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# Allotransplantation for Patients Age ≥40 Years with Non-Hodgkin Lymphoma: Encouraging Progression-Free Survival

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A B S T R A C T

Non-Hodgkin lymphoma (NHL) disproportionately affects older patients, who do not often undergo allogeneic hematopoietic cell transplantation (HCT). We analyzed Center for International Blood and Marrow Transplant Research data on 1248 patients age ≥40 years receiving reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) conditioning HCT for aggressive (n = 668) or indolent (n = 580) NHL. Aggressive lymphoma was more frequent in the oldest cohort 49% for age 40 to 54 versus 57% for age 55 to 64 versus 67% for age ≥65; $P = .0008$). Fewer patients aged ≥65 had previous autografting (26% versus 24% versus 9%; $P = .002$). Rates of relapse, acute and chronic GVHD, and nonrelapse mortality (NRM) at 1 year post-HCT were similar in the 3 age cohorts (22% [95% confidence interval (CI), 19% to 26%] for age 40 to 54, 27% [95% CI, 23% to 31%] for age 55 to 64, and 34% [95% CI, 24% to 44%] for age ≥65. Progression-free survival (PFS) and overall survival (OS) at 3 years was slightly lower in the older cohorts (OS: 54% [95% CI, 50% to 58%] for age 40 to 54; 40% [95% CI, 36% to 44%] for age 55 to 64, and 39% [95% CI, 28% to 50%] for age ≥65; $P < .0001$). Multivariate analysis revealed no significant effect of age on the incidence of acute or chronic GVHD or relapse. Age ≥55 years, Karnofsky Performance Status <80, and HLA mismatch adversely affected NRM, PFS, and OS. Disease status at HCT, but not histological subtype, was associated with worse NRM, relapse, PFS, and OS. Even for patients age ≥55 years, OS still approached 40% at 3 years, suggesting that HCT affects long-term remission and remains underused in qualified older patients with NHL.



## INTRODUCTION

The use of allogeneic hematopoietic cell transplantation (HCT) to treat non-Hodgkin lymphoma (NHL) is increasing in patients with high-risk and relapsed/refractory disease [1]. Considering that more than one-half of such NHL cases are diagnosed in individuals age >65 years, this represents a growing population of patients for whom allogeneic HCT may provide long-term disease-free survival and improve outcomes [2]. It has been postulated that conventional myeloablative conditioning before HCT is not feasible for the vast majority of older patients owing to limited physiological resilience and accompanying comorbidities. Nonmyeloablative (NMA) conditioning and reduced-intensity conditioning (RIC) strategies have made HCT available to less-fit individuals with relapsed or poor-risk hematologic malignancies amenable to allogeneic HCT. Recent studies have reported acceptable nonrelapse mortality (NRM) rates of 10% to 20% and 2- to 3-year progression-free survival rates of 25% to 75% depending on NHL subtype [3-7]; however, data specific to older patients with NHL remain limited.

We recently examined the influence of age on outcomes in older patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) in first complete remission (CR) and found similar outcomes as seen in younger patients when given an RIC HCT regimen [8]. In the present study, we examined the same question in older patients undergoing RIC or NMA allogeneic HCT for NHL of aggressive or indolent histology, with the aim of defining post-HCT outcomes in older patients and evaluating patient, disease, and treatment characteristics influencing these outcomes.

## PATIENTS AND METHODS

Data for this analysis were submitted to the Center for International Blood and Transplant Research (CIBMTR), a voluntary working group of more than 450 transplant centers worldwide who contribute data on consecutive allogeneic HCTs to a statistical center housed at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program in Minneapolis. Patients are followed longitudinally with yearly follow-up. Computerized checks for errors and onsite audits of participating centers ensure data quality. Physician review of data and additional requested information from reporting centers are included. Observational studies conducted by the CIBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

### *Patient Selection*

The study group included patients age ≥40 years undergoing RIC or NMA HCT between 2001 and 2007 for aggressive NHL (ie, diffuse large B cell [n = 202], mantle cell [n = 279], immunoblastic/anaplastic B/T cell [n = 52], peripheral T cell [n = 60], peripheral T cell lymphoma not otherwise specified [n = 25], Burkitt lymphoma [n = 4], other [n = 46]) and indolent NHL (ie, small lymphocytic lymphoma [SLL]/chronic lymphocytic leukemia [CLL] [n = 156], follicular [n = 387], marginal zone [n = 13], and other [n = 24]). Patients were classified as being in first (n = 87) or second (n = 231) complete remission (CR), in first (n = 478) or second (n = 304) partial remission (PR), or with resistant disease (RD; n = 304) as known before HCT. Grafts were from a related donor or an unrelated donor (URD); cord blood grafts were not studied. Patients who underwent previous autologous HCT were included.

A total of 1248 cases were identified, including 668 patients with aggressive NHL and 580 patients with indolent NHL treated at 165 centers. There were 1119 patients with B cell histology and 106 patients with T cell histology; 3 patients were not classifiable. Patients ranged in age from 40 to 75 years and were divided into 3 age cohorts for analysis: 40 to 54 years (n = 614); 55 to 64 years (n = 552), and ≥65 years (n = 82). Previously established criteria for donor–recipient HLA matching were used to define well-matched, partially matched, and mismatched categories [9]. Preparative regimens were classified as either RIC or NMA. RIC regimens included ≤500 cGy total body irradiation as a single fraction or ≤800 cGy if fractionated, ≤9 mg/kg busulfan oral (or i.v. equivalent), <140 mg/m2 melphalan, <10 mg/kg thiotepa, and BEAM (carmustine, etoposide, cytarabine, and melphalan) [10,11]. Other regimens were classified as NMA when hematopoietic recovery without transplantation within 28 days could be reasonably expected [12]. T cell depletion accomplished via ex vivo or in vivo methods was included.

### *Study Endpoints and Definitions*

Primary outcomes were overall survival (OS) and progression-free survival (PFS), defined as survival from allogeneic HCT without death and without disease progression or relapse, respectively. NRM was defined as any death occurring in the first 28 days post-transplantation or any death after day +28 without documented NHL progression or relapse. All data were censored at the date of last reported follow-up. Secondary endpoints included neutrophil recovery, defined as the time to an absolute neutrophil count of ≥500 cells/μL sustained for 3 consecutive days, and the cumulative incidence of acute (grade II-IV) and chronic graft-versus-host disease (GVHD) as defined by consensus criteria [13,14].

### *Statistical Analysis*

Patient-, disease-, and transplantation-related variables were compared in the 3 age cohorts using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of PFS and OS were calculated using the Kaplan-Meier estimator, with variance estimated using Greenwood's formula. Probabilities of neutrophil recovery, acute and chronic GVHD, NRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks. The 95% confidence intervals (CIs) for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques.

The influence of age cohort on neutrophil recovery was compared using logistic regression. Cox proportional hazards regression models were used for all other outcomes. The proportional hazards assumption was tested for all variables. Variables were stratified in the model when the proportionality assumption did not hold [15]. Patient-, disease-, and transplantation-related variables were considered in the model building procedure, with recipient age—the main focus of this study—included in all steps of model building. Separate analyses of patients in CR1 versus those in CR2 and of patients in PR1 versus those in PR2 identified no significant differences in major endpoints, and thus these groups were combined for subsequent analysis. Patient-related variables considered were sex and Karnofsky Performance Status (KPS) of <80 versus ≥80. Disease-related variables included histology subtype (aggressive versus indolent), disease status at time of HCT (CR1/2+ versus PR1/2+ versus RD), and interval from diagnosis to perfomance of HCT (<2 years versus ≥2 years). The International Prognostic Index (IPI) was considered, but lactate dehydrogenase was not reported for 69% of the patients, and thus it could not be assigned. The presence of extranodal sites and the number of pre-transplantation therapies were considered as well.

Transplantation-related variables included era of transplantation (2001 to 2004 versus 2005 to 2007), donor/recipient cytomegalovirus (CMV) serostatus (−/− versus −/+ versus +/− versus +/+), HLA matching (HLA-matched sibling donor versus well-matched URD versus partially matched URD versus mismatched URD), stem cell source (bone marrow versus peripheral blood stem cells [PBSCs]), GVHD prophylaxis (cyclosporine [CSA] ± methotrexate [MTX] ± other versus tacrolimus [Tac] ± MTX ± other versus T cell depletion), donor–recipient sex match (male–male versus male–female

**Table 1**
Characteristics of 1248 Patients Age ≥40 Years Undergoing RIC or NMA Allogeneic HCT for NHL

| Characteristic | Age 40-54 | Age 55-64 | Age ≥65 | *P* Value |
|---|---|---|---|---|
| Number of patients | 614 | 552 | 82 | |
| Number of centers | 120 | 112 | 45 | |
| Age, yr, median (range) | 49 (40-54) | 59 (55-64) | 67 (65-75) | <.0001 |
| Male sex, n (%) | 406 (66) | 359 (65) | 64 (78) | .06 |
| KPS ≥80% before HCT, n (%) | 512 (83) | 481 (87) | 71 (87) | .24 |
| Missing KPS, n (%) | 38 (6) | 30 (5) | 2 (2) | |
| Previous autologous HCT, n (%) | 160 (26) | 131 (24) | 7 (9) | .002 |
| NHL histology, n (%)* | | | | .0008 |
| Aggressive | 299 (49) | 314 (57) | 55 (67) | |
| Indolent | 315 (51) | 238 (43) | 27 (33) | |
| Disease status at HCT, n (%) | | | | .79 |
| CR1/CR2+ | 173 (28) | 160 (29) | 19 (23) | |
| PR1/PR2+ | 233 (38) | 218 (39) | 32 (39) | |
| RD | 155 (25) | 126 (23) | 25 (30) | |
| Unknown or untested sensitivity | 53 (9) | 48 (9) | 6 (7) | |
| Interval from diagnosis to HCT, n (%) | | | | .12 |
| <2 yr | 217 (35) | 167 (30) | 31 (38) | |
| ≥2 yr | 397 (65) | 385 (70) | 51 (62) | |
| Donor–recipient sex match, n (%) | | | | .04 |
| Male–male | 262 (43) | 230 (42) | 51 (62) | |
| Male–female | 122 (20) | 109 (20) | 9 (11) | |
| Female–male | 144 (23) | 129 (23) | 13 (16) | |
| Female–female | 86 (14) | 84 (15) | 9 (11) | |
| Donor/recipient CMV serostatus, n (%) | | | | .41 |
| −/− | 193 (31) | 142 (26) | 19 (23) | |
| −/+ | 171 (28) | 171 (31) | 24 (29) | |
| +/+ | 173 (28) | 170 (31) | 31 (38) | |
| +/− | 60 (10) | 55 (10) | 6 (7) | |
| Unknown | 17 (3) | 14 (3) | 2 (2) | |
| Graft source, n (%) | | | | .53 |
| Bone marrow | 84 (14) | 78 (14) | 15 (18) | |
| PBSCs | 530 (86) | 474 (86) | 67 (82) | |
| HLA match, n (%) | | | | .29 |
| HLA-identical sibling | 262 (43) | 208 (38) | 29 (35) | |
| URD, well matched | 222 (36) | 234 (42) | 39 (48) | |
| URD, partially matched | 95 (15) | 76 (14) | 9 (11) | |
| URD, mismatched | 15 (2) | 17 (3) | 1 (1) | |
| URD, missing | 20 (3) | 17 (3) | 4 (5) | |
| Year of HCT, n (%) | | | | <.0001 |
| 2001-2004 | 363 (59) | 243 (44) | 36 (44) | |
| 2005-2007 | 251 (41) | 309 (56) | 46 (56) | |
| Conditioning regimen intensity, n (%) | | | | .05 |
| RIC | 333 (54) | 260 (47) | 43 (52) | |
| NMA | 281 (46) | 292 (53) | 39 (48) | |
| Conditioning regimen | | | | .25 |
| TBI ≤200 cGy | 111 (18) | 129 (23) | 17 (21) | |
| TBI >200 cGy | 21 (3) | 22 (4) | 4 (5) | |
| Alkylator only (Cy, Mel, Bu, Thio); no TBI | 443 (72) | 359 (65) | 57 (70) | |
| Other | 39 (6) | 42 (8) | 4 (5) | |
| GVHD prophylaxis | | | | .43 |
| CSA ± MTX ± other | 205 (33) | 162 (29) | 19 (23) | |
| Tac ± MTX ± other | 179 (29) | 172 (31) | 25 (30) | |
| T cell depletion† | 230 (37) | 218 (39) | 38 (46) | |
| Follow-up of survivors, mo, median (range) | 56 (3-111) | 47 (2-111) | 47 (2-86) | |

RIC indicates reduced-intensity conditioning; NMA, nonmyeloablative; HCT, hematopoietic cell transplantation; NHL, Non-Hodgkin lymphoma; KPS, Karnofsky Performance Status; CR1/CR2+, complete remission; PR1/PR2+, partial remission; RD, resistant disease; CMV, cytomegalovirus; PBSCs, peripheral blood stem cells; HLA, human leukocyte antigen; URD, unrelated donor; TBI, total body irradiation; Cy, cyclophosphamide; Mel, melphalan; Bu, busulfan; Thio, thiotepa; GVHD, graft-versus-host disease; CSA, cyclosporine; MTX, methotrexate; Tac, tacrolimus.

* Detailed in Methods, Patient Selection.

† Includes in vivo (antithymocyte globulin or alemtuzumab) and ex vivo T cell depletion.

versus female–male versus female–female), and conditioning regimen intensity (RIC versus NMA). All risk factors with a $P$ value <.05 were included in the models. The potential interaction between the main effect of age and all significant covariates were examined. To analyze any possible impact of specific histology on outcomes, we divided patients into 5 histological groups (diffuse large B cell, mantle cell, SLL/CLL, follicular, and other) and included these in the models for relapse/progression, PFS, and OS. All computations were performed using SAS version 9.1 (SAS Institute, Cary, NC).

## RESULTS

### *Patient Characteristics*

Table 1 summarizes patient-, disease-, and transplantation-related variables for the 3 age cohorts. The 1248 patients in the study population included 614 (49%) age 40 to 54 years, 552 (44%) age 55 to 64 years, and 82 (7%) age ≥65 years. The majority of patients underwent transplantation for aggressive NHL subtypes, which were most frequent in the oldest patient group (49% for 40 to 54 years versus 57% for 55 to 64 years versus 67% for ≥65 years; $P = .0008$). The oldest group also had the lowest rate of previous autologous HCT (26% for 40 to 54 years versus 24% for 55 to 64 years versus 9% for ≥65 years; $P = .002$). A total of 225 patients with aggressive NHL and 73 patients with indolent NHL had undergone previous autologous HCT. Across the age cohorts, 23% to 30% of all patients underwent transplantation with RD, including 30% of the oldest group. Use of an HLA-matched related sibling donor or URD was similar across the age cohorts. The remaining variables—sex, KPS, interval from diagnosis to transplantation, donor–recipient sex match, donor and recipient CMV serostatus, and donor–recipient HLA match—were balanced across age cohorts. GVHD prophylaxis most often included a calcineurin inhibitor with or without methotrexate, but 37% to 46% of patients underwent T cell depletion, with the highest rate in the oldest age cohort. Median follow-up for the 3 age cohorts ranged from 47 to 56 months.

### *Neutrophil Recovery and GVHD*

Neutrophil recovery by day +28 post-transplantation was similar across the 3 age cohorts (Table 2). Multivariate analysis demonstrated that older age (odds ratio [OR], 0.32; 95% CI, 0.14 to 0.75; $P = .0085$), KPS <80% (OR, 0.28; 95% CI, 0.21 to 1.85; $P = .0002$), and RD status at HCT (OR, 0.25; 95% CI, 0.10 to 0.60; $P = .002$) were associated with a lower likelihood of prompt engraftment. The use of PBSC grafts versus bone marrow grafts was associated with faster neutrophil recovery (OR, 3.09; 95% CI, 1.64 to 5.85; $P = .0005$).

The incidence of grade II-IV acute GVHD (33% to 35% by day +100; $P = .92$) and chronic GVHD (48 to 56% by 3 years; $P = .39$) was similar across the 3 age cohorts (Table 2). Multivariate analysis demonstrated no impact of age on acute or chronic GVHD, but did show a higher risk of acute GVHD in patients not in CR at time of HCT (PR1/PR2: risk ratio [RR], 1.37; 95% CI, 1.08 to 1.75; $P = .01$; RD: RR, 1.46; 95% CI, 1.12 to 1.91; $P = .0005$) and with the use of RIC versus an NMA conditioning regimen (RR, 1.31; 95% CI, 1.08 to 1.59; $P = .007$). The use of a non-CSA-containing GVHD prophylaxis regimen was associated with less acute GVHD (Tac ± MTX ± other: RR, 0.76; 95% CI, 0.60 to 0.96; $P = .02$; T cell depletion: RR, 0.45; 95% CI, 0.35 to 0.57; $P < .001$). Compared with HLA-matched sibling HCT, URD HLA-mismatched (URD well-matched: RR, 1.45; 95% CI, 1.20 to 1.75; $P = .002$; URD partially HLA-matched: RR, 1.75; 95% CI, 1.35 to 2.26; $P < .001$), and RIC conditioning regimen (RR, 1.29; 95% CI, 1.32 to 3.36; $P < .002$) were all associated with a higher incidence of chronic GVHD.

### *NRM*

The cumulative incidence of NRM did not differ significantly among the 3 age cohorts at either day +100 (13% to 18%; $P = .11$) or 1 year (22% to 34%; $P = .05$) post-transplantation (Table 2). Univariate analyses stratified by disease histology (aggressive versus indolent) also showed no impact of age on NRM at these same time points (Table 3). Because too few patients in the oldest cohort (n = 7) had undergone previous autologous HCT, we performed a separate analysis in the 2 younger cohorts comparing outcomes in those with and those without previous autologous HCT. We found a higher 3-year NRM in patients who had received an autograft before undergoing allogeneic HCT (previous autograft: 42%; 95% CI, 25% to 31%; no previous autograft: 28%; 95% CI, 37% to 48%; $P < .0001$). In multivariate analysis, older age was associated with worse NRM (age 55 to 64 years: RR, 1.52; 95% CI, 1.24 to 1.86; $P < .001$; age ≥65 years: RR, 1.57; 95% CI, 1.08 to 2.29: $P = .02$), although NRM was similar in the 2 older age cohorts (Table 4). Lower KPS, advanced disease at HCT, and less favorable HLA match also adversely impacted NRM.

**Table 2**
Univariate Analysis of Outcomes for All Patients Age ≥ 40 Years Undergoing RIC or NMA Allogeneic HCT for NHL

| Outcome event | Age 40-54 | | Age 55-64 | | Age ≥65 | | $P$ Value* |
|---|---|---|---|---|---|---|---|
| | n | Probability (95% CI), % | n | Probability (95% CI), % | n | Probability (95% CI), % | |
| Neutrophil engraftment | 614 | | 552 | | 82 | | |
| 28 d | | 96 (95-97) | | 96 (94-97) | | 89 (82-95) | .09 |
| Acute GVHD grade II-IV | 614 | | 552 | | 82 | | |
| 100 d | | 35 (31-39) | | 34 (30-38) | | 33 (23-44) | .92 |
| Chronic GVHD | 612 | | 551 | | 82 | | |
| 3 yr | | 56 (52-60) | | 54 (49-58) | | 48 (37-59) | .39 |
| NRM | 605 | | 552 | | 82 | | |
| 100 d | | 13 (10-16) | | 17 (14-20) | | 18 (11-28) | .11 |
| 1 yr | | 22 (19-26) | | 27 (23-31) | | 34 (24-44) | .05 |
| Progression/relapse | 605 | | 552 | | 82 | | |
| 3 yr | | 28 (24-32) | | 33 (29-37) | | 33 (23-44) | .22 |
| PFS | 605 | | 552 | | 82 | | |
| 3 yr | | 44 (39-48) | | 32 (28-36) | | 27 (17-37) | <.0001 |
| OS | 614 | | 552 | | 82 | | |
| 3 yr | | 54 (50-58) | | 40 (36-44) | | 39 (28-50) | <.0001 |

RIC indicates reduced-intensity conditioning; NMA, nonmyeloablative; HCT, hematopoietic cell transplantation; NHL, Non-Hodgkin lymphoma; GVHD indicates graft-versus-host disease; NRM, nonrelapse mortality; PFS, progression-free survival; OS, overall survival.

* Pointwise $P$ value.

**Table 3**
Univariate Outcomes by Disease Histology for Patients Age ≥40 Years Undergoing RIC or NMA Allogeneic HCT for NHL

| Outcome Event | Age 40-54 | | Age 55-64 | | Age ≥65 | | *P* Value* |
|---|---|---|---|---|---|---|---|
| | n | Probability (95% CI), % | n | Probability (95% CI), % | n | Probability (95% CI), % | |
| Aggressive NHL | | | | | | | |
| NRM | 297 | | 314 | | 55 | | |
| 100 d | | 13 (9-17) | | 16 (12-20) | | 24 (13-36) | .15 |
| 1 yr | | 22 (17-27) | | 26 (22-32) | | 38 (26-51) | .05 |
| Progression/relapse | 297 | | 314 | | 55 | | |
| 3 yr | | 34 (28-39) | | 36 (31-42) | | 29 (18-42) | .55 |
| PFS | 297 | | 314 | | 55 | | |
| 3 yr | | 38 (32-44) | | 30 (25-35) | | 25 (14-37) | .04 |
| OS | 299 | | 314 | | 55 | | |
| 3 yr | | 50 (44-56) | | 37 (31-43) | | 34 (21-47) | .003 |
| Indolent NHL | | | | | | | |
| NRM | 308 | | 238 | | 27 | | |
| 100 d | | 13 (9-17) | | 18 (13-23) | | 8 (1-20) | .10 |
| 1 yr | | 23 (18-27) | | 27 (22-33) | | 24 (10-42) | .46 |
| Progression/relapse | 308 | | 238 | | 27 | | |
| 3 yr | | 23 (18-27) | | 28 (22-34) | | 41 (23-61) | .11 |
| PFS | 308 | | 238 | | 27 | | |
| 3 yr | | 49 (43-55) | | 35 (29-41) | | 30 (13-50) | .003 |
| OS | 315 | | 238 | | 27 | | |
| 3 yr | | 58 (52-63) | | 44 (38-51) | | 50 (30-79) | .013 |

RIC indicates reduced-intensity conditioning; NMA, nonmyeloablative; HCT, hematopoietic cell transplantation; NHL, Non-Hodgkin lymphoma; NRM, non-relapse mortality; PFS, progression-free survival; OS, overall survival.
* Pointwise *P* value.

### *Relapse and Progression*

Relapse and progression rates at 3 years post-transplantation were similar across the 3 age cohorts, as confirmed in a separate analysis stratified by disease histology (Tables 2 and 3; Figure 1A and C). In the youngest and middle cohorts, relapse incidence was similar in patients who underwent previous autologous HCT (30% at 3 years; $P = .88$). Multivariate analysis demonstrated no significant impact of age, but advanced disease at HCT and GVHD prophylaxis were associated with increased risk of progression or relapse. T cell depletion was associated with a significantly increased risk of progression or relapse (RR, 1.52; 95% CI, 1.18 to 1.95; $P = .001$). The number of extramedullary sites involved and number of pretransplantation therapies did not influence the risk of relapse ($P > .10$).

### *PFS and OS*

In univariate analysis, PFS at 3 years was highest in the youngest age cohort, and there was no difference in PFS between the 2 older cohorts (Table 2 and Figure 2A). PFS also differed among the age cohorts when patients were stratified by aggressive/indolent disease histology (Table 3; Figures 1B and D and 2A). Multivariate analysis showed that older age (≥55 and >65 years), lower KPS (<80%), disease status other than CR1/CR2, GVHD prophylaxis, and greater HLA mismatch were all associated with inferior PFS (Table 4).

Three-year OS also differed significantly across the 3 age cohorts (Table 2 and Figure 2B), although even in the oldest cohort, 39% of patients survived beyond 3 years. In the youngest and middle cohorts, previous autologous HCT was associated with lower 3-year OS (previous autograft: 35%; 95% CI, 30% to 41%; no previous autograft: 52%; 95% CI, 48% to 55%; $P < .0001$). In multivariate analysis, older age was associated with worse OS, as were disease status at allogeneic HCT, KPS <80%, HLA mismatch, and use of an RIC regimen (Table 4). After HCT, the primary causes of death were similar in the 3 age cohorts: relapse (33% to 37%), infection (17% to 21%), GVHD (14% to 17%), and organ failure (13% to 15%).

To examine the effect of histology on outcomes, we assessed the impact of 5 specific histological subgroups on the incidence of relapse/progression, PFS, and OS. Multivariate analysis revealed no significant influence of these histological subgroups on any outcome ($P > .10$ for all). In addition, NHL subtype (B cell or a T cell subtype) had no significant effect on any outcome ($P > .30$ for all). Neither the number of extramedullary sites involved nor the number of pretransplantation therapies influenced PFS or OS ($P > .10$ for both).

## DISCUSSION

We examined the impact of age in a large group of older patients undergoing RIC or NMA allogeneic HCT for NHL. In this sizeable cohort, we found that only a modest number of patients over age 65 years underwent allogeneic HCT to treat their disease. Although age had a modest adverse effect in patients over age 55 compared with those age 40 to 54, outcomes were equivalent in patients age 55 to 64 and those age ≥65, with no significant differences in NRM, relapse, PFS, or OS. Older age also did not influence the incidence of acute or chronic GHVD, major complications that might be less well tolerated by older patients.

It is not surprising that HLA disparity, poorer KPS, T cell depletion, and advanced disease status at time of transplantation adversely affected major HCT outcomes, given that each has been reported to have prognostic implications [9,16-20]. Aggressive NHL is also generally associated with worse outcomes [21,22]. Although histological subgroup had no significant association with any HCT outcome in multivariate analysis, 67% of all patients age ≥65 years and 57% of those age 55 to 64 years had aggressive NHL. The small number of patients in the oldest age cohorts might have limited these analyses. Few patients in the oldest cohort had undergone previous autologous HCT, which precluded the inclusion of this cohort in the analysis for the effect of previous autologous HCT. In the 2 younger cohorts, however, we found an adverse effect of previous autologous HCT on both NRM and OS. Two previous small series also reported a

**Table 4**
Multivariate Analysis of NRM, Relapse/Progression, PFS, and OS after RIC or NMA Allogeneic HCT for NHL

| Variable | n | Relative Risk (95% CI) | *P* Value* | Overall *P* Value |
|---|---|---|---|---|
| NRM | | | | |
| Age, yr | | | | |
| 40-54 | 614 | | | .0002 |
| 55-64 | 552 | 1.52 (1.24-1.86) | <.0001 | |
| ≥65 | 82 | 1.57 (1.08-2.29) | .0189 | |
| Significant covariates | | | | |
| KPS | | | | |
| ≥80 | 1064 | | | .0001 |
| <80 | 114 | 1.87 (1.40-2.50) | <.0001 | |
| NHL disease status | | | | |
| CR1/CR2+ | 352 | | | <.0001 |
| PR1/PR2+ | 483 | 1.27 (0.99-1.63) | .0576 | |
| RD | 306 | 1.90 (1.45-2.49) | <.0001 | |
| HLA match | | | | |
| HLA-identical sibling | 499 | | | <.0001 |
| URD well matched | 495 | 1.36 (1.07-1.71) | .0116 | |
| URD partially matched | 180 | 2.30 (1.74-3.03) | <.0001 | |
| URD mismatched | 33 | 2.9 (1.76-4.77) | <.0001 | |
| Relapse | | | | |
| Age, yr | | | | |
| 40-54 | 614 | | | .059 |
| 55-64 | 552 | 1.29 (1.05-1.59) | .0176 | |
| ≥65 | 82 | 1.18 (0.78-1.77) | .4321 | |
| Significant covariates | | | | |
| NHL disease status | | | | |
| CR1/CR2+ | 352 | | | <.0001 |
| PR1/PR2+ | 483 | 1.67 (1.27-2.19) | .0002 | |
| RD | 306 | 2.73 (2.04-3.64) | <.0001 | |
| GVHD prophylaxis | | | | |
| CSA ± MTX ± other | 386 | | | <.0001 |
| Tac ± MTX ± other | 376 | 0.88 (0.67-1.16) | .3607 | |
| T cell depletion | 486 | 1.52 (1.18-1.95) | .0011 | |
| PFS | | | | |
| Age, yr | | | | |
| 40-54 | 614 | | | .0001 |
| 55-64 | 552 | 1.37 (1.18-1.59) | <.0001 | |
| ≥65 | 82 | 1.34 (1.01-1.76) | .0397 | |
| Significant covariates | | | | |
| KPS | | | | |
| ≥80 | 1064 | | | <.0001 |
| <80 | 114 | 1.63 (1.30-2.05) | <.0001 | |
| NHL disease status | | | | |
| CR1/CR2+ | 352 | | | <.0001 |
| PR1/PR2+ | 483 | 1.45 (1.21-1.75) | <.0001 | |
| RD | 306 | 1.45 (1.88-2.78) | <.0001 | |
| GVHD prophylaxis | | | | |
| CSA ± MTX ± other | 386 | | | .0001 |
| Tac ± MTX ± other | 376 | 0.87 (0.72-1.06) | .1655 | |
| T cell depletion | 486 | 1.26 (1.05-1.50) | .0129 | |
| HLA match | | | | |
| HLA-identical sibling | 499 | | | <.0001 |
| URD well matched | 495 | 1.13 (0.96-1.34) | .1468 | |
| URD partially matched | 180 | 1.39 (1.12-1.72) | .0029 | |
| URD mismatched | 33 | 2.28 (1.56-3.32) | <.0001 | |
| OS | | | | |
| Age, yr | | | | |
| 40-54 | 614 | | | <.0001 |
| 55-64 | 552 | 1.47 (1.25-1.72) | <.0001 | |
| ≥65 | 82 | 1.47 (1.09-1.98) | .0127 | |
| Significant covariates | | | | |
| NHL disease status | | | | |
| CR1/CR2+ | 352 | | | <.0001 |
| PR1/PR2+ | 483 | 1.29 (1.06-1.58) | .0113 | |
| RD | 306 | 1.97 (1.60-2.44) | <.0001 | |
| KPS | | | | |
| ≥80 | 1064 | | | <.0001 |
| <80 | 114 | 1.87 (1.48-2.37) | <.0001 | |
| HLA match | | | | |
| HLA-identical sibling | 499 | | | <.0001 |
| URD well matched | 495 | 1.30 (1.09-1.56) | .0043 | |
| URD partially matched | 180 | 1.90 (1.52-2.38) | <.0001 | |
| URD mismatched | 33 | 2.21 (1.48-3.30) | .0001 | |
| Conditioning regimen | | | | .03 |
| NMA | 612 | | | |
| RIC | 636 | 1.19 (1.02-1.39) | .03 | |

NRM indicates nonrelapse mortality; PFS, progression-free survival; OS, overall survival; RIC, reduced-intensity conditioning; NMA, nonmyeloablative; HCT, hematopoietic cell transplantation; NHL, Non-Hodgkin lymphoma; KPS, Karnofsky Performance Status; CR1/CR2+, complete remission; PR1/PR2+, partial remission; RD, resistant disease; HLA, human leukocyte antigen; URD, unrelated donor; GVHD, graft-versus-host disease; CSA, cyclosporine ; MTX, methotrexate; Tac, tacrolimus.

* Compared with reference group.

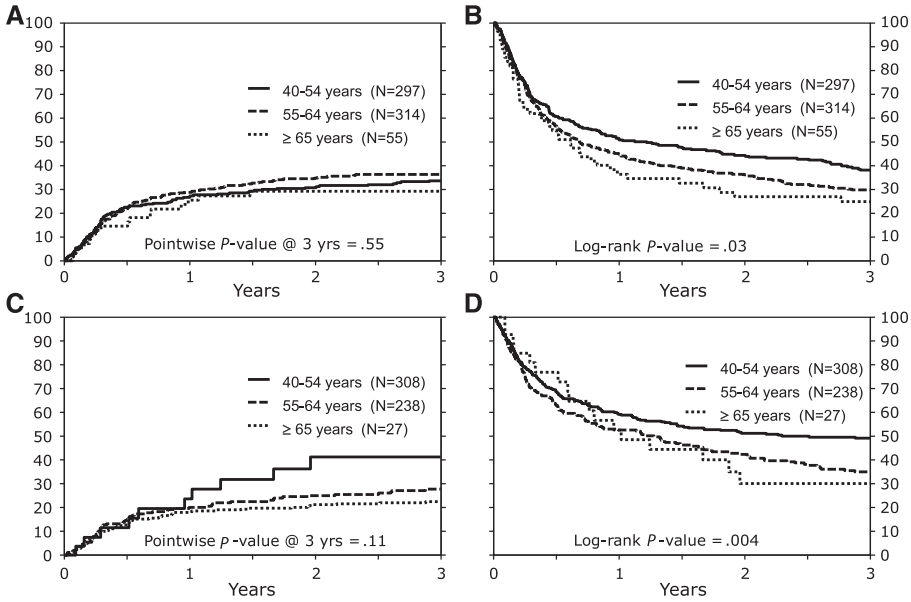


**Figure 1.** Three-year relapse and PFS based on histology. (A) Progression/relapse, aggressive NHL. (B) PFS, aggressive NHL. (C) Progression/relapse, indolent NHL. (D) PFS, indolent NHL.

modest negative influence of previous autologous HCT on subsequent allogeneic HCT. Thomson et al. [23] found no influence of previous autologous HCT on outcomes, whereas Rodriguez et al. [24] reported an association between previous autologous HCT and worse relapse and OS, and a trend toward an association with worse NRM. Given that autologous HCT remains the initial HCT option for most patients with NHL, the impact of previous autografting directly influences the selection of patients for allografting.

Even for patients with advanced NHL, the outcomes of RIC or NMA allogeneic HCT seen in the present study are encouraging. This is important, considering that patients who relapse after autologous HCT have very poor median survival, ranging from 3 to 8 months depending on NHL histological type [25-27]. One study found a median survival of just 23 months in patients with mantle cell lymphoma who relapsed after autologous HCT, and only 6 months if relapse occurred within 1 year after HCT [28]. In another study of patients with relapsed/refractory diffuse large B cell lymphoma, 36% of patients who received second-line salvage therapy failed to respond, and in those who did respond, the median duration of response was only 4 months [29]. A study of survival after relapse post-autografting using an age-adjusted IPI found a PFS of only 16% and an OS of only 18% at 4 years, even in patients with chemosensitive disease [27]. In the present study, 3-year OS was 39% in the oldest age cohort, suggesting that selected older patients can benefit from allogeneic HCT and can achieve extended survival that cannot be attained with other salvage approaches.

We were surprised at how few patients age ≥65 years underwent allogeneic HCT, even though more than one-half of all NHL cases occur in patients age ≥60 years [30]. Similar to observations in patients with acute myelogenous leukemia and myelodysplastic syndrome, the majority of patients with NHL eligible for allogeneic HCT are not referred and never receive this therapy [31]. Contemporary registry analyses from the European Group for Blood and Marrow Transplantation and the CIBMTR examining relapsed high-grade lymphomas have emphasized the curative potential of this therapy [32,33], yet recognize the rarity of its use. Thus, HCT remains

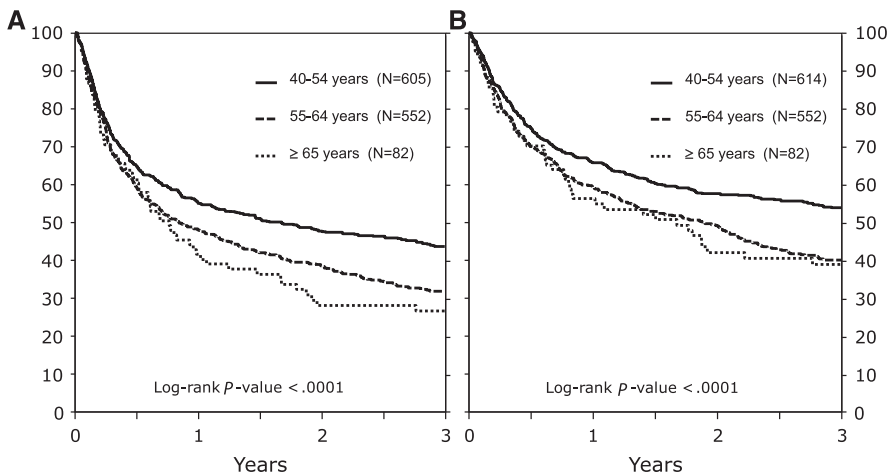


**Figure 2.** Three-year PFS (A) and OS (B) after allogeneic HCT for NHL.

not widely applied despite recent reports of improved HCT outcomes for patients in the modern era [34-37].

We note some limitations of our study owing to the heterogeneity of pre-HCT therapies and lack of direct data to clarify the medical decision making when selecting patients for allogeneic HCT. Detailed comorbidity information other than KPS was not available for this study, although this information may directly inform patient selection by physicians considering allogeneic HCT. Although some appropriate clinical selection bias exists in choosing only the fittest older patients for an allograft, these promising outcomes suggest that careful pretransplantation evaluation can identify patients able to tolerate this curative therapeutic approach.

Although our results suggest that outcome differences are only modestly influenced by age, even our oldest patients had encouraging outcomes. Attention to disease stage, HLA disparity, and performance status before HCT could further improve these results by identifying those patients with NHL most likely to benefit from RIC allogeneic HCT. Our analysis supports the referral of selected older patients with NHL for allogeneic HCT.

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