47.0	64.9	51.4	52.0
SD	11.3	10.6	13.4	12.0	12.5
Median	50.0	50.0	67.0	54.0	54.0
Gender, (%)					
Male	51.8	53.0	59.7	55.4	53.3
Female	48.2	47.0	40.3	44.6	46.7
Geographic region, (%)					
Northeast	21.1	22.7	19.9	20.6	24.8
Midwest	31.4	29.4	30.1	31.2	29.8
South	39.0	40.1	32.0	40.0	37.3
West	8.5	7.8	18.0	8.2	8.1
Payer type, (%)					
Commercial	65.0	63.5	55.1	64.7	62.2
Self-insured	32.9	34.2	33.0	33.4	34.7
Medicare risk	0.0	0.0	5.6	0.5	0.7
Medicaid	1.7	1.9	1.6	0.8	1.6
Unknown	0.5	0.5	4.8	0.6	0.8
Health plan type, (%)					
HMO	8.5	8.3	12.3	9.4	10.3
PPO	81.3	81.6	72.6	82.4	79.5
POS	5.3	4.7	3.3	3.6	3.8
Consumer-directed	0.9	1.5	0.5	0.4	1.3
Indemnity	3.4	3.6	10.8	3.7	4.4
All other	0.5	0.3	0.5	0.5	0.7

HIC=high-intensity chemotherapy; HMO=health maintenance organization; HSCT=hematopoietic stem cell transplantation; LIC=low-intensity chemotherapy; POS=point of service; PPO=preferred provider organization; R/R=relapsed/refractory; SD=standard deviation.

Bleeding events and infections were excluded from the final model as they were correlated with blood and lymphatic system disorders. Results of independent variable parameter estimates were reported as exponentiated values with corresponding 95% confidence intervals to provide the relative contribution to costs associated with SxTox of interest.

Results

Patient Sample and Baseline Characteristics

A total of 21,994 patients with ≥ 2 outpatient claims with an AML diagnosis >30 days apart or one inpatient claim with an AML diagnosis were identified. After applying all inclusion criteria, 7,883 patients with AML remained in the sample. Of the 7,883 patients with AML, 1,542 (19.6%) patients were further identified as having an HIC-I episode; 591 (7.5%) with an HIC-C episode; 628 (8.0%) with an LIC episode; 1,000 (12.7%) with an HSCT episode; and 707 (9%) with an R/R episode of care. Patients with AML who were not classified as HIC, LIC, HSCT, or R/R could have undergone HIC, LIC, and/or HSCT

but may have failed to meet specific criteria used to define the treatment episode due to data incompleteness.

Patient demographics and baseline characteristics can be seen in Table 1. Patient ages were similar across groups (range=47.0-52.0 years) except for patients with an LIC episode (mean=64.9 years). The proportion of males were similar across each group, ranging from 51.8% in the HIC-I episode group to 59.7% in the LIC episode group. Patients were most often located in the southern United States, and the majority were commercially insured and participated in a preferred provider organization plan. The most frequently observed comorbid conditions were hypertension (34.9%), dyslipidemia (29.4%), and osteoarthritis (25.4%).

The duration (mean $\pm$ standard deviation [SD]) of each episode of care was longest in patients with R/R AML (14.77 [15.21] months), followed by patients with HSCT (6.35 [9.77] months), the HIC-I cohort (2.09 [0.37] months), the LIC cohort (1.99 [0.99] months), and the HIC-C cohort (1.52 [1.04] months). The mean (SD) length of hospital stay was longest in the HIC-I sample (26 [13] days), followed by the HSCT (19 [14] days), R/R (174 [32] days), and HIC-C (7 [4] days) samples. The mean (SD) number of total days in the hospital was largest in the R/R sample (75 [394] days), followed by the HIC-I (44 [22] days), HSCT (38 [32] days), and HIC-C (16 [13] days) samples. The majority of patients had at least one outpatient physician office visit (range=93.7%-99.0%).

Health Care Resource Cost and Utilization

Total mean (SD) episode costs were highest in the R/R episodes (\$439,104 [\$405,475]; note: 67.3% of patients with R/R had HSCT), followed by HSCT (\$329,621 [\$288,707]), HIC-I (\$198,657 [\$190,751]), HIC-C (\$73,428 [\$72,811]), and LIC (\$53,081 [\$56,715]) episodes (Table 2). Hospitalization was the largest contributor to cost, accounting for roughly 70% of costs across all treatment groups. Within hospitalization, intensive care unit (ICU) mean (SD) admission costs were a noteworthy contributor, ranging from \$307,446 (\$291,748) in HSCT to \$52,727 (\$87,926) for LIC among patients who were admitted to the ICU. For R/R, the majority of costs (70%) were associated with hospitalization (mean $\pm$ SD=\$308,978 [\$306,987]), followed by nonphysician office visits (\$30,909 [\$49,315]) and outpatient pharmacy costs (\$24,640 [\$46,275]). Similarly, for HSCT, the majority of the costs (79%) were associated with hospitalization (\$259,873 [\$247,198]), followed by nonphysician office visits (\$20,746 [\$47,692]) and outpatient pharmacy costs (\$12,203 [\$26,716]). Unlike other treatment episodes, HIC-I episodes required hospitalization in all (100%) patients, which accounted for the majority of the HIC-I episode costs (\$179,590 [\$187,478]), with \$2,972 (\$3,868) attributed to physicians' office visits and \$3,186 (\$4,715) attributed to outpatient pharmacy. The HIC-C episodes were also likely to require hospitalization (98.1%; Table 3), but the associated costs (SD) were relatively low (\$56,645 [\$67,388]) compared

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TABLE 2 All-Cause Direct Health Care Costs

	HIC		LIC	HSCT	R/R
	Induction (n = 1,542) \$	Consolidation (n = 591) \$	(n = 628) \$	(n = 1,000) \$	(n = 707) \$
Total costs					
Mean	198,657	73,428	53,081	329,620	439,104
SD	190,751	72,811	56,715	288,707	405,475
Median	155,485	55,160	36,659	252,245	340,862
Physician office visits					
Incidence of ≥ 1 visit, n (%)	1,482 (96.1)	554 (93.7)	613 (97.6)	990 (99.0)	690 (97.6)
Mean	2,972	1,090	1,531	6,090	10,926
SD	3,868	1,259	2,416	12,869	13,645
Median	1,345	668	832	3,196	7,215
Emergency visits					
Incidence of ≥ 1 visit, n (%)	441 (28.6)	154 (26.1)	174 (27.7)	269 (26.9)	385 (54.5)
Mean	1,179	1,043	1,235	3,956	4,301
SD	4,641	2,660	2,065	21,005	20,941
Median	390	344	586	706	861
Inpatient visits					
Incidence of ≥ 1 visit, n (%)	1,542 (100.0)	580 (98.1)	225 (35.8)	949 (94.9)	664 (93.9)
Mean	179,590	56,645	49,580	259,873	308,978
SD	187,478	67,388	61,154	247,198	306,987
Median	135,942	38,831	27,914	199,765	228,916
Outpatient pharmacy utilization					
Incidence of ≥ 1 visit, n (%)	1,389 (90.1)	545 (92.2)	562 (89.5)	936 (93.6)	637 (90.1)
Mean	3,186	2,465	2,895	12,203	24,640
SD	4,715	4,156	5,226	26,716	46,275
Median	1,044	571	744	4,579	11,548

HIC = high-intensity chemotherapy; HSCT = hematopoietic stem cell transplantation; LIC = low-intensity chemotherapy; R/R = relapsed/refractory; SD = standard deviation.

with HSCT, R/R, and HIC-I episodes. While patients with LIC had the lowest hospitalization rate (35.8%), these made up the largest component of total episode costs (\$49,580 [\$61,154]).

Effect of SxTox on Episode Costs and Their Rate of Occurrence

Patients discussed in this study experienced a wide range of SxTox, some of which made a noteworthy effect on episode costs (Table 4). After adjusting for age, gender, and CCI score, multivariate GLM results revealed cardiovascular SxTox were significant predictors of total episode costs among patients with HIC-I, HIC-C, LIC, and R/R episodes: HIC-I (22% higher; $P < 0.001$), HIC-C (23% higher; $P = 0.005$), LIC (36% higher; $P < 0.001$), and R/R code episodes (26% higher; $P = 0.001$). The remaining SxTox of interest (blood and lymphatic system disorders, GI disorders, liver disorders, nervous system disorders, renal disorders, skin and subcutaneous tissue disorders, and vascular disorders) had varying degrees of effect depending on the episode type. SxTox events had the greatest effect on total costs of R/R episodes, with significantly increased costs ($P \leq 0.05$), relative to patients without SxTox, observed in all 8 SxTox categories of interest.

The most frequently observed categories of interest were blood and lymphatic system disorders and infections and

infestations (Table 5). The patients receiving HIC-I experienced blood and lymphatic system disorders (98.8%), infections and infestations (91.1%), GI disorders (69.1%), and nervous system disorders (56.2%). The patients receiving HIC-C experienced blood and lymphatic system disorders (96.4%), infections and infestations (89.5%), and bleeding events (73.6%). The patients receiving LIC experienced blood and lymphatic system disorders (84.1%), infections and infestations (64.3%), and bleeding (54.0%). Patients who received HSCT experienced blood and lymphatic system disorders (96.6%), infections and infestations (95.7%), GI disorders (81.5%), bleeding events (60.0%), and nervous system disorders (54.4%). Patients with R/R AML experienced blood and lymphatic system disorders (97.2%), infections and infestations (97.3%), GI disorders (86.6%), bleeding (72.0%), cardiovascular disorders (69.6%), and nervous system disorders (65.8%). It is worth noting that patients in the HIC-I, HSCT, and R/R cohorts appeared to experience SxTox of interest at higher frequencies compared with patients in the HIC-C and LIC cohorts.

Discussion

Between 2017 and 2019, a number of therapies have come to the U.S. market, including enasidenib (IDH2-mutated R/R AML),

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TABLE 3 All-Cause Health Care Resource Utilization During Episodes of Care

	HIC		LIC	HSCT	R/R
	Induction (n = 1,542)	Consolidation (n = 591)	(n = 628)	(n = 1,000)	(n = 707)
Duration of episode, months					
Mean	2.1	1.5	2.0	6.4	14.8
SD	0.4	1.0	1.0	9.8	15.2
Median	2.0	1.2	2.0	2.9	9.9
Physician office visits					
Incidence of ≥ 1 visit, n (%)	1,482 (96.1)	554 (93.7)	613 (97.6)	990 (99.0)	690 (97.6)
Number of unique visits in all patients					
Mean	22.9	8.8	13.0	39.2	76.8
SD	28.5	8.7	13.6	42.8	71.2
Median	10.0	6.0	9.0	24.5	58.0
Emergency department visits					
Incidence of ≥ 1 visit, n (%)	441 (28.6)	154 (26.1)	174 (27.7)	269 (26.9)	385 (54.5)
Number of unique visits in all patients					
Mean	1.3	1.4	1.6	2.7	3.4
SD	1.5	1.5	1.4	7.7	10.0
Median	1.0	1.0	1.0	1.0	2.0
Inpatient visits					
Incidence of ≥ 1 visit, n (%)	1,542 (100)	580 (98.1)	225 (35.8)	949 (94.9)	664 (93.9)
Number of unique visits in all patients					
Mean	1.9	2.2	1.4	2.3	4.5
SD	0.8	1.2	0.8	1.8	3.9
Median	2.0	2.0	1.0	2.0	3.0
Outpatient pharmacy utilization					
Incidence of ≥ 1 visit, n (%)	1,389 (90.1)	545 (92.2)	562 (89.5)	936 (93.6)	637 (90.1)
Number of unique visits in all patients					
Mean	9.1	8.3	11.0	37.5	83.1
SD	5.2	6.1	8.8	62.1	99.1
Median	8.0	7.0	9.0	19.0	50.0

HIC=high-intensity chemotherapy; HSCT=hematopoietic stem cell transplantation; LIC=low-intensity chemotherapy; R/R=relapsed/refractory; SD=standard deviation.

midostaurin, gemtuzumab ozogamicin, venetoclax (1L-unfit AML), ivosidenib (IDH1-mutated R/R AML), glasdegib, and gilteritinib (*FLT3*-mutated R/R AML), with several additional agents in the late stages of investigation (e.g., quizartinib and crenolanib). These therapies may help improve prognosis of patients with AML, especially R/R AML, thanks to varied mechanisms of action and/or targets. As data for this analysis were collected before approval for these new therapies, this study serves as a baseline for the clinical and economic burden associated with AML, allowing for comparisons related to the cost-benefit of emerging treatments.

The data show HRU, cost, and clinical burden varied depending on AML episode type. Specifically, R/R, HSCT, and HIC-I AML episodes were associated with the highest resource, economic, and SxTox-related burden. These findings are similar to other work done in this area,^{5,9,10} where the majority of costs for AML episodes appeared to be driven by inpatient hospitalization (average of roughly 70% of cost, across all episodes), relative to other common cost-accruing events such as

outpatient office visits and pharmacy costs (each average >7% of cost, across all episodes). This suggests opportunities to avoid inpatient care, in favor of outpatient care, should be used.

Not surprisingly, SxTox during treatment were associated with significant clinical and economic burden, especially during R/R episodes where all 8 categories of SxTox (cardiovascular disorders, blood and lymphatic system disorders, GI disorders, liver disorders, nervous system disorders, renal disorders, skin and subcutaneous tissue disorders, and vascular disorders) contributed to higher costs. Cardiovascular disorders consistently increased total costs across episodes: HIC-I (22% higher; $P<0.001$), HIC-C (23% higher; $P=0.005$), LIC (36% higher; $P<0.001$), and R/R code episodes (26% higher; $P<0.001$); this may be due to the inherently expensive nature of testing and treating cardiovascular disorders as well as the link between AML and cardiovascular disorders.¹¹

While dollar-for-dollar comparisons are difficult to make, the findings discussed here are generally consistent with previous studies. Preussler et al. (2017) reported mean adjusted

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TABLE 4 Symptom and Toxicity Events That Significantly Affect Episode Costs^a

Select AML Treatment Episodes	P Value	Exp (Parameter) ^b	95% CI	
HIC induction - episode cost GLM (n = 1,542)				
Cardiovascular disorders	<0.0001	1.22	1.141	1.315
Nervous system disorders	0.005	1.11	1.031	1.185
Skin and subcutaneous tissue disorders	0.007	1.11	1.028	1.191
Vascular disorders	0.0002	1.2	1.093	1.324
HIC consolidation - episode cost GLM (n = 591)				
Cardiovascular disorders	0.005	1.23	1.064	1.422
Gastrointestinal disorders	<0.0001	1.298	1.148	1.467
Nervous system disorders	0.001	1.232	1.087	1.396
LIC - episode cost GLM (n = 628)				
Blood and lymphatic system disorders	<0.0001	3.05	2.501	3.732
Cardiovascular disorders	0.0004	1.36	1.148	1.608
Skin and subcutaneous tissue disorders	0.012	1.5	1.096	2.062
R/R - episode cost GLM (n = 707)				
Blood and lymphatic system disorders	<0.0001	3.62	2.546	5.151
Cardiovascular disorders	0.001	1.26	1.102	1.451
Gastrointestinal disorders	<0.0001	2.01	1.680	2.397
Liver disorders	0.0002	1.35	1.155	1.583
Nervous system disorders	<0.0001	1.31	1.146	1.489
Renal disorders	0.0004	1.26	1.110	1.434
Skin and subcutaneous tissue disorders	<0.0001	1.34	1.186	1.517
Vascular disorders	0.047	1.14	1.002	1.293

^aSymptom and toxicity events are listed in this table only if they significantly affected episode costs.

^bAfter adjusting to baseline age, gender, and comorbidity index. Exponentiated parameter estimate equals the multiplicative effect of this level versus the reference level (e.g., 1.22 equals 22% higher costs) where the reference level is defined as patients without the disorder.

AML=acute myeloid leukemia; CI=confidence interval; Exp=exponentiated; GLM=generalized linear models; HIC=high-intensity chemotherapy; LIC=low-intensity chemotherapy; R/R=relapsed/refractory.

costs accrued in the year following initial AML diagnosis of \$280,788 in patients aged 50 to 64 years who received chemotherapy alone and \$544,178 in patients who received HSCT.⁷ While the dollar amounts presented by Preussler et al. differ from amounts presented in the current study—likely due to differences in study methodology—results are similar since HSCT, which is curative in nature and the goal for patients with AML with a poor prognosis, is substantially more expensive than chemotherapy. Preussler et al. also reported patients receiving chemotherapy alone had a mean of 4 hospitalizations, 52.9 inpatient days, and 52.4 outpatient visits in the year after AML diagnosis; patients receiving allogeneic HSCT had 5 hospitalizations, 92.5 inpatient days, and 74.5 outpatient visits.⁷ Again, trends in the current study are consistent with this, despite differences in data output.

Although Stein et al. (2018) reported substantially lower costs compared with the current study, similar trends emerged as induction therapy was associated with higher costs relative to consolidation therapy. Stein et al. reported mean cost of induction therapy in the United States in 2015 was \$145,189 for commercially insured patients, with newly diagnosed patients with AML who received consolidation therapy in inpatient settings incurring mean costs of \$28,137. Outpatient consolidation therapy costs averaged \$11,271.⁸ Similar to Stein et al., our data suggest HSCT is more expensive than chemotherapy; indeed, when costs related to R/R episodes were stratified by HSCT status, a pattern of higher costs among patients with HSCT, relative to patients without HSCT, emerged (mean±SD total episode costs without HSCT: \$263,310±\$222,357; with HSCT: \$524,596±\$445,149). In a separate analysis, Pandya et al. (2019) suggested this trend may be due to the costs associated with the transplant procedure itself and the accompanying inpatient stays, as well as pretransplant preparation and the treatment of posttransplant toxicities (acute and long-term).¹² This trend is also supported by Mahmoud et al. (2012) who reported HSCT was the most expensive of the episodes examined.⁹ Broder et al. (2017) examined the cost of HSCT in the United States and found the total health care cost at 100 days was \$289,283,¹³ which is below our estimate of \$329,621 and the Preussler et al. estimate of \$544,178 and above the Mahmoud et al. estimate of \$154,739.^{7,9} Given the differences in study methodologies, this discrepancy in dollar amount is to be expected. Nevertheless, it is important to highlight how expensive HSCT can be.

While the need to visit the ED was not the primary driver of cost in the current study, utilization of the ED during these events has been a concern in patients with AML. Bryant et al. (2015) found 75% of patients had ≥1 ED or hospitalization event in the year following induction therapy.⁶ Similarly, Meyers et al. (2013) found roughly 66% of patients with AML had ≥1 ED event.¹⁰ Unfortunately, Bryant et al. did not report a breakdown for those events, so no details on the proportion of patients who visited the ED only or the hospital only are available. The data in the current study delineated between visits to the ED and other types of hospital visits and found, in general, less than 30% of patients required a visit to the ED; however, 54.5% of patients in the R/R cohort visited the ED. It is important to note in the current study that an ED visit that led to subsequent inpatient care was categorized as part of that inpatient visit. Nevertheless, such data illustrate both the significant financial and physical burden faced by individuals with R/R AML.

Limitations

This study has some limitations to consider. No data from patients receiving best supportive care alone were included

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TABLE 5 Occurrence of Symptom and Toxicity Events During Each Episode^a

SxTox of Interest	HIC-Induction (n = 1,542)	HIC-Consolidation (n = 591)	LIC (n = 628)	HSCT (n = 1,000)	R/R (n = 707)
Blood and lymphatic system disorders	98.8	96.4	84.1	96.6	97.2
Infections and infestations	91.1	89.5	64.3	95.7	97.3
Gastrointestinal disorders	69.1	48.6	47.5	81.5	86.6
Bleeding events	39.0	73.6	54.0	60.0	72.0
Nervous system disorders	56.2	36.4	17.4	54.4	65.8
Cardiovascular disorders	44.6	27.7	36.5	52.8	69.6
Skin and subcutaneous tissue disorders	31.2	9.1	6.1	33.1	41.7
Vascular disorders	14.2	9.1	7.0	17.4	33.7
Renal disorders	17.8	11.0	27.9	26.6	37.5
Liver disorders	6.7	3.0	4.0	9.4	16.8

^aOccurrence reported as percentage.

HIC = high-intensity chemotherapy; HSCT = hematopoietic stem cell transplantation; LIC = low-intensity chemotherapy; R/R = relapsed/refractory; SxTox = symptom and toxicity events.

in this analysis. Capturing the data for best supportive care separately with this methodology is difficult due to the barriers in defining the beginning and end of such an episode. Patients who receive active therapy typically also receive best supportive care. Therefore, a retrospective claims database is not a reliable means to gain this information.

It is also possible that not all study patients receiving active treatments, such as HIC/LIC, were captured in this study. In the current study for example, patients with AML who were not classified as HIC, LIC, HSCT, or R/R could have undergone HIC, LIC, and/or HSCT but may have failed to meet specific criteria used to define the treatment episode due to data incompleteness. Furthermore, the 3-month postindex requirement may also have introduced a mortality bias in the population as patients who lost enrollment due to death within 3 months of index were excluded from the final study sample, thereby yielding a final study sample with different underlying characteristics when compared with the general population.

The results from the current study may be limited by coding errors made by providers. As the study sample was anonymized to comply with HIPAA regulations, such errors cannot be identified or corrected. As such, these results should be interpreted in the context of the current study sample. Nevertheless, any resulting bias due to coding errors is likely to be random in nature, affecting all patients to an equal degree.

Finally, as the study sample was principally composed of commercially insured patients, the findings are not necessarily generalizable to the uninsured, Medicare fee-for-service, or Medicaid populations. This is especially relevant in AML, considering the median age of the disease; younger, commercially insured patients represented in this sample may include more patients with HSCT, compared with older patients with less commercial coverage.

Conclusions

This study constitutes the largest retrospective RWD analysis of the economic and clinical burden of AML episodes of care in the United States before approval of targeted agents. Our findings suggest AML episodes are characterized by varying, yet substantial, levels of economic burden. AML is also characterized by substantial physical burden due to disease- and treatment-related SxTox that are responsible for increases to the total cost of care. This, paired with the fact that patients who are diagnosed with AML have poor survival rates, suggests there is a need for therapies with lower toxicity and better efficacy. Emerging treatments that draw on the genetic underpinnings of AML subtypes may help address these needs.

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DISCLOSURES

This study was funded by Astellas Pharma. Astellas employees were involved in the study design, interpretation of data, writing of the manuscript, and the decision to submit the manuscript for publication. Pandya and Wilson are employees of Astellas Pharma U.S. Walsh was an employee of Astellas Pharma U.S. while the study was conducted. Chen, McGuiness, and Wade are employees of IQVIA, which received funding from Astellas Pharma U.S. Madeiros was employed at Stanford University while this study was conducted and received a consulting fee from Astellas for work on this study.

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DATA-SHARING STATEMENT

Researchers may request access to anonymized participant level data, trial level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com.

For the Astellas criteria on data sharing, see <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: leukemia—acute myeloid leukemia (AML). 2016. Available at: <https://seer.cancer.gov/statfacts/html/amyl.html>. Accessed March 22, 2020.
3. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9):1969-78.
4. Ganzel C, Sun Z, Cripe LD, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: The ECOG-ACRIN experience. *Am J Hematol*. 2018;93(8):1074-81. Available at: <https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25162>. Accessed April 1, 2020.
5. Hagiwara M, Sharma A, Chung KC, Delea TE. Burden of acute myeloid leukemia (AML) in a U.S. commercially insured population. *J Clin Oncol*. 2017;35(15 Suppl):e18330.
6. Bryant AL, Deal AM, Walton A, Wood WA, Muss H, Mayer DK. Use of ED and hospital services for patients with acute leukemia after induction therapy: one year follow-up. *Leuk Res*. 2015;39(4):406-10.
7. Preussler JM, Meyer CL, Mau LW, et al. Healthcare costs and utilization for patients age 50 to 64 years with acute myeloid leukemia treated with chemotherapy or with chemotherapy and allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(6):1021-28.
8. Stein EM, Bonifacio G, Latremouille-Viau D, et al. Treatment patterns, healthcare resource utilization, and costs in patients with acute myeloid leukemia in commercially insured and Medicare populations. *J Med Econ*. 2018;21(6):556-63.
9. Mahmoud D, Skikne B, Kucmin-Bemelmans I, Alleman C, Hensen M. Overall economic burden of total treatment costs in acute myeloid leukemia throughout the course of the disease [abstract]. *Blood*. 2012;120(21):3614. Available at: <https://ashpublications.org/blood/article/120/21/3614/86271/Overall-Economic-Burden-of-Total-Treatment-Costs>. Accessed April 1, 2020.
10. Meyers J, Yu Y, Kaye JA, Davis KL. Medicare fee-for-service enrollees with primary acute myeloid leukemia: an analysis of treatment patterns, survival, and healthcare resource utilization and costs. *Appl Health Econ Health Policy*. 2013;11(3):275-86.
11. Shaw LJ, Goyal A, Mehta C, et al. 10-year resource utilization and costs for cardiovascular care. *J Am Coll Cardiol*. 2018;71(10):1078-89.
12. Pandya BJ, Chen CC, Medeiros BC, et al. Economic and clinical burden of relapsed and/or refractory active treatment episodes in patients with acute myeloid leukemia (AML) in the USA: a retrospective analysis of a commercial payer database. *Adv Ther*. 2019;36(8):1922-35.
13. Broder MS, Quock TP, Chang E, et al. The cost of hematopoietic stem-cell transplantation in the United States. *Am Health Drug Benefits*. 2017;10(7):366-74.

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APPENDIX A Study Design and Time Frame

AML = acute myeloid leukemia; HRU = health resource utilization.

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APPENDIX B Overview of Symptom and Toxicity Events

Adverse events were grouped into the following categories:

Blood and lymphatic system disorders

- Diagnostic proxies:
 - o Anemia
 - o Leukopenia
 - o Neutropenia
 - o Thrombocytopenia
- Treatment proxies:
 - o Erythropoietin
 - o Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage CSF
 - o Blood product administration

Gastrointestinal disorders

- Diagnostic proxies:
 - o Constipation
 - o Diarrhea
 - o Nausea and vomiting
 - o Decreased appetite and weight loss
 - o Mucositis
- Treatment proxies:
 - o Laxatives, anti-diarrheals
 - o Antiemetics
 - o Androgenic hormones

Bleeding events

- Diagnostic proxies:
 - o Intracranial hemorrhage
 - o Pulmonary hemorrhage
 - o Gastrointestinal hemorrhage
- Treatment proxies:
 - o Packed red cells, whole blood
 - o Surgical intervention

Infections and infestations

- Diagnostic proxies:
 - o Cellulitis
 - o Pneumonia
 - o Pyelonephritis
 - o Bacteremia/sepsis
 - o Urinary tract infection
 - o Candidiasis
 - o Empyema
 - o Cytomegalovirus
 - o Mucormycosis
 - o Aspergillus
- Treatment proxies:
 - o Broad-spectrum antibiotics
 - o Systemic antifungals

Adverse events were grouped into the following categories:

Nervous system disorders

- Diagnostic proxies:
 - o Dizziness
 - o Headache
 - o Mental confusion
 - o Cerebellar toxicity, ataxia (in combination with, for example, adverse event of antineoplastic drugs)
 - o Keratoconjunctivitis, Sicca syndrome
 - o Palmar plantar erythrodysesthesia
 - o Anxiety, depression, insomnia
- Treatment proxies:
 - o Tricyclic antidepressants (only with diagnosis of dizziness, headache, ataxia)

Skin and subcutaneous tissue disorders

- Diagnostic proxy: Rash

Vascular disorders

- Diagnostic proxies:
 - o Hypotension
- Treatment proxies: pressor agents

Renal disorders

- Diagnostic proxies:
 - o Renal insufficiency

- Treatment proxies:
 - o Diuretics
 - o Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs)

Liver disorders

- Diagnostic proxies:
 - o Hepatotoxicity, nonalcoholic and nonviral cirrhosis

Cardiovascular disorders

- Diagnostic proxies:
 - o Arrhythmia (excluding QT prolongation)
 - o Congestive heart failure
- Treatment proxies:
 - o Antiarrhythmics
 - o ACEIs, ARBs, beta blockers, digoxin