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RESEARCH ARTICLE

Allogeneic Hematopoietic Stem Cell Transplantation for Elderly Acute Lymphoblastic Leukemia Patients: A Registry Study From the Société Francophone de Greffe de Moelle et Thérapie Cellulaire (SFGM-TC)

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ABSTRACT

There are very limited data regarding the outcomes of elderly patients with acute lymphoblastic leukemia (ALL) who undergo allogeneic hematopoietic stem cell transplantation (alloHSCT). A total of 316 ALL patients aged ≥60 years who underwent alloHSCT between 2010 to 2022 were identified in the SFGM-TC registry. The primary objective was to evaluate progression-free survival (PFS), non-relapse mortality (NRM), relapse incidence (RI), and graft-versus-host disease (GvHD)-free relapse-free survival (GRFS), as well as their risk factors. The median age was 63.8 years (range 60–75.8), 49.8% of patients had Philadelphia-positive B-ALL (Ph + ALL), and 70.9% were in first complete remission (CR1) at transplantation. The donor was an unrelated donor in 52.1%, a matched related donor (MRD) in 26.3%, and a haplo-identical donor in 17.7%. Reduced-intensity conditioning (RIC) was administered to 64.6% of patients, while total body irradiation (TBI) was used in 35.8%. The 3-year overall survival (OS) was 46% (95% CI 40%–53%). The 3-year PFS, NRM, RI, and GRFS were 41% (95% CI 35%–48%), 23% (95% CI 18%–28%), 36% (95% CI 31%–42%), and 30% (95% CI 25%–37%), respectively. Multivariable analyses confirmed poorer OS and PFS in patients with advanced disease, with an HR of 1.79 (95% CI 1.22–2.64), $p = 0.0032$. Additionally, the ALL subtype significantly impacted outcomes, with an HR of 1.99 (95% CI 1.42–2.79) for non-Ph + ALL. This study suggests that alloHSCT is a viable option for elderly ALL patients, as age itself did not impact outcomes. However, advanced disease and non-Ph + ALL were associated with significantly worse survival.

1 | Introduction

Acute lymphoblastic leukemia (ALL) is predominant in children and young adults, and significant progress in treatments has been made for this population over the last decade, with a 5-year overall survival (OS) rate exceeding 90% [1]. In adults, there has also been an improvement in outcomes with pediatric-inspired strategies, particularly in younger adults under 60 years

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[2–4], but for the older population (over 60 years old), results have been less satisfactory, with a 5-year OS rate below 30%. For Philadelphia positive (Ph+) ALL, which represents an important proportion of ALL in the elderly population (35%–50%) [5], the advent of tyrosine kinase inhibitors (TKI) has revolutionized treatment strategies and improved the outcomes of Ph + ALL patients, with an OS at 2 years ranging from 36% with the first-generation TKI imatinib to 97% with the third-generation TKI ponatinib [6]. However, for elderly patients, the results remain suboptimal, with a 5-year OS of 36% in the EWALL-PH-01 study [7]. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a therapeutic strategy that offers a chance to cure high-risk patients suffering from ALL [8–10]. With the introduction of reduced intensity conditioning regimens, which decrease non-relapse mortality (NRM), transplantation has been increasingly used in the older population at the cost of a higher incidence of relapse (RI) [11–14]. A Danish population-based study on alloHSCT for adult ALL patients also showed improved outcomes over the years, with a 2-year OS of 49% (95% CI 27%–66%) in 2000 versus 77% (95% CI 59%–88%) in 2019 [15].

The type of conditioning also seems to be important for ALL patients, particularly in the case of myeloablative conditioning (MAC), with retrospective analyses suggesting an advantage of the incorporation of total body irradiation (TBI) into the regimens compared to a chemotherapy-only regimen in terms of OS as well as leukemia-free survival (LFS), related to a lower RI [16–18]. On the other hand, a recent randomized phase 3 study from China involving ALL patients aged 14–65 years showed that busulfan-cyclophosphamide (BuCy) was non-inferior to CyTBI, but used 4.5 Gy × 2 days, which is not the usual TBI MAC dosing [19]. In the older population, patients are usually not eligible for MAC regimens, and the question of RIC with or without TBI remains a matter of debate, with conflicting results. A retrospective analysis by the European Society for Blood and Marrow Transplantation (EBMT) showed improved LFS due to a lower RI with the Fludarabine-TBI 8 Gy (4 × 2 Gy) conditioning regimen compared to fludarabine-busulfan (6.4 mg/kg or 9.6 mg/kg) [20], however, another study from the same group did not show any significant difference between fludarabine-Bu, fludarabine-melphalan, and fludarabine-TBI [21].

There are very few studies focused on alloHSCT for elderly ALL. The one published dataset by the EBMT group suggested that for a selected group of elderly patients, including patients in first complete remission (CR1) with matched sibling donors and with cytomegalovirus (CMV) donor-recipient matching other than CMV donor+/recipient+, alloHSCT is a viable option with 3-year OS and LFS rates of 42% and 35%, respectively [22].

We, therefore, wanted to analyze the outcomes of ALL patients aged 60 years or over in a recent era within the Société Francophone de Greffe de Moelle et Thérapie Cellulaire (SFGM-TC) registry database and also to determine if TBI conditioning could be beneficial or not in this population.

2 | Patients and Methods

This is a retrospective, multicenter, registry-based analysis approved by the SFGM-TC. The SFGM-TC is a non-profit, scientific society representing 54 transplant centers in French-speaking countries. Data is entered, managed, and maintained in a central database with internet access; each center is represented within this database. Patient selection included patients aged 60 years or older undergoing their first alloHSCT for ALL between 2010 and 2022 from a matched (10/10) or mismatched (< 10/10) related or unrelated donors. Performance status was assessed via the reported Karnofsky Performance Status (KPS) and comorbidities via the hematopoietic cell transplantation-specific comorbidity index (HCT-CI). Based on these criteria, 316 adults were identified in the registry database.

Neutrophil engraftment was defined as the time at which the absolute neutrophil count was $> 0.5 \times 10^9$/L for 3 consecutive days, and platelet engraftment as a platelet count $> 20 \times 10^9$/L for 7 consecutive days without transfusion support. Primary graft failure (PGF) was defined as failing to reach a neutrophil count of $> 0.5 \times 10^9$/L within the first 28 days post stem cell transplantation or as documentation of autologous reconstitution by chimerism analysis in the absence of relapse. Secondary graft failure was defined by the treating physician: standard criteria across Europe define it as loss of a functioning graft demonstrated by cytopenia in at least two lineages and loss of donor chimerism. Complete remission (CR) was defined as meeting all the following criteria: Hb > 10 g/dL, platelet count $> 100 \times 10^9$/L and neutrophils $> 1.5 \times 10^9$/L with fewer than 5% blasts in the bone marrow. Relapse was defined as the loss of CR. In this study, CR and relapse were determined by the treating physician. Conditioning regimens were defined as MAC if they contained either TBI at a dose greater than 6 Gy, oral busulfan at a dosage greater than 8 mg/kg, or intravenous busulfan at a dose greater than 6.4 mg/kg. Grading of acute GvHD (aGvHD) was performed according to two different criteria depending on the year of aGvHD diagnosis [23, 24]. Chronic GvHD (cGvHD) was assessed using two established NIH criteria [25, 26]. Based on the information reported in the registry, the severity of cGvHD was graded according to the classical criteria (limited vs. extensive).

SFGM-TC studies are approved by an institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. SFGM-TC centers commit to obtaining informed consent in compliance with the local regulations applicable at the time of transplantation to report pseudonymized data.

3 | Statistics

The median and interquartile range (IQR) were used to summarize quantitative variables, and frequencies and percentages were used to summarize categorical variables. The study endpoints were OS, progression-free survival (PFS), RI, NRM, aGvHD, cGvHD, and GvHD-free relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. OS was defined as the time from transplantation to death from any cause. PFS was defined as survival with no evidence of relapse or progression. NRM was defined as death from any cause without a prior relapse or progression. We applied modified GRFS criteria. GRFS events were defined as the first event

among grade III-IV aGvHD, extensive cGvHD, relapse, or death from any other cause [27].

The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. The RI and NRM were calculated using cumulative incidence (CI) functions in a competing risk setting, with death in remission considered a competing event for relapse. To estimate the CI of acute or chronic GvHD, relapse and death were considered competing events. Univariable analyses were performed using the log-rank test for LFS and OS, while Gray's test was used for CI. Multivariable analyses were performed using the Cox proportional-hazards regression model [28]. All factors known to be associated with outcomes were included in the models. To account for heterogeneity across centers, a random effect (also referred to as a frailty effect) was introduced in Cox multivariable models. This random effect was shared by all patients within the same center [29].

4 | Results

4.1 | Patient Characteristics

Between 2010 and 2022, a total of 316 patients aged ≥ 60 years received alloHSCT for ALL at 36 participating centers. The median follow-up was 34.5 months (IQR: 29.5–38.8 months). The median time from diagnosis to transplantation was 7 months (IQR: 5.7–10.3 months). Fifteen patients received blinatumomab and eight received inotuzumab ozogamicin prior to transplantation. Patients' characteristics are described in Table 1. The median age at transplantation was 63.8 (range 60–75.8) years. Most patients had Ph + ALL (49.8%), were in CR1 at transplantation (70.9%), had an intermediate disease risk index (71.3%) [30], and received a matched-unrelated donor (MUD) transplantation (44.9%) with peripheral blood stem cells (PBSC) as the stem cell source (93%). Anti-thymocyte globulin (ATG) was given in 69.6% of cases; 157 patients received Thymoglobuline, 46 Grafalon, and it was unknown for 16 patients. TBI (all doses) was administered to only 35.8% and RIC to 64.6%. Cytogenetic results were known for 47.5% of patients, with 92% of them in cytogenetic CR. Molecular results were known for 66.3% of patients, of whom 60.5% were in molecular CR (defined as the absence of a molecular marker if present at the time of diagnosis) at transplantation. Seventy-four patients received TKIs after transplantation, although the specific indication was not documented. TKIs were likely administered either as maintenance therapy, in response to molecular progression, or at relapse. Moreover, 33 patients received at least one donor lymphocyte infusion (DLI), with a median time from alloHSCT to the first DLI of 7.6 months (IQR: 3.5–14.3 months), administered for molecular progression, mixed chimerism, or hematological relapse.

4.2 | Engraftment, Acute and Chronic GvHD

The cumulative incidence of engraftment at day 28 was 96% (95% CI 93%–98%).

At day 180, the cumulative incidence of acute GvHD grade II–IV was 33% (95% CI 28%–38%, Figure 1A) and the cumulative incidence of grade III–IV was 11% (95% CI 8%–15%, Figure 1B). In univariable analysis, the only factor that affected the incidence of acute GvHD grade III–IV was the Ph + ALL subtype, with 15% (95% CI 10%–22%) at day 180 versus all other types at 8% (95% CI 4%–13%), $p = 0.043$ (Table S1). This was not confirmed in the multivariable analysis (Table 2). All other factors, notably age (< or > 65 years), year of transplantation, female donor for a male patient, conditioning (MAC or RIC), and whether the patient had received TBI or not, did not have a significant impact (Table S1, univariable analysis and Table 2, multivariable analysis). At 36 months, the cumulative incidence of chronic GvHD was 35% (95% CI 30%–41%, Figure 1C), and the incidence of extensive chronic GvHD was 21% (95% CI 16%–26%, Figure 1D). The factors influencing the incidence of chronic GvHD were the time from diagnosis to alloHSCT (49% [95% CI 37%–59%] if < 6 months versus 30% [95% CI 23%–36%] if > 6 months), a CMV-negative serology donor for a CMV-positive patient (49% [95% CI 38–60] vs. 30% [95% CI 24–37]), and having received TBI (46% [95 CI 35%–56%] vs. no TBI at 29% [95% CI 23%–36%]) (Table S1). In addition to the previous risk factors, extensive cGVHD was also influenced by the ALL subtype, with a higher incidence at 36 months for Ph + ALL (28% [95% CI 20%–37%]) compared to other subtypes (14% [95% CI 9%–21%]) (Table S1). In multivariable analysis, the only significant risk factor for chronic GVHD was a short interval between diagnosis and transplantation (< 6 months, HR: 0.6, 95% CI 0.37–0.95), Table 2.

4.3 | Relapse Incidence and NRM

There were 101 relapses, of which 7 were extramedullary and 12 both extramedullary and hematological. The 3-year cumulative relapse incidence (RI) was 36% (95% CI 31%–42%), Figure 2A. In univariable analysis, the factors that influenced RI were the year of alloHSCT (2018–22: 30% [95% CI 22%–39%] vs. 2010–17, 42% [95% CI 34%–50%], $p = 0.022$), the disease status at alloHSCT (advanced disease/≥ CR2 patients: 54% [95% CI 42%–65%] vs. CR1: 29% [95% CI 23%–36%], $p = 0.0042$), the donor type, with lower RI observed in patients transplanted with UD (UD: 31% [95% CI 23%–38%], haploidentical donors: 34% [95% CI 20%–49%] vs. MSD: 50% [95% CI 38%–61%], $p = 0.011$), the CMV serostatus (donor-negative/patient-positive: 19% [95% CI 11%–29%] vs. other combinations: 43% [95% CI 35%–50%], $p < 0.001$), having received or not (TBI: 27% [95% CI 18%–36%] versus no TBI: 42% [95% CI 34%–49%], $p = 0.0069$), and finally the ALL subtype, with a lower RI observed in patients with Ph + ALL (Ph + ALL: 26% [95% CI 19%–34%] versus other ALL: 47% [95% CI 38%–55%], $p < 0.001$), Table S2. In multivariable analyses, the factors that remained significant were the ALL subtype, with an HR of 0.5 (95% CI 0.33–0.76) for Ph + vs. all other types, $p = 0.0011$, the disease status at alloHSCT, with an HR of 2.4 (95% CI 1.5–3.84) for advanced disease/≥ CR2 versus CR1, $p = 0.0003$, and the CMV serostatus, with an HR of 0.40 (95% CI 0.23–0.69) for donor-negative/recipient-positive versus all other combinations, $p = 0.001$, Table 3.

The 3-year cumulative incidence of NRM was 23% (95% CI 18%–28%), Figure 2B. In univariable analysis, none of the factors had a significant impact on NRM (Table S2), as well as in multivariable analysis (Table 3).

TABLE 1 | Patient characteristics.

Characteristics	*N* = 316
Median age at HSCT (IQR)	63.8 (61.8–66.5)
Median age at diagnosis (IQR)	63. (61–65.4)
Median time from diagnosis to HSCT (IQR) months	7.05 (5.7–10.3)
Median year of HSCT (IQR)	2017.5 (2015–2020)
Median age of the donor (IQR)	37.4 (26.7–54.7)
Missing	7
Median follow-up of alive patients (IQR) months	34.5 (29.5–38.8)
ALL subtype	
B-ALL Ph—	81 (25.9%)
B-ALL Ph+	156 (49.8%)
T-ALL	42 (13.4%)
Other/unknown	37 (11.7%)
Patient's sex	
Female	156 (49.4%)
Male	160 (50.6%)
Disease status at HSCT	
CR1	224 (70.9%)
≥ CR2	74 (23.4%)
Not in CR (advanced)	18 (5.7%)
Cytogenetic CR	
Cytogenetic CR	138 (43.7%)
No cytogenetic CR	12 (3.8%)
Missing	166 (52.5%)
Molecular CR	
Molecular CR	121 (38.3%)
No molecular CR	79 (25%)
Missing	116 (36.7%)
DRI	
High	72 (22.9%)
Intermediate	224 (71.3%)
Very high	18 (5.7%)
Missing	2
Type of donor	
Haplo-identical	56 (17.7%)
MSD	83 (26.3%)
MUD	142 (44.9%)
MMUD	23 (7.3%)
UD missing HLA	12 (3.8%)
Source of stem cell	
BM	22 (7%)
PBSC	294 (93%)
Comorbidity index (Sorror)	
≥ 3	76 (32.5%)
1–2	53 (22.6%)
0	105 (44.9%)
Missing	82
Donor's sex	
Female	93 (29.5%)
Male	222 (70.5%)
Missing	1
Donor to patient's sex	
Female to male	44 (14%)
Other	271 (86%)
Missing	1
CMV donor/patient	
Neg/Neg	84 (26.8%)
Neg/Pos	93 (29.7%)
Pos/Neg	24 (7.7%)
Pos/Pos	112 (35.8%)
Missing	3
PTCY	
Yes	64 (20.3%)
No	252 (79.7%)
ATG	
Yes	220 (69.6)
No	96 (30.4%)
GvHD prophylaxis	
Calcineurin inhibitors	292 (92.4%)
MMF	163 (51.6%)
Methotrexate	92 (29.1%)
Conditioning	
RIC	204 (64.6%)
MAC	112 (35.4%)

(Continues)

TABLE 1 | (Continued)

Characteristics	*N* = 316
Missing	0
TBI	
No TBI	203 (64.2%)
BU-FLU	127 (40.2%)
BU-FLU-THIO	45 (14.2%)
Others	31 (9.8%)
TBI	113 (35.8%)
Missing	0
TBI and dose	
No TBI	203 (64.4%)
TBI < 8 Gy (2 Gy *n* = 31, 4 Gy *n* = 4, 6 Gy *n* = 8)	43 (13.7%)
TBI 8 Gy	69 (21.9%)
Missing	1

Abbreviations: ALL: acute lymphoblastic leukemia, ATG: antithymocyte globulin, BM: bone marrow, BU-FLU: Busulfan-Fludarabine, BU-FLU-THIO: Busulfan-Fludarabine-Thiotepa., CR: complete remission, DRI: disease risk index, Gy: gray, HSCT: hematopoietic stem cell transplantation, IQR: interquartile range, MAC: myeloablative conditioning, MMF: mycophenolate mofetil, MMUD: mismatched unrelated donor, MSD: matched sibling donor, MUD: matched unrelated donor, PBSC: peripheral blood stem cell, Ph−: Philadelphia negative, Ph+: Philadelphia positive, PTCY: post-transplant cyclophosphamide, RIC: reduced intensity conditioning, TBI: total body irradiation.

4.4 | OS, PFS and GRFS

The estimated 3-year OS was 46% (95% CI 40%–53%), Figure 2C. In univariable analyses, the factors that significantly affected OS were the disease status at transplantation with a lower OS of 29% (95% CI 20%–43%) at 36 months for advanced disease/≥ CR2 patients compared to 53% (95% 46%–60%) for patients in CR1, $p < 0.001$, and the ALL subtype, with better OS observed in patients with Ph + ALL (OS at 36 months: 59% [95% CI 51%–68%] vs. 33% [95% CI 26%–43%] for all other subtypes, $p < 0.001$); Table S2. This was confirmed in multivariable analyses, with an HR of 1.79 (95% CI 1.22–2.64) for advanced disease/≥ CR2 vs. patients in CR1, $p = 0.003$ and an HR of 0.5 (95% CI 0.39–0.70) for Ph + ALL vs. all other ALL subtypes, $p < 0.0001$; Table 3.

The 3-year estimate of PFS was 41% (95% CI 35%–48%), Figure 2D. In univariable analyses, the factors that significantly affected PFS were the year of alloHSCT with better PFS at 36 months for patients transplanted during 2018–22 (48% [95% CI 39%–59%] vs. 35% [95% CI 28%–43%] for 2010–17), the disease status at transplantation with lower PFS at 36 months for those with advanced disease/CR ≥ 2 (22% [95% CI 14%–35%] vs. 49% [95% 42%–57%] for patients in CR1), conditioning with TBI, with higher PFS observed in patients who received TBI (PFS of 49% [95% CI 39%–61%] vs. 37% [95% CI 30%–45%] for those without TBI, and finally the ALL subtype), with better PFS at 36 months observed in patients with Ph + ALL (51% [95% CI 43%–61%] vs. 32% [95% CI 24%–41%] for all other subtypes); Table S2. The factors that remained significant in multivariable analysis were the

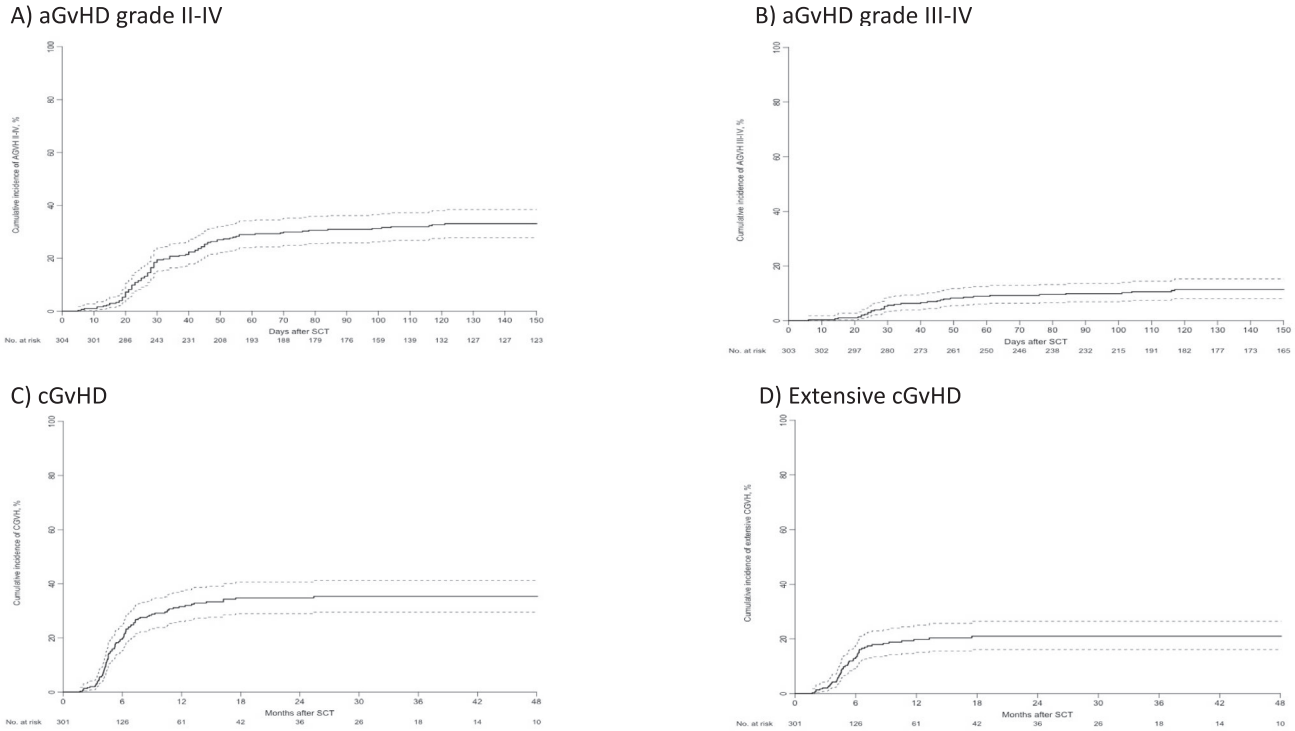

FIGURE 1 | (A) Cumulative incidence of acute graft-versus-host disease (aGvHD) grade II–IV of ALL patients who received allogeneic hematopoietic stem cell transplantation (allo-HSCT) was 33% (95% CI 28%–38%) at 180 days. (B) Cumulative incidence of aGvHD grade III–IV was 11% (95% CI 8%–15%) at 180 days. (C) Cumulative incidence of chronic GvHD (cGvHD) at 3 years was 35% (95% CI 30%–41%). (D) Cumulative incidence of extensive cGvHD at 3 years was 21% (95% CI 16%–26%). Numbers below the graph show the number of patients at risk.

TABLE 2 | Multivariable analysis for acute and chronic GvHD and GRFS at 36 months.

	aGvHD		cGvHD		GRFS	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age						
Five years increase	0.71 (95% CI 0.5–1)	0.053	1.04 (95% CI 0.76–1.43)	0.805	0.96 (95% CI 0.76–1.22)	0.733
ALL subtype						
Other vs. B Phi+	1.17 (95% CI 0.78–1.76)	0.439	0.75 (95% CI 0.5–1.12)	0.157	1.34 (95% CI 1.01–1.78)	0.046
Time form Dx to SCT						
Above 6 months vs. under 6 months	1.1 (95% CI 0.69–1.76)	0.680	0.6 (95% CI 0.37–0.95)	0.0289	0.56 (95% CI 0.4–0.79)	0.00085
Disease status at SCT						
CR2+/Not in CR vs. CR1	0.82 (95% CI 0.5–1.34)	0.429	1.52 (95% CI 0.9–2.56)	0.114	1.94 (95% CI 1.38–2.73)	0.00013
Donor to patient CMV						
Other vs. Neg/Pos	0.72 (95% CI 0.47–1.1)	0.131	0.58 (95% CI 0.38–0.89)	0.0132	1.09 (95% CI 0.79–1.49)	0.599
Donor to patient sex						
Female to male vs. other	0.93 (95% CI 0.52–1.65)	0.802	0.88 (95% CI 0.49–1.59)	0.674	0.86 (95% CI 0.57–1.31)	0.495
ATG						
No ATG vs. ATG	1.4 (95% CI 0.87–2.23)	0.163	0.62 (95% CI 0.38–1.02)	0.0594	0.95 (95% CI 0.68–1.34)	0.773
Conditioning						
MAC vs. RIC	0.91 (95% CI 0.56–1.48)	0.707	1.01 (95% CI 0.59–1.71)	0.981	1.09 (95% CI 0.76–1.56)	0.657
TBI						
TBI vs. no TBI	1.16 (95% CI 0.71–1.89)	0.552	1.34 (95% CI 0.79–2.29)	0.277	0.89 (95% CI 0.62–1.28)	0.531

Abbreviations: aGvHD: acute graft-versus-host disease, ALL: acute lymphoblastic leukemia, ATG: antithymocyteglobulin, cGvHD: chronic graft-versus-host disease, cGvHDext: chronic extensive graft-versus-host disease, CMV: cytomegalovirus, CR: complete remission, Dx: diagnosis, GRFS: GvHD free relapse free survival, MAC: myeloablative conditioning, Ph−: Philadelphia negative, Ph+: Philadelphia positive, SCT: stem cell transplantation, TBI: total body irradiation.

disease stage with an HR of 2.07 (95% CI 1.43–3) for advanced disease/CR ≥2 vs. CR1 patients, $p = 0.0001$, and the ALL subtype with an HR of 0.61 (95% CI 0.45–0.85) for Ph + ALL vs. all other ALL subtypes, $p = 0.0029$, Table 3.

The 3-years estimate of GRFS was 30% (95% CI 25%–37%). In univariable analyses, the factors that significantly affected GRFS were the year of alloHSCT, with better GRFS at 36 months for patients transplanted during 2018–22 (40% [95% CI 31%–51%] vs. 23% [95% CI 9%–59%] for 2010–17), the disease status at transplantation, with lower GRFS at 36 months for advanced disease/≥CR2 patients (20% [95% CI 13%–32%] vs. 35% [95% 28%–43%] for patients in CR1), and the ALL subtype, with better GRFS at 36 months observed in patients with Ph + ALL (37% [95% CI 30%–47%] vs. 24% [95% CI 18%–33%] for all other subtypes, $p = 0.027$), Table S1. In multivariable analyses, three factors significantly affected GRFS: the time from diagnosis to transplant (HR: 0.56 [95% CI 0.4–0.79] for a time of 6 months vs. less than 6 months), the advanced disease status at SCT (HR: 1.94 [95% CI 1.38–2.73] for advanced vs. CR1) and the ALL subtype (HR: 0.74 [95% CI 0.56–0.99] for Ph + vs. other subtypes); Table 2.

5 | Discussion

As alloHSCT is considered the standard of care for high-risk ALL patients, including Ph− and Ph+ ALL [8, 9], the question of an age cutoff for this procedure arises. Most prospective trials involving ALL patients that recommend alloHSCT have included patients with an upper age limit of 60 years because of the increased risk of NRM related to the procedure [10, 31–36]. Therefore, we analyzed retrospective data from the SFGM-TC registry to evaluate the outcomes of alloHSCT and to explore the

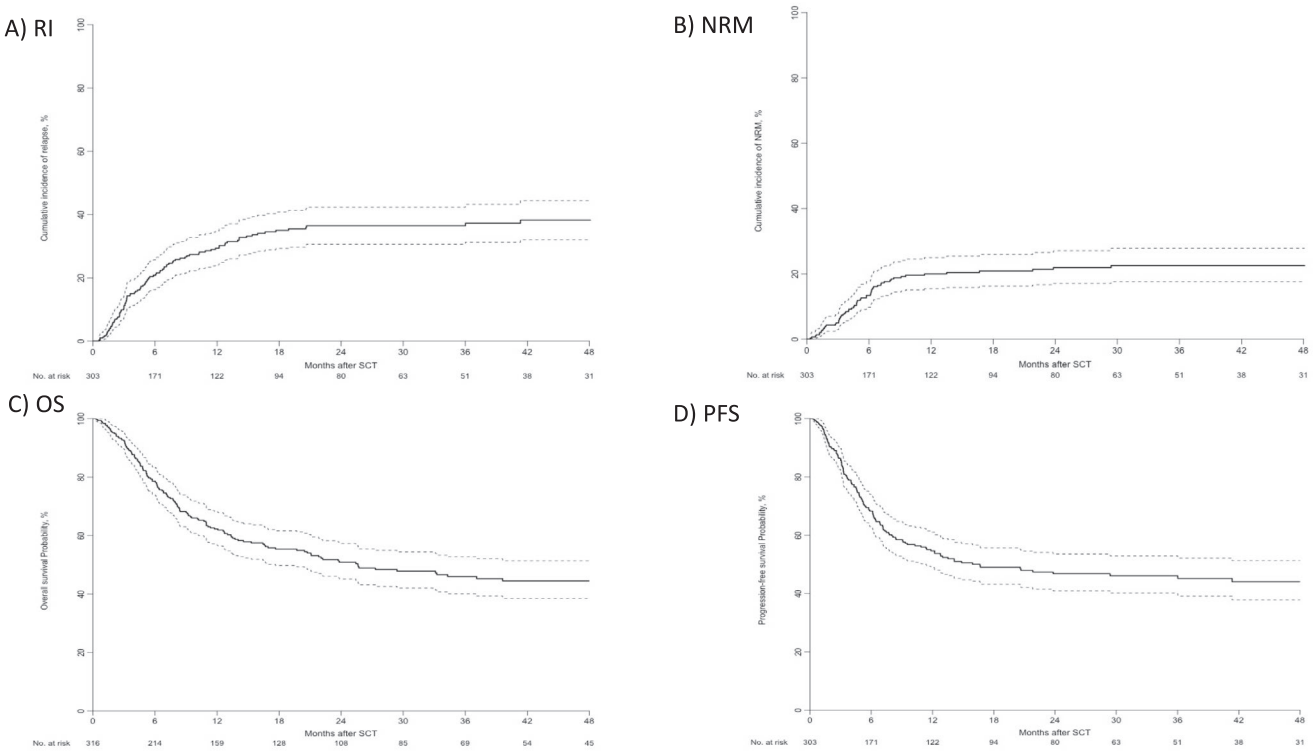

FIGURE 2 | (A) Relapse incidence (RI) at 3 years: 36% (95% CI 31%–42%), (B) non-relapse mortality (NRM) at 3 years: 23% (95% CI 18%–28%), (C) overall survival (OS) at 3 years; 46% (95% CI 40%–53%), and (D) progression free survival (PFS) at 3 years: 41% (95% CI 35%–48%) of ALL patients who received allogeneic hematopoietic stem cell transplantation (allo-HSCT). Numbers below the graph show the number of patients at risk.

feasibility of this procedure in patients over 60 years, identifying key factors that may influence its success.

This registry study describes the outcomes of an elderly ALL population aged 60 to 75 years who underwent alloHSCT with various donor types between 2010 and 2022. We demonstrated that, in a substantial number of patients ($n = 316$), alloHSCT can be a viable option for a carefully selected population fit for transplantation. Despite the fact that a third of patients had a high HCT-CI (≥ 3), the 3-year OS and PFS were 46% and 41%, respectively, and even 56% and 51% for the Ph + ALL subtype. Within this age range (60 to 75 years), age did not significantly impact any outcome, neither on univariable (< 65 years vs. 65 years) nor multivariable analysis (by 5-year increase). That suggests that, within this age range, transplantation is feasible when patients are appropriately selected. This contrasts with the study by the CIBMTR which spanned an earlier period between 2001 and 2011 and had a median age of 61 years, showing an increased overall mortality for patients aged 66 years and above, with a hazard ratio (HR) of 1.51 (95% CI 1.00–2.229), $p = 0.05$ [13]. It is difficult to compare both studies, as they were conducted in different periods and involved different patient populations (the CIBMTR study included only B-ALL patients). However, improvements in supportive care, new antibiotics, anti-infectious prophylaxis, and the increased use of RIC in recent years have all contributed to reducing NRM incidence across all age groups, making age less of a limiting factor today. Notably, there was no influence of age (by 5-year increase) in multivariable analysis on aGvHD, cGvHD, or GRFS. On the other hand, the Acute Leukemia Working Party of the EBMT reported on patients who underwent transplantation between 2005 and 2014, exclusively with RIC, with median age and high HCT-CI proportions similar to those in the SFGM-TC study [22]. Both studies, although retrospective registry-based, suggest that alloHCT is feasible for a specific, carefully selected elderly population, yielding reasonable outcomes in terms of OS and PFS for this age group. These findings may assist physicians in decision-making when treating elderly ALL patients.

The conditioning regimen also plays a crucial role, both in terms of intensity and type, particularly regarding the inclusion of TBI [16–18]. In our analysis, MAC accounted for 35% of conditioning regimens, which remains relatively high for this older population. However, the patients who received MAC were likely highly selected. The intensity of conditioning did not impact OS or RFS in either univariable or multivariable analyses. As expected, this was due to a tendency toward increased RI with RIC and increased NRM with MAC, which ultimately neutralized each other, resulting in comparable outcomes. This is in accordance with other recent studies that did not find any impact of conditioning intensity on OS or PFS [37–40].

Another aspect of conditioning is whether to incorporate TBI or not. In ALL, TBI has been shown to decrease RI, particularly with MAC [38, 39, 41, 42]. The role of lower doses of TBI used in RIC, particularly in the elderly population, remains a matter of debate regarding whether it is as effective as in MAC. A small single-center study compared RIC TBI with fludarabine and melphalan to MAC TBI regimens including VP16/TBI or cyclophosphamide-TBI. This study did not find any statistically

TABLE 3 | Multivariable analysis for OS, PFS, RI, and NRM at 36 months post-transplantation.

	OS		PFS		RI		NRM	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age								
Five years increase	0.98 (0.74–1.28)	0.858	1 (0.78–1.28)	0.995	0.89 (0.65–1.23)	0.492	1.21 (0.81–1.82)	0.359
All subtype								
Other vs. Ph+	1.99 (1.42–2.79)	< 0.0001	1.63 (1.18–2.24)	0.0029	2.01 (1.32–3.07)	0.0011	1.19 (0.71–1.98)	0.515
Time form Dx to SCT								
> 6 months vs. < 6 months	0.81 (0.53–1.21)	0.300	0.71 (0.48–1.05)	0.0838	0.68 (0.4–1.15)	0.146	0.72 (0.4–1.31)	0.289
Disease status at SCT								
CR2+/Not in CR vs. CR1	1.79 (1.22–2.64)	0.0032	2.07 (1.43–3)	0.00011	2.4 (1.5–3.84)	0.00026	1.55 (0.83–2.86)	0.166
Donor to pt CMV								
Other vs. Neg/Pos	1.36 (0.92–2.01)	0.118	1.43 (0.99–2.07)	0.055	2.49 (1.45–4.29)	0.0010	0.69 (0.4–1.18)	0.172
Donor to pt sex								
F to M vs. other	0.74 (0.45–1.21)	0.232	0.67 (0.41–1.08)	0.102	0.68 (0.37–1.22)	0.197	0.59 (0.25–1.39)	0.227
ATG								
No ATG vs. ATG	0.84 (0.55–1.28)	0.410	0.81 (0.54–1.21)	0.304	0.66 (0.39–1.12)	0.122	1.07 (0.57–2)	0.839
Conditioning								
MAC vs. RIC	1.08 (0.71–1.62)	0.724	0.94 (0.63–1.41)	0.765	0.71 (0.41–1.24)	0.229	1.36 (0.73–2.53)	0.324
TBI								
TBI vs. no TBI	0.87 (0.57–1.34)	0.537	0.79 (0.52–1.2)	0.268	0.76 (0.45–1.31)	0.328	0.82 (0.42–1.6)	0.554

Abbreviations: ALL: acute lymphoblastic leukemia, ATG: antithymocyte globulin, CI: confidence interval, CMV: cytomegalovirus, CR: complete remission, Dx: diagnosis, F: female, M: male, MAC: myeloablative conditioning, NRM: non-relapse mortality, OS: overall survival, PFS, Ph+: Philadelphia positive, progression-free survival, pt.: patient, RI: relapse incidence, RIC: reduced intensity conditioning, SCT: stem cell transplant, TBI: total body irradiation.

significant difference in OS (56% with RIC [median age: 61 years] vs. 69.9% with MAC [median age: 36 years]), while the relapse rate was lower with MAC (HR: 0.21, $p = 0.02$) [38]. In our cohort, only a minority of patients received TBI (all doses) as part of the conditioning (35.8% of whom 21.9% received 8 Gy). We nevertheless studied the impact of TBI on RI and found a lower RI in univariable analysis with 8 Gy TBI (22% vs. 42% without TBI, $p = 0.017$), which was also associated with improved PFS (52% vs. 37%, $p = 0.044$). However, this was not confirmed in multivariable analysis when comparing TBI (all doses) vs. no TBI (we did not analyze TBI in more subgroups due to the low number of patients who had < 8 Gy TBI [$n = 43$] vs. ≥ 8 Gy TBI [$n = 69$] vs. 203 patients without TBI). Therefore, a prospective trial comparing 8 Gy TBI to non-TBI RIC is needed to determine the benefit of lower-dose TBI in elderly ALL patients. We also found an increased incidence of cGvHD with TBI (all doses) in univariable analysis, but this was not the case in multivariable analysis.

All of this suggests that for elderly ALL patients, alloHSCT with RIC can be considered, despite the increased risk of relapse. A potential explanation is the development of improved post-transplant strategies, including the use of TKI for Ph + ALL, administered as a maintenance, preemptively, or as a relapse treatment strategy [43–46], as well as the advent of blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T-cells (CAR-T) [47–49]. Moreover, post-transplant monitoring with measurable residual disease (MRD) assessment enables earlier intervention, increasing the chances of successful rescue therapy [50].

An interesting finding was that relapse incidence was lower in patients with a CMV donor-negative/recipient positive (D-R+) combination compared to all other combinations, and this was confirmed in multivariable analysis. This observation has already been reported, particularly in acute myeloid leukemia (AML), and is thought to be related to a higher frequency of CMV reactivation in this setting, which is associated with an anti-leukemic effect. This effect is believed to result from immune system reactivation—involving T lymphocytes, natural killer (NK) cells, and inflammatory cytokines—thereby reenforcing the graft-versus-leukemia (GvL) effect [51–54].

As expected, disease status significantly impacted outcomes, which was confirmed in multivariable analysis, showing better OS (HR: 1.79, $p = 0.0032$), PFS (HR: 2.07, $p = 0.0001$) and lower RI (HR: 2.4, $p = 0.0003$) for patients in CR1 compared to those with more advanced diseases. However, this was also the case for the ALL subtype, as multivariable analysis showed improved OS (HR: 1.99, $p < 0.0001$), PFS (HR: 1.63, $p = 0.0029$) and lower RI (HR: 2.01, $p = 0.0011$) for patients with Ph+ ALL compared to other subtypes. This contrasts with the EBMT study, which did not find any difference at 3 years, with OS rates of 47.2% for Ph+ ALL versus 36.5% for Ph− ALL ($p = 0.31$), and LFS rates of 39.3% versus 31% for Ph+ versus Ph- ALL, respectively [22]. The difference may be due to the study period, as improved TKI use, deeper molecular responses before transplantation, and greater use of TKIs in maintenance or preemptively upon molecular relapse are more common today. On the other hand, a more recent EBMT study comparing autologous versus alloHSCT found the same advantage for Ph+ ALL patients, with improved OS (HR: 0.74 95% CI 0.55–0.98, $p = 0.04$) and decreased RI (HR: 0.7 95% CI 0.51–0.98, $p = 0.04$), supporting the above hypothesis [55]. This trend is also observed in other recent studies analyzing different conditioning regimens, which have reported better OS, LFS, and lower RI for Ph+ ALL compared to non-Ph+ ALL, further supporting our findings [40, 56]. The beneficial effect of Ph+ ALL was also evident in our study for GRFS in multivariable analysis, with an HR of 1.34 (95% CI 1.01–1.78, $p = 0.046$) when comparing Ph+ ALL to non-Ph+ ALL patients. Altogether, these findings suggest that in the elderly population, Ph+ ALL is associated with a better prognosis and improved outcomes after alloHSCT compared to non-Ph+ ALL.

The treatment approach for Ph+ ALL has recently evolved from chemotherapy plus TKI to immunotherapy plus TKI, showing promising results with blinatumomab combined with dasatinib or ponatinib, achieving 4-year OS rates of up to 80% [57–59]. This challenges the need for alloHSCT, particularly in MRD-negative patients. However, concerns remain regarding an increased risk of central nervous system (CNS) relapse in this setting, as well as the long-term use of TKIs, which carry potential toxicities, particularly cardiovascular and hematological effects. Longer follow-up in randomized studies comparing these strategies is needed to determine the most beneficial approach for each patient. The same applies to Ph- B-ALL in elderly patients, as combining blinatumomab with chemotherapy in first-line treatment has shown encouraging results with 3-year OS rates reaching 85% [60]. Similarly, inotuzumab ozogamicin combined with chemotherapy, as reported by Chevallier et al. in a population with a median age of 68 years, showed a 2-year OS of 55%, with particularly favorable outcomes for the 10 patients who underwent alloHSCT, achieving a 2-year OS/RFS of 90% [61].

The limitations of this study are inherent to its registry-based design, which may introduce bias. The study population was heterogeneous, and detailed molecular risk stratification was not available. Additionally, this represents a selective population deemed fit for a high-risk procedure such as alloHSCT. Another limitation is the lack of cytogenetic and molecular remission data at transplantation, making it difficult to analyze and interpret the results related to these factors.

In summary, this study suggests that for ALL patients aged 60 to 75 years, alloHSCT is feasible and may be a valid option for high-risk ALL, offering a chance for cure in a substantial number of patients. Age itself did not impact outcomes, but advanced disease and non-Ph+ALL negatively influenced prognosis. Further collaborative and prospective studies are necessary to confirm these findings in the era of combined immunotherapy and chemotherapy. Additionally, questions remain regarding the optimal conditioning regimen and the role of TBI in this population.

Author Contributions

Y.C., M.R. and S.M.-L. designed the study. Y.C., R.D., S.N., C.-E.B., P.C., E.B., M.-T.R., H.L.-W., J.M., P.C., N.M., X.P., C.C.-L., Y.B., J.C., S.M., T.M., E.D., J.-O.B., P.T., M.J., K.B., G.G., S.F., A.B., S.C., P.L., A.M., M.L., M.B., P.C., E.F., A.H., M.R., S.M.-L. contributed data and reviewed the manuscript. Y.C., A.B., M.R. and S.M.-L. analyzed the data. Y.C., A.B., M.R. and S.M.-L. wrote the manuscript.

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Ethics Statement

The SFGM-TC is a non-profit, scientific society representing 54 transplant centers from French speaking countries. SFGM-TC studies are

approved by an institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. SFGM-TC centers commit to obtain informed consent according to the local regulations applicable at the time to report pseudonymized data stored in a central database.

Conflicts of Interest

Y.C. has received consulting fees for advisory board from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier, Takeda, Pierre Fabre, Medac; travel support from MSD, Roche, Novartis, Pfizer, BMS, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz, Pierre Fabre, Sanofi all via the institution. E.F. received funding for congress participation from Alexion, Gilead, Jazz, MSD, Novartis; and honoraria for boards and speaker bureau participation from Alexion, GSK, Novartis, Gilead, Astellas. E.B. received research funding, honorarium, speaker's fees and travel expenses from Novartis, Astellas, Alexion, Jazz Pharmaceuticals, Gilead, MSD, Keocyt, Amgen, Beigen, Pierre Fabre, Pfizer, Celgene/BMS, Sanofi. M.L. received funding for honoraria: Alexion, Astra Zeneca, BMS Celgene, Gilead, GSK, Jazz, Kartos, Medac, MSD, Novartis, Pfizer, Sanofi, Sobi, Telios. T.M. has received consulting fees from Servier, Jazz Pharmaceutical, Sobi, Astellas. Travel support from Servier, Jazz Pharmaceutical. A.H. has received consulting fees advisory board from Jazz, Pfizer, Servier, Novartis, Astellas; Travel support from Medac, Jazz, Neovii all via the Institution. M.R. support for research from Neovii, Medac, Abbvie, Novartis. S.M.-L. received funding for congress participation from Gilead, Jazz, BeiGene, Sanofi all via institution.

Data Availability Statement

As for SFGM-TC Policy, data cannot be shared but are available on reasonable request to: nicole.raus@chu-lyon.fr.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.