

Characteristics, Treatment Patterns, and Predictors of Outcomes in Treatment-Naive Acute Myeloid Leukemia Patients Judged Ineligible for Intensive Chemotherapy in Sweden

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INTRODUCTION

- ❖ Survival outcomes for adults diagnosed with acute myeloid leukemia (AML) have improved in recent years¹, with remission-inducing treatment such as intensive chemotherapy providing curative potential. However, relative toxicity means that older and medically-unfit patients are often judged ineligible for intensive treatment
- ❖ The standard of care for patients judged unfit for an intensive treatment approach include low-dose cytarabine (LDCA) or the hypomethylating agents (HMAs) azacitidine and decitabine, however outcomes for these patients remain poor (<5% two-year survival rate)²
- ❖ Emerging novel therapies for AML such as venetoclax have the potential to change the treatment landscape for patients judged ineligible for intensive treatment³
- ❖ Population-based, real-world data are important to understand treatment outcomes for this patient group with significant unmet medical need
- ❖ The current analysis describes recent frontline treatment patterns, overall survival (OS) and treatment response for patients in Sweden with AML ineligible for intensive chemotherapy

METHODS

Data sources

- ❖ Patients ≥18 years of age newly diagnosed with AML in Sweden between January 2012 to October 2019 (National cohort) or May 2020 (Regional subgroup) were identified in the National Cancer Registry and linked to relevant national population registries (i.e., the Cause of Death Registry, Prescribed Drug Registry, and Patient Registry) as well as the National Quality Registry for AML

Patients and study design

- ❖ Patients were included in the study if they were judged ineligible for intensive chemotherapy by the treating physician and received frontline HMA (azacitidine or decitabine), venetoclax or palliative treatment (including LDCA)
- ❖ Detailed information on treatment patterns and response was obtained through electronic medical records (EMRs) for a regional cohort of patients from the Stockholm and Skåne regions for subgroup analyses
- ❖ For OS, median and 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method
- ❖ Multivariable Cox regression was used to analyse hazard ratios, with age, year of diagnosis, sex, AML etiology, cytogenetic risk and treatment type as covariates. Time-varying effects for treatment, AML etiology and cytogenetic risk were included to account for non-constant hazard

- ❖ Healthcare resource utilization (HRU) was presented as proportion of time spent in healthcare calculated as the total number of days in care divided by the total contributed follow up time for the follow-up year
- ❖ Response was defined as complete remission (CR) including CR with incomplete hematological recovery (CRI) or primary induction failure (PIF)

RESULTS

Baseline Patient Characteristics

- ❖ A total of 1335 patients newly diagnosed with AML and judged ineligible for intensive chemotherapy were identified in the time period between January 2012 to October 2019 (**Table 1**)
- ❖ Median age at diagnosis remained stable over both calendar periods at 82 and 78 years for palliative (including LDCA) and HMA treatment, respectively
- ❖ The number of patients receiving frontline HMA treatment increased from 122 (19.3%) in 2012-2015 to 278 (39.6%) in 2016-2019
- ❖ In the later calendar period (2016-2019) over half of all patients still received only palliative treatment (n= 419; 59.7%)
- ❖ Patients who received palliative care had poorer performance status at baseline compared to patients treated with HMAs (WHO status 2-4; 57% vs 25%), and over a quarter of palliative treatment patients received no cytogenetic testing (n= 257; 27.6%)

Table 1. Baseline Characteristics for AML Patients Judged Ineligible for Intensive Chemotherapy Stratified by Frontline Treatment Type and Calendar Period of Diagnosis					
	2012-2015			2016-2019	
Characteristic	HMA N = 122	Palliative N = 511	Venetoclax N = 5	HMA N = 278	Palliative N = 419
Age at AML diagnosis					
Mean (SD)	75.5 (9.24)	80.4 (8.61)	63.0 (18.3)	76.6 (8.48)	80.0 (10.1)
Median (IQR)	78.0 (72.0-81.8)	82.0 (76.0-86.0)	71.0 (51.0-77.0)	78.0 (73.0-82.0)	82.0 (75.0-88.0)
Age at diagnosis, n (%)					
<60	7 (5.7%)	9 (1.8%)	2 (40.0%)	10 (3.6%)	16 (3.8%)
60-69	13 (10.7%)	43 (8.4%)	0 (0%)	31 (11.2%)	30 (7.2%)
70-79	59 (48.4%)	132 (25.8%)	3 (60.0%)	129 (46.4%)	127 (30.3%)
≥80	43 (35.2%)	327 (64.0%)	0 (0%)	108 (38.8%)	246 (58.7%)
Male, n (%)	66 (54.1%)	260 (50.9%)	3 (60.0%)	162 (58.3%)	210 (50.1%)
WHO status					
0 (Full daily activity)	20 (16.4%)	35 (6.8%)	0 (0%)	44 (15.8%)	32 (7.6%)
1 (Not bedridden)	72 (59.0%)	175 (34.2%)	4 (80.0%)	143 (51.4%)	108 (25.8%)
2 (Bedridden <50%)	21 (17.2%)	122 (23.9%)	0 (0%)	51 (18.3%)	105 (25.1%)
3 (Bedridden ≥50%)	3 (2.5%)	94 (18.4%)	1 (20.0%)	17 (6.1%)	94 (22.4%)
4 (Bedridden all the time)	2 (1.6%)	62 (12.1%)	0 (0%)	6 (2.2%)	55 (13.1%)
Missing	4 (3.3%)	23 (4.5%)	0 (0%)	17 (6.1%)	25 (6.0%)
Cytogenetic risk, n (%)					
Low	2 (1.6%)	14 (2.7%)	1 (20.0%)	12 (4.3%)	15 (3.6%)
Intermediate	72 (59.0%)	245 (47.9%)	1 (20.0%)	151 (54.3%)	208 (49.6%)
High	41 (33.6%)	115 (22.5%)	3 (60.0%)	95 (34.2%)	76 (18.1%)
Missing	7 (5.7%)	137 (26.8%)	0 (0%)	20 (7.2%)	120 (28.6%)
AML etiology, n (%)					
De novo	57 (46.7%)	300 (58.7%)	3 (60.0%)	139 (50.0%)	234 (55.8%)
Secondary: AHD-AML	53 (43.4%)	165 (32.3%)	2 (40.0%)	104 (37.4%)	140 (33.4%)
Secondary: t-AML	12 (9.8%)	46 (9.0%)	0 (0%)	35 (12.6%)	45 (10.7%)
Bone marrow blast cells (%)					
Mean (SD)	33.3 (16.0)	49.4 (23.7)	39.6 (20.9)	36.3 (18.0)	44.4 (23.9)
Median (IQR)	28.0 (23.3-40.0)	46.0 (29.5-70.0)	34.0 (28.0-36.0)	30.0 (23.0-47.3)	38.0 (25.0-60.0)
Missing	4 (3.3%)	80 (15.7%)	0 (0%)	10 (3.6%)	85 (20.3%)

AML, acute myeloid leukemia; HMA, hypomethylating agent; IQR, interquartile range; SD, standard deviation; WHO, World Health Organization; AHD, antecedent hematological disease; t, therapy-related

Survival

- ❖ Among all Swedish AML patients newly diagnosed 2012-2019 and judged ineligible for intensive chemotherapy, the median OS was 2.52 (95% CI 2.28-2.88) months
- ❖ Median survival for HMA treated patients was 8.40 (6.84-9.84) months compared to 1.32 (1.20-1.56) months for palliative treatment

- ❖ Median survival for low, medium and high cytogenetic risk groups was 4.68 (2.64-7.68), 3.12 (2.64-3.72) and 2.88 (2.4-3.6) months respectively
- ❖ In a time-varying multivariable model, first line treatment exposure to novel agents (HMA or venetoclax) compared to palliative (including other low intensive treatment) was associated with lower risk of death at 0-0.5 years, >0.5-1 years and > 1 years after AML diagnosis (**Figure 1**)

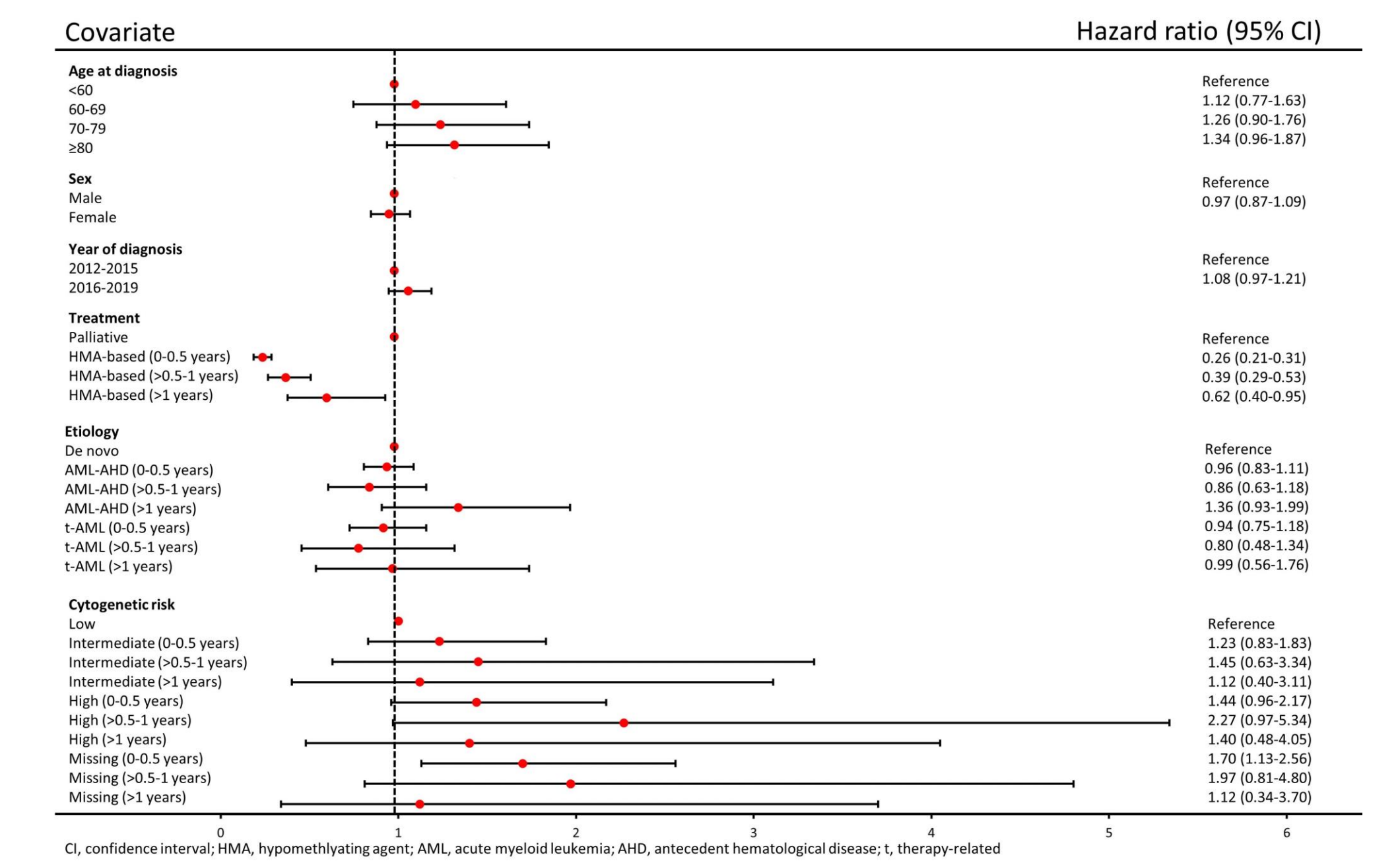


Figure 1. Multivariable analysis of hazard ratios for overall survival for AML patients judged ineligible for intensive chemotherapy.

Healthcare Resource Utilization

- ❖ Patients receiving HMA-based treatment spent less time in inpatient care, and more time in outpatient care (**Figure 2**).

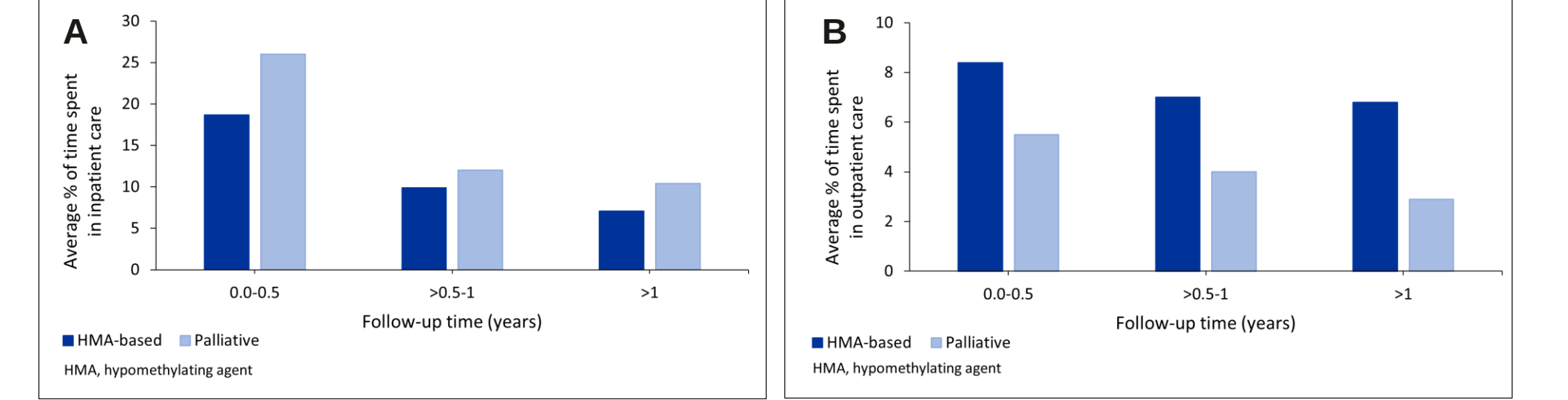


Figure 2. Average proportion of time spent in (A) inpatient and (B) outpatient care for AML patients judged ineligible for intensive chemotherapy.

Treatment Patterns and Response

- ❖ EMR investigation in the Stockholm and Skåne regions (n=138) indicated 98 patients received azacitidine (71%), 4 received decitabine (3%) and 18 received other HMA-based combinations (13%). 18 patients received LDCA (13%)
- ❖ Other HMA-based include azacitidine + venetoclax (n=2), azacitidine + LDCA (n=3), guadecitabine (n=3), azacitidine + venetoclax/placebo (n=3), azacitidine + tioguanine (n=2), azacitidine + hydroxyurea (n=2)

- ❖ Median time to start of HMA-based treatment from diagnosis was 14 days (IQR 6.0-21.0) compared to 8.5 days (IQR 3.0-44.0) for palliative care (**Table 2**)
- ❖ Of those patients receiving HMA-based therapy, 46.7% patients received <5 cycles
- ❖ CR rates were 20% for patients receiving HMA-based regimes compared to 0% for LDAC

Table 2. Treatment description and response for regional cohort		
	HMA-based	LDCA
Number of cycles in first line treatment	N = 120	N = 18
1-2 cycles	32 (26.7%)	18 (100%)
3-4 cycles	24 (20%)	0 (0%)
5 or more cycles	62 (51.7%)	0 (0%)
Missing	2 (2.5%)	0 (0%)
Days from diagnosis to treatment start		
Mean (SD)	15.7 (20.4)	27.8 (40.7)
Median (IQR)	14.0 (6.8-21.0)	8.50 (3.0-44.0)
Response		
CR	20 (16.7%)	0 (0%)
CR(i)	4 (3.3%)	0 (0%)
PIF	96 (80%)	18 (100%)
Number of cycles to reach response		
CR after ≤4 cycles	11 (9.2%)	0 (0%)
CR after ≥5 cycles	8 (6.7%)	0 (0%)
PIF	101 (84.2%)	18 (100%)

HMA, hypomethylating agent; LDCA, low dose cytarabine; SD, standard deviation; IQR, interquartile range; CR, complete remission; CRI, complete remission with incomplete hematologic recovery; PIF, primary induction failure

CONCLUSIONS

- ❖ Among patients judged ineligible for intensive chemotherapy, survival remained poor at less than a year despite improved outcomes associated with HMA-based treatments
- ❖ More than half of recent patients received palliative treatment (including LDAC) rather than HMA-based treatment
- ❖ An increasing number of patients received first line treatment with HMA over time however:
 - ❖ Most patients treated with HMA became refractory to HMA treatment, highlighting the need for optimized treatment strategies
 - ❖ Patients that received HMA often experienced longer time to treatment start and limited treatment cycles
- ❖ HMA-based treatment was associated with less time in inpatient care, which may suggest improved quality of life, but still a significant proportion of time spent in care
- ❖ Despite increased numbers of patients receiving novel treatments and subsequent improved survival, there remains a notable unmet need for novel treatments for patients with AML who are judged ineligible for intensive chemotherapy