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Clinical outcome of older adults with acute myeloid Leukemia: An analysis of a large tertiary referral Center over two decades

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ABSTRACT

Objective: In older adults with acute myeloid leukemia (AML), the overall outcome is still dismal and long-term data on survival are scarce, particularly outside of clinical trials. Here, we assess characteristics, prognostic factors and long-term survival in patients ≥60 years who were treated for AML at our center over the past 17 years.
Methods: 590 older adults with newly diagnosed AML were characterized according to Eastern Cooperative Oncology Group (ECOG) score, Charlson comorbidity index (CCI), European LeukemiaNet (ELN) risk, type of therapy, serum ferritin (SF) and further baseline characteristics. Survival analysis was performed accordingly.
Results: Median age was 68 years and most patients were in good general condition. Median follow-up was 55.8 months. Of all patients, 66% received intensive chemotherapy (IC) +/− allogeneic hematopoietic stem cell transplantation (allo-HSCT). The remaining cohort received palliative chemotherapy (PC, 26%) or best supportive care only (BSC, 8%). Enrollment rate for interventional clinical trials was 26%. 5-year overall survival (OS) and relapse-free survival (RFS) were 18% (median 12.5 months) and 11,5% (median 10.0 months). Long-term survival was independently influenced by ECOG score, ELN risk group, baseline SF, previous myocardial infarction, and choice of therapy, but not consistently by age or CCI. Considering therapeutic subgroups, the contribution of particular parameters in predicting OS was most compelling in IC patients, but less consistent with PC or BSC.
Conclusion: Our results provide thorough insights into prognostication within therapeutic subgroups and emphasize the need for more detailed prognostic algorithms and routine geriatric assessment in the treatment of older adults with AML.

1. Introduction

The incidence of AML is increasing with age. Median age at primary diagnosis of AML is 69 years [1]. In older adults with AML, the overall clinical outcome is particularly dismal due to a higher frequency of adverse patient- and disease-related factors as compared to younger patients. Furthermore, age itself is generally accepted as an adverse prognostic factor. This makes older patients one of the most vulnerable subgroups in treatment for AML [2–5]. Over the past decades, long-term-survival in patients with AML has improved in general and the characterization of more distinct genetic subgroups has led to several personalized therapies. However, achieving long-term survival remains particularly challenging in the subgroup of older adults [6,7]. Older patients with AML are often not eligible for interventional clinical trials or allo-HSCT and are an underrepresented patient cohort in large secondary or tertiary admission centers such as university hospitals [8]. Besides a few population-based analyses, data on long-term survival and patient- and disease related risk factors in older adults with AML outside of clinical trials are still scarce [2,9–11]. In addition to age, performance status, comorbidity burden, cytogenetic/molecular features and subtype of AML, further parameters such as geriatric assessment and early treatment response seem to be potential variables for a more accurate prediction of clinical outcome [12–19].

Unfortunately, an ideal diagnostic tool that enables determination of individual chances and risks of intensive versus non-intensive therapy and prediction of response to a particular targeted therapy is still elusive.

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The aim of this study was to provide a detailed analysis of clinical characteristics, prognostic factors and long-term survival in different therapeutic subgroups within a large cohort of older adults that had been treated for AML at our clinic over the past two decades. In the course of this analysis, particular focus was set on the influence of age and CCI on long-term survival, since their independent prognostic impact is an ongoing matter of debate [14,17–21]. Furthermore, the prognostic value of baseline SF that has previously been described by our group and others in younger patients with AML [15,22–24] was evaluated in this cohort of older adults treated for AML.

2. Patients and Methods

2.1. Patients

631 patients aged ≥60 years with newly diagnosed AML were treated at Charité University Medical Center Berlin, Campus Virchow-Clinic, within the past two decades (1st January 2000 through 31st December 2017). Diagnosis of AML was confirmed by cytologic, flow cytometric, histopathologic, cytogenetic, and molecular evaluation of bone marrow aspirates and/or biopsies. 41 patients were excluded for the following reasons: acute promyelocytic leukemia (n = 11), mixed phenotype acute leukemia/acute undifferentiated leukemia (n = 28), and incomplete data set (n = 2). Finally, 590 patients were eligible for the analysis. The study was performed in accordance with local ethical guidelines (institutional ethics committee approval: EA4/231/19) and the declaration of Helsinki.

Measurement of initial performance status was based on the ECOG performance score [25]. Comorbidity burden was specified using the CCI [26]. Remission status and molecular/cytogenetic risk groups were classified according to the 2010 ELN criteria, since many of the molecular data that are necessary for the 2017 ELN risk classification were not available for patients analyzed in the period 2000–2017 [27,28]. As previously suggested in younger patients [22,29,30], a cutoff value of 1000 μg/l was used for the assessment of the prognostic impact of SF. AML subtypes were defined according to the WHO classification of 2016: sAML was defined as AML with myelodysplasia-related changes with either previous myelodysplastic syndrome (MDS), myeloproliferative neoplasia (MPN) or MDS/MPN overlap syndrome [31]. Therapy-related AML (t-AML) was defined as AML following cytotoxic therapy. For the survival analysis, the entire cohort was subdivided according to ECOG score, CCI, ELN risk group, subtype of AML, treatment modality, age, and SF.

2.2. Statistical Analysis

Data collection and statistical analysis were performed using IBM SPSS Statistics®, Version 23 (IBM® 2015, Armonk, NY, USA). Kruskal-Wallis-H-test, Mann-Whitney-*U* test and chi-square test were applied for the analysis of baseline characteristics. In multiple comparisons, Kruskal-Wallis-H-test and chi-square test were followed by Bonferroni adjustment and post-hoc testing. Overall survival (OS), relapse-free survival (RFS) and event-free survival (EFS) were analyzed using the Kaplan-Meier method. To specify median follow-up, the reverse Kaplan-Meier method was applied [32]. A logrank-test followed by a stratified univariate Cox regression was used to determine significant survival factors. In multiple comparisons, logrank-test was followed by the Benjamini Hochberg Procedure [33]. In order to calculate a hazard ratio (HR), certain variables were transformed into categorical

Table 1
Baseline characteristics of 590 older patients treated for AML.

Characteristics	Entire cohort (n = 590)	Intensive CHT (n = 390)	Palliative CHT (n = 154)	BSC (n = 46)	p*
Gender, n [%]					0.150
Female	255 [43.2]	159 [40.8]	71 [46.1]	25 [54.3]	
Male	335 [56.8]	231 [59.2]	83 [53.9]	21 [45.7]	
Median age, y [IQR]	68 [63–74]	**66 [62–70]**	**74.5 [71–79]**	**71.0 [66–78]**	**<0.001**
- Age 60–65 y, n [%]	215 [36.4]	**193 [49.5]**	**13 [8.4]**	9 [19.6]	**<0.001**
- Age 66–70 y, n [%]	159 [26.9]	**123 [31.5]**	**23 [14.9]**	13 [28.3]	**<0.001**
- Age 71–75 y, n [%]	112 [19.0]	**55 [14.1]**	**49 [31.8]**	8 [17.4]	**<0.001**
- Age > 75 y, n [%]	104 [17.6]	**19 [4.9]**	**69 [44.8]**	**16 [34.8]**	**<0.001**
- Age > 80 y, n [%]	45 [7.6]	**5 [1.3]**	**33 [21.4]**	7 [15.2]	**<0.001**
Median ECOG score [IQR]	1 [0–1]	**1 [0–1]**	**1 [1–2]**	**2 [1–2.5]**	**<0.001**
Median CCI [IQR]	1 [0–2]	**0 [0–2]**	**2 [1–3]**	**2 [1–3]**	**<0.001**
Median blast count (BM), % [IQR]	70 [30−100]	60 [21–80]	60 [20−100]	60.0 [21.0–80.0]	0.190
Median WBC count, x 10^9/l [IQR]	9.1 [2.1–42.3]	6.4 [1.9–38.9]	13 [3.7–50.1]	7.9 [1.5–32.1]	0.058
Median hemoglobin, g/dl [IQR]	9.2 [8.1–10.3]	9.3 [8.2–10.6]	9.0 [8.1–9.9]	8.9 [8.1–10.5]	0.187
Median platelet count, x 10^9/l [IQR]	55.5 [32−103]	56 [34–105]	53.5 [32.3–102.8]	45.5 [17.3–93.5]	0.062
Median SF, μg/l [IQR]	974 [509.6–1797.0]	884 [538–1430]	1130.6 [448–1896]	1908 [781–6009]	0.126
Severe infection at initial diagnosis	98 [16.6]	68 [17.4]	20 [13.0]	10 [21.7]	0.381
Cytogenetic risk (ELN 2010), n [%]					0.127
- Favorable	49 [8.3]	41 [10.5]	7 [4.5]	1 [2.2]	
- Intermediate	269 [45.6]	198 [30.8]	58 [37.7]	13 [28.3]	
- Adverse	159 [26.9]	104 [26.7]	45 [29.2]	10 [21.7]	
- Unknown	114 [19.3]	47 [12.1]	16 [10.4]	22 [47.8]	
Type of AML, n [%]					**0.001**
- De-novo AML	281 [47.6]	**209 [53.6]**	**52 [33.8]**	20 [43.5]	**<0.001**
- Secondary AML	229 [38.8]	**136 [34.9]**	**77 [50.0]**	16 [34.8]	**0.003**
- Previous MDS	172 [75.1]	112 [82.4]	49 [63.6]	11 [68.8]	0.086
- Previous MPN	33 [14.4]	15 [11.0]	15 [19.5]	3 [18.7]	
- Previous MDS/MPN overlap	24 [10.5]	9 [6.6]	13 [16.9]	2 [12.5]	
- Therapy-related AML	72 [12.2]	43 [11.0]	21 [13.6]	8 [17.4]	0.180
- Unknown	8 [1.4]	2 [0.5]	4 [2.6]	2 [4.3]	0.134
Interventional clinical trial, n [%]	155 [26.3]	**140 [35.9]**	**15 [9.7]**	**0 [0]**	**< 0.001**

Note: *All groups were compared to each other and Bonferroni-adjustment was applied subsequently. Significant differences between groups and significance levels are highlighted in bold letters.
Abbreviations: number of observations (n), chemotherapy (CHT), best supportive care (BSC), interquartile range (IQR), Eastern cooperative oncology group score (ECOG), Charlson Comorbidity Index (CCI), bone marrow (BM), serum ferritin (SF), peripheral white blood cell count (WBC), hemoglobin (Hb), c-reactive protein (CRP), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), European LeukemiaNet (ELN), allogeneic hematologic stem cell transplantation (allo-HSCT).

dichotomous data. Subsequently, the independence of factors with a significant impact on OS was analyzed in a stepwise multivariate Cox proportional hazards model. A p-value of $p < 0.05$ was considered statistically significant in two-by-two analyses. In comparisons between three or more subgroups, this level of significance was divided by the respective number of conducted tests (Bonferroni correction).

Table 2
Overall Survival and baseline characteristics in 590 AML patients by type of therapy.

A	Entire cohort				Intensive CHT +/- allo-HSCT				Intensive CHT without allo-HSCT				Intensive CHT with allo-HSCT			
Variable	n	Median	95% CI	p	n	Median	95% CI	p	n	Median	95% CI	p	n	Median	95% CI	p
OS (m)	590	12.0	10.6–13.5	–	390	21.6	17.1–26.1	–	171*	11.1	8.5–13.7	–	216	32.7	25.3–40.2	–
RFS (m)	590	10.5	8.5–12.6	–	343	11.1	8.5–13.4	–	137	8.0	6.2–9.7	–	205	14.8	11.3–18.3	–
EFS (m)	590	8.3	7.1–9.6	–	390	11.9	10.4–13.5	–	171	7.6	6.0–9.2	–	216	15.9	12.9–18.8	–
Age (OS, m)				**<0.001**				0.051				0.616				0.834
60–65 years	215	10.6	8.3–13.0		193	12.3	8.6–15.9		58	8.0	5.4–10.7		134	32.4	24.9–40.5	
66–70 years	159	9.4	7.3–11.5		123	12.2	9.7–14.7		53	14.9	6.5–23.4		69	31.4	16.7–46.2	
71–75 years	112	7.6	5.5–9.6		55	11.7	9.7–13.8		41	13.5	8.9–18.1		13	35.8	11.3–60.4	
> 75 years	104	3.9	2.4–5.5		19	10.3	4.9–15.7		19	10.3	4.9–15.7		–	–	–	
> 80 years	45	2.8	1.4–4.2		5	5.3	2.0–8.5		5	5.3	2.0–8.5		–	–	–	
ECOG (OS, m)				**<0.001**				**<0.001**				**<0.001**				0.348
ECOG 0	191	11.2	8.8–13.6		157	12.4	9.3–15.6		67	13.5	7.9–19.1		89	40.6	14.8–66.4	
ECOG 1	237	7.0	5.7–8.4		162	10.3	7.9–12.8		82	9.1	6.7–11.5		79	30.5	21.2–40.0	
ECOG 2	73	1.8	1.2–3.4		14	6.1	2.3–10.0		7	6.0	0.0–15.1		6	10.0	0.0–36.5	
ECOG 3	19	1.3	1.0–1.5		2	1.3	–		1	1.3	–		1	17.1	–	
ECOG 4	4	0.4	0.0–1.2		1	0.1	–		1	0.1	–		–	–	–	
CCI (OS, m)				**<0.001**				0.102				**<0.001**				0.388
CCI 0–1	359	10.4	8.7–12.2		276	12.7	10.5–14.8		110	12.3	9.4–15.1		163	35.4	27.9–42.9	
CCI 2–3	187	6.7	5.5–7.9		97	9.3	7.4–11.2		54	9.0	6.2–11.8		43	20.2	10.7–29.7	
CCI 4–5	34	3.0	1.0–4.9		14	3.7	0.0–13.5		6	3.1	0.0–16.5		8	25.1	n. r - n. r.	
CCI 6–7	7	0.8	0.3–1.3		2	0.9	–		1	0.9	–		1	16.4	–	
CCI 8–10	2	0.8	–		–	–	–		–	–	–		–	–	–	
Subtype (OS, m)				**0.021**				0.620				0.440				0.062
De novo AML	281	14.2	9.5–18.9		209	11.3	9.2–13.4		91	13.2	9.2–17.1		115	39.4	27.2–51.5	
sAML	229	11.7	9.9–13.6		136	12.0	9.5–14.6		62	11.3	9.0–13.6		74	26.0	15.4–36.5	
tAML	72	8.9	5.6–12.2		43	10.6	6.4–14.8		17	8.4	6.4–10.4		26	15.0	9.3–20.6	
ELN risk (OS, m)				**<0.001**				**<0.001**				**<0.001**				**0.002**
Favorable	49	25.5	5.2–45.7		41	14.8	10.4–19.1		13	43.2	13.3–73.0		28	53.5	35.3–71.6	
Intermediate	268	18.2	12.5–23.9		198	14.9	10.7–19.2		90	14.5	10.3–18.8		106	36.5	27.4–45.6	
Adverse	159	8.9	10.9–15.9		104	7.6	4.9–10.2		41	5.3	2.8–7.8		63	16.4	8.8–24.0	

B	Palliative CHT +/- HMA				HMA 1st-line				Other palliative CHT				BSC only			
Variable	n	Median	95% CI	p	n	Median	95% CI	p	n	Median	95% CI	p	n	Median	95% CI	p
OS, m	154	3.9	2.4–5.3	–	58	11.7	7.0–16.4	–	96	2.5	1.8–3.2	–	46	1.3	0.4–2.2	–
RFS, m	3	4.5	0.8–8.3	–	3	4.5	0.8–8.3	–	–	–	–	–	–	–	–	–
EFS, m	154	3.9	2.4–5.3	–	58	11.2	6.7–15.6	–	96	2.5	1.8–3.2	–	46	1.3	0.4–2.2	–
Age (OS, m)				0.399				0.732				0.799				0.425
60–65 years	13	2.5	2.0–3.0		–	–	–		13	2.5	2.0–3.0		9	1.0	0.0–2.5	
66–70 years	23	3.0	0.0–6.0		6	5.6	0.0–37.9		17	1.8	0.9–2.8		13	1.3	0.0–2.7	
71–75 years	49	4.7	1.8–7.6		20	8.1	1.9–14.4		29	2.6	0.8–4.3		8	0.9	0.0–4.5	
> 75 years	69	4.0	2.1–5.9		32	11.8	3.7–19.9		37	2.8	1.1–4.4		16	1.6	0.4–2.2	
> 80 years	33	2.8	0.8–4.8		12	11.8	0–29.9		21	1.1	0.0–2.1		7	2.2	0.0–6.9	
ECOG (OS, m)				**<0.001**				**0.005**				**<0.001**				0.420
ECOG 0	30	8.1	6.1–10.2		14	11.4	1.9–21.0		16	5.0	2.9–7.0		3	3.3	0.0. - 8.0	
ECOG 1	57	5.4	4.2–6.7		21	17.8	7.5–28.0		36	3.9	1.2–6.7		18	1.6	0.0–3.6	
ECOG 2	46	1.6	1.0–2.1		12	2.0	1.2–2.9		34	1.3	0.6–2.1		13	1.3	0.0–2.6	
ECOG 3	8	3.5	0.0–7.1		1	15.7	–		7	3.5	0.0–9.4		9	0.6	0.0–1.8	
ECOG 4	1	0.9	–		1	0.9	–		–	–	–		2	0.4	–	
CCI (OS, m)				**<0.001**				0.814				**<0.001**				0.819
CCI 0–1	68	3.9	3.0–4.7		34	11.4	3.3–19.6		34	2.6	1.5–3.7		15	1.6	0.4–2.7	
CCI 2–3	66	5.4	2.2–8.6		20	17.6	1.9–33.3		46	2.8	1.6–4.0		23	1.0	0.8–1.8	
CCI 4–5	15	3.0	0.0–6.2		4	17.3	0.0–42.4		11	1.3	0.0–3.6		5	1.9	0.0–5.0	
CCI 6–7	3	0.6	0.0–1.3		–	–	–		3	0.6	0.0–1.3		2	0.03	–	
CCI 8–10	1	0.8	–		–	–	–		1	0.8	–		1	1.7	–	
Subtype (OS, m)				**0.004**				0.724				0.192				0.543
De novo AML	52	1.8	1.2–2.5		15	11.2	5.1–17.2		37	1.8	1.0–2.6		20	1.3	0.0–3.8	
sAML	76	5.6	3.5–7.7		37	12.6	2.4–22.8		39	3.1	1.5–4.7		16	1.2	0.6–1.8	
tAML	21	2.6	0.0–6.6		5	22.2	0.0–53.7		16	2.2	0.0–4.7		8	1.0	0.0–2.5	
ELN risk (OS, m)				**<0.001**				**<0.001**				**0.006**				0.089
Favorable	7	0.8	0.7–0.9		1	1.4	–		6	0.8	0.5–1.1		1	0.2	–	
Intermediate	57	6.7	3.7–9.6		24	20.6	7.5–33.6		33	3.9	1.9–6.0		13	3.3	1.5–5.1	
Adverse	45	5.1	2.1–8.1		18	6.6	2.4–22.8		27	2.6	0.0–6.4		10	1.2	0.7–1.6	

A: entire cohort and patients with intensive CHT, B: patients with palliative CHT (HMA and non-HMA) or BSC only.
Note: Significant differences between all categories of each subgroup are highlighted in bold letters.
Abbreviations: months (m), number of patients (n), confidence interval (CI), overall survival (OS), relapse-free survival (RFS), event-free survival (EFS), chemotherapy (CHT), best supportive care (BSC), Eastern Cooperative Oncology group Score (ECOG), Charlson Comorbidity Index (CCI), secondary/therapy-related AML (sAML/tAML), European LeukemiaNet (ELN), hypomethylating agents (HMA), allogeneic hematopoietic stem cell transplantation (allo-HSCT), not reached (n.r.)
* 3 Patients were lost to follow-up and therefore excluded from the subgroup-analyses.

3. Results

3.1. Entire Cohort – Baseline Characteristics, Therapy and Survival

590 patients aged ≥60 years were included in this analysis. Baseline characteristics and treatment modalities are shown in Table 1 and Supplementary Fig. 1. Median age at diagnosis was 68 years in the entire cohort (range: 60–90 years). Median follow-up was 55.8 months. 390 patients (66%) underwent IC with curative intent containing cytarabine and anthracycline (7 + 3 or high dose cytarabine and mitoxantrone (HAM)). Of these patients, 42.3% (n = 165) received a second induction cycle, 59% (n = 230) were treated with a high-dose Cytarabine-based (HD Ara-C 1 g/m^2) consolidation therapy and 55.3% (n = 216) underwent allo-HSCT.

Of all patients, 10% (n = 58/590) were treated with hypomethylating agents (HMA). The other patients received either PC with low-dose Ara-C (LDAC, n = 51), Hydroxyurea (n = 21), oral Etoposide, Thioguanine, Mercaptopurine (n = 24) or BSC (n = 46). Before January 2008, only 6% of the patients with PC had received LDAC (n = 2/31) and none of the patients had been treated with HMA. Since 2008, 40% of patients with PC were treated with LDAC (n = 49/123) and 47% received HMA (n = 58/123). Enrollment into interventional clinical trials (Supplementary Fig. 1) decreased significantly with age (60–65 years, 34%, 66–70 years: 23%, ≥70 years: 5%, ≥80 years: 0%, p < 0.001).

5-year OS and EFS were 18% and 11.5% in the entire cohort. 10-year OS and EFS were 9% and 7%, respectively. Considering the different therapeutic strategies (IC, PC, and BSC), the only modality associated with improved OS in the multivariate analysis was IC followed by allo-HSCT (Table 3). Since this is a retrospective study over a rather long period of time, no consistent algorithm can be described, that led to the allocation of patients to the different treatment modalities. However, a comparison of baseline characteristics within the entire cohort and the different therapeutic subgroups (Tables 1 and 2) suggests that – as expected – age, ECOG performance status, ELN risk group and CCI were major drivers for therapeutic decision. Furthermore, de novo AML was associated with IC, whereas PC was more commonly used in sAML (Table 1).

With regard to baseline characteristics potentially predicting OS, the following findings were made in the entire cohort: ELN risk group and ECOG performance status had an independent prognostic impact OS (Table 3). Additionally, elevated baseline SF values of ≥1000 μg/l and a history of myocardial infarction were independent negative predictors of OS (Table 3 and Supplementary Table 1). In contrast, age and comorbidity were not generally maintained as significant prognostic parameters in the multivariate analysis (Table 3, Fig. 2). However, CCI remained significant in patients receiving IC without allo-HSCT, in the entire PC cohort and the non-HMA PC subgroup (Fig. 2B, D, F).

3.2. ECOG Performance Status, Comorbidity, and Age: Impact on Clinical Outcome in Therapeutic Subgroups

In order to gain more insight into the prognostic role of baseline characteristics within the different subgroups with regard to type of therapy, the impact of baseline characteristics on OS was analyzed for each subgroup separately:

3.2.1. Intensive Therapy with or without Allogeneic HSCT

As expected, patients with intensive therapy and particularly those undergoing allo-HSCT were the youngest and fittest in our cohort (Table 1). Allo-HSCT was performed up to an age of 75 years. In 95% of cases, reduced intensity conditioning regimens were applied (n = 203/216). OS was significantly longer in patients who underwent allo-HSCT as compared to patients who did not (Supplementary Fig. 3B). A survival benefit for patients with allo-HSCT was obvious across different age groups (Supplementary Fig. 3G–H). In the multivariate analysis, this allo-HSCT-associated benefit was maintained in the entire cohort (Table 3) and for patients aged <70 years (p < 0.001, HR 0.2, not shown).

Amongst patients with de novo AML, IC was the most frequent treatment modality (Table 1). In all patients receiving IC, age > 80 years (HR 8.2, 95% CI 1.7–38.8), an intermediate or adverse ELN risk group (HR 3.4, 95% CI 1.1–11.4) and baseline SF > 1000 μg/l (HR 1.7, 95% CI 1.0–3.0) had an independent negative impact on OS (Fig. 2A).

In the non-transplant subgroup of intensively treated patients, ECOG, CCI and ELN risk group maintained their prognostic value in the multivariate analysis (Fig. 2B).

In the transplant group, an adverse ELN risk was the only parameter that maintained its independent negative prognostic impact on OS, whereas CCI and ECOG did not (Figs. 1E and 2C).

3.2.2. Palliative Chemotherapy

PC comprised therapy with HMA and other cytoreductive drugs (see above). In the entire PC group, median age was 74.5 years. These patients had a higher CCI and a more unfavorable ECOG score than patients treated with IC (Table 1, Supplementary Fig. 1B and C) Notably, 50% of PC patients had sAML (Table 1). Interestingly, a favorable ELN risk score was associated with a higher risk of death in the PC group (HR 3.3), whereas sAML was not (HR 0.6, Fig. 2D, Supplementary Fig. 4B).

Particularly in the non-HMA group, ECOG and CCI were independent risk factors which apparently shaped results in the entire PC group (Fig. 2D–F). Therapy with HMA was associated with a significantly better OS as compared with non-HMA chemotherapy. This was a consistent finding in patients <70 years and ≥ 70 years of age (Supplementary Fig. 4G). Comparing the periods of time before and after 2008 (5-Azacytidine was licensed by the EMA in 2008), there was a significant OS difference in favor of the period 2008–2017 (Supplementary Fig. 4H).

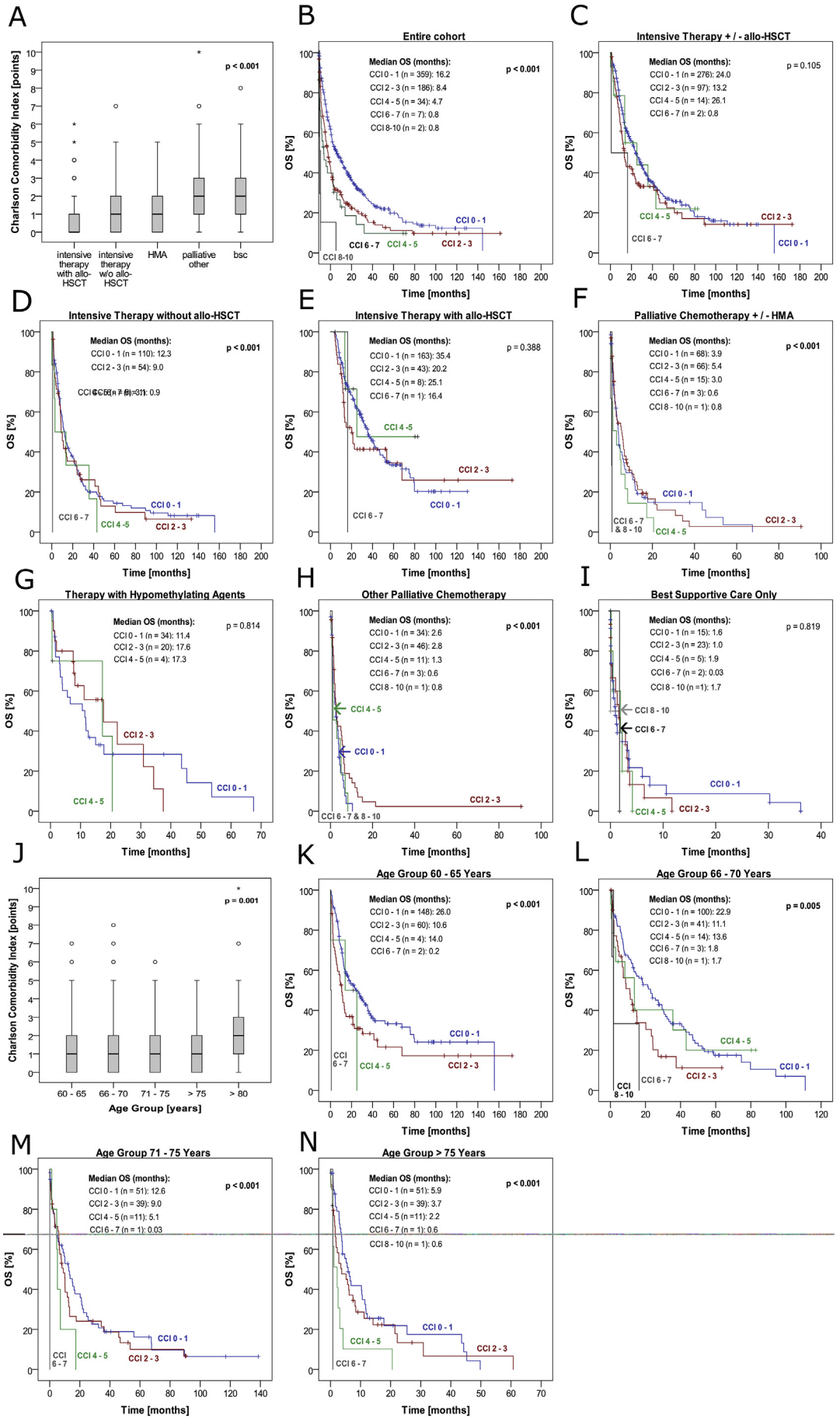
3.2.3. Best Supportive Care

Median age of patients with BSC was 71 years. Median OS was inferior to all other groups which was most likely driven by ECOG score and CCI (Tables 1 and 2B). Within this subgroup of patients, no significant prognostic factor could be identified (Table 2B, Fig. 2G).

Table 3
Univariate and multivariate cox regression of prognostic baseline characteristics for OS in 590 older patients with AML.

Variable	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Gender, male	0.99	0.82–1.20	0.919	–	–	–
Age ≥ 70 years	1.72	1.43–2.08	**<0.001**	1.08	0.65–1.79	0.760
ECOG score > 1	3.81	2.99–4.85	**<0.001**	3.69	1.86–7.30	**<0.001**
CCI ≥ 2	2.04	1.12–3.69	**0.019**	1.14	0.72–1.80	0.578
Subtype sAML/tAML	1.23	1.07–1.55	**0.009**	0.83	0.51–1.33	0.438
ELN risk group adverse	2.00	1.61–2.49	**<0.001**	2.37	1.47–3.81	**0.001**
Intensive therapy followed by allo - HSCT	0.26	0.21–0.32	**<0.001**	0.50	0.29–0.86	**0.012**
Severe infection at initial diagnosis	1.21	0.94–1.56	0.146	–	–	–
WBC < 1.0 × 10^9/l	1.33	0.91–1.94	0.141	–	–	–
WBC > 100 × 10^9/l	1.20	0.87–1.66	0.260	–	–	–
Platelet count <50 × 10^9/l	1.20	0.99–1.46	**0.070**	1.34	0.86–2.10	0.197
Hb ≤ 10 mg/dl	1.27	0.73–2.21	0.400	–	–	–
SF > 1000 μg/l	1.69	1.16–2.46	**0.006**	1.64	1.04–2.57	**0.033**

Abbreviations: overall survival (OS), hazard ratio (HR), confidence interval (CI), Eastern cooperative oncology group score (ECOG), Charlson Comorbidity Index (CCI), secondary AML (sAML), therapy related AML (tAML), European LeukemiaNet (ELN), allogeneic hematopoietic stem cell transplantation (allo-HSCT), peripheral white blood cell count (WBC), hemoglobin (Hb), serum ferritin (SF).
Significant differences between groups are marked in bold (p < 0.005).


A
Charlson Comorbidity Index [points]
p < 0.001
intensive therapy with allo-HSCT
intensive therapy w/o allo-HSCT
HMA
palliative other
bsc
B
Entire cohort
Median OS (months):
CCI 0 - 1 (n = 359): 16.2
CCI 2 - 3 (n = 186): 8.4
CCI 4 - 5 (n = 34): 4.7
CCI 6 - 7 (n = 7): 0.8
CCI 8-10 (n = 2): 0.8
p < 0.001
OS [%]
Time [months]
C
Intensive Therapy + / - allo-HSCT
Median OS (months):
CCI 0 - 1 (n = 276): 24.0
CCI 2 - 3 (n = 97): 13.2
CCI 4 - 5 (n = 14): 26.1
CCI 6 - 7 (n = 2): 0.8
p = 0.105
D
Intensive Therapy without allo-HSCT
Median OS (months):
CCI 0 - 1 (n = 110): 12.3
CCI 2 - 3 (n = 54): 9.0
p < 0.001
E
Intensive Therapy with allo-HSCT
Median OS (months):
CCI 0 - 1 (n = 163): 35.4
CCI 2 - 3 (n = 43): 20.2
CCI 4 - 5 (n = 8): 25.1
CCI 6 - 7 (n = 1): 16.4
p = 0.388
F
Palliative Chemotherapy + / - HMA
Median OS (months):
CCI 0 - 1 (n = 68): 3.9
CCI 2 - 3 (n = 66): 5.4
CCI 4 - 5 (n = 15): 3.0
CCI 6 - 7 (n = 3): 0.6
CCI 8 - 10 (n = 1): 0.8
p < 0.001
G
Therapy with Hypomethylating Agents
Median OS (months):
CCI 0 - 1 (n = 34): 11.4
CCI 2 - 3 (n = 20): 17.6
CCI 4 - 5 (n = 4): 17.3
p = 0.814
H
Other Palliative Chemotherapy
Median OS (months):
CCI 0 - 1 (n = 34): 2.6
CCI 2 - 3 (n = 46): 2.8
CCI 4 - 5 (n = 11): 1.3
CCI 6 - 7 (n = 3): 0.6
CCI 8 - 10 (n = 1): 0.8
p < 0.001
I
Best Supportive Care Only
Median OS (months):
CCI 0 - 1 (n = 15): 1.6
CCI 2 - 3 (n = 23): 1.0
CCI 4 - 5 (n = 5): 1.9
CCI 6 - 7 (n = 2): 0.03
CCI 8 - 10 (n =1): 1.7
p = 0.819
J
Charlson Comorbidity Index [points]
p = 0.001
60 - 65
66 - 70
71 - 75
> 75
> 80
Age Group [years]
K
Age Group 60 - 65 Years
Median OS (months):
CCI 0 - 1 (n = 148): 26.0
CCI 2 - 3 (n = 60): 10.6
CCI 4 - 5 (n = 4): 14.0
CCI 6 - 7 (n = 2): 0.2
p < 0.001
L
Age Group 66 - 70 Years
Median OS (months):
CCI 0 - 1 (n = 100): 22.9
CCI 2 - 3 (n = 41): 11.1
CCI 4 - 5 (n = 14): 13.6
CCI 6 - 7 (n = 3): 1.8
CCI 8 - 10 (n = 1): 1.7
p = 0.005
M
Age Group 71 - 75 Years
Median OS (months):
CCI 0 - 1 (n = 51): 12.6
CCI 2 - 3 (n = 39): 9.0
CCI 4 - 5 (n =11): 5.1
CCI 6 - 7 (n = 1): 0.03
p < 0.001
N
Age Group > 75 Years
Median OS (months):
CCI 0 - 1 (n = 51): 5.9
CCI 2 - 3 (n = 39): 3.7
CCI 4 - 5 (n =11): 2.2
CCI 6 - 7 (n = 1): 0.6
CCI 8 - 10 (n = 1): 0.6
p < 0.001
Time [months]

3.3. Secondary AML and Therapy-Related AML

Distribution of AML subtypes is shown in Supplementary Fig. 1E. As expected, patients with sAML/tAML showed an accumulation of adverse cytogenetic characteristics as compared to patients with de novo AML. Median age with sAML or tAML was 68 years. Of note, 43% of patients with sAML or tAML (n = 129/301) showed at least one adverse cytogenetic or molecular feature (complex karyotype, monosomal karyotype, t(6;9), MLL/11q23, inv3/t(3,3), del (5q)/−5, del (7q)/−7, TP53-mutation or FLT3-ITD/NPM1 wildtype), whereas these adverse prognostic features were only present in 29% (n = 82/281) of patients with de novo AML (p = 0.001).

Patients with sAML were less frequently treated with intensive therapy than patients with de novo AML (59% vs. 74%, p = 0.003). Instead, HMA therapy was applied more frequently in patients with sAML (65%, Table 3).

OS with sAML/tAML was significantly worse than with de novo AML (HR 1.23). This can most likely be explained by an accumulation of adverse cytogenetic features in patients with sAML/tAML. However, in the multivariate analysis, this difference was neither maintained in the entire cohort (Table 3) nor within subgroups (Fig. 2). Interestingly, sAML seemed to fare better in the entire PC subgroup as compared to de novo AML (Fig. 2D). This was apparently caused by the fact that patients with de novo AML treated with PC were in a particular unfavorable general health condition at baseline (de novo AML: ECOG/CCI = 2/2 vs. sAML/t-AML: ECOG/CCI = 1/1, p = 0.022/0.039).

3.4. Baseline Serum Ferritin: An Additional Risk Factor

Median SF was elevated above the normal range in the entire cohort (974 μg/l, normal range: 200–300 μg/l) with the highest values in patients receiving PC and BSC (Table 1). Of all patients, 12.5% (n = 74/590) had elevated baseline SF levels >1000 μg/l. Neither treatment modalities (p = 0.3) nor AML subtypes (p = 0.3) differed significantly between patients with high and low SF levels at baseline. Clinical outcome with highly elevated baseline SF was particularly dismal as compared to lower SF levels (OS 6.8 months vs. 12.8 months, p < 0.001). As previously reported in younger patients [15,22], highly elevated baseline SF was confirmed to be an adverse prognostic factor in this cohort of older adults with AML (Table 3). This was maintained in the multivariate subgroup analyses particularly for patients aged 71–74 years (p = 0.001, HR 5.7, not shown) and for the entire subgroup of intensively treated patients (HR 1.7, p = 0.05, Fig. 2A). The negative prognostic impact of baseline SF was independent from other (inflammation-associated) factors such as severe infections (Table 3).

3.5. Referrals of Older AML Patients and Changes in Therapeutic Strategies over Time

In order to analyze changes in referrals and therapeutic strategies over time, our cohort was divided according to three periods: 1) 2000–2005, 2) 2005–2010 and 3) 2010–2017 (Supplementary Fig. 2). There was a significant increase of referrals of older patients treated for AML over time with concurrent improvement of OS. Interestingly, between 2000 and 2017, the percentage of patients who were finally treated with PC rose from 18% to 27%, whereas the percentage with BSC only dropped from 14% to 4%, reflecting changes in the landscape of AML therapy over time, in particular after introduction of HMA in routine AML management. The percentage of intensively treated patients remained stable throughout the whole period of time (Supplementary Fig. 2).

4. Discussion

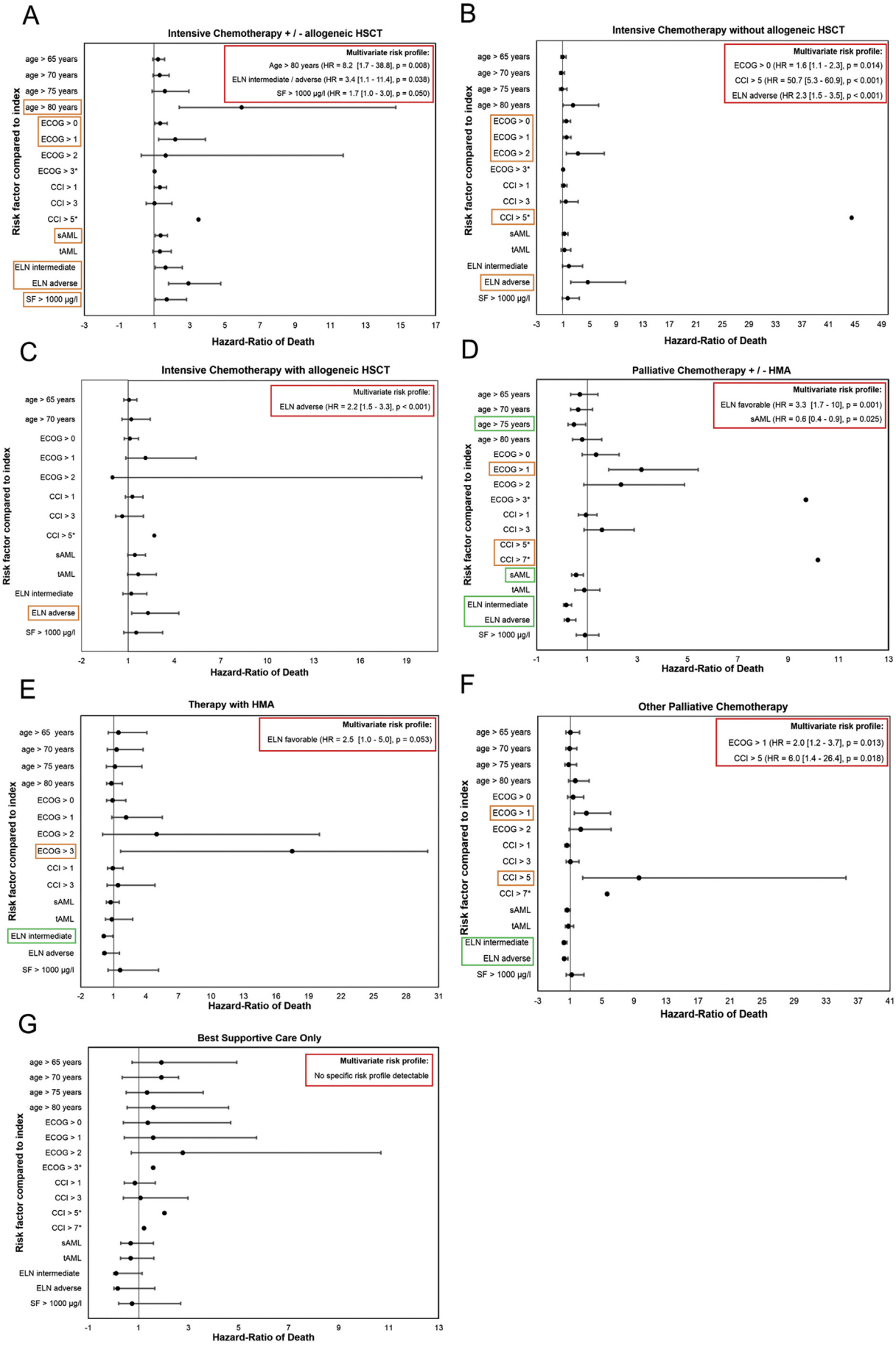
This single-center retrospective study provides long-term survival data in a large cohort of older adults with AML aged from 60 to 90 years with a median follow-up of 55.8 months. The patient cohort reported on – in particular patients who have not been treated within clinical trials – represents a subgroup in which data on long-term outcome are scarce. Our study gives detailed insights into clinical characteristics and prognostic parameters of older patients with AML within major therapeutic subgroups including treatment with intensive chemotherapy (with or without allo-HSCT), palliative chemotherapy (with or without HMA) and best supportive care only. We analyzed widely established risk factors such as ECOG score and ELN risk classification [2,4,16,20,28,34] across these subgroups, with an additional focus on chronological age and comorbidity, since their independent prognostic impact is less consistent in the literature [13,14,17–21,35]. Moreover, our study shows that baseline SF and a history of myocardial infarction are also useful as prognostic parameters in older adults treated for AML.

Long-term survival was only observed in intensively treated patients. 5-year OS with IC followed by allo-HSCT was 24% and is consistent with the results from other studies (14% - 27%) [2,10,36–41]. IC followed by allo-HSCT was confirmed as an independent predictor for long-term survival and was frequently used in the entire cohort (29%). The latter is most likely caused by a selection bias (towards a better general health condition) that is seen in large academic medical centers, leading to underrepresentation of frail patients [8]. Our trial enrollment rate (26%) was comparable with data from current literature [2,3,10,36].

Overall, our study confirms widely established patient- and AML-related prognostic variables such as ELN risk group, ECOG performance status and CCI [2,4,13,16,20,28,42]. However, their contribution in predicting clinical outcome within the different therapeutic subgroups is very heterogeneous. In our cohort, decisions against intensive chemotherapy (in favor of palliative chemotherapy) were mainly driven by age and comorbidity burden. In contrast, the main selection criterion for BSC (instead of PC) seemed to be ECOG score (Table 1). Furthermore, patients with sAML were more likely to receive HMA.

Interestingly, the impact of age was neither prognostic in the multivariate analysis of the entire cohort nor within particular subgroups, except for patients >80 years undergoing allo-HSCT (Table 3, Fig. 2). In the literature, age is generally accepted as a powerful risk factor in AML [4,16,28,43]. However, the strong prognostic impact of age is particularly apparent in studies that compare patients who are younger than 60 years with older patients treated for AML [4,43]. In contrast, the role of age as an independent risk factor amongst older patients with AML (> 60–65 years) is less clear-cut owing to many other aspects such as performance status, comorbidity and genetic alterations in the leukemia cells that modulate both tolerance of therapy and the susceptibility of leukemia cells to chemotherapy [28,42,44,45]. Thus, the adverse prognostic impact of age may be substantially modified by other patient- or leukemia-specific factors. In fact, in some studies that describe age as an independent risk factor, the genetic ELN risk stratification was not included into the analysis [3]. In other studies (within

Fig. 1. Comorbidity in 590 older patients with AML (univariate analysis). A–I: Association between CCI and OS with regard to type of therapy: Patients receiving palliative chemotherapy or best supportive care only showed higher CCI scores than patients who were eligible for intensive therapy (A). There was an inverse association between CCI and OS in the entire cohort (B) and within the non-transplant group receiving intensive chemotherapy (D). The influence of CCI on OS was not statistically significant within the entire subgroup of patients receiving intensive therapy with or without allo-HSCT (C) and within the subgroup receiving allo-HSCT (E). Amongst patients receiving palliative chemotherapy, CCI had a significant impact on OS (F). This latter effect was mainly driven by patients who were treated with non-HMA chemotherapy (H), whereas the influence of CCI was not significant in the HMA subgroup (G). In patients receiving BSC only, CCI did not impact OS (I). J–N: CCI and OS with respect to age: Median CCI was comparable in all age groups except for patients >80 years who had the highest CCI score (J). In the univariate analysis, CCI had a significant impact on OS across all age groups (K–N). Note: °outlyers, *extreme outlyers, significant p-values are highlighted in bold. Abbreviations: Charlson-Comorbidity Index (CCI), overall survival (OS), number of patients (n), hematopoietic stem cell-transplantation (HSCT), hypomethylating agents (HMA).


A
Intensive Chemotherapy + / - allogeneic HSCT
Multivariate risk profile:
Age > 80 years (HR = 8.2 [1.7 - 38.8], p = 0.008)
ELN intermediate / adverse (HR = 3.4 [1.1 - 11.4], p = 0.038)
SF > 1000 µg/l (HR = 1.7 [1.0 - 3.0], p = 0.050)
Risk factor compared to index
age > 65 years
age > 70 years
age > 75 years
age > 80 years
ECOG > 0
ECOG > 1
ECOG > 2
ECOG > 3*
CCI > 1
CCI > 3
CCI > 5*
sAML
tAML
ELN intermediate
ELN adverse
SF > 1000 µg/l
Hazard-Ratio of Death
B
Intensive Chemotherapy without allogeneic HSCT
Multivariate risk profile:
ECOG > 0 (HR = 1.6 [1.1 - 2.3], p = 0.014)
CCI > 5 (HR = 50.7 [5.3 - 60.9], p < 0.001)
ELN adverse (HR 2.3 [1.5 - 3.5], p < 0.001)
Hazard-Ratio of Death
C
Intensive Chemotherapy with allogeneic HSCT
Multivariate risk profile:
ELN adverse (HR = 2.2 [1.5 - 3.3], p < 0.001)
Hazard-Ratio of Death
D
Palliative Chemotherapy + / - HMA
Multivariate risk profile:
ELN favorable (HR = 3.3 [1.7 - 10], p = 0.001)
sAML (HR = 0.6 [0.4 - 0.9], p = 0.025)
Hazard-Ratio of Death
E
Therapy with HMA
Multivariate risk profile:
ELN favorable (HR = 2.5 [1.0 - 5.0], p = 0.053)
Hazard-Ratio of Death
F
Other Palliative Chemotherapy
Multivariate risk profile:
ECOG > 1 (HR = 2.0 [1.2 - 3.7], p = 0.013)
CCI > 5 (HR = 6.0 [1.4 - 26.4], p = 0.018)
Hazard-Ratio of Death
G
Best Supportive Care Only
Multivariate risk profile:
No specific risk profile detectable
Hazard-Ratio of Death

the subgroup of older patients with AML > 60 years), age also lost its multivariate significance [46,47] or only maintained statistically significant in very old patients, respectively [48]. Regarding our own data in the context of the literature, we assume that the relative weight of age for prognostication can easily be overridden by other factors, thus explaining a certain degree of heterogeneity in retrospective studies.

Likewise, our study suggests that CCI as a prognostic factor should be used with caution, since analyses in therapeutic subgroups did not show a consistent independent impact of CCI, except for patients receiving IC without allo-HSCT and non-HMA PC (Fig. 2). In general, CCI records less comorbidities than other scores and functional abilities may substantially modulate comorbidity [49,50]. Despite these disadvantages, CCI belongs to the most commonly used indices for comorbidity in the literature. However, the independent prognostic value of comorbidity is controversial, since there are studies which do not show an independent correlation between CCI and outcome [14,20,21,35]. This discrepancy may be explained by several factors: an association between CCI and age, a transient nature of leukemia-associated comorbidities measured at baseline (due to improvement under treatment) and a strong association between CCI and type of therapy being administered.

In contrast to age and CCI, ELN risk group and ECOG status had a more consistent prognostic impact in our study. ELN risk was strongly prognostic in the entire cohort and particularly within the intensively treated subgroup (Table 3, Fig. 2A–C), which is in line with the present literature [16,28,42,44]. ECOG also had an independent prognostic impact in the entire cohort and within particular subgroups (Table 3, Fig. 2). However, this was lost in patients undergoing HSCT, since this subgroup is usually highly selected towards a more favorable general health condition. Moreover, the therapeutic modality of HSCT has an independent influence on OS itself. In the PC group receiving HMA, the loss of multivariate significance of ECOG is most likely caused by sample size (Fig. 2E). In previous studies, ECOG score has been a strong predictor for OS irrespective of age [4,20]. However, assessing performance status is afflicted with a high degree of subjectivity and is not equivalent to the functional status that reflects “biological age” or the level of autonomy achieved by individuals in daily life [20]. In fact, further age-related components such as functional capacities or cognitive impairment might have influenced OS in our cohort [49,51,52]. Activities of daily living [50,53], short physical performance battery (measuring physical function) [54], or Mini-Mental State Exam (assessing cognitive function) [55,56] are only a few examples of diagnostic tools that have been validated to quantify the functional status. Therefore, a routine comprehensive geriatric assessment at baseline would be helpful as an additional component of initial treatment decision and might substantially improve prognostication [49,51,52].

Besides well-established risk factors, the independent negative prognostic impact of high SF at baseline, that has recently been described in intensively treated patients with AML by our group and others [15,22–24] was confirmed in this study. Thus, we propose an implementation of baseline SF into the assessment of older patients with AML, particularly in the context of intensive therapy (Table 3, Fig. 2A). Furthermore, a history of myocardial infarction was found to be a factor of prognostic relevance in our cohort (Supplementary Table 1) and it is yet to be determined to what extent this finding might be linked to inflammation-related clonal hematopoiesis [57].

Since our study extents over a period of nearly two decades, we were able to provide an analysis of clinical outcome within different time periods. In the subgroup of patients receiving PC, the increase of survival rates over time (2000–2007 vs. 2008–2017, Supplementary Figs. 2 and 4H) is an interesting observation that is likely caused by the improvement of supportive care in AML therapy (e.g. introduction of modern systemic antimycotics) [2,58,59], but also by the use of HMA in Europe since 2008 [60–62]. Correspondingly, an OS benefit with HMA was found in patients <70 and >70 years of age as compared to non-HMA chemotherapy (Supplementary Fig. 3G). Obviously, the advent of HMA therapy was accompanied by an increase of referrals of older patients with AML who were not eligible for intensive chemotherapy. This finding is also reflected by an increase of median age over time (Supplementary Fig. 2). The improvement of OS (as compared to non-HMA chemotherapy) is in line with the literature [60,63]. In a prospective randomized trial (AZA001) that compared 5-Azacytidine to conventional intensive and non-intensive chemotherapy regimens in older patients with AML, 5-Azacytidine was superior to conventional chemotherapy, particularly in the subgroup of patients with adverse genetic features according to ELN [63,64]. In line with these results, we observed a lower risk of death for sAML in the entire PC subgroup (Fig. 2D). However, this advantage of patients with sAML and intermediate/adverse ELN risk observed in the PC subgroup (Fig. 2D–F) can also be explained by a particular unfavorable health condition of patients with de novo AML and favorable ELN risk, who were treated with PC and not with IC instead. In our cohort, the latter aspect is supported by higher ECOG and CCI scores in patients with de novo AML as compared to patients with sAML or tAML. This example shows that standard risk factors must be interpreted with caution in the context of a palliative treatment strategy.

The major limitation of our study is caused by its retrospective nature. Although our analysis was performed in a comparatively large cohort of patients, some subgroups tend to be rather small, particularly in the setting of palliative treatment. Obviously, this restrains statistical power which is reflected by the broad width of confidence intervals in these subgroups. Furthermore, a selection bias towards younger age, lower ECOG performance status and lower CCI scores that is observed in large academic referral centers might have improved long-term outcome in our cohort.

The heterogeneity of health conditions at baseline and the increasing number of therapeutic options emphasize the need for a more accurate prediction of long-term survival in older adults with AML [14,49,50]. A few, partly web-based algorithms have already been proposed [65]. Our current study shows that ECOG performance status, cytogenetic/molecular risk, SF and (to a lesser extent) comorbidity burden are more reliable in informing therapeutic decisions for or against intensive therapy than chronological age. However, in PC and BSC, these established parameters for prognostication are less consistent.

For the future, an algorithm for therapeutic decision making that is based on large data sets, including clinical and molecular parameters, geriatric assessment and new targeted approaches such as FLT3-, IDH1/IDH2- and BCL2-inhibitors will probably help to improve long-

Fig. 2. Detailed risk factor profiles within subgroups of older patients treated for AML according to type of therapy (both univariate and multivariate analysis). Forest-Plots were grouped by type of treatment. Univariate cox regression was performed for each parameter. Index parameters were age < 65 years, ECOG 0, CCI 0, de novo AML and favorable ELN risk. Unfavorable variables that were significant in the univariate analysis are highlighted in orange boxes. Favorable variables are highlighted in green boxes. Parameters with multivariate significance are indicated in red boxes at the top right corner of each figure, together with 95% confidence intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) A–C: In patients receiving intensive therapy (n = 390), ELN-risk was the most consistent driver of a dismal prognosis (A–C). Elevated baseline SF was an adverse prognostic parameter in the entire cohort of intensively treated patients (A). Within the subgroups IC without allo-HSCT and IC with allo-HSCT, a tendency towards inferior OS was observed in patients with elevated SF, however, this difference in the subgroups did not reach the level of statistical significance (B, C). D–F: In patients receiving palliative chemotherapy (n = 154), established prognostic factors were less consistent. G: In patients receiving BSC only (n = 46), no significant independent risk factors were found. Note: * 95% CI could not be provided here due to sample sizes (n = 1–2). Abbreviations: Hazard Ratio (HR), Eastern Cooperative Oncology Group (ECOG), Charlson-Comorbidity Index (CCI), European Leukemia Net (ELN), secondary AML (sAML), therapy-related AML (tAML), serum ferritin (SF), hematopoietic stem cell transplantation (HSCT), hypomethylating agents (HMA).

term survival and unfold the potential of less toxic therapies in older patients treated for AML [66–68].

Contributions

Conceptualization: Ihlow J, Westermann J. Patient recruitment: Westermann J, Bullinger L, Flörcken A, Schwarz, M, Neuendorff NR, Singh A, Blau IW. Diagnostics (cytology, pathology, flow cytometry, cytogenetics, molecular genetics): Anagnostopoulos I, Turkmen S, Burmeister T, Westermann J. Data curation: Ihlow J, Gross S, Herneth A, Busack L. Statistical analysis: Ihlow J, Westermann J. Supervision: Westermann J, Bullinger L. Writing: Ihlow J, Westermann J, Neuendorff NR. Critical revision: all authors.

Declaration of Competing Interest

The authors declare that there is no conflict of interest with respect to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2020.11.001.

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