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Reduced Intensity T-Replete Allogeneic Stem Cell Transplantation Provides Long-Term Survival in Relapsed Angioimmunoblastic T-Cell Lymphoma Post-Autologous Transplant in patients over the age of 50

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Abstract

Background

Relapsed angioimmunoblastic T-cell lymphoma (AITL) following autologous transplantation carries poor prognosis. Reduced-intensity T-replete allogeneic transplant may provide durable disease control via immune-mediated graft effects.

Methods

We retrospectively analyzed 21 patients over the age of 50 with relapsed AITL who underwent reduced-intensity T-replete allo-HCT across three transplant centers between 2013 and 2022. Following salvage treatment, all patients experienced chemo sensitive disease and proceeded to transplantation. Responses were PET-based, and survival outcomes were assessed.

Results

All patients achieved hematologic engraftment, with 13 in complete metabolic remission and 8 in partial remission at the time of transplant. At a median follow-up of 7.55 years, OS was 100%, 81%, and 71% at 1, 2, and 5 years, respectively, with PFS of 95%, 95%, and 84%. Seven deaths occurred, four due to disease progression and three related to transplantation. Acute and chronic GvHD were observed in 30% and 22% of patients respectively. Five patients received donor lymphocyte infusion, showing a trend toward improved survival.

Conclusion

Reduced-intensity T-replete allo-HCT is a feasible and potentially curative therapeutic option for patients over 50 with chemo sensitive relapsed AITL after autologous transplantation. Early disease control and long-term remission suggest a clinically meaningful graft-versus-lymphoma (GVL) effect in appropriately selected individuals.

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare subtype of primary nodal peripheral T-cell lymphoma (PTCL), accounting for approximately 1–2% of all non-Hodgkin lymphomas (NHLs) [1]. The majority of patients present with advanced disease, frequently manifesting as generalized lymphadenopathy, hepatosplenomegaly, and hypergammaglobulinemia [2]. Even when AITL is treated with intensive induction regimens, the prognosis can be poor. Standard first-line therapy typically consists of anthracycline-based chemotherapy, with or without etoposide, depending on the patient's age, and, for those who are CD30 positive, brentuximab combined with chemotherapy [1, 3]. Patients

who achieve complete remission (CR) and have a favorable performance status often proceed with autologous hematopoietic cell transplantation (auto-HCT) consolidation to achieve long term remission.

Despite this approach, outcomes remain unsatisfactory due to significant relapse rates[4]. Allogeneic hematopoietic cell transplantation (allo-HCT) has emerged as a potentially curative strategy for patients with relapsed AITL following auto-HCT [5–8], possibly owing to the graft-versus-lymphoma (GVL) effect mediated by donor immune cells [9, 10]. AITL originates from follicular helper T-cells and is characterized by immune dysregulation and EBV-induced B-cell proliferation, factors that may influence the response to immune-mediated GVL effects [11]. Allogeneic grafts can be categorized as T-cell-replete or T-cell-depleted depending on whether donor T-cells remain in the graft or are eliminated. T-depleted techniques minimize the risk of graft-versus-host disease (GvHD), but they may compromise disease control. On the other side, T-replete transplantation preserves donor T-cells, which can mediate a positive GVL effect but at the expense of increased GvHD risk [9, 12].

Donor lymphocyte infusion (DLI), which can employ donor immune cells to improve disease control in certain hematologic malignancies, including AITL, may also be beneficial for treating relapse following allogeneic stem cell transplantation [8]. Reduced-intensity conditioning (RIC) regimens, being less toxic and intense, allo-HCT to be offered to older or frail patients while preserving graft immunologic function [13]. Nevertheless, few studies have specifically evaluated reduced-intensity, T-replete allo-HCT in this setting, and the evidence for an early GVL effect remains limited.

In an effort to channel a potential graft-versus-lymphoma effect following previous unsuccessful auto-HCT, we examined the therapeutic role of reduced-intensity, T-replete allogeneic transplantation in patients over 50 with relapsed AITL who achieved a chemo sensitive response to salvage therapy.

Methodology

Study Design and Patient Population

This was a retrospective, multicenter cohort study designed to evaluate the efficacy of reduced-intensity, T-replete allogeneic hematopoietic cell transplantation in patients with relapsed angioimmunoblastic T-cell lymphoma. The study included three bone marrow transplant (BMT) centers and comprised 21 patients who underwent allo-HCT following prior autologous HCT between 2013 and 2019. All patients were aged 50 years and above at the time of diagnosis and had experienced relapse after auto-HCT. Patients received salvage chemotherapy with GDP (gemcitabine, dexamethasone, cisplatin), ICE (ifosfamide, carboplatin, etoposide), or mini-BEAM (carmustine, etoposide, cytarabine, melphalan). Those achieving complete response (CR) or partial response (PR) to salvage therapy were considered chemosensitive and were eligible for transplantation [14].

Response Evaluation and Definitions

Pre-transplant response to salvage chemotherapy was assessed using ^{18}F-FDG PET/CT. Patients who demonstrated a complete or partial metabolic response by PET criteria [15] proceeded to reduced-intensity T-replete allo-HCT. The following endpoints were established according to the Revised Response Criteria for Malignant Lymphoma [14]. Overall survival (OS) was defined as the time between stem cell transplantation and death from any cause. Progression-free survival (PFS) was defined as the time between stem cell transplantation and lymphoma relapse, progression, or death from any cause, whichever occurred first. Non-relapse mortality (NRM) was defined as death from any cause without prior disease progression. Acute (grades I-IV) and chronic (limited or extensive) graft-versus-host disease (GvHD) were graded according to international consensus standards [16, 17].

Transplant Procedure

Among the 21 patients included in this study, 15 were males, and 6 were females, with a median age of 58.3 years (50–73). Eight patients were in partial remission, and thirteen were in complete remission at the time of transplantation, based on PET/CT criteria. Five patients received an HLA-matched sibling allogeneic transplant, and sixteen received a fully matched volunteer unrelated donor transplant. Eligible donors were matched at the allele level for HLA-A, -B, -C, -DQ, and -DRB1. The conditioning regimen was classified as reduced-intensity according to the established EBMT criteria [18] and consisted of fludarabine, cyclophosphamide, and a single fraction 2Gy total body irradiation (TBI). In total, 5 patients received donor lymphocyte infusion (DLI) at a dose of 1 x 10^6 cells/kg for post-transplant relapse.

All patients received peripheral blood stem cell transplants. The median infused stem cell dose was 4.7X 10^6 CD34/kg (4.0-6.2 x 10^6 CD34/kg). Neutrophil engraftment was defined as an absolute neutrophil count (ANC) greater than 0.5 X 10^9/L for two consecutive days following allo-HCT, and platelet engraftment as a platelet count greater than 20 X 10^9/L for two consecutive days, unsupported. Cyclosporine and methotrexate were used for graft-versus-host disease (GvHD) prophylaxis.

Statistical Analysis

A descriptive analysis was initially performed to summarize the demographic and clinical characteristics of the study population. Patients were censored at the date of last contact for survival analyses. Median age and ranges were reported, along with transplantation- and treatment-related characteristics. Survival outcomes were assessed using the Kaplan–Meier method. Overall survival (OS) was estimated from the date of transplantation until the date of death due to any cause or the last follow-up. Progression-free survival (PFS) was defined as the time between transplantation and disease progression, relapse, or death, whichever came first. Survival probabilities at 1, 2, and 5 years were estimated using 95% confidence intervals. Comparisons of survival between patient subgroups (e.g., patients receiving donor lymphocyte infusion versus those who did not) were conducted using the log-rank test. Mortality analysis was further performed to classify deaths into disease progression and HSCT-related mortality. Engraftment kinetics and graft-versus-host disease (GvHD) incidence were also reported descriptively.

All statistical analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) within the RStudio environment. A two-sided significance level of $\alpha = 0.05$ was applied throughout.

Ethical Issues

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of all participating BMT centers. Informed consent for data use was obtained according to institutional policy. All patient data were anonymized prior to analysis to ensure confidentiality.

Results

The dataset included 21 patients with relapsed AITL who received allogeneic stem cell transplantation following a previous autologous transplant. Table 1 summarizes the demographic and clinical characteristics of patients. The median age at diagnosis was 61 years (40–73), with a male predominance (n = 15). The median follow-up after allogeneic transplantation was 7.55 years (0.3–10.7). Cytogenetic analysis was normal in most patients (n = 15), while isolated abnormalities were less common and included 5q gain (n = 3), 13q changes (n = 2), and gain of chromosome 21 (n = 1). The median infused stem cell dose was $5x10^6$ ($3.9\text{-}6.2x10^6$). Patients mostly received grafts from unrelated donors (n = 16), while 5 had sibling donors. Donor–recipient CMV serostatus was concordantly positive in 10 cases and negative in 5, with 6 pairs showing discordance (either donor/recipient positive). In total, 14 out of 21 patients were CMV seropositive. Donor lymphocyte infusion (DLI) was administered in 5 patients. All patients achieved hematologic engraftment, both for neutrophils and platelets. Median neutrophil engraftment occurred on day + 17 (D + 14 - D + 25) and median platelet engraftment occurred on day + 20 (D + 18 - D + 26). Ten patients experienced acute GvHD (grades I–III), while 11 had no acute GvHD. Chronic GvHD occurred in 4 patients (all limited). In total, 13 patients (62%) had a complete metabolic response, and 8 patients (38%) had a partial metabolic response to salvage chemotherapy prior to allogeneic transplant. There were 7 deaths, 4 of which were due to disease progression, and 3 were HSCT-related.

Table 1
Patients' characteristics

Variable	N = 21
Age at diagnosis	61 (40–73)
Follow-up (in years)	7.55 (0.3–10.7)
Sex	
Male	15
Female	6
Cytogenetics	
Normal	15
5 gain	3
13q	2
Gain 21	1
Stem cell dose	$5x10^6$ ($3.9–6.2 x 10^6$)
Donor type	
Sibling	5
Unrelated	16
Donor/Recipient CMV status	
Both negative	5
Both positive	10
Either donor/recipient +	6
CMV status (patient)	
Positive	14
Negative	7
CMV status (donor)	
Positive	10
Negative	11
Donor DLI	
Yes	5
No	16

Variable	N = 21
Engraftment	D + 17 (D + 14 - D + 25)
Neutrophil Engraftment	D + 20 (D + 18 - D + 26)
Platelet Engraftment	
Acute GvHD	
Grade 0	11
Grade I	3
Grade II	4
Grade III	3
Chronic GvHD	
None	17
Limited	4
Metabolic Response	13
Complete	8
Partial	7
Mortality	
Cause of death	
Progression	4
HSCT related	3

Relapse and Non-Relapse Mortality

At the latest follow-up, 7 patients (33%) had passed away and 14 patients (67%) were still alive. Analysis of the cohort's mortality causes showed that, of the 7 patients with a documented cause of death, 4 (57.1%) died due to disease progression, and 3 (42.9%) succumbed as a result of hematopoietic stem cell transplantation (HSCT), indicating non-relapsed mortality. The median time to relapse among relapsed cases was 22 months (8–92 months) following transplantation. These findings highlight the substantial impact that transplantation-related complications and disease progression have on patient survival.

Overall Survival

The Kaplan-Meier overall survival analysis (Fig. 1) showed OS rates of 100% at 1 year, 81% at 2 years, and 71% at 5 years. The survival probability remains high for the first year, followed by a gradual decline over the 5-year follow-up period.

Progression-Free Survival

Figure 2 depicts a Kaplan-Meier analysis of PFS, which revealed a probability of 95% at 1 year, 95% at 2 years, and 84% at 5 years. The survival curve remains steady for the first two years but declines after five years, indicating disease progression in a subset of patients.

Acute and Chronic GvHD

At three months post transplant, the cumulative incidence of grade II-IV acute GvHD was 38% (95% CI 32–45), and grade III-IV acute GvHD was 15% (95% CI 8–21). Acute GvHD predominantly affects the skin, gastrointestinal tract, and liver. The 1-year cumulative incidence of chronic GvHD was 46% (95% CI 39–54), while the 1-year cumulative incidence of extensive chronic GvHD was 35% (95% CI 29–44).

DLI & Survival

Kaplan-Meier survival analysis comparing patients who received DLI versus those who did not (Fig. 3) showed a trend toward improved survival in the DLI group. Although this difference was not statistically significant (log-rank test, $p = 0.5544$), DLI appeared to contribute to durable immune-mediated disease control. Among DLI recipients, 4 of them (80%) remained alive at the end of the follow-up, while one (20%) experienced HSCT-related mortality.

Discussion

In this retrospective multicenter cohort study, reduced intensity T-replete allogeneic stem cell transplantation showed promising long-term survival in patients with relapsed AITL following prior autologous transplantation, a population that has traditionally been linked to few therapeutic options and poor outcomes. Of the 21 individuals in this sample, 8 achieved a partial metabolic response while 13 achieved a complete response. All patients achieved hematologic engraftment, and both OS (100% at 1 year and 71% at 5 years) and PFS (95% at 1–2 years and 84% at 5 years) remained high during the early post-transplant period, suggesting that elderly patients with chemosensitive relapse may benefit from the potentially curative approach of T-replete grafts. At the end of the study, 7 patients had died; disease progression accounted for 57.1% of these deaths, while HSCT-related causes (non-relapsed mortality) accounted for the remaining instances.

Several factors may have contributed to the favorable outcomes observed. Firstly, all patients proceeded to transplantation with chemosensitive disease, which has been consistently associated with an improved post-transplant outcome in T-cell lymphomas, including AITL. Achieving a complete or partial remission prior to allo-HCT may have decreased disease burden, allowing donor immune reconstitution

in the context of minimal residual lymphoma. Moreover, the use of a T-replete graft may have preserved donor T-cell function, supporting a stronger immunologic GvL effect. The early disease control, together with sustained remission observed in a significant portion of patients, supports the hypothesis that donor immune activity plays a critical role in long term lymphoma eradication. The universal engraftment and prompt neutrophil and platelet recovery further suggest the viability of allo-HCT in older transplant candidates over the age of 50.

When compared to previous research, the results of our study appear promising. Epperla et al. achieved in their research a 4-year OS of 56% and PFS of 47–49% in relapsed AITL following allo-HCT, while Kyriakou et al. demonstrated durable remission although with more heterogeneous conditioning regimens. The improved survival rates observed in our cohort could be related to the combination of chemosensitive disease at transplantation and a uniform reduced-intensity T-replete transplant strategy. This highlights again the need of preserving donor T-cells for the development of an early and clinically relevant GvL response. In general, our findings indicate that for those patients with relapsed AITL who respond to salvage therapy, reduced-intensity T-replete allo-HCT may provide a viable option to long-term remission even if autologous transplant fails. Despite the sample size being limited, the increased survival observed in patients receiving DLI supports the notion that immune-mediated disease control may play an important role in this context.

Although these findings are promising, GvHD still remained a transplant-related risk, with both acute and chronic GvHD observed in the study. The occurrence of GvHD reflects the inherent balance between desirable GvL activity and unwanted immune toxicity. Nonetheless, non-relapse mortality in older allo-HCT recipients remained limited relative to historical expectations, indicating that reduced-intensity conditioning may decrease toxicity while preserving immunologic benefit.

The limitations of this study should be taken into consideration. Our findings have limited generalizability due to the intrinsic retrospective study design and the small sample size used in this research. Furthermore, due to a lack of molecular or genomic patient data, biological predictors of allo-HCT response cannot be established. This study only included chemosensitive patients, which could introduce selection bias toward favorable biology or treatment response. Future prospective multicenter studies should be conducted to confirm these findings, investigate biomarkers of transplant response, and optimize approaches that improve GvL activity while minimizing GvHD-related morbidity.

Conclusion

AITL has an uncertain prognosis when treated with conventional therapies, hence novel approaches are needed. This research comprised patients over the age of 50 who have relapsed AITL after autologous transplantation and for whom reduced-intensity T-replete allogeneic stem cell transplantation yields promising OS and PFS outcomes. Hematologic engraftment was achieved in all patients, suggesting that this approach is feasible even in elderly populations. This study demonstrates that the T-replete approach may offer long-term survival and induce an early GVL effect to the patients. Moreover, reduced-

intensity conditioning can balance toxicity while preserving the donor immune function. Therefore, donor-derived immune activity is crucial to maintaining remission as seen by the favorable results achieved in patients receiving DLI. Due to the disease's rarity and the limited data given, new and larger research studies, possibly with integrated biologic profiling, are required to confirm our findings and identify effective strategies that preserve GVL effect while diminishing GvHD.

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Figures

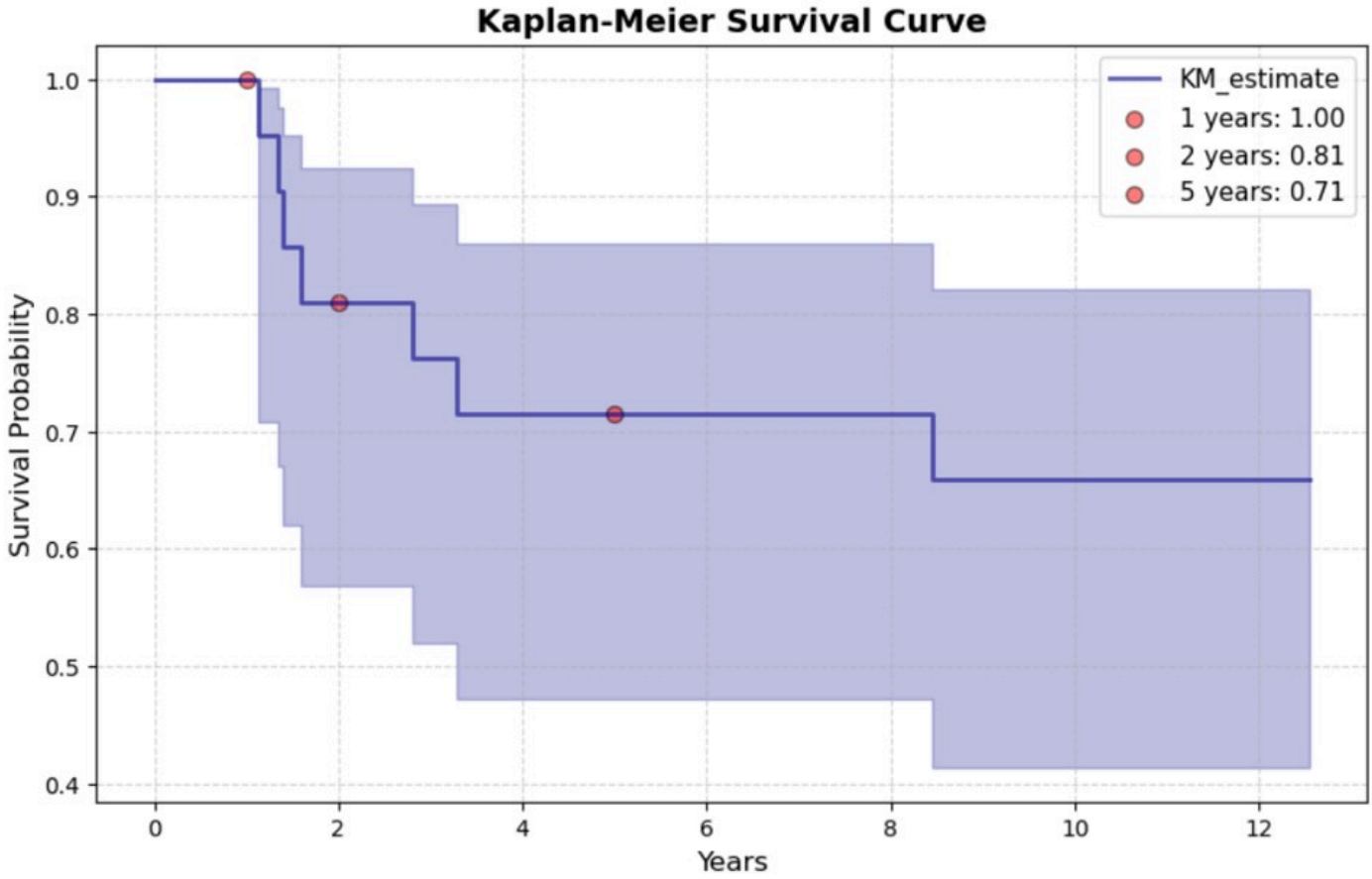

Figure 1

Kaplan-Meier overall survival (1-year OS, 2-year OS, 5-year OS)

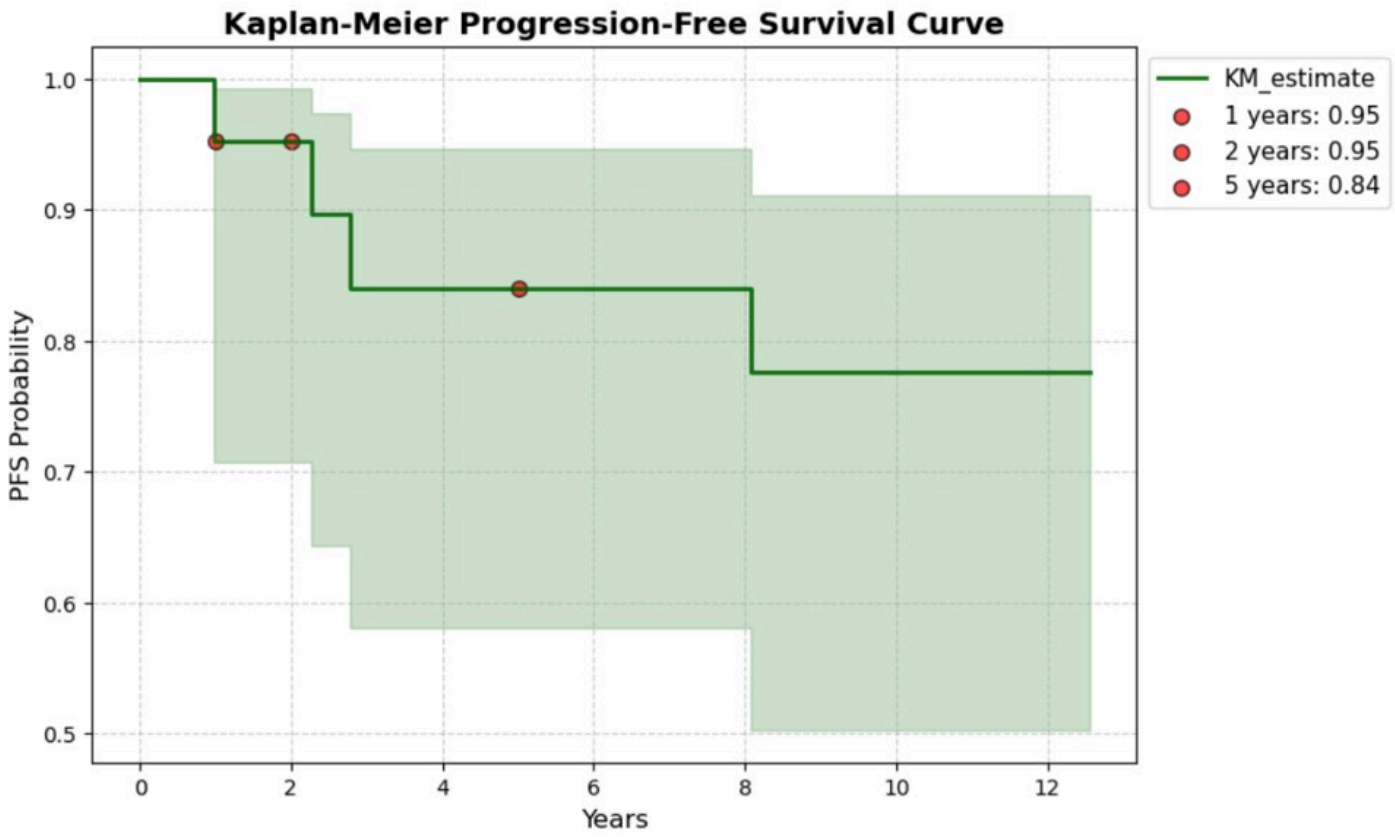

Figure 2

Kaplan-Meier progression-free survival (1-year PFS, 2-yearPFS, 5-yearPFS)

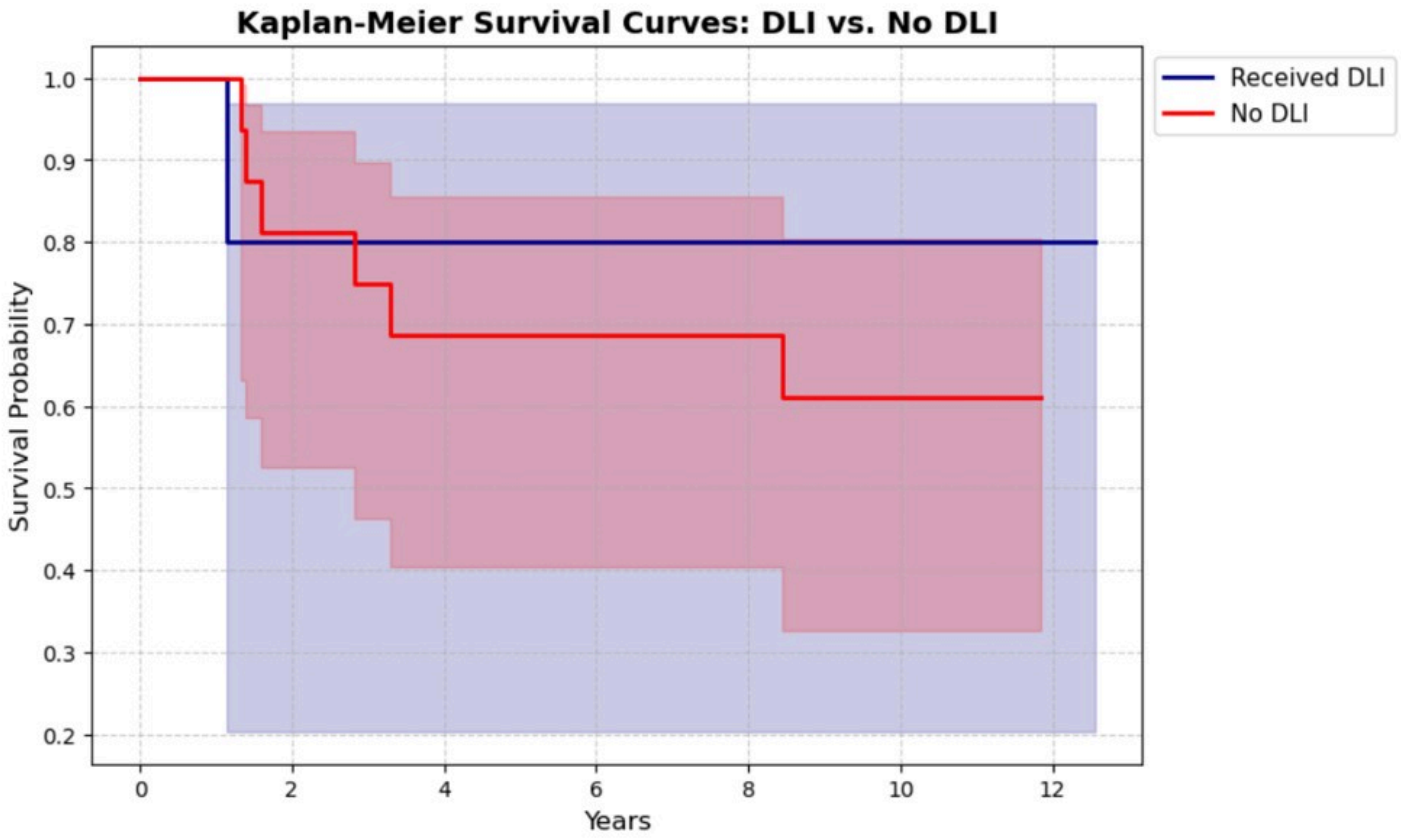

Figure 3

Kaplan-Meier survival curve with and without DLI