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Real-World Outcomes of FLAG-Ida Regimen in 1079 Adult Patients With First Relapsed/Refractory AML: A PETHEMA Study

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ABSTRACT

In a large multicenter real-world cohort, we aimed to evaluate outcomes of FLAG-Ida salvage therapy for relapsed/refractory (R/R) acute myeloid leukemia (AML) and validated the SALFLAGE prognostic score. We analyzed 1079 adults with R/R AML treated across 112 PETHEMA institutions over 26 years (1998–2024), including patients with primary refractory disease (36.9%) and first relapse episode (63.1%), with a median age of 52 years. Complete remission composite (CRc) was achieved 56.8%, including complete remission (CR) in 51.0%, CR with incomplete recovery in 4.0%, and morphological-free-state in 1.8%, enabling 35.2% of patients and 62% of responders to proceed to allogeneic transplantation without morphological disease. With median follow-up of 50.9 months, median overall survival (OS) was 10.2 months, with 5-year OS rate of 21.6%. Prior allogeneic transplantation (HR 0.54; $p < 0.001$) and relapse-free interval ≥ 1 year (HR 0.75; $p = 0.024$) independently predicted improved OS, whereas modified high-risk cytogenetics including *t*(8; 21) (HR 3.58; $p < 0.001$), *FLT3*-ITD mutation at primary diagnosis (HR 1.61; $p < 0.001$), and age ≥ 60 (HR 1.43; $p < 0.001$) conferred inferior OS. Validation of the SALFLAGE score demonstrated moderate discrimination (C-index 0.67), with 5-year survival of 38.4%, 27.2%, and 12.7% across risk categories ($p < 0.001$). Outcomes improved over periods (1998–2005 vs. 2006–2016 vs. 2017–2024): 30-day mortality was 6.9% vs. 9.3% vs. 5.0%, respectively ($p = 0.030$), and median OS was 7.8 versus 9.4 versus 11.1 months, respectively ($p = 0.16$). We confirm FLAG-Ida as a reference salvage regimen in fit R/R AML and validate the SALFLAGE score in this setting.

For affiliations refer to page 1703.

1 | Introduction

Relapse and primary refractoriness remain the leading causes of treatment failure in acute myeloid leukemia (AML) patients. Although 60%–80% of adults achieve complete remission (CR) after intensive induction schedules, approximately 20% show refractory disease, and more than 50% of responders will eventually relapse [1, 2]. Outcomes after relapse remain poor, and no standard salvage regimen has been established [3].

For younger and fit patients, the goal of salvage therapy is to achieve a second remission and proceed to allogeneic hematopoietic cell transplantation (allo-HCT), the most potentially curative option [3]. Intensive chemotherapy remains the backbone of treatment in this setting. Among available regimens, the combination of fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) is one of the most widely used [4], with reported CR and CR with incomplete recovery (CRi) rates of 40%–60% and providing an effective bridge to transplantation [4–12]. However, these studies were developed in relatively small series without long-term follow-up [4]. Although novel agents (venetoclax, *Menin-1*, *FLT3*, and *IDH* inhibitors) have recently emerged, their role in the relapsed/refractory setting remains under investigation [3, 13, 14]. Large real-world series could settle the efficacy of FLAG-Ida salvage regimen in first relapse/refractory episode, establishing its usefulness compared with newer promising strategies in this setting.

In 2016, the Programa Español de Tratamientos en Hematologia (PETHEMA) group proposed the SALFLAGE score to predict OS after FLAG-Ida for first relapsed/refractory AML in adult patients [12]. This scoring system stratified patients into three risk categories using five widely available favorable prognostic factors (prior allogeneic transplantation, relapse-free interval ≥ 1 year, low/intermediate modified cytogenetic risk, *FLT3*-ITD wild type, and age < 60 years old). Validating this predictive tool could help to identify patients who may benefit from FLAG-Ida versus those who may benefit from alternative approaches.

We conducted a large real-world retrospective analysis of adults with relapsed or refractory (R/R) AML treated with FLAG-Ida, encompassing 1079 patients from 112 institutions over 26 years. Our objectives were to: (1) characterize response and survival outcomes in a contemporary real-world cohort; (2) identify prognostic factors for response and survival; (3) evaluate temporal trends in outcomes and transplant utilization; and (4) validate the SALFLAGE prognostic model.

2 | Patients and Methods

2.1 | Patients and Study Design

This was a retrospective, multicentre analysis including all consecutive adult patients with de novo or secondary non-M3 AML registered in the multinational PETHEMA AML epidemiological registry (NCT02006004), who received FLAG-Ida as salvage therapy for primary refractory disease or first relapse after one or two courses of intensive induction chemotherapy. Refractory AML was defined as the persistence of $\geq 5\%$ bone marrow blasts or extramedullary disease after one or two identical intensive chemotherapy induction cycles. Patients who received alternative second-line regimens were excluded from this study.

The analysis encompassed institutions of Spain, Portugal, Chile, and Colombia, covering patients treated between 1998 and 2024. Clinical, cytogenetic, and molecular data, as per local practice, were prospectively recorded and retrospectively analyzed for this study.

The study was conducted in accordance with the Declaration of Helsinki. The protocols of the participating registries were approved by the respective institutional review boards or ethics committees of the participating centers, and written informed consent for data collection and anonymized research use was obtained as per local regulations.

2.2 | Cytogenetic and Molecular Analysis

Conventional cytogenetics was performed using standard G-banding techniques at diagnosis. Cytogenetic risk was classified according to the UK Medical Research Council (MRC) 2010 criteria [15], modified by assigning AML with *t*(8; 21) to the high-risk category in the relapsed/refractory setting [16]. The ELN 2022 risk stratification was not applied due to incomplete molecular data in earlier cohorts.

Molecular profiling evolved over the study period, reflecting changes in standard-of-care diagnostics. *FLT3* and *NPM1* mutation testing were widely performed at primary diagnosis from 2010 onwards, while *IDH1/2* assessment became routine after 2015. *FLT3* internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations, as well as *NPM1* and *IDH1/2* mutations, were assessed at participating institutions as part of routine diagnostic workup at the time of initial diagnosis. Molecular testing was performed using polymerase chain reaction (PCR)–based assays or next-generation sequencing (NGS) platforms available at each center.

2.3 | Treatment Protocols

2.3.1 | Frontline Therapy

Frontline induction strategies varied, though the vast majority of patients received intensive chemotherapy. The predominant regimen was standard "3 + 7" combining cytarabine with idarubicin (62.9%) or daunorubicin (7.3%), "3 + 7" plus midostaurin (4.0%), idarubicin plus cytarabine "2 + 5" (2.3%), FLAG-Ida (2.3%), idarubicin plus cytarabine plus etoposide (2.0%), and CPX-351 (1.6%), and other regimens (17.6%).

2.3.2 | Salvage Therapy With FLAG-Ida

According to PETHEMA cooperative group recommendations, FLAG-Ida was widely used as a salvage regimen. In the PETHEMA front-line protocols, FLAG-Ida was indicated for patients with (i) relapsed AML, (ii) failure to achieve at least a

partial remission (PR) [17] after the first cycle of intensive induction therapy, or (iii) failure to achieve CR after a second identical induction course, provided a partial remission had been obtained with the first. Elderly or comorbid patients who had received de-intensified frontline regimens could be treated with FLAG-Ida as salvage therapy at the investigator's discretion.

The FLAG-Ida regimen consisted of granulocyte colony-stimulating factor (G-CSF) at 300 μg on days 1–3 and thereafter from day 10 until hematopoietic recovery, idarubicin 10 mg/m^2 on days 2–4, fludarabine 30 mg/m^2 on days 2–5, and cytarabine 2 g/m^2 on days 2–5, administered 4 h after fludarabine infusion. Antifungal and antibacterial prophylactic and treatment agents were generally recommended, as well as full-length hospitalization until hematopoietic recovery. Patients were recommended to undergo allo-HCT whenever possible after achieving CR/CRi or MLFS, at the discretion of the treating physicians.

The FLAG-Ida regimen was administered as a single salvage course, with response assessment performed after hematologic recovery or at day 28–35, whichever occurred first. Second courses of FLAG-Ida were not routinely administered.

2.4 | Endpoints and Definitions

The primary endpoint was overall survival (OS), defined as the time from initiation of salvage therapy with FLAG-Ida to death from any cause or last follow-up if alive. Secondary endpoints included complete remission composite (CRc) (i.e., CR plus CR with incomplete hematologic recovery (CRi) plus morphologic leukemia-free state [MLFS]), event-free survival (EFS), disease-free survival (DFS), early mortality, the proportion of patients proceeding to allo-HCT, and the validation of the previously published SALFLAGE prognostic score in this expanded real-world cohort. In addition, outcomes were compared across treatment periods (1998–2005, 2006–2016, and 2017–2024) to evaluate temporal trends in efficacy, survival, and transplant utilization.

Response categories were defined according to modified International Working Group (IWG) criteria [17] and the ELN 2022 recommendations [2]. CR required < 5% bone marrow blasts, absence of extramedullary disease and peripheral blood blasts, and recovery of peripheral counts (neutrophils $\geq 1.0\times10^9$/L, platelets $\geq 100\times10^9$/L). CRi met all CR criteria except for residual cytopenia. MLFS was defined as < 5% blasts in an aplastic bone marrow and absence of peripheral blood blasts and extramedullary disease, without requirements for peripheral count recovery. PR was defined as a decrease in marrow blasts to 5%–25% and at least a 50% reduction from baseline. CRc was defined as achieving CR, CRi or MLFS. MLFS was included within the CRc composite endpoint because it represents a clinically relevant response category that frequently prompts consideration for allo-HCT, and because the distinction between CRi and MLFS can be ambiguous in multi-institutional registry data. A sensitivity analysis excluding MLFS confirmed that all findings remained unchanged (see Results).

EFS was calculated from the start of FLAG-Ida to the first event (failure to achieve CRc after a single cycle of FLAG-Ida, relapse, or death) or last follow-up if none occurred. DFS was measured from the date of CRc to relapse, death, or last follow-up, whichever came first. Relapse was defined as the reappearance of ≥ 5% bone marrow blasts, circulating blasts, or new extramedullary disease after a documented remission. Early death was assessed at Day 30, day 60, and 90 from treatment initiation.

2.5 | Statistical Analysis

Categorical variables were presented as number (percentages) and compared using Pearson's chi-square. Continuous variables were reported as median (range) and compared using the Mann–Whitney *U* or Kruskal–Wallis test, as appropriate. Kaplan–Meier estimates were used for unadjusted time-to-event analysis of OS, DFS and EFS, with log-rank tests for comparisons. Multivariate models included SALFLAGE components and age as specified in the final models by Bergua et al. [12]. Cox proportional hazards regression was used to assess associations with OS, DFS and EFS, provided the proportional hazards assumption was met. When this assumption was violated, variables were excluded from the final model fit. Regarding CR, a multivariate logistic regression model was computed using the same covariables. Cross-validation and penalized regression (LASSO and elastic net) did not yield models with better concordance index or calibration than the prespecified model by Bergua et al. For model discrimination, the concordance index for OS at 2-year and 5-year was computed and 95% confidence intervals (95% CI) were derived through bootstrapping (2000 iterations). A 2-sided p value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.4.1. Missing data were reported for each variable, and patients with missing values were excluded from the corresponding analyses (complete case approach). The SALFLAGE score could not be computed for 258 (23.9%) patients lacking one or more of its components. Model discrimination of the SALFLAGE score was assessed using the concordance index (C-index).

3 | Results

3.1 | Study Population

A total of 1229 adult patients with R/R AML treated with FLAG-Ida salvage therapy among 112 participating sites were identified in the PETHEMA registry between 1998 and 2024. Of them, 1079 (88%) were evaluable for treatment outcomes and survival and therefore included in the analyses. Those patients were distributed across treatment periods as follows: 101 (9.4%) in 1998–2005, 475 (44.0%) in 2006–2016, and 503 (46.6%) in 2017–2024 (Table 1).

The median age at first salvage was 52 years (range, 18–88), with 327 (30.3%) aged ≥ 60 years. Males constituted 55.5% of the cohort. Median leukocyte count at diagnosis was 11.3×10^9/L (range, 0.12–417), and secondary AML (antecedent MDS/MPN or therapy-related) accounted for 165 (15.5%) cases. Using the modified MRC 2010 cytogenetic stratification (with *t*(8; 21) assigned to the high-risk group), 69 (6.4%) patients were low risk, 621 (57.6%) intermediate risk, and 345 (32.0%) high risk; cytogenetic risk was missing in 44 (4.0%) patients.

TABLE 1 | Patient and disease characteristics.

	All patients	1998–2005	2006–2016	2017–2024	*p*
No. of patients	1079	101 (9.4)	475 (44.0)	503 (46.6)	
Sex, male, *n* (%)	599 (55.5)	67 (66.3)	252 (53.1)	280 (55.7)	0.051
Age, years, median (range)	52 (18–88)	52 (18–72)	54 (18–88)	52 (18–72)	0.216
Age groups, years, *n* (%)					< 0.001
< 60	752 (69.7)	64 (63.4)	314 (66.1)	374 (74.4)	
≥ 60	327 (30.3)	37 (36.6)	161 (33.9)	129 (25.6)	
Leukocytes, median (range) at diagnosis	11.3 (0.12–417)	10.8 (0.12–269)	12.4 (0.35–345)	10.8 (0.24–417)	0.675
Secondary AML, *n* (%)	165 (15.5)	14 (14.4)	71 (15.1)	80 (16.0)	0.889
Modified MCR 2010, *n* (%)					0.327
Low	69 (6.4)	10 (9.9)	27 (5.7)	32 (6.4)	
Intermediate	621 (57.6)	62 (61.4)	270 (56.8)	289 (57.5)	
High	345 (32.0)	26 (25.7)	163 (34.3)	156 (31.0)	
Missing	44 (4.0)	3 (3.0)	15 (3.2)	26 (5.2)	
NPM1, *n* (%)					
Positive	192 (17.8)	3 (3.0)	93 (19.6)	96 (19.1)	0.124
Negative	623 (57.7%)	20 (19.8%)	255 (53.7%)	348 (69.2%)	
Missing	264 (24.5)	78 (77.2)	127 (26.7)	59 (11.7)	—
FLT3-ITD, *n* (%)					
Positive	172 (15.9)	8 (7.9)	80 (16.8)	84 (16.7)	0.488
Negative	689 (63.9%)	33 (32.7%)	286 (60.2%)	370 (73.6%)	
Missing	218 (20.2)	60 (59.4)	109 (22.9)	49 (9.7)	—
IDH1/IDH2, *n* (%)					
Positive	77 (7.1)	0	12 (2.5)	65 (12.9)	0.029
Negative	298 (27.6%)	1 (1.0%)	20 (4.2%)	277 (55.1%)	
Missing	704 (65.2)	100 (99.0)	443 (93.3)	65 (32.0)	—
inv(16), *n* (%)					0.515
Positive	57 (5.3)	8 (7.9)	24 (5.1)	25 (5.0)	
Missing	130 (12.0)	8 (7.9)	37 (7.8)	85 (16.9)	—
Previous transplant, *n* (%)					< 0.001
No	721 (68.7)	75 (74.3)	335 (71.6)	312 (64.7)	
Autologous	115 (11.0)	20 (19.8)	59 (12.6)	36 (7.5)	
Allogeneic	214 (20.4)	6 (5.9)	74 (15.8)	134 (27.8)	
Missing	29 (2.7)	0 (0.0)	7 (1.5)	21 (4.2)	
Relapse free interval (RFI), *n* (%)					0.344
Resistant	398 (36.9)	38 (37.6)	183 (38.5)	177 (35.2)	
RFI < 1 year	426 (39.4)	35 (34.7)	176 (37.1)	214 (42.5)	
RFI ≥ 1 year	255 (23.7)	28 (27.7)	116 (24.4)	112 (22.3)	

TABLE 2 | Response to salvage therapy with FLAG-Ida.

	All patients	1998–2005	2006–2016	2017–2024	*p*
No. of patients	1079	101 (9.4)	475 (44.0)	503 (46.6)	
FLAG-Ida response, *n* (%)					0.379
CR	550 (51.0)	56 (55.4)	227 (48.0)	267 (53.1)	
CRi	43 (4.0)	2 (2.0)	21 (4.4)	20 (4.0)	
MLFS	19 (1.8)	0	8 (1.7)	11 (2.2)	
PR	57 (5.3)	4 (4.0)	31 (6.5)	22 (4.4)	
No response	319 (29.6)	32 (31.7)	140 (29.3)	147 (29.2)	
Death	91 (8.4)	7 (6.9)	48 (10.1)	36 (7.2)	
FLAG-Ida composite response, *n* (%)					0.266
CRc[a]	612 (56.8)	58 (57.4)	256 (54.1)	298 (59.2)	
Non-CRc[b]	467 (43.2)	43 (42.6)	219 (45.9)	205 (40.8)	

Note: The *p* value corresponds to the comparison of the distribution of response categories (CR, CRi, MLFS, PR, no response, and death) across the three eras (chi-squared test).
Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; PR, partial remission.
[a]CRc (composite complete remission) = CR + CRi + MLFS.
[b]Non-CRc = PR + NR + death.

Among patients with available molecular data, *NPM1* and *FLT3*-ITD mutations were detected in 192 (17.8%) and 172 (15.9%), respectively, while *IDH1/2* mutations were reported in 77 (7.1%). Substantial missing data for *IDH1/2* (704 patients; 65.2%) reflects the progressive implementation of molecular testing over the study period (Table 1).

At FLAG-Ida initiation, 398 (36.9%) patients had primary refractory disease, 426 (39.4%) relapsed within < 1 year from first remission, and 255 (23.7%) had a relapse-free interval ≥ 1 year. Prior transplantation status was available for most patients: 721 (68.7%) had no prior transplant, 115 (11.0%) had undergone autologous transplantation, 214 (20.4%) prior allo-HCT, and missing in 2.7%.

3.2 | Response to FLAG-Ida

Overall response after FLAG-Ida salvage therapy was CR in 550 patients (51.0%), CRi in 43 (4.0%), and MLFS in 19 (1.8%), yielding a CRc rate of 56.8% ($n = 612$). The remaining patients achieved PR in 57 (5.3%), resistance in 319 (29.6%), or died during induction in 91 without documented resistance (8.4%) (Table 2).

Several baseline covariates were associated with CRc achievement in univariate analysis. Longer relapse-free interval conferred a significant advantage (≥ 1 year: 72.3% vs. primary refractory: 52.3% vs. < 1 year: 51.8%; $p < 0.001$). Prior allo-HCT was associated with higher response rates (78.5% vs. 50.8% for no/autologous HCT; $p < 0.001$). Cytogenetic risk also discriminated response, with CRc rates of 73.6% for low risk, 55.2% for intermediate risk, and 53.9% for modified high risk ($p < 0.001$). *FLT3*-ITD positivity was associated with lower CRc (48.8% vs. 59.8% in wild-type; $p = 0.011$).

In multivariable logistic regression analysis for CRc achievement, prior allo-HCT was the strongest favorable predictor (Odds Ratio [OR] 3.45; 95% CI 2.22–5.26; $p < 0.001$), followed by relapse-free interval ≥ 1 year (OR 2.04; 95% CI 1.25–3.33; $p = 0.005$). Conversely, high-risk cytogenetics including *t*(8; 21) (OR 0.10; 95% CI 0.02–0.30; $p < 0.001$), intermediate-risk cytogenetics (OR 0.17; 95% CI 0.04–0.49; $p = 0.004$), and *FLT3*-ITD positivity (OR 0.58; 95% CI 0.39–0.87; $p = 0.008$) were independently associated with lower CRc probability. Age ≥ 60 years was not independently associated with response (OR 0.89; 95% CI 0.63–1.25; $p = 0.51$) (Table 3).

Among the 46 patients with *t*(8; 21), the CRc rate was 69.6% (95% CI 55.2%–80.9%) and the median OS was 8.97 months (95% CI 6.01–15.28), with 2-year and 5-year OS rates of 29.0% and 20.3%, respectively. Although *t*(8; 21) patients showed numerically superior outcomes compared with other high-risk patients ($n = 271$; median OS 6.97 months), this difference did not reach statistical significance ($p = 0.138$; Figure S3), supporting the reclassification of *t*(8; 21) as high-risk in the R/R setting.

In a sensitivity analysis excluding MLFS from the composite endpoint, the CR + CRi rate was 55.0% (593/1079), compared with the CRc rate of 56.7% (612/1079) when MLFS was included. This 1.8 percentage-point difference was consistent across all subgroups analyzed. Importantly, all prognostic factors identified in the multivariable logistic regression for CRc remained unchanged in direction, magnitude, and statistical significance when MLFS was excluded.

Early mortality rates after initiation of FLAG-Ida were 7.1% (95% CI: 5.5%–8.6%) at 30 days, 13.3% (95% CI: 11.3%–15.4%) at 60 days, and 18.8% (95% CI: 16.7%–21.4%) at 90 days. Causes of death within the first 90 days are shown in Table S1. Infection was the leading cause of death during the first 30 days (52.6%), while disease progression/refractory disease became the predominant cause in subsequent periods (41.8% at Days 31–60 and 53.3% at Days 61–90).

TABLE 3 | Multivariable logistic regression analysis for CRc achievement.

		OR (95% CI)	*p*
Age (years)	< 60	Reference	
	≥ 60	0.89 (0.63–1.25)	0.51
RFI	Resistant	Reference	
	≤ 1 year	0.58 (0.41–0.83)	0.003
	> 1 year	2.04 (1.25–3.33)	0.005
Previous HCT	No	Reference	
	Autologous	1.03 (0.58–1.82)	0.91
	Allogeneic	3.45 (2.22–5.26)	< 0.001
Modified MRC2010[a]	Low	Reference	
	Intermediate	0.17 (0.04–0.49)	0.004
	High	0.10 (0.02–0.30)	< 0.001
FLT3-ITD	Wild-type	Reference	
	Mutated	0.58 (0.39–0.87)	0.008

Note: Odds ratios (OR) greater than 1 indicate increased likelihood of CRc achievement. The model included all SALFLAGE score components and age. Goodness-of-fit was assessed using the Hosmer–Lemeshow test.
Abbreviations: CI, confidence interval; CRc, composite complete remission (CR + CRi + MLFS); HCT, hematopoietic cell transplantation; MRC, Medical Research Council; OR, odds ratio; RFI, relapse-free interval.
[a]Modified MRC classification with *t*(8; 21) reclassified as high risk given its diminished prognostic value in the relapsed/refractory setting.

When stratified by age, 30-day mortality was 5.9% (95% CI 4.4%–7.8%) in patients < 60 years and 9.8% (95% CI 7.0%–13.5%) in patients ≥ 60 years ($p = 0.021$). At 60 days, mortality rates were 11.3% vs. 18.1% ($p = 0.002$), and at 90 days, 16.6% vs. 24.7% ($p = 0.002$), respectively. An age-dependent gradient in early mortality was observed across five age groups (p-trend for early mortality: $p < 0.001$ at 60 and 90 days, $p = 0.066$ at 30 days; Table S4).

3.2.1 | Post-FLAG-Ida Therapy

Following FLAG-Ida salvage, allo-HCT was performed in subsequent CRc in 379 patients (35.2% of the entire cohort), autologous HCT in 9 (0.8%), and no HCT was performed in subsequent CRc in 691 (64.0%). Among the 612 patients achieving CRc after FLAG-Ida, 379 (61.9%) proceeded to allo-HCT, 9 (1.5%) to autologous HCT, and 224 (36.6%) did not undergo HCT consolidation. Patients with prior allo-HCT were more likely to receive a second transplant compared with those without prior allo-HCT (69.6% vs. 32.5%; $p < 0.001$).

3.3 | Survival Outcomes After Salvage Therapy

With a median follow-up of 50.9 months (reverse Kaplan–Meier; 95% CI 44.2–59.2), the median OS of the entire cohort was 10.2 months (95% CI 9.0–11.7) (Figure 1A), with estimated 2-year and 5-year OS rates of 30.0% (95% CI 27.1–33.1) and 21.6% (95% CI 18.9–24.7), respectively.

In univariate analysis, age significantly influenced survival, with median OS progressively declining from 16.0 months in patients < 40 years to 14.5 months (40–49 years), 8.5 months (50–59 years), 7.9 months (60–69 years), and 5.8 months in patients ≥ 70 years ($p < 0.001$) (Figure 1B). Cytogenetic risk strongly discriminated survival, with median OS of 29.4 months for low-risk, 11.2 months for intermediate-risk, and 7.2 months for high-risk including *t*(8; 21) ($p < 0.001$) (Figure 1C). *FLT3*-ITD positivity was associated with inferior survival (median OS: 8.4 vs. 12.2 months; $p < 0.001$) (Figure 1D). Among molecular markers, *IDH1/IDH2* mutations were associated with favorable outcomes (median OS: 17.0 months vs. 10.4 months for wild-type; $p = 0.007$) (Figure 1E), whereas *NPM1* mutational status did not significantly influence survival (median OS: 9.9 months for mutated vs. 11.1 months for wild-type; $p = 0.393$) (Figure 1F). Longer relapse-free interval conferred superior OS (median OS: 15.4 months for ≥ 1 year vs. 9.9 months for refractory vs. 7.8 months for < 1 year; $p < 0.001$) (Figure 1G). Prior allo-HCT was associated with significantly better outcomes (median OS: 22.5 months vs. 8.2 months for no prior HCT; $p < 0.001$) (Figure 1H).

In multivariable Cox regression analysis for OS showed that prior allo-HCT was the strongest protective factor (HR 0.54; 95% CI 0.43–0.68; $p < 0.001$), while relapse-free interval ≥ 1 year was associated with significantly better survival compared with primary refractory disease (HR 0.75; 95% CI 0.59–0.96; $p = 0.024$). Conversely, high-risk cytogenetics including *t*(8; 21) conferred the highest risk of death (HR 3.58; 95% CI 2.09–6.12; $p < 0.001$), followed by intermediate-risk cytogenetics (HR 2.09; 95% CI 1.23–3.53; $p = 0.006$). *FLT3*-ITD mutation was associated with a 61% increased risk of death (HR 1.61; 95% CI 1.30–2.00; $p < 0.001$). Early relapse (< 1 year) conferred worse OS than primary refractory disease (HR 1.39; 95% CI 1.14–1.70; $p = 0.001$). Age ≥ 60 years was also independently associated with inferior OS (HR 1.43; 95% CI 1.19–1.72; $p < 0.001$) (Table 4).

Median EFS for the entire cohort was 4.5 months (95% CI 3.8–5.2), with 2-year and 5- EFS rates of 20.9% (95% CI 18.4–23.7) and 16.2% (95% CI 13.9–18.9), respectively. Among patients achieving CRc, median DFS was 5.0 months (95% CI 4.3–5.6), with 2-year and 5-year DFS rates of 21.5% (95% CI 19.0–24.3) and 16.9% (95% CI 14.5–19.6), respectively. Multivariable analyses for EFS (Table S2) and DFS (Table S3) confirmed the independent prognostic impact of modified cytogenetic risk, *FLT3*-ITD status, relapse-free interval, and prior allo-HCT.

The median OS (mOS) varied according to response after FLAG-Ida (23.1 months for CR, 9.9 months for CRi, 7.1 months for MLFS, 11.2 months for PR, and 5.3 months for resistance, $p < 0.0001$) (Figure S1A). The rate of subsequent allo-HCT was 64% for CR ($n = 353$), 58.1% for CRi ($n = 25$), and 10.5% for MLFS ($n = 2$).

The mOS according to post-CRc treatment were: 49.8 months for allo-HCT, 13.4 months for auto-HCT and 11.4 months for no HCT, $p < 0.0001$ (Figure S1B).

3.4 | Temporal Trends

Outcomes were compared across three treatment eras: 1998–2005 ($n = 101$), 2006–2016 ($n = 475$), and 2017–2024 ($n = 503$). CRc rates

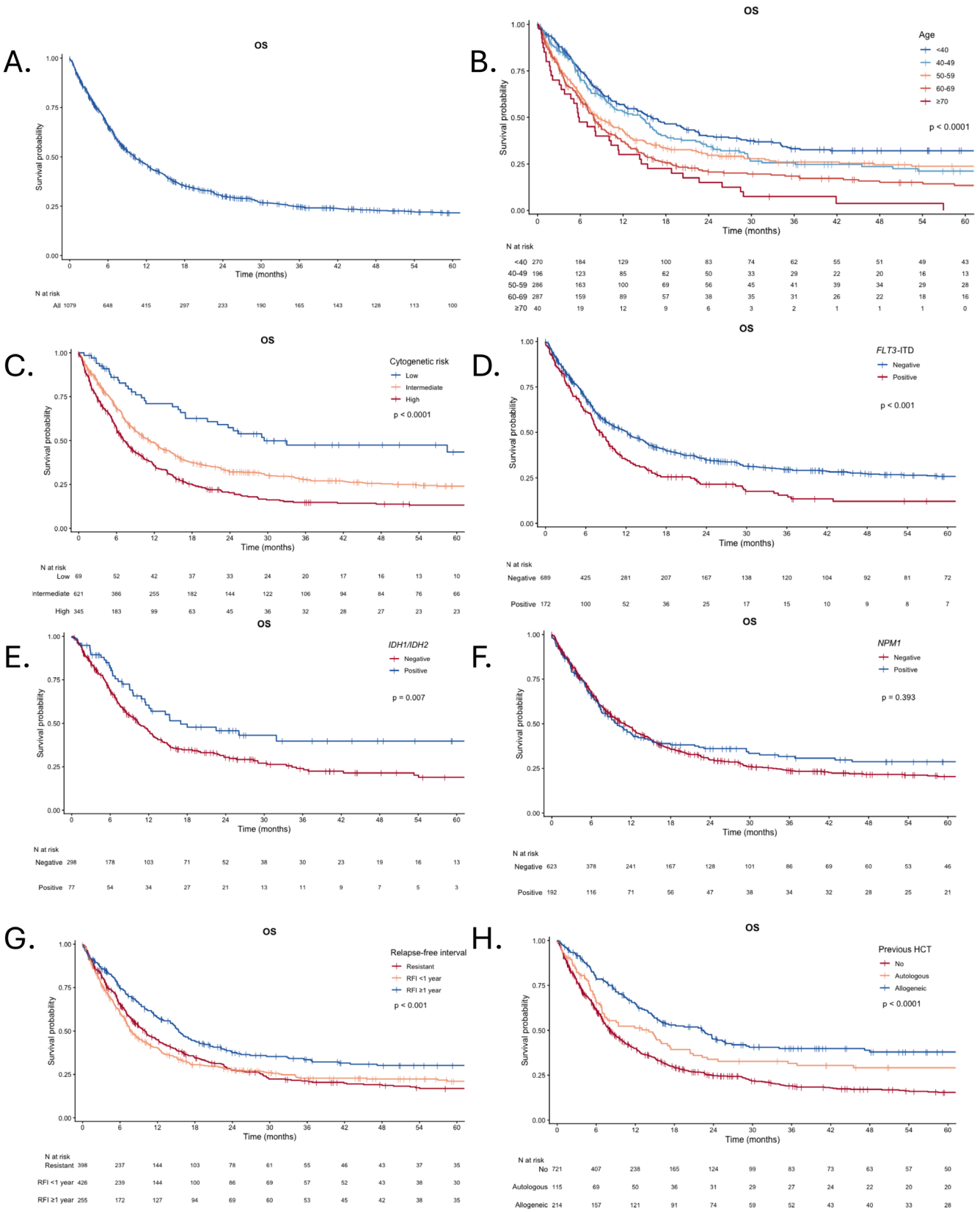

FIGURE 1 | Overall survival after FLAG-Ida salvage therapy. OS after salvage therapy with FLAG-Ida: (A) OS in the whole cohort ($n = 1079$), (B) OS according to age group, (C) OS according to modified MRC 2010 cytogenetic risk, (D) OS according to FLT3-ITD mutation status, (E) OS according to IDH1/2 mutation status, (F) OS according to NPM1 mutation status, (G) OS according to RFI category (primary refractory, relapse < 1 year, relapse ≥ 1 year), (H) OS according to prior hematopoietic cell transplantation in first remission (none, autologous, allogeneic). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 | Multivariable Cox regression analysis for overall survival.

Variable	HR (95% CI)	*p*
Age (years)		
< 60	Reference	—
≥ 60	1.43 (1.19–1.72)	< 0.001
Relapse free interval		
Refractory	Reference	—
< 1 year	1.39 (1.14–1.70)	0.001
≥ 1 year	0.75 (0.59–0.96)	0.024
Previous Allo-HCT		
No/Autologous	Reference	—
Allogeneic	0.54 (0.43–0.68)	< 0.001
Modified MRC2010[a]		
Low	Reference	—
Intermediate	2.09 (1.23–3.53)	0.006
High	3.58 (2.09–6.12)	< 0.001
FLT3-ITD		
Negative	Reference	—
Positive	1.61 (1.30–2.00)	< 0.001

Note: Multivariable Cox proportional hazards regression model including 766 patients (71.0%) with complete data for all covariates. Hazard ratios (HR) greater than 1 indicate increased risk of death. The model demonstrated adequate discriminative ability (C-index = 0.653) and the proportional hazards assumption was satisfied (global test $p = 0.199$).
Abbreviations: CI, confidence interval; HCT, hematopoietic cell transplantation; HR, hazard ratio; MRC, Medical Research Council.
[a]Modified MRC classification with *t*(8; 21) reclassified as high risk given its diminished prognostic value in the relapsed/refractory setting.

remained stable over time (57.4% vs. 54.1% vs. 59.2%; $p = 0.266$) (Table 2). Median OS showed a numerical but non-significant improvement across periods (7.8 months (95% CI 6.9–11.7) versus 9.4 months (95% CI 7.8–12.3) versus 11.1 months (95% CI 9.7–12.7); $p = 0.16$) (Figure S2). The proportion of patients proceeding to allo-HCT in CRc after FLAG-Ida rose from 22.8% in 1998–2005 to 34.7% in 2006–2016 and 41.9% in 2017–2024 ($p < 0.001$). Autologous HCT was not performed after 2016 (0% vs. 6.9% in 1998–2005; $p < 0.001$).

Thirty-day mortality was 6.9% in 1998–2005, 9.3% in 2006–2016, and 5.0% in 2017–2024 ($p = 0.030$). Similarly, 90-day mortality decreased from 21.8% in 1998–2005 and 2006–2016 to 15.9% in 2017–2024 ($p = 0.034$). The improvement was driven by the most recent era, with significant differences between 2006–2016 and 2017–2024 at both 30 days (9.3% vs. 5.0%; $p = 0.013$) and 90 days (21.8% vs. 15.9%; $p = 0.016$).

3.5 | Validation of the SALFLAGE Score

The SALFLAGE prognostic scoring system, originally developed by Bergua et al. in a cohort of 190 patients, was applied to this expanded real-world cohort. Complete data for score calculation were available in 811 patients (75.2%). The distribution across risk categories was 211 (26.0%) low-risk, 222 (27.4%) intermediate-risk, and 378 (46.6%) high-risk, comparable to the proportions reported in the Bergua et al. study [12].

Median OS was 22.2 months (95% CI 15.4–36.8) in the low-risk, 13.4 months (95% CI 11.2–19.8) in the intermediate-risk, and 6.9 months (95% CI 6.0–7.5) in the high-risk group ($p < 0.001$; Figure 2). Two-year OS rates were 46.2% (95% CI 39.4–54.2), 40.2% (95% CI 33.7–47.9), and 19.0% (95% CI 15.0–24.0), respectively, while 5-year OS rates were 38.4% (95% CI 31.4–47.0), 27.2% (95% CI 21.2–35.0), and 12.7% (95% CI 9.1–17.7), respectively. The SALFLAGE score also predicted response to FLAG-Ida, with CRc rates of 76.0%, 63.3%, and 42.2% in low-, intermediate-, and high-risk groups, respectively ($p < 0.001$).

At 2 years, the C-index for the numerical SALFLAGE score (0 to 11 points) was 0.64 (95% CI 0.61–0.67), with similar performance at 5 years (C-index 0.64; 95% CI 0.61–0.67). The three categories score showed slightly better discrimination (C-index 0.67; 95% CI 0.63–0.76 at 2 years; C-index 0.67; 95% CI 0.63–0.70 at 5 years). These values indicate moderate discriminatory capability, consistent with the original validation (C-index 0.68) and confirm the reproducibility of the SALFLAGE score in an extended, contemporary real-world cohort.

To compare prognostic frameworks, the Breems/HOVON and Chevallier/GOELAMS scores were applied to the 766 patients with complete data for all three systems. SALFLAGE demonstrated the highest discriminatory ability (C-index: 0.615; 95% CI: 0.591–0.638) compared with the Chevallier score (C-index: 0.595; 95% CI: 0.571–0.618) and the Breems score (C-index: 0.552; 95% CI: 0.531–0.572). Notably, the Breems score classified 71.1% of patients as unfavorable, 21.9% as intermediate, and only 6.9% as favorable, limiting its clinical utility for risk-guided decision-making. In contrast, SALFLAGE provided a more balanced three-tier distribution (25.8% low, 27.4% intermediate, 46.7% high), with significantly different median OS across groups (23.8, 13.8, and 7.0 months, respectively; $p < 0.001$; Figure 3).

4 | Discussion

This study shows that FLAG-Ida offers consistently, in a real-world setting, remarkable CR rates, and additional CRi and MLFS in the first relapse/refractory AML setting. In spite of substantial toxicity, including an early mortality rate of 7.1% within the first month, we demonstrate that this regimen is a valid option as bridge to transplant. We also show improvements across a large inclusion period, with lower early death and higher subsequent transplant rate in the later study cohort, leading to improved median and 5-year OS. Nevertheless, short and long-term outcomes after salvage with FLAG-Ida remain disappointing, especially for patients identified as intermediate and high SALFLAGE score risk, which was herein validated and may allow for risk-adapted selection of patients for alternative approaches.

As far as we know, this is the largest retrospective analysis of FLAG-Ida salvage therapy in relapsed/refractory AML to date, encompassing 1079 patients over a 26-year period. We should highlight that there were no selection criteria (apart from

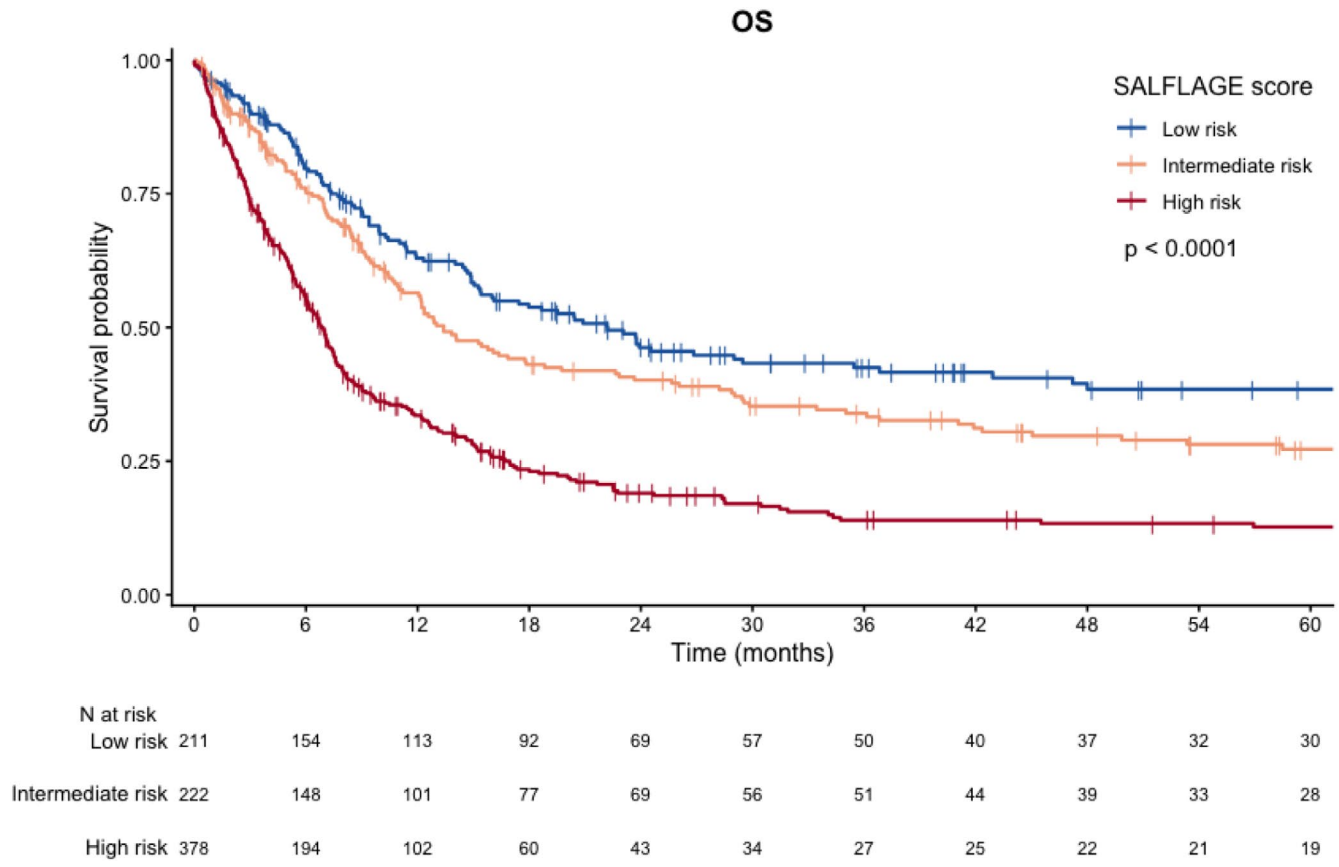

FIGURE 2 | Overall survival according to SALFLAGE prognostic score. Kaplan–Meier curves of overall survival according to SALFLAGE prognostic score risk categories: low (0–4 points; $n = 211$), intermediate (5–6 points; $n = 222$), and high (≥7 points; $n = 378$). Median OS was 22.2 months (95% CI 15.4–36.8), 13.4 months (95% CI 11.2–19.8), and 6.9 months (95% CI 6.0–7.5), respectively. Five-year OS rates were 38.4%, 27.2%, and 12.7%, respectively. Log-rank $p < 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

pediatric age and completeness of data regarding response and survival), so this series could serve as a reference for other real-world studies. On the other hand, the database collected limited information on toxicities (beyond early death and causes of death), so this study cannot serve as a comparator for less toxic approaches and for safety measurements in clinical trials. Interestingly, we observe that the few randomized trials performed in relapsed/refractory AML generally lack clearly defined control-arm regimens, and the CR rates to exceed are around 20% to 30% (based on high- or intermediate-dose cytarabine monotherapy) [18–22]. However, we report a CR rate of 51% after FLAG-Ida, and a CRc of 56.8%, consistent with prior series reporting response rates of 40%–60% [4, 6, 12, 23, 24], suggesting that estimated CR rates and control-arm selection should be revisited. Of course, we can speculate that stricter criteria for CR definition in clinical trials could lead to decreased rates as compared to that observed in registry studies.

Our CRc rate of 56.8% compares favorably with previously published FLAG-Ida series. Westhus et al. [24] reported a CR/CRi rate of 56% in 132 patients, while Pastore et al. [23] achieved 52% CR in 46 patients. The systematic review by Megías-Vericat et al. [4] reported CR rates ranging from 44% to 59% for cytarabine-based combinations with purine analogues. In the UK NCRI AML17 randomized trial comparing FLAG-Ida with daunorubicin/clofarabine, CR rates were 74% in the R/R cohort with no significant difference between arms, although patients not receiving transplantation survived beyond 21 months [25]. Although FLAG-Ida salvage enabled up to 35.2% of patients and 62% of responders to proceed to potentially curative allo-HCT, the median OS was disappointing (10.2 months, with 2-year and 5-year probabilities of 30.0% and 21.6%, respectively). Moreover, despite almost doubling the rate of patients undergoing allograft in CRc, we observed modest mOS improvement in the 2017–2024 cohort (11.1 months) as compared to the 1998–2005 period (7.8 months). We can speculate that, while allo-HCT is regarded as the "only" curative option in relapse/refractory AML, its efficacy remains limited in the majority of patients.

A notable finding is the significant improvement in early mortality across treatment eras. Three-month survival improved from 78.2% in 1998–2005 to 84.1% in 2017–2024 ($p = 0.043$), while 30-day mortality decreased from 6.9% to 5.0% ($p = 0.030$). These improvements likely reflect advances in supportive care, including antimicrobial prophylaxis and growth factor support. Another contributing factor could be the lower percentage of patients aged 60 years or more in the later period, probably because FLAG-Ida was less used in the last years in favor of non-intensive options in older patients.

Several prognostic factors emerged as independent predictors of CRc achievement. Remarkably, age was not an independent predictor, suggesting that FLAG-Ida could be also an efficacious option in >60 years AML patients. Supporting this

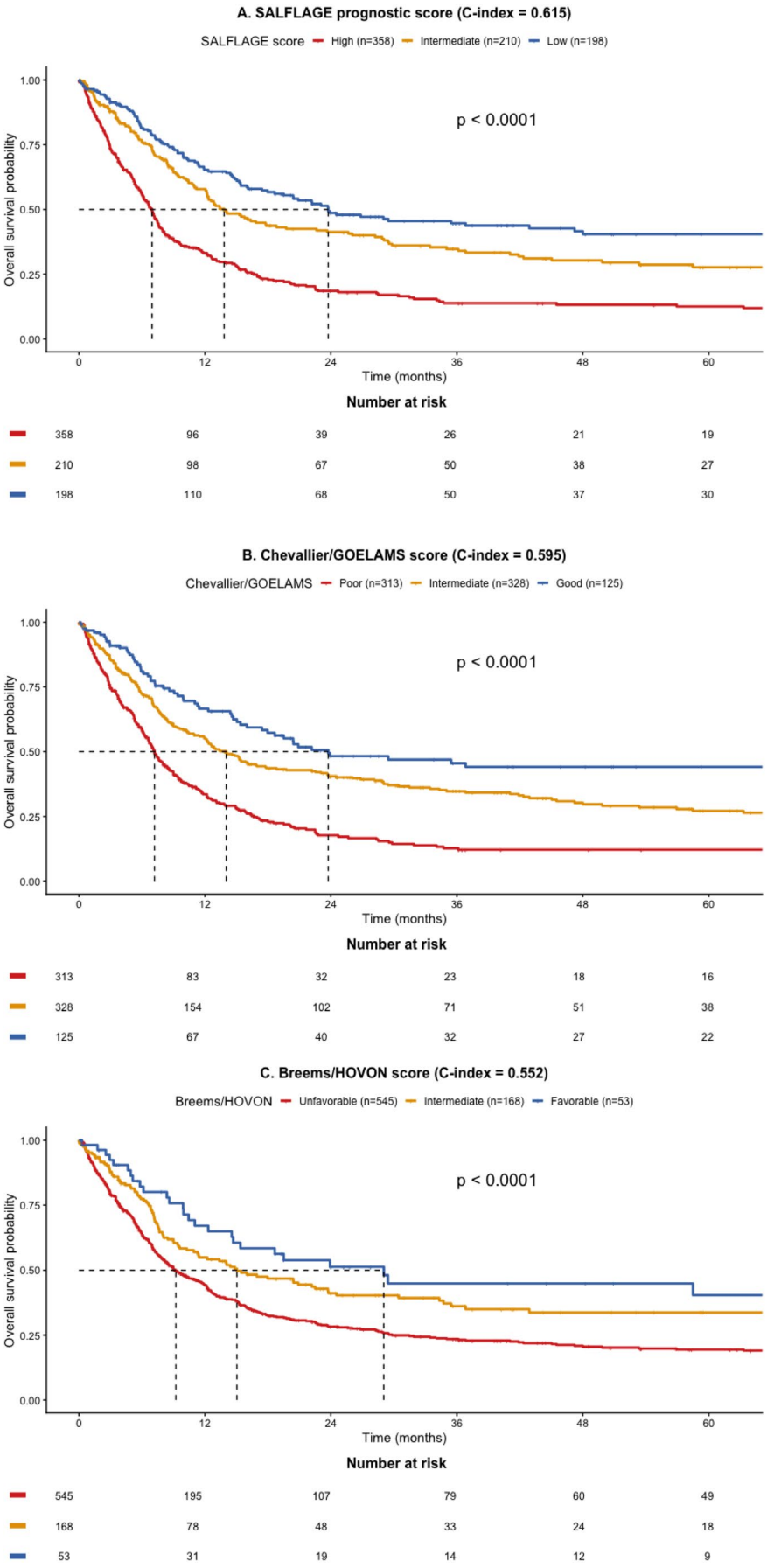

FIGURE 3 | Legend on next page.

FIGURE 3 | Comparison of prognostic scoring systems for overall survival in relapsed/refractory AML treated with FLAG-Ida. Kaplan–Meier estimates of overall survival stratified by risk categories according to (A) the SALFLAGE score (low, $n = 198$; intermediate, $n = 210$; high, $n = 358$), (B) the Chevallier/GOELAMS score (good, $n = 125$; intermediate, $n = 328$; poor, $n = 313$), and (C) the Breems/HOVON score (favorable, $n = 53$; intermediate, $n = 168$; unfavorable, $n = 545$). Analysis was restricted to 766 patients with complete data for all three scoring systems to enable direct comparison of discriminatory ability. Harrell's C-index was 0.615 (95% CI 0.591–0.638) for SALFLAGE, 0.595 (95% CI 0.571–0.618) for Chevallier, and 0.552 (95% CI 0.531–0.572) for Breems. Dashed lines indicate median overall survival. *p* values were calculated using the log-rank test. [Color figure can be viewed at wileyonlinelibrary.com]

observation, while early mortality was significantly higher in patients ≥ 60 years (30-day: 9.8% vs. 5.9%, $p = 0.021$; 90-day: 24.7% vs. 16.6%, $p = 0.002$; Table S4), the absolute 30-day mortality rate of 9.8% in older patients remains comparable to other intensive salvage regimens. Notably, patients aged 60–69 years showed 30-day mortality of 9.1%, suggesting that, with appropriate patient selection, fit elderly R/R AML patients can tolerate FLAG-Ida salvage therapy. Interestingly, patients with prior allo-HCT demonstrated significantly higher response rates (78.5% vs. 50.8%; $p < 0.001$), likely reflecting selection of fitter patients and potentially preserved graft-versus-leukemia effect, but also longer relapse-free intervals. Additionally, the immunomodulatory properties of fludarabine—a potent lymphodepleting agent that induces prolonged T-cell depletion, particularly in the CD4+ subset [26]—may enhance donor T-cell-mediated antileukemic activity in patients with residual donor chimerism [11], thereby contributing to the superior outcomes observed in this subgroup. A relapse-free interval ≥ 1 year was associated with superior CRc rates (72.3% vs. 51.8%; $p < 0.001$), consistent with the original SALFLAGE study [12] and the prognostic index proposed by Breems et al. [16]. We employed the modified MRC 2010 cytogenetic classification, which reclassifies *t*(8; 21) as high-risk in the R/R setting based on evidence of inferior outcomes upon relapse [15]. Notably, no cytogenetic risk stratification has been specifically developed for R/R AML; the existing classifications (MRC 2010, ELN 2017/2022) were all derived from newly diagnosed cohorts. The modified MRC 2010, which incorporates the reclassification of *t*(8; 21) as high-risk based on the Breems et al. data [16], represents the most adapted available framework for this setting. This classification was adopted to maintain consistency with the original SALFLAGE model [12] and to allow direct comparison with its validation cohort. Although the MRC classification did not distinguish CRc rates between intermediate- and high-risk categories (55.2% vs. 53.9%), it significantly discriminated survival outcomes, suggesting that its prognostic value in the R/R setting is primarily reflected in long-term endpoints rather than initial chemosensitivity. Separate analysis of the *t*(8; 21) subgroup ($n = 46$) confirmed that, despite a higher initial CRc rate (69.6%), these patients exhibited a median OS of 8.97 months, comparable to other high-risk categories ($p = 0.138$). This is consistent with the findings reported by Breems et al. [16] and validates the reclassification of *t*(8; 21) as high-risk in the relapsed/refractory context. *FLT3*-ITD positivity was associated with lower CRc rates (48.8% vs. 59.8%; $p = 0.011$) and inferior OS (median 8.4 vs. 12.2 months; $p < 0.001$), highlighting the unmet need for targeted therapies in this subgroup [27].

We provide the first large-scale validation of the SALFLAGE prognostic score, which should be considered specific for patients receiving FLAG-Ida. Importantly, head-to-head comparison with the Breems/HOVON [16] and Chevallier/GOELAMS [27] prognostic systems demonstrated that SALFLAGE achieved the highest discriminatory ability (C-index 0.615 vs. 0.595 and 0.552, respectively), the most clinically balanced risk-group distribution, and the widest separation between survival curves (Figure 3). The Breems score, while historically influential, classified over 70% of patients as unfavorable, limiting its clinical utility for treatment individualization. SALFLAGE, developed specifically for FLAG-Ida-treated patients, identified a meaningful 25.8% of patients with favorable long-term outcomes (5-year OS 40.4%), enabling risk-adapted selection of salvage strategies. While SALFLAGE remains useful for risk stratification and OS prediction in the relapse/refractory setting, future iterations could incorporate measurable residual disease (MRD) status, *IDH1/2* mutations, *RUNX1*, *ASXL1*, and *TP53* status [2, 3].

The combination of venetoclax with hypomethylating agents (HMA) has emerged as an important therapeutic option in R/R AML, particularly for patients unfit for intensive chemotherapy. In the large Italian AVALON real-world study, Todisco et al. [28] reported CR/CRi rates of 43% in 148 R/R AML patients (median age 73 years) treated with venetoclax plus HMA, with a median OS of 6.3 months. More recently, Shahswar et al. [29] established a multicenter prognostic risk model based on 240 R/R AML patients (median age 68.6 years) treated with venetoclax plus HMA, reporting an overall response rate of 44% and a median OS of 7.9 months. These large real-world cohorts consistently demonstrate that, while venetoclax-HMA combinations offer a less toxic approach, response rates remain lower than those achieved with intensive FLAG-Ida salvage (CRc 56.7% in our series), particularly in transplant-eligible patients. Aldoss et al. [30] reported encouraging results with venetoclax plus HMA in R/R AML, demonstrating CR/CRi rates of 33%–64% depending on prior therapy exposure. A systematic review and meta-analysis by Bewersdorf et al. [31] encompassing multiple studies of venetoclax-based regimens in R/R AML reported pooled CR/CRi rates of 21% for venetoclax monotherapy, increasing to 38% when combined with HMA or low-dose cytarabine. Notably, Shahswar et al. [32] compared FLAVIDA (FLA-IDA + venetoclax) with standard FLA-IDA in 118 R/R AML patients, demonstrating a significantly higher ORR with the addition of venetoclax (78% vs. 47%; $p = 0.001$), although without a significant impact on OS. For fit patients with R/R AML who are candidates for transplantation, intensive regimens such as FLAG-Ida may offer advantages over venetoclax-HMA combinations by achieving faster and deeper cytoreduction, and perhaps higher CRc rates, thereby enabling more timely progression to allo-HCT. Prospective trials comparing these two approaches in transplant-eligible patients are warranted to optimize salvage therapy selection. Furthermore, recent data suggest combining venetoclax with FLAG-Ida. DiNardo et al. [33] reported 67% CR + CRi + MLFS and 12 months mOS in a series of 61 R/R AML

(median age 47 years, 69% of them in the first R/R episode), and notably, 57% of them were successfully bridged to allo-HCT.

The emergence of targeted therapies has transformed R/R AML treatment. *FLT3* inhibitors (gilteritinib, quizartinib) [19, 34], *IDH1/2* inhibitors (ivosidenib, enasidenib) [35, 36], and *Menin-1* inhibitors [14] have demonstrated efficacy in molecularly defined subsets, but results with monotherapy remain very poor. The addition of targeted agents to FLAG-Ida represents a promising strategy to further enhance both response rates and successful transition to allo-HCT.

This study has several important limitations: (1) the retrospective design and absence of a control arm preclude direct comparison with alternative salvage strategies; (2) *FLT3*-ITD positivity was not routinely tested at relapse in this series and therefore prognostication was based on the primary AML diagnosis *FLT3*-ITD status; (3) baseline molecular characterization was missing in many patients, and critical prognostic markers such as *TP53* were not systematically available, limiting risk stratification precision; (4) the SALFLAGE score could not be calculated for 24% of patients due to missing components, which may introduce bias in the validation analysis; (5) MRD assessment was not collected preventing evaluation of response depth; and (6) the extended study period (1998–2024) encompasses substantial heterogeneity in supportive care, transplant conditioning regimens, and donor availability.

In summary, FLAG-Ida remains an effective salvage regimen in R/R AML, achieving remission in over half of patients (with notable CRc rates in post-allo-HCT relapses). FLAG-Ida serves as an effective bridge-to-transplant strategy, enabling 35.2% of all patients and 62% of responders to proceed to potentially curative allo-HCT. The validated SALFLAGE score provides useful risk stratification predicting OS and CRc in R/R patients treated with FLAG-Ida. Future efforts should focus on integrating FLAG-Ida with targeted agents to further improve remission rates while reducing the backbone chemotherapy schedule, enhancing the bridge-to-transplant success; and possibly incorporating maintenance phase with targeted agents to prevent further relapses.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Overall survival according to response and post-remission treatment. (A) Overall survival by response to FLAG-Ida salvage therapy ($n = 988$, excluding induction deaths). (B) Overall survival by post-CRc treatment among patients achieving composite complete remission ($n = 612$). **Figure S2:** Overall survival according to treatment era after FLAG-Ida salvage therapy. Kaplan–Meier curves depicting overall survival stratified by treatment period. Median OS: 7.8 months (95% CI 6.9–11.7) for 1998–2005 ($n = 101$), 9.4 months (95% CI 7.8–12.3) for 2006–2016 ($n = 475$), and 11.1 months (95% CI 9.7–12.7) for 2017–2024 ($n = 503$); log-rank $p = 0.16$. **Figure S3:** Overall survival of patients with *t*(8; 21) compared with other high-risk cytogenetic categories. Kaplan–Meier curves comparing OS in patients with *t*(8; 21) ($n = 46$; median OS 8.97 months, 95% CI 6.01–15.28) versus other high-risk patients ($n = 271$; median OS 6.97 months). The difference was not statistically significant (log-rank $p = 0.138$). High-risk cytogenetics were defined according to the modified MRC 2010 classification. **Table S1:** Causes of early mortality following FLAG-Ida salvage therapy. **Table S2:** Multivariable Cox regression analysis for event-free survival. **Table S3:** Multivariable Cox regression analysis for disease-free survival. **Table S4:** Early mortality rates following FLAG-Ida salvage therapy stratified by age group.