Received: 20 March 2024 | Revised: 24 June 2024 | Accepted: 25 June 2024

DOI: 10.1111/ejh.14272

ORIGINAL ARTICLE

European Journal of Haematology

WILEY

Treatment and clinical outcomes of patients with acute myeloid leukemia in Finland 2010–2020: A retrospective analysis of electronic health records

Juha Ranti[1] | Hanna Pudas[2] | Martta Ranta[2] | Samuli Tuominen[3] | Kristiina Uusi-Rauva[3] | Johanna Lammela[2]

[1]Turku University Hospital, Turku, Finland

[2]AbbVie, Inc., Helsinki, Finland

[3]Medaffcon Oy, Espoo, Finland

Correspondence
Juha Ranti, Turku University Hospital, PO Box 52, 20521 Turku, Finland.
Email: juha.ranti@tyks.fi

Abstract

Our retrospective study (2010–2020) examined treatment patterns, outcomes, and healthcare resource utilization in Finnish acute myeloid leukemia (AML) patients. Data covered 153 patients diagnosed at Hospital District of Southwest Finland (HDSF) and 107 from other districts who underwent allogeneic stem cell transplantation (aSCT) at HDSF. Of the 153 patients, 56.2% received intensive chemotherapy (IC), while 43.8% deemed ineligible for IC received low-intensity therapies or best supportive care (BSC). Median overall survival for IC patients was 31.2 months, compared to 5.3 months for those under azacytidine and 1.2 months on BSC. Majority (57.5%) of patients over 60 with intermediate/high European leukemia network risk had poor outcomes with IC and couldn't proceed to aSCT. These patients carried the highest costs and hospital resource use per patient month. Most common reasons for transplant ineligibility after IC were refractory disease and infection. Our data provides a comprehensive view on AML treatment landscape from a period when the latest treatment advancements were not yet accessible. The data describes patient groups with poor prognosis and increased healthcare burden, emphasizing the need to improve treatment practices and identify better ways to get more patients to transplant, in a rapidly evolving treatment landscape.

KEYWORDS

acute myeloid leukemia, best supportive care, eligible/ineligible, intensive chemotherapy, low intensity therapy, stem cell transplantation

Novelty statements

What is the new aspect of your work?

Our study is the most comprehensive dataset describing AML treatment landscape in Finland, including treatment outcomes and HCRU in both fit and unfit AML patient populations.

What is the central finding of your work?

Unfit patients receiving azacytidine monotherapy or palliative care, as well as the majority of patients aged over 60 with an intermediate or high ELN-risk who undergo intensive chemotherapy, experience very poor prognoses.

What is (or could be) the specific clinical relevance of your work?

Our research emphasizes the significance of improving treatment approaches for these particular patient populations and underscores the need to determine the most effective criteria for selecting patients who are eligible or ineligible for intensive chemotherapy, as well as how to achieve the most favorable long-term results for elderly patients.

1 | INTRODUCTION

Acute myeloid leukemia (AML) is typically disease of the elderly and is characterized by the proliferation of myeloid blasts in bone marrow leading to progressive peripheral blood cytopenias and rather rapid decline in the patient's condition.[1] Genetic and cytogenetic heterogeneity is typical of AML, forming the basis for AML risk classification.[2]

Traditionally, AML treatments have consisted of different chemotherapy combinations with anthracycline-cytarabine backbone followed by allogeneic stem cell transplantation (aSCT). This intensive approach has been applied for patients mainly under 70 years and fit, as determined by treating physician according to Ferrara criteria. Approximately 50% of patients under 60 years achieve cure, whereas the prognosis for elderly patients is significantly worse.[3] With increasing age, adverse risk genetic abnormalities, concomitant disease burden, poor performance status, and decreased tolerability for chemotherapy become more common, leading to inferior outcomes with intensive approach.[4]

Recently, new targeted therapies have expanded the treatment landscape of AML patients ineligible for intensive chemotherapy (IC) and venetoclax+azacytidine therapy has become the new standard of care for these patients.[2] Previously, ineligible patients were treated with low intensity therapies (LIT), such as hypomethylating agents or given only best supportive care (BSC). Data from the Finnish Cancer Registry shows that median overall survival (mOS) for AML patients diagnosed and treated between 2007 and 2018 was 3 months for patients over 75 years (Finnish Cancer registry 2020, www.canceregistry.fi).

To further understand AML treatment patterns and outcomes in both intensively and non-intensively treated patients, we conducted a retrospective analysis of electronic health records from a tertiary care center in Hospital District of Southwest Finland (HDSF). Our analysis characterizes AML patients treated between 2010 and 2020, describes their treatments and outcomes, and assesses healthcare resource utilization (HCRU) and associated costs, providing a view into treatment landscape prior to the introduction of new therapies. Additionally, our dataset included patients from other regions who underwent transplantation at HDSF, providing insights into national leukemia treatment practices.

2 | METHODS

2.1 | Data collection and inclusion criteria

In this retrospective registry study, existing electronic health record (EHR) data generated during routine clinical practice and available in the data lake of the HDSF were compiled for the analyses by Auria Clinical Informatics. The extracted data were complemented by a manual chart review performed by the clinical expert of the study to cover observed data gaps.

The study included all adult patients diagnosed with acute myeloid leukemia (AML) based on the International Classification of Diseases 10th edition (ICD-10) code C92.0 in the HDSF patient information system between January 1st, 2010, and October 31st, 2020. Following patients were excluded: non-incident patients (first AML diagnosis recorded before January 1, 2010, or actual diagnosis before the first available ICD-10 record as confirmed by the clinical expert), patients with incorrect AML diagnosis or acute promyelocytic leukemia (ICD-10 C92.4) or acute lymphoblastic leukemia (ICD-10 C91.0), and patients treated elsewhere or treated in a clinical trial. Diagnoses and diagnosis dates were validated by the clinical expert.

Index date was defined as the date of the first AML diagnosis code or the date of the first AML treatment, if earlier. End of follow-up was defined as end of study (December 31, 2020) or death, if the patient deceased before end of study. Length of follow-up was defined as 12*(end of follow-up−index+1)/365.25 months.

All patients were retrospectively followed and data collected from earliest available data point until end of follow-up. Data collected

included demographic and clinical characteristics, including age at index, sex, Eastern Cooperative Oncology Group performance status at index (ECOG; range: 0–5), diagnoses, procedures, laboratory tests, hospital-administered cancer treatments (including chemotherapies and immunosuppressants), date and type of aSCT, prescriptions of hospital administrated medications, date and cause of death as well as all healthcare contacts (see section on healthcare resource utilization for more details). Diagnoses were available from 2004 onwards and the other data from 2010 onwards until December 31, 2020 European leukemia network (ELN) risk status was assessed by chart review according to 2017 risk stratification[2] based on available genetic data. For patients, ineligible for IC in particular, data coverage was poor for ELN and ECOG. ICD-10 codes recorded 2 years prior to index were used to determine secondary AML (sAML) status (including transformed and treatment related sAML) and Charlson comorbidity index (CCI).[5] Data were also incomplete in the cohort referred to HDSF for aSCT from other hospital districts, and thus CCI index, comorbidities and sAML determinations could not be completed for this cohort. Group sizes between 1 and 4 are reported as "<5," as a requirement from the permission authority to ensure patient anonymity.

2.2 | Patient subgroups and characteristics

Patients residing at HDSF were divided into patients eligible for IC and patients ineligible for IC, based on received treatment. Patients who received IC were further assessed in two subgroups; patients who received aSCT by the end of follow-up and patients who did not. Patients who were ineligible for IC were divided into patients treated with LIT and patients receiving BSC. All aSCT procedures in Finland are centralized to HDSF or Hospital District of Helsinki and Uusimaa, hence the outcomes of stem cell transplantations were also analyzed in all patients transplanted at HDSF regardless of home municipality (Figure 1).

Descriptive statistics were used to report the demographic and clinical characteristics, comorbidities, and infections at baseline and during follow-up, including the number and proportion of patients, and median numbers stratified according to the patient subgroup. Differences in categorial variables between IC eligible and ineligible patients as well as ineligible treated with LIT and unfit with BSC were tested using the Chi-squared test or Fisher's exact test (with group size 1–5; *p*-value omitted if any cell had value 0), while differences in continuous variables were tested using the Student's *t*-test.

2.3 | Outcomes

Overall survival (OS) was defined as time from index (all eligible and ineligible patients and patients without aSCT), from date of aSCT (transplanted patients), or treatment initiation (ineligible, LIT treated patients; first administration of the respective regimen) until death (all-cause; event) or end of study (December 31, 2020; censoring event). OS was analyzed with the Kaplan–Meier method and stratified according to indicated patient subgroups. The median survival with 95% confidence interval (CI) was reported, if reached. Cox proportional hazards model was used to estimate the association of age, sex, CCI, and ELN and aSCT status with OS in patients who received IC. aSCT was included as a time varying covariate. The hazard ratios with 95% CIs and *p*-values were reported.

Progression free survival (PFS) was defined as time from the initiation of therapy until disease progression (myeloblast proportion ≥5% in bone marrow; event), death, or end of study (December 31, 2020; censoring event). Both PFS and OS were analyzed according to the cause of death with the Aalen-Johansen estimator, which accounts for the competing risks setting between multiple alternative outcome events. The cumulative incidences of the different outcome events were plotted in addition to the PFS or OS curve.

2.4 | Healthcare resource utilization and related costs

HCRU data included all hospitalizations, emergency room (ER) and outpatient visits, procedures (including blood transfusions), operations

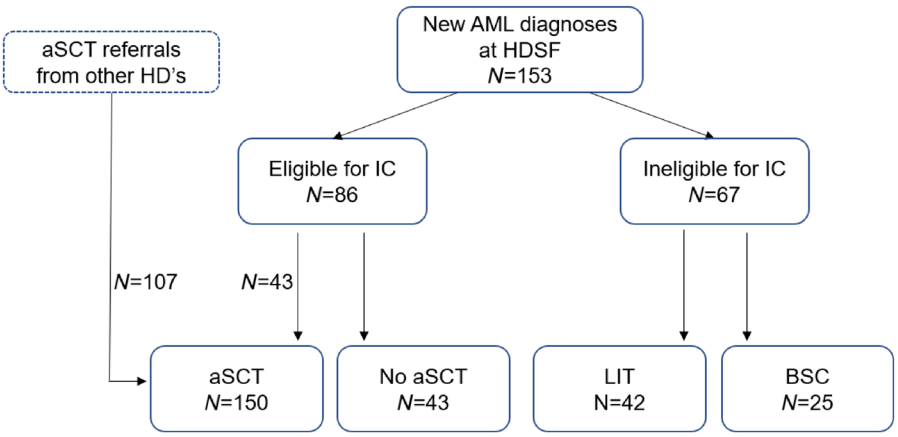

FIGURE 1 Flowchart of patient cohorts and subgroups. aSCT, allogeneic stem cell transplantation; BSC, best supportive care; HD, Hospital district; HDSF, Hospital District of Southwest Finland; IC, intensive chemotherapy; LIT, low intensity therapy.

(procedures requiring operation room reservation), and laboratory tests of the diagnosed AML (C92.0) patients whose home municipality was within HDSF, regardless of the diagnosis associated with the contact (all-cause; all HCRU of AML diagnosed patients). The number of outpatient and ER visits, and the number of inpatient days were reported. The HCRU related costs were reported according to the HCRU type, and the costs were derived according to the unit cost method and using publicly available service price listings obtained from the HDSF. Both the number of contacts and total costs were reported per patient (PP; total number divided by the total number of patients) and per patient year (PPY; total number divided by the total follow-up length). The 95% CIs were estimated with the bootstrap method using 10 000 samples.

2.5 | Statistical analysis

Statistical analyses were performed using R version 4.0.3.[6] *p*-Values less than .05 were considered statistically significant. *p*-Values were not adjusted for multiple testing. The proportion of missing values were reported, where applicable.

3 | RESULTS

3.1 | Patient cohorts

One hundred and fifty three new AML patients were diagnosed at HDSF between January 1, 2010 and October 31, 2020, with a median follow-up of 20.7 months (Figure 1). Of these, 56.2% (86/153) were treated with an intensive approach and 43.8% (67/153) were considered as ineligible for IC and treated with LIT (62.7%, 42/67) or with BSC (37.3%, 25/67).

One hundred and seven AML patients were referred to HDSF for aSCT from other hospital districts during 2010–2020. Altogether 150 patients received an aSCT at HDSF during 2010–2020 with median follow-up of 45.9 months (Figure 1). Characteristics of different subgroups are described in Table 1.

3.2 | Treatments and outcomes

3.2.1 | Patients treated with intensive chemotherapy

Altogether 56.2% (86/153) of the HDSF's AML patients were treated with IC (Figure 1). Median age of these patients was 62.7 years (IQR 50.1–68.2), 3.3% had sAML and majority (62.8%) had ECOG 1–2. Further characteristics, including ELN risk profiles are presented in Table 1.

The majority of intensively treated patients had comorbidities recorded prior to or at the time of AML diagnosis. The most common comorbidities were arterial hypertension 22.1%, non-hematological cancer 10.5%, non-insulin-dependent diabetes mellitus 8.1%, atrial fibrillation or flutter 7.0% and dyslipidemia 7.0%.

In most cases (>90%), the first induction was standard combination of cytarabine plus idarubicin. Less than five patients received cytarabine plus daunorubicin. The majority (72.1%) of patients were given one induction, 27.9% presented with induction failure and received ≥2 inductions.

Median OS for all patients who received IC was 31.2 months (95% CI: 11.5–68.3) (Figure 2A). Survival was significantly associated with patient's age and ELN risk status (Figure 2A–C). Median OS for patients <65 years was 68.3 months (95% CI: 35.8–not reached), whereas for ≥65-year-olds mOS was 8.1 months (95% CI: 5.3–12.9) (Figure 2B). 3-year survival estimate for <65-year-olds was 61.7% (95% CI: 49.5–77.1) versus 22.2% (95% CI: 11.3–43.7) for ≥65-year-olds.

Median OS for patients with intermediate ELN risk (IR) was 41.7 months (95% CI: 17.2–not reached), whereas for high-risk (HR) patients mOS was 7.5 months (95% CI: 4.9–18.9) (Figure 2C). The mOS in low-risk group was not reached during the follow-up.

3.2.2 | Allogeneic stem cell transplantation

Expectedly, being able to proceed to aSCT was associated with better OS in patients treated with IC after adjusting with age and risk-class (hazard ratio for death 0.29, $p = .007$) (Figure 2A). Half (43/86) of the patients diagnosed at HDSF who received IC proceeded to aSCT after induction (Figure 1.). In addition, 107 patients referred from other hospital districts received aSCT at HDSF between 2010 and 2020. Among all 150 aSCT patients, median age was 58.1 years (IQR: 43.9–63.7). 22.0%, 34.7% and 43.3% represented LR, IR and HR ELN profiles, respectively. The majority were recorded with ECOG 0 (42.6%) or ECOG 1–2 (56.6%) (Table 1).

Most of the patients (94.0%, 141/150) received one stem cell transplantation; 6.0% (9/150) had a second transplant. At 3 years after aSCT, PFS was 48.6% (95% CI: 40.9–57.7) and OS was 65.0% (95% CI: 57.3–73.7) (Figure 3A,B). Causes of death included relapse (18.2% of all patients), infections (4.7%), and other reasons (12.0%, including GHVD-related mortality) (Figure 3B). 60.0% (95% CI: 51.8–69.6) of patients were alive at 5 years. The median time from diagnosis to transplantation was 123 days.

According to the HDSF guidelines, AML patients with highest relapse risk were treated with azacytidine as a maintenance therapy. Typically, it was started prophylactically for patients with measurable residual disease. Altogether 45.3% (68/150) of the patients received azacytidine after the aSCT. The 3-year survival for this group was 64.5% (95% CI: 51.6–80.6), which did not differ from the whole cohort (Supplementary Figure 1).

A relatively high proportion of IR and HR patients who received IC at HDSF were not able to proceed to aSCT (35.1% [13/37] of IR,

TABLE 1 Patient characteristics.

	AML patients diagnosed at HDSF ($n = 153$)						aSCT at HDSF $N = 150$
	Eligible for IC $N = 86$	Ineligible for IC $N = 67$	p-Value Eligible versus ineligible	Ineligible for IC: LIT $N = 42$	Ineligible for IC: BSC $N = 25$	p-Value LIT versus BSC	
Sex			.282			.925	
Male	59.3% ($n = 51$)	49.3% ($n = 33$)		47.6% ($n = 20$)	52.0% ($n = 13$)		52.7% ($n = 79$)
Female	40.7% ($n = 35$)	50.7% ($n = 34$)		52.4% ($n = 22$)	48.0% ($n = 12$)		47.3% ($n = 71$)
Age							
Median, years (IQR)	62.7 (50.1–68.2)	80.1 (75.6–83.7)	<.005	77.1 (72.6–80.9)	83.6 (80.8–87.4)	<.005	57.8 (43.5–63.3)
<50	24.4% ($n = 21$)	0% ($n = 0$)		0% ($n = 0$)	0% ($n = 0$)		36.7% ($n = 55$)
50–64	37.2% ($n = 32$)	$n < 5$		$n < 5$	0% ($n = 0$)		46.7% ($n = 70$)
65–74	32.6% ($n = 28$)	17.9% ($n = 12$)		21.4% ($n = 9$)	$n < 5$		16.7% ($n = 25$)
75–84	5.8% ($n = 5$)	58.2% ($n = 39$)		66.7% ($n = 28$)	44.0% ($n = 11$)		0% ($n = 0$)
≥85	0% ($n = 0$)	17.9% ($n = 12$)		$n < 5$	44.0% ($n = 11$)		0% ($n = 0$)
sAML	23.3% ($n = 20$)	38.8% ($n = 26$)	.057	50.0% ($n = 21$)	20.0% ($n = 5$)	.029	
ELN risk			.177				
Low	23.5% ($n = 20$)	$n < 5$		$n < 5$	0% ($n = 0$)		22.0% ($n = 33$)
Intermediate	43.5% ($n = 37$)	50.0% ($n = 21$)		48.5% ($n = 16$)	55.6% ($n = 5$)		34.7% ($n = 52$)
High	32.9% ($n = 28$)	40.5% ($n = 17$)		39.4% ($n = 13$)	$n < 5$		43.3% ($n = 65$)
Missing	$n < 5$	37.3% ($n = 25$)		21.4% ($n = 9$)	64.0% ($n = 16$)		0% ($n = 0$)
ECOG			<.005				
0	33.7% ($n = 29$)	$n < 5$		$n < 5$	0% ($n = 0$)		42.6% ($n = 58$)
1–2	62.8% ($n = 54$)	54.0% ($n = 34$)		65.9% ($n = 27$)	31.8% ($n = 7$)		56.6% ($n = 77$)
3–4	$n < 5$	42.9% ($n = 27$)		29.3% ($n = 12$)	68.2% ($n = 15$)		$n < 5$
Missing	0% ($n = 0$)	$n < 5$		$n < 5$	$n < 5$		9.3% ($n = 14$)
CCI			.027			.029	
0–1	$n < 5$	$n < 5$		$n < 5$	$n < 5$		
2–3	87.2% ($n = 75$)	70.1% ($n = 47$)		81.0% ($n = 34$)	52.0% ($n = 13$)		
4+	11.6% ($n = 10$)	25.4% ($n = 17$)		16.7% ($n = 7$)	40.0% ($n = 10$)		
Missing	0% ($n = 0$)	0% ($n = 0$)		0% ($n = 0$)	0% ($n = 0$)		
Follow-up, months			<.005			.058	
Mean	32.4	5.6		7.0	3.3		45.9
Median	17.8	3.0		3.6	1.1		36.5
IQR	6.6–50.3	0.8–7.6		1.1–8.6	0.3–5.5		14.1–66.2

Note: Determination of sAML and CCI was not applicable in the aSCT ($n = 150$) cohort due to incomplete data coverage of previously recorded diagnoses as most of the transplanted patients were referred from other hospital districts.

Abbreviations: aSCT, allogeneic stem cell transplantation; BSC, best supportive care; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group performance status; ELN, European Leukemia Network; IC, intensive chemotherapy; IQR, interquartile range; LIT, low intensity therapy; sAML, secondary AML.

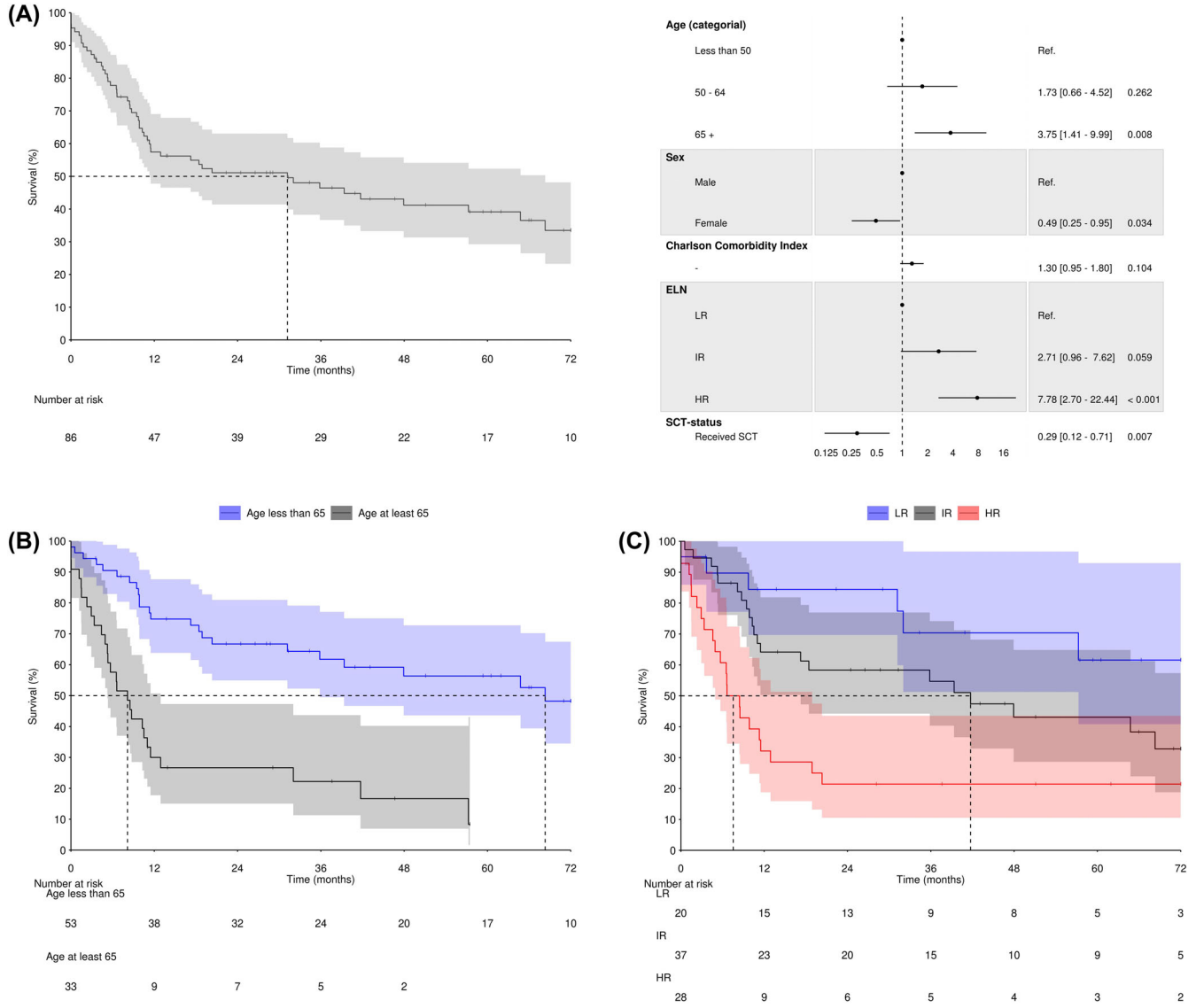

FIGURE 2 (A) OS in patients treated with IC at HDSF ($n = 86$) and variables associated with survival (Cox proportional hazards analysis). Impact of (B) age and (C) ELN risk status on OS. Kaplan–Meier curve representing OS stratified by age of 60 years is shown in Supplementary Figure 3. aSCT, allogeneic stem cell transplantation; CI, confidence interval; ELN, European Leukemia Network; HDSF, Hospital District of Southwest Finland; HR, high risk; IC, intensive chemotherapy; IR, intermediate risk; LR, low risk; mOS, median overall survival; NR, not reached.

53.6% [15/28] of HR patients). Most common reasons were refractory disease (35.7%, 10/28), infection (32.1%, 9/28), high comorbidity burden, or low performance status (10.7%, 3/28) or death (other than infection-related) during induction/before aSCT (10.7%, 3/28). mOS was 8.7 months for IR patients who were not able to proceed to aSCT (95% CI:5.3–) and 3.4 months for HR patients who were not able to proceed to aSCT (95% CI:1.5–8.5) (Figure 3C), while it was not reached (95% CI: 64.1–, IR) and 52.5 months (95% CI: 28.1–, HR) in patients who were able to proceed to aSCT.

Compared to transplanted IR/HR patients (37/65), IR/HR patients who were not able to proceed to aSCT (28/65) were significantly older (median 68.2 [IQR 64.7–70.6] vs. 59.4 [IQR 49.8–64.3] years, $p = .002$) and had higher ECOG (ECOG 0: $n < 5$, ECOG 1–2: 85.7% (24/28), ECOG 3–4: $n < 5$ vs. ECOG 0: 51.4% [19/37], ECOG 1–2: 48.6% [18/37], ECOG 3–4: 0%). Increasing age decreased the likelihood of IR/HR patients to proceed to aSCT after intensive induction. Of <60-year-old intensively treated IR/HR patients, 80.0% (20/25) proceeded to aSCT, whereas only 42.5% (17/40) and 23.1% (6/26) of >60-year-olds and >65-year-olds, respectively, were able to proceed to aSCT after IC. Associated outcomes are shown in Supplementary Figure 2.

3.2.3 | Patients ineligible for intensive chemotherapy

Less than half, 43.8% (67/153), of HDSF patients were considered as ineligible for IC and treated with LIT or BSC. Compared to eligible

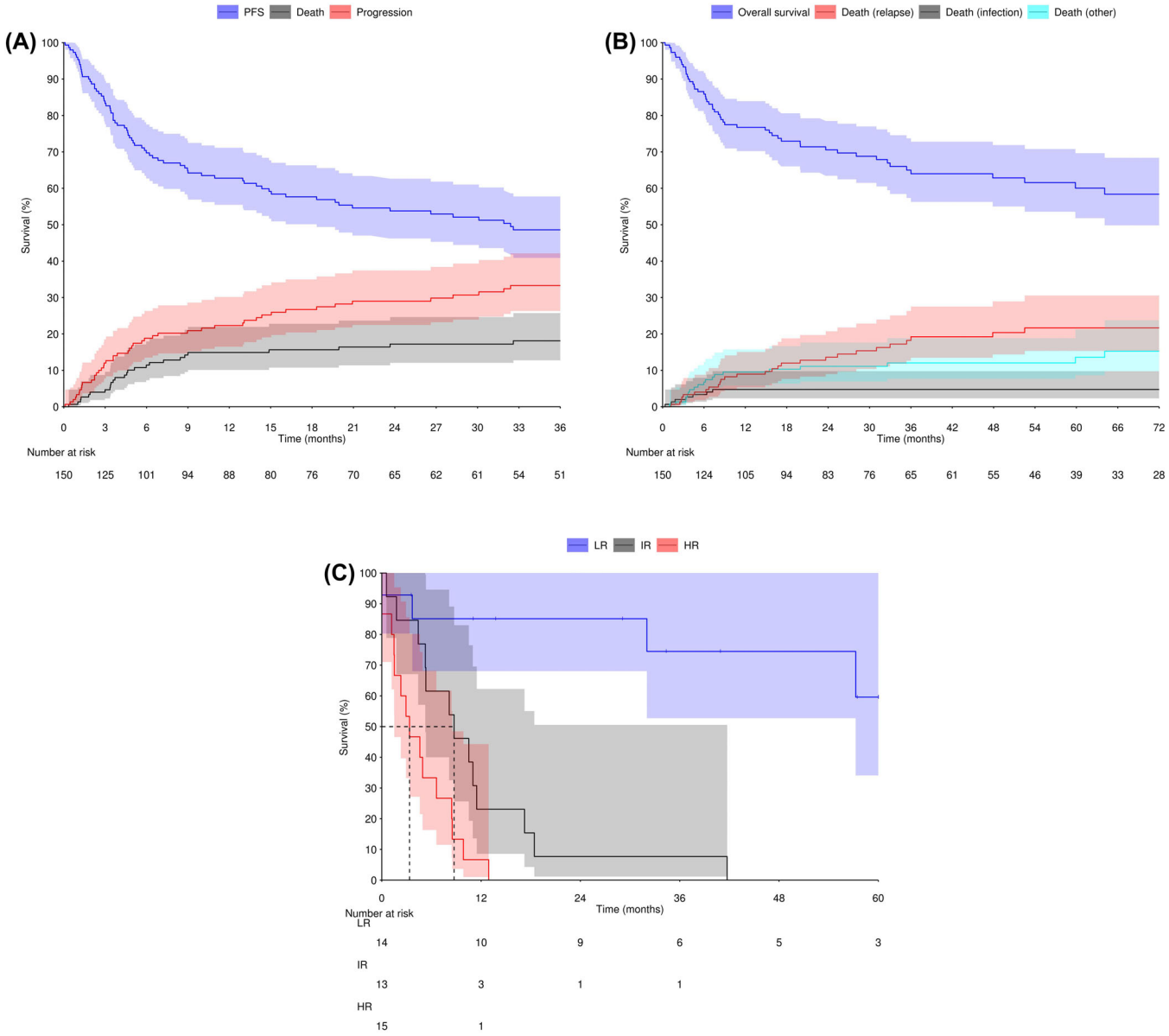

FIGURE 3 (A) PFS and (B) OS and causes of death of patients who received aSCT at HDSF ($n = 150$). (C) OS by ELN risk status in patients who didn't proceed to aSCT after IC ($n = 43$). aSCT, allogeneic stem cell transplantation; ELN, European Leukemia Network; HDSF, Hospital district of Southwest Finland; HR, high risk; IR, intermediate risk; LR, low risk; mOS, median overall survival; NR, not reached; PFS, progression-free survival.

patients, ineligible patients were older, presented more often with sAML, high/intermediate ELN risk, and low performance status (Table 1). Patients who were ineligible for IC also had higher burden of comorbidities at index compared to patients who received IC, especially heart-related comorbidities, such as atrial fibrillation and flutter (37.3% vs. 7.0%), chronic ischemic heart disease (16.4% vs. n < 5 [less than 5.8%]) and congestive heart failure (14.9% vs. $n < 5$).

Slight majority, 62.7% (42/67), of ineligible patients were treated with LIT. Azacytidine monotherapy was the most used treatment ($n = 20$), followed by mercaptopurine monotherapy ($n = 9$) and low dose cytarabine (LDAC, $n = 8$). For a few patients, LDAC was combined with tioguanine or idarubicin (without intention to treat with aSCT). Median OS for azacytidine monotherapy and LDAC-based treatments was 5.2 (95% CI: 3.5–13.7) and 5.4 (95% CI: 2.4–) months, respectively. For mercaptopurine, which was mainly used at the beginning of the follow-up period for palliative purposes, mOS was 0.9 months (95% CI: 0.7–). (Figure 4).

Approximately one third, 37.3% (25/67), of patients ineligible for IC did not receive any anti-leukemic treatment, that is, received only BSC (e.g., granulocyte colony stimulating factors, antibiotics, corticosteroids, antianemics, hydroxycarbamide, blood transfusions).

Compared to patients treated with LIT, patients receiving only BSC were clearly older, had poorer performance status and had higher comorbidity burden (Table 1.), especially chronic ischemic heart

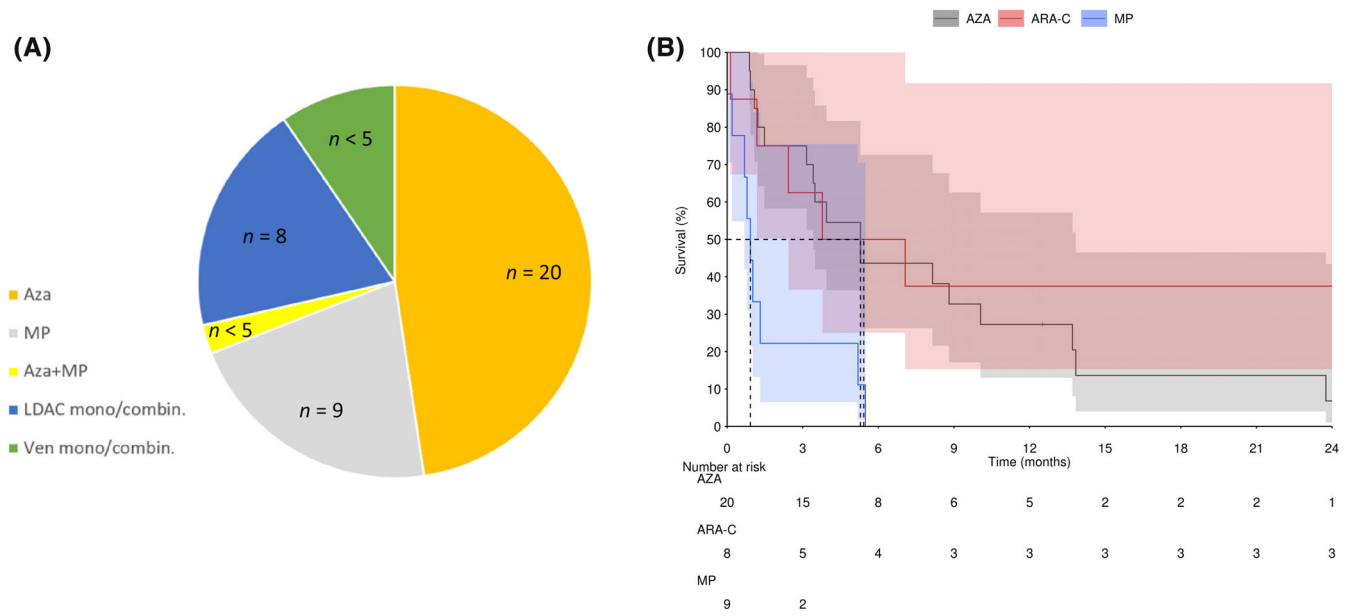

FIGURE 4 (A) First line treatments (B) overall survival for patients ineligible for IC. Aza, azacytidine; LDAC, low dose cytarabine; MP, mercaptopurine; Ven, venetoclax.

disease (24.0% vs. 11.9%) and congestive heart failure (20.0% vs. 11.9%) were more common in the BSC group. Median OS was 1.2 months (95% CI: 0.5–5.6) in patients receiving only BSC.

3.2.4 | Healthcare resource utilization

HCRU was assessed in HDSF's patients ($n = 153$). In patients who were ineligible for IC, HRCU was assessed for patients who received BSC or azacytidine, as these patient groups were the largest ones ($n \geq 20$). The total use of hospital resources (total number of inpatient days, outpatient visits and ER visits) was highest among patients with longest survival/follow-up, that is, for patients who received aSCT (Figure 5A). However, the resource use per patient month was highest for patients who received IC but were not able to proceed to aSCT and for patients who were ineligible for IC and received azacytidine, indicating a high burden for healthcare and for patients during their short-term survival/follow-up (Figure 5B). It is notable that patients who received IC but were not able to proceed to aSCT had significant number of inpatient days per month that lead to increased burden of hospitalization. Patients who were ineligible for IC and received azacytidine, had greater amount of outpatient visits.

Expectedly, the total costs were highest for the patients with longest follow-up (transplanted patients) (Figure 5C). However, the relative costs (cost per month) of transplanted patients were close to azacytidine treated patients with short follow-up highlighting the cost-effectiveness of aSCT (Figure 5D). For the IR/HR patients who received IC but were not able to proceed to aSCT, the total costs were substantial despite of their short follow-up (Figure 5C). In fact, when calculating the relative costs, treatment of this patient group was the most expensive (Figure 5D).

4 | DISCUSSION

This retrospective single-center study delved into the treatment patterns, outcomes and HCRU among Finnish patients with AML. It offers a comprehensive view on patient populations urgently requiring more effective therapies. The study also corroborates previous findings regarding the beneficial long-term outcomes achieved with aSCT.[7]

HDSF cohort had 153 patients of which 86 (56.2%) were considered eligible for IC. In a large Swedish registry study, the treatment distribution was similar with 62% of patients treated intensively.[8] In a real-world study on AML treatment in 27 US hospital institutions the proportion of intensively treated patients was lower, 47%.[9] The difference in treatment distribution might be attributed to the tertiary nature of AML-treating centers in Nordic countries, where the most unfit patients receive diagnosis and treatment locally.

Ineligible patients were significantly older with worse performance status compared to eligible patients. Considering the previously described poor outcomes in patients over 75 years of age or with ECOG ≥2 treated with IC, the patient selection seems appropriate and consistent with the Ferrara criteria.[10,11]

Treatment outcomes for the ineligible population were suboptimal with mOS of 5.2 and 5.4 months among patients treated with azacytidine monotherapy and LDAC-based treatments, respectively. Outcomes in the present study match the results reported from a large retrospective community based nationwide Flatiron Health database study in US, where mOS of 6.3 months was achieved with azacytidine therapy.[12] In another retrospective chart review from 112 community or hospital medical centers across 22 countries, Miyamoto and colleagues reported mOS of 9.9 months reached with azacytidine.[13] Similar results have also been reported previously in

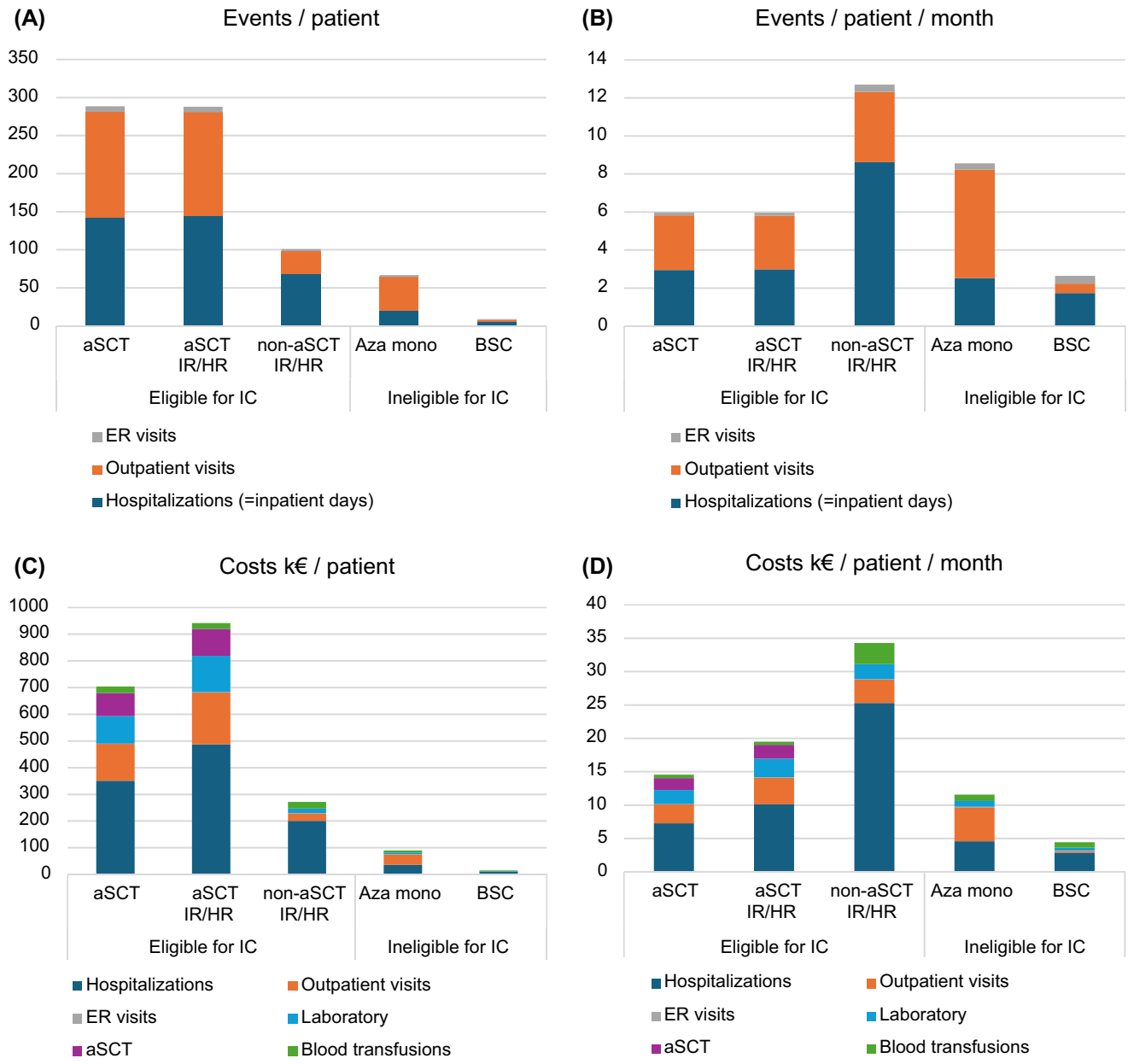

FIGURE 5 (A) HCRU-related events, (B) events per patient per month, (C) HCRU-related costs, and (D) costs per patient per month in HDSF's patients who received aSCT (aSCT, $n = 43$), transplanted IR/HR patients (aSCT IR/HR, $n = 37$), IR/HR patients who didn't proceed to aSCT (non-aSCT IR/HR, $n = 28$) and patients who were ineligible for intensive chemotherapy and received azacytidine monotherapy (Aza mono, $n = 20$) or only best supportive care (BSC, $n = 25$). Mean follow-up time (years) per patient: aSCT (4.03), aSCT IR/HR (4.02), non-aSCT IR/HR (0.66), Aza mono (0.65), BSC (0.28). The length of the follow-up was defined as time from index until the end of study (December 31, 2020) or death. aSCT, allogeneic stem cell transplantation; BSC, best supportive care; ER, emergency room; HCRU, healthcare resource utilization; HR, high risk; IC, intensive chemotherapy; IR, intermediate risk.

clinical trials with achieved mOS of 8–10 months by hypomethylating agents.[14,15]

In our cohort, the patient population having the worst prognosis were the patients assigned to BSC or mercaptopurine therapy. Mercaptopurine has been previously used to control hyperleukocytosis with fading use in the last years of the follow-up. The patients in BSC group were significantly older than those assigned to LIT and carried a higher disease burden and worse performance status highlighting the frail nature of this most prognostically adverse group.

Adverse cytogenetic abnormalities and comorbidities increase with age impairing the outcomes of conventional intensive chemotherapy. Abuelgasim and colleagues reported 2-year OS of 15.8% in intensively treated AML patients aged over 60 years.[16] Furthermore, in the M.D Anderson's data set mOS of 5.4 months was reported for intensively treated patients of age 65 years or older.[11] Similarly, in our dataset, patient's age proved to be of prognostic significance among the intensively treated group. The best outcomes were noted in patients under the age of 50 as compared with patients over

65 years-old having markedly worse outcomes (HR for death 3.75, $p = .008$). The mOS for intensively treated over 65-year-old patients was 8.1 months (95% CI: 5.3–12.9).

Increasing age decreased the probability of IR/HR patients to proceed to aSCT after intensive induction. 57.5% (23/40) and 76.9% (20/26) of >60-year-olds and >65-year-olds were not able to proceed to aSCT after IC, respectively, and for these patients mOS was less than 6 months. However, for patients >65 years mOS was not improved even if they were able to proceed to aSCT (mOS 6.2 months, 95% CI:1.8–). The most frequent reasons for omitting the aSCT in IR/HR patients included refractory disease and difficult-to-treat infections during the chemotherapy treatment. Poor outcomes observed in older population further stress the previously raised question of how to optimally select patients who are eligible/ineligible for conventional intensive chemotherapy.[17] Ongoing trials will shed light on new improved ways to get more patients to transplant. Will less intensive venetoclax-based approach serve as a beneficial alternative bridging therapy for some patients or, alternatively, combining novel agents with less intensive chemotherapy backbone. The potential benefits of reducing the dose or replacing cytotoxic components like anthracyclines are under investigation. By reducing treatment-related toxicities without compromising efficacy, these alternative approaches may have potential to increase the chances to proceed to transplant and achieve better long-term outcomes.

Our HCRU analyses expectedly revealed that patients receiving aSCT, that is, patients with longest survival and follow-up, had most HCRU-related events and costs. This is in line with results from a nationwide Swedish registry study.[18] However, the relative resource use and costs (events and k€ per month) were highest particularly for patients who received IC but were not able to proceed to aSCT. This was mostly driven by a high need for hospitalization (inpatient days) during the short survival of this patient group. These results underscore the importance of identifying more effective and well-tolerated ways to prepare more patients to transplant. It is notable that HCRU and related costs were assessed based on the EHRs and do not cover primary healthcare resource use or open care medications. As most patients who are ineligible for IC shift to primary healthcare for the rest of their care, it is probable that these patients cause more HCRU-related costs than we have shown.

Although the HDSF data lake utilized in this study has good temporal coverage and accurate data on multiple variables to answer the questions posed, some limitations with these data and their interpretation do exist. Due to the retrospective nature of the study and the reliance on the accuracy and completeness of the recorded registry data, some data gaps and missing information were observed, although both structural and text mining searches were utilized to extract the relevant data. Data on characteristics were partly incomplete—for the genetic data in particular the coverage was poor for most of the aberrations due to the unavailability of complete mutation panel analyses until the late 2010s, coinciding with their uptake into routine clinical practice. Additionally, the variability of patient texts can complicate text-mining of key terms, affecting completeness of variables such as the ELN status and myeloblast proportions. The extracted data were complemented by a manual chart review performed by the clinical expert of the study to cover observed data gaps. Our study focused on the HDSF regional patients, thus limiting the generalizability of the study and resulted in low patient numbers for certain subgroup analyses. The Cox proportional hazards analysis was limited by a small sample size and the results should be interpreted with care. Particularly the hazard ratio for proceeding to aSCT could be overestimated due to the inability to properly control for confounding covariates. Additionally, the cohort was limited to the information on tertiary care, which may distort the findings especially in the unfit population and medications administered in primary care.

In conclusion, the present study provides insights into treatment patterns, outcomes, and health care costs for Finnish AML patients diagnosed and treated from 2010 to 2020. Our cohort clearly demonstrates poor outcomes in patients ineligible for IC during time when novel targeted treatments were not yet available. Fortunately, new targeted therapies have expanded the treatment landscape of AML patients ineligible for IC and venetoclax+azacytidine therapy has recently become the recommended standard of care for these patients.[2] Our findings also highlight a disparity in results between patients who underwent successful aSCT and those who could not proceed to the transplantation after IC. The majority of patients aged over 60 with an intermediate or high risk could not proceed to aSCT post-IC, primarily due to refractory disease or infection. These findings prompt a reevaluation of strategies to achieve optimal long-term outcomes for these patients, including selection of optimal induction treatment to increase the possibility to proceed to stem cell transplantation.

AUTHOR CONTRIBUTIONS

JR, JL, HP, MR, ST, and KU-R contributed to the study design and objectives, interpretation of results and writing of the manuscript. In addition, ST performed the data analysis and JR performed manual chart review. All authors have reviewed and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We wish to thank Auria Clinical Informatics (www.auria.fi/tietopalvelu/en/index.html) of the Hospital District of Southwest Finland (called The wellbeing services county of Southwest Finland starting from January 1, 2023) for providing the data for this study. We also thank Kai Kysenius for the medical writing and Maija Itälä-Remes and Mika Kontro for valuable discussions and advice during the study.

CONFLICT OF INTEREST STATEMENT

JL, HP, and MR are employees of AbbVie and own AbbVie stock; ST and KU-R are employees of Medaffcon Oy; JR is a hematologist at Turku University Hospital and has received consultation fees or speaker honorarium from AbbVie, Janssen-Cilag, Astra-Zeneca and

travel grants from AbbVie, Janssen-Cilag. This study was funded by AbbVie. Medaffcon Oy received funds from AbbVie for conducting the study, analysis, and reporting of findings.

DATA AVAILABILITY STATEMENT

This study is based on secondary use of health care register data. Thus, data cannot be shared openly.

REFERENCES

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152. doi:10.1056/NEJMra1406184
2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood J Am Soc Hematol*. 2022;140(12):1345-1377. doi:10.1182/blood.2022016867
3. Thein MS, Ershler WB, Jemal A, Yates JW, Baer MR. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer*. 2013;119(15):2720-2727. doi:10.1002/cncr.28129
4. Kantarjian H, Kadia T, DiNardo C, et al. Acute myeloid leukemia: current progress and future directions. *Blood Cancer J*. 2021;11(2):41. doi:10.1038/s41408-021-00425-3
5. Quan H, Li B, Couris CM, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433
6. R Core Team (2022). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/
7. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. *Br J Haematol*. 2020;188(1):129-146. doi:10.1111/bjh.16355
8. Juliusson G, Antunovic P, Derolf Å, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. *Blood*. 2009;113(18):4179-4187. doi:10.1182/blood-2008-07-172007
9. Kwon C, Brandt P, Manson S, Fuentes-Alburo A, Forsythe A. Treatment patterns and health care resources use (HCRU) in patients with acute myeloid leukemia (AML): real world evidence (RWE) from 30 US institutions. *Blood*. 2017;130:5655. doi:10.1182/blood.V130.Suppl
10. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia*. 2013;27(5):997-999. doi:10.1038/leu.2012.303
11. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106(5):1090-1098. doi:10.1002/cncr.21723
12. Pardee TS, Oschwald J, Ma E, et al. Treatment patterns and outcomes of patients with newly diagnosed acute myeloid leukemia (AML) treated with hypomethylating agents (HMA) in the United States (US). *Blood*. 2020;136(1):14-16. doi:10.1182/blood-2020-134830
13. Miyamoto T, Sanford D, Tomuleasa C, et al. Real-world treatment patterns and clinical outcomes in patients with AML unfit for first-line intensive chemotherapy*. *Leuk Lymphoma*. 2022;63(4):928-938. doi:10.1080/10428194.2021.2002321
14. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299. doi:10.1182/blood-2015-01-621664
15. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30(21):2670-2677. doi:10.1200/JCO.2011.38.9429
16. Abuelgasim KA, Albuhayri B, Munshi R, et al. Impact of age and induction therapy on outcome of 180 adult patients with acute myeloid leukemia; retrospective analysis and literature review. *Leuk Res Rep*. 2020;14:100206. doi:10.1016/j.lrr.2020.100206
17. Kantarjian HM, Kadia TM, DiNardo CD, Welch MA, Ravandi F. Acute myeloid leukemia: treatment and research outlook for 2021 and the MD Anderson approach. *Cancer*. 2021;127(8):1186-1207. doi:10.1002/cncr.33477
18. Hernlund E, Redig J, Paulsson B, et al. Socioeconomic cost of AML in Sweden—a population-based study using multiple nation-wide registers. *eJHaem*. 2021;2(3):385-393. doi:10.1002/jha2.208

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ranti J, Pudas H, Ranta M, Tuominen S, Uusi-Rauva K, Lammela J. Treatment and clinical outcomes of patients with acute myeloid leukemia in Finland 2010–2020: A retrospective analysis of electronic health records. *Eur J Haematol*. 2024;1-11. doi:10.1111/ejh.14272