American Journal of Hematology

WILEY

CORRESPONDENCE

Outcome of Patients With Acute Myeloid Leukemias or Myelodysplastic Syndromes After Relapsing From Allogeneic Stem Cell Transplantation: The GITMO AML/MDS-Relapse Registry Study

Michele Malagola[1,2] | Luca Castagna[3] | Domenica Matranga[4] | Vera Radici[1,2] | Mirko Farina[1,2] | Marco Galli[1,2] | Eugenia Accorsi Buttini[5] | Vicky Rubini[6] | Caterina Alati[7] | Simona Bassi[8] | Alessandra Biffi[9] | Carlo Borghero[10] | Alessandro Busca[11] | Chiara Nozzoli[12] | Michele Carella Angelo[13] | Irene Cavattoni[14] | Raffaella Cerretti[15] | Patrizia Chiusolo[16] | Michele Cimminiello[17] | Angela Cuoghi[18] | Marco De Gobbi[19,20] | Federico Vincenzo[21] | Piero Galieni[22] | Paola Iori Anna[23] | Attilio Olivieri[24] | Matteo Parma[25] | Francesca Patriarca[26] | Vincenzo Pavone[27] | Alessandra Picardi[28] | Eugenia Piras[29] | Nicola Polverelli[30] | Lucia Prezioso[31] | Benedetta Rambaldi[32] | Elvira Scalisi[33] | Carmine Selleri[34] | Cristina Skert[35] | Alessandro Spina[36] | Cristina Tecchio[37] | Elena Oldani[32] | Degrandi Eliana[38] | Russo Domenico[1,2] | Massimo Martino[7]

Correspondence: Michele Malagola (michele.malagola@unibs.it)

Received: 17 March 2025 | **Revised:** 27 June 2025 | **Accepted:** 8 July 2025

Keywords: acute myeloid leukemia | allogeneic stem cell tansplantation | disease burden | myelodysplastic syndrome | relapse

To the Editor,

Disease relapse represents the main cause of treatment failure after allogeneic stem cell transplantation (Allo-SCT) in Acute Myeloid Leukemia (AML) and myelodysplastic syndrome (MDS) patients [1]. Thus, minimal residual disease (MRD) monitoring following allo-SCT is a mainstay of good clinical practice. The prognosis following relapse is dismal, and recently new treatment options, such as hypomethylating agents (HMAs) alone or in combination with venetoclax (VEN), have been used also in the setting of post-transplant disease relapse, but data from prospective trials are lacking [2].

With the aim to describe the real-life management of AML/MDS post-transplant relapses in Italy, we conducted this retrospective registry study, involving 33/63 (52%) transplant centers in Italy and including 859 cases of disease relapse registered between 2015 and 2021 (GITMO-AML/MDS relapse study; ClinicalTrials.gov: NCT06790680). All patients included in the registry provided informed consent for data registration in the PROMISE database. Clinically available data were extracted from the PROMISE database, and additional queries on the relapse event were submitted to each center to minimize missing data.

The probability of Overall Survival (OS) was estimated using the Kaplan–Meier method. Cox proportional hazards model and log-rank test were used to compare OS across groups. Subdistribution hazard model and Gray's test were used to compare Treatment Related Mortality (TRM) and Relapse Mortality (RM) across groups. For non-proportional OS risks, interaction with time was modeled as an unrestricted smooth cubic spline function. No correction for non-proportional risks was applied in the Fine and Gray model. Statistical analysis was performed in R (https://cran.r-project.org/) [3].

Table 1 reports the patients' and transplants' characteristics. The median age of the patients at transplant was 57.4 years (range 18.7–74.8). Ninety percent of the patients ($n = 768$) were affected by AML, and 507/859 (59%) received the transplant in first complete remission (CR), following one line of therapy in 48% of the cases. The donor was unrelated in 48% of the cases ($n = 416$), matched sibling in 28% of the cases ($n = 242$) and haploidentical in 23% of the cases ($n = 197$), and more than two thirds of the patients (75%) received peripheral blood stem cells (PBSC). The conditioning was myeloablative in 71% of the cases ($n = 611$) and graft versus host disease (GVHD) prophylaxis included anti-thymocytes globulin (ATG) or anti-T lymphocytes

[Correction added on 19 November 2025, after first online publication: The author's first and last names were inadvertently inverted has been updated.]

TABLE 1 | Clinical and transplant characteristics of the 859 AML/MDS patients relapsing after allo-SCT included in the study.

	***n* = 859**
Age at diagnosis (years)	
Mean (SD)/median (Min, Max)	58.5 (12.1)/61.0 [23.0–80.0]
Age at SCT (years)	
Mean (SD)/median [Min, Max]	52.9 (12.2)/54.7 [18.7–74.8]
Diagnosis at SCT	
AML/MDS	768 (90%)/91 (10%)
Disease status at SCT	
No-CR/CR	352 (41%)/507 (59%)
Lines of therapy before SCT	
> 1/1	419 (49%)/415 (48%)
Missing	25 (3%)
Donor type	
Sibling	242 (28%)
MUD/MMUD	416 (48%)
Haploidentical	197 (23%)
Missing	4 (1%)
SCs source	
BM	203 (24%)
PBSC	646 (75%)
UCB	10 (1%)
MAC regimen	
No/Yes	248 (29%)/611 (71%)
GVHD prophylaxis	
ATG/ATLG	600 (70%)
PTCy	188 (22%)
aGVHD	
No/Yes	508 (59%)/210 (24%)
Grade II/IV aGVHD	141 (17%)
cGVHD	
No	680 (79%)
Yes	110 (13%)
Extensive cGVHD	69 (8%)
Time SCT-relapse (months)	
Mean (SD)/Median [Q1, Q3]	8.85 (10.1)/5.49 [3.0–11.1]
Survivors follow-up time (months)	
Mean (SD)/Median [Q1, Q3]	47.0 (24.5)/41.8 [29.2–65.57]

Abbreviations: aGVHD, acute graft versus host disease; AML, acute myeloid leukemia; ATG, anti thymocytes globulin; ATLG, anti T-lymphocytes globulin; BM, bone marrow; cGVHD, chronic graft versus host disease; CR, complete remission; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MMUD, mismatched unrelated donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cells; SC, stem cells; SCT, stem cell transplantation; UCB, umbilical cord-blood.

globulin (ATLG) in 70% of the cases ($n = 600$). At the time of disease recurrence, 757/859 patients (88%) had hematological relapse (more than 5% of blast cells in the bone marrow), whereas 102/859 patients (12%) showed minimal residual disease positivity or molecular mixed chimerism (either on CD34+ or mononuclear BM cells or on peripheral blood neutrophils and/or lymphocytes) (Figure S1). Moreover, 647/859 patients (75%) received a treatment for the relapse. In detail, 558/647 patients (86%) were treated with evidence of morphological relapse (more than 5% BM blasts), whereas 89/647 patients (14%) were treated in a pre-emptive setting (MRD positivity and/or mixed chimerism). HMAs±venetoclax therapy was the most frequently used salvage treatment (308/647 patients, 48%). 144/647 patients (22%) were treated with intensive chemotherapy at relapse, and 76/647 patients (12%) received an anti-FLT3 inhibitor. Twenty-one patients (3%) were addressed to a second allo-SCT, and 243/647 (38%) patients received DLI as part of the salvage therapy (Figure S1).

The cumulative incidence of post-transplant (pre-relapse) acute GVHD was 24% ($n = 210$), and this was clinically significant (grade II to IV) in 17% of the cases ($n = 141$). In parallel, 110 patients (13%) developed chronic GVHD following allo-SCT, before relapse. With a median follow up for survivors of 41.8 months (29.2–65.57), the 1- and 2-year OS of the whole population was 55% and 28%, respectively (Figure 1A). The 1- and 2-year RM was 39% and 56%, whereas the 1- and 2-year TRM was 6% and 15%, respectively (Figure 1B). Receiving a treatment for the relapse was associated with a significantly longer OS (at 1 and 2 years: 64% and 34% vs. 25% and 10%; $p < 0.001$; Figure 1C). By multivariable analysis, the age as a continuous variable (HR 1.01) was independently associated with impaired OS, whereas relapse occurring at least 12 months after transplant (HR 0.00), disease relapsing with MRD positivity and/or molecular mixed chimerism (HR 0.37), being in CR at allo-SCT (HR 0.59), transplant performed after 1 line of therapy (HR 0.82), and post-relapse therapy including DLI (HR 0.62) were significantly associated with an advantage in OS (Table S1). Focusing on RM, by multivariable analysis, the age at transplant as a continuous variable was the only factor independently associated with an increased risk (HR 1.01). On the other hand, relapse occurring at least 12 months from transplant (HR 0.38), disease relapsing with MRD positivity and/or molecular mixed chimerism (HR 0.47), disease in CR at allo-SCT (HR 0.59), and post-relapse therapy based on HMA±venetoclax (HR 0.56) were independently associated with reduced risk of RM. Post-relapse therapy including DLI confirmed its independent prognostic impact on TRM by multivariable analysis (HR 1.45) (Table S2).

Interestingly, 86% of the patients in the present series were treated at the time of hematological relapse. This point reflects the historical attitude of clinicians to wait for overt relapse after allo-SCT before giving any treatment. Consequently, the results of this study suffer from a bias selection, including mostly very high-risk patients. Nevertheless, we observe a significantly improved outcome if the relapse is treated (Figure 1C). Interestingly, 48% of the patients who were treated for disease relapse received HMAs±venetoclax, and only 22% of the treated patients received intensive chemotherapy as part of the salvage therapy (Figure S1). This is a consequence of the well-known toxic profile associated with the low cure rate of conventional

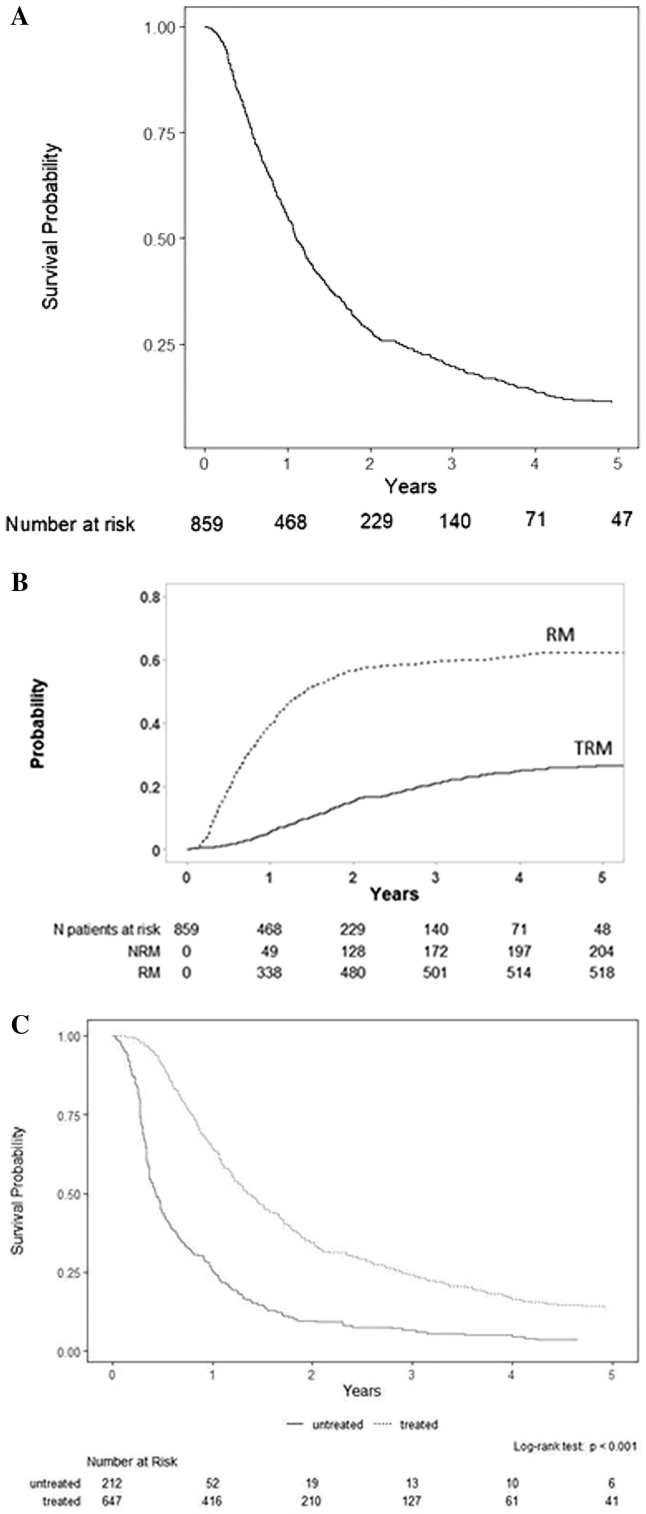

FIGURE 1 | Overall survival (OS) of the series (A; 1-year OS = 55%, 2-year OS = 28%); Cumulative Incidence of RM and $_{T}$RM (B; 1-year RM = 39%, 2-year RM = 56%; 1-year TRM = 6%, 2-year TRM = 15%); OS of treated versus untreated patients (C; treated: 1-year OS = 64%, 2-year OS = 34%; Untreated: 1-year OS = 25%, 2-year OS = 10%).

chemotherapy in patients relapsing after allo-SCT. The extremely low rate of second allo-SCT (3%) similarly reflects the reluctance of clinicians to perform such a procedure, frequently associated with high transplant-related mortality, particularly in the presence of active disease, and with such a short median time from transplant to relapse (5.49 months). Moreover, the second transplant has become more frequently and easily performed following the spread in the world of haploidentical allo-SCT with post-transplant cyclophosphamide, and in Italy, between 2015 and 2021, this latter procedure was starting to become widely adopted. The results of the multivariable analysis on OS, RM, and TRM are somehow expected, with the conventional factors independently associated with better or dismal prognosis (Tables S1 and S2). An interval from transplant to relapse ≥ 12 months was independently associated with both improved OS and reduced RM. Moreover, patients with morphological evidence of disease at relapse (more than 5% of BM blast cells) show a dismal OS and an increase in RM. This strongly suggests the benefit of a pre-emptive approach at the time of MRD positivity and/or molecular mixed chimerism. Similar results were observed in our Italian and French retrospective study on 134 patients [4] and by Zuanelli Brambilla and colleagues on a case series of 148 AML/MDS relapses [5]. Moreover, the favorable impact of DLI in association with post-relapse therapy is the indirect proof of the graft versus leukemia effect, and this is confirmed also in the subset of patients treated with HMAs±venetoclax (data not shown). The benefit of DLI in association with salvage therapy is also highlighted in the multivariable analysis on RM (HR 0.56). Notably, the increased risk of TRM when DLI are used (HR 1.45) does not hamper their benefit on OS and RM (Table S2). Several single-center and registry studies highlighted the efficacy of administration of DLI following disease relapse after allo-SCT, in particular if these were administered in a pre-emptive setting, and other preliminary data suggest some benefit of prophylactic DLI for high-risk AML [6].

The major limit of our study is its retrospective design. As a consequence, many data have been collected following specific queries with possible biases and limiting the availability of more detailed analysis. In the meantime, the multicentric nature of this study and the relatively large number of patients included make the findings quite strong and reliable. These results may be the starting point to design prospective studies including early pre-emptive therapy in the presence of MRD positivity and/or molecular chimerism failure, possibly including new agents (e.g., HMAs±venetoclax) in combination with DLI.

Affiliations

[1]Chair of Hematology, University of Brescia, Brescia, Italy | [2]Adult Bone Marrow Transplant Unit, Program of Cellular Therapy and Research in Hematology, ASST Spedali Civili di Brescia, Brescia, Italy | [3]BMT Unit, AOR Villa Sofia Cervello, Palermo, Italy | [4]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Italy | [5]Department of Clinical and Experimental Science, University of Brescia, Brescia, Italy | [6]University of Milan, Milan, Italy | [7]Hematology and Stem Cell Transplantation and Cellular Therapies Unit, Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy | [8]UO Ematologia e CTMO, Ospedale Guglielmo da Saliceto, Piacenza, Italy | [9]Division of Pediatric Hematology, Oncology and Stem Cell Transplant, Padova University Hospital, Padova, Italy | [10]Dipartimento di Ematologia, Presidio Ospedaliero S. Bortolo, Vicenza, Italy | [11]SS Trapianto Allogenico Cellule Staminali, AOU Citta' della Salute e della Scienza, Torino, Italy | [12]Cell Therapy and Transfusion Medicine Unit, Careggi University Hospital, Florence, Italy | [13]Hematology and

Transplant Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy | [14]Ematologia e Centro Trapianti di Midollo, Comprensorio di Bolzano, Azienda Ospedaliera Alto Adige, Bolzano, Italy | [15]Department of Onco Hematology, UOC Stem Cell Transplant, Fondazione Policlinico Tor Vergata, Rome, Italy | [16]Department of Diagnostic Imaging, Oncological Radiotherapy and Hematology, Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy | [17]Unità Operativa di Ematologia con TMO, A.O.R. S. Carlo, Potenza, Italy | [18]Struttura Complessa Ematologia, Unità Trapianti di Midollo, AOU Policlinico di Modena, Italy | [19]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy | [20]Internal Medicine and Haematology Division, San Luigi University Hospital, Turin, Italy | [21]UOC Hematology and Transplant, Vito Fazzi, Lecce, Italy | [22]UOC di Ematologia e Terapia Cellulare, Ospedale C e G Mazzoni, Ascoli Piceno, Italy | [23]UOC Ematologia, AOU Policlinico Umberto I, Sapienza University of Rome, Rome, Italy | [24]Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy | [25]Haematology Unit, San Gerardo Hospital, Monza, Italy | [26]Hematologic Clinic and Transplant Center, University Hospital of Central Friuli, DMED, University of Udine, Udine, Italy | [27]Department of Hematology and Bone Marrow Transplantation, "Card. G. Panico" Hospital, Tricase, Italy | [28]Stem Cell Transplant Program AORN Cardarelli, Naples, Italy and Biomedicine and Prevention Department of Tor Vergata University, Rome, Italy | [29]SC Ematologia e CTMO", Ospedale Businco, ARNAS Brotzu, Cagliari, Italy | [30]Unit of Bone Marrow Transplantation – Division of Hematology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy | [31]Hematology and BMT Unit, AOU of Parma, Parma, Italy | [32]BMT Unit. ASST Papa Giovanni XXIII, Bergamo, Italy | [33]Clinica Ematologica, Universita' di Catania, Catania, Italy | [34]Hematology and Transplant Unit, AOU San Giovanni di Dio e Ruggi d'Aragona, Department of Medicine and Surgery, University of Salerno, Fisciano, Italy | [35]UOC Ematologia Ospedale dell'Angelo Venezia Mestre, Venezia Mestre, Italy | [36]Ematologia con Trapianto, Ospedale A. Perrino, Brindisi, Italy | [37]Department of Medicine, Hematology and Bone Marrow Transplant Unit, Verona University, Verona, Italy | [38]GITMO Trial Office, Geno, Italy

Ethics Statement

All patients included in the registry provided informed consent for data registration in the PROMISE database. The study was conducted in compliance with current national and European legislation on clinical trials and in accordance with the Declaration of Helsinki and the principles of good clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. F. Kreidieh, I. Abou Dalle, N. Moukalled, et al., "Relapse After Allogeneic Hematopoietic Stem Cell Transplantation in Acute Myeloid Leukemia: An Overview of Prevention and Treatment," *International Journal of Hematology* 116, no. 3 (2022): 330–340, https://doi.org/10.1007/s12185-022-03416-7.

2. M. Gooptu, H. M. Murdock, and R. J. Soiffer, "How I Treat AML Relapse After Allogeneic HCT," *Blood* 24 (2024): 2024025705, https://doi.org/10.1182/blood.2024025705.

3. A. Latouche, R. Porcher, and S. Chevret, "A Note on Including Time-Dependent Covariate in Regression Model for Competing Risks Data," *Biometrical Journal* 47 (2005): 807–814.

4. E. Accorsi Buttini, C. Doran, M. Malagola, et al., "Donor Lymphocyte Infusion in the Treatment of Post-Transplant Relapse of Acute Myeloid Leukemias and Myelodysplastic Syndromes Significantly Improves Overall Survival: A French-Italian Experience of 134 Patients," *Cancers* 16, no. 7 (2024): 1278, https://doi.org/10.3390/cancers16071278.

5. C. Zuanelli Brambilla, S. M. Lobaugh, J. D. Ruiz, et al., "Relapse After Allogeneic Stem Cell Transplantation of Acute Myelogenous Leukemia and Myelodysplastic Syndrome and the Importance of Second Cellular Therapy," *Transplant Cell Therapy* 27, no. 9 (2021): 771.e1–771.e10, https://doi.org/10.1016/j.jtct.2021.05.011.

6. F. Patriarca, A. Sperotto, F. Lorentino, et al., "Donor Lymphocyte Infusions After Allogeneic Stem Cell Transplantation in Acute Leukemia: A Survey From the Gruppo Italiano Trapianto Midollo Osseo (GITMO)," *Frontiers in Oncology* 15, no. 10 (2020): 572918, https://doi.org/10.3389/fonc.2020.572918.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Univariable and Multivariable analysis on Overall Survival. **Table S2:** Univariable and Multivariable analysis on Relapse Mortality and Treatment-Related Mortality. **Figure S1:** Flow chart of the post-relapse treatment of our series.