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Prospective implementation of the HCT frailty scale in adults with lymphoproliferative syndromes candidates for autologous haematopoietic stem cell transplantation: Results from a multicentre GETH-TC study

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Summary

This prospective study evaluated the incidence and dynamics of frailty in 156 adults with lymphoproliferative syndromes undergoing autologous haematopoietic stem cell transplantation (HSCT). Frailty was assessed using the haematopoietic cell transplantation (HCT) frailty scale in patients from 15 Spanish institutions at initial consultation, transplant admission and day +100. Quality of life (QoL) was measured using the EuroQoL. At first consultation, 45 patients (28.8%) were classified as fit, 93 (59.6%) as pre-frail and 18 (11.6%) as frail. Frailty was more frequent among older patients, those with Karnofsky performance status (KPS) below 90%, and abnormal Mini-Cog scores (<3). Rates of relapse, death, readmission and median hospital stay were similar across frailty groups. However, frail patients reported significantly worse QoL. One-year non-relapse mortality was higher in frail patients than in pre-frail and fit patients, although differences were not statistically significant ($p = 0.19$). At day +100, 33.6% of patients were fit, 57.9% pre-frail and 8.5% frail, demonstrating significant transitions in frailty over time ($p = 0.001$). Moreover, frail patients showed lower relapse-free [53.3% (17.7–79.6) vs. 85.3% (68.3–93.6), $p = 0.05$] and overall survival [77.8% (36.5–93.9) vs. 100%, $p = 0.16$], and worse perceived QoL than fit ones. Overall, frailty was dynamic and clinically relevant, supporting routine assessment and targeted interventions to mitigate adverse outcomes.

KEYWORDS

autologous haematopoietic stem cell transplantation, dynamic assessment, frailty, lymphoproliferative syndrome, quality of life

For affiliations refer to page 12.

INTRODUCTION

Autologous haematopoietic stem cell transplantation (auto-HSCT) is a cornerstone in the treatment of several lymphoproliferative syndromes (LPS),[1] aiming to prolong progression-free survival (PFS) following induction regimens.[2] Advances in transplant procedures and supportive care have expanded eligibility beyond young and fit patients to include older adults and those with comorbidities.[3] However, auto-HSCT remains associated with substantial morbidity and a non-negligible risk of mortality,[4] highlighting the need for accurate candidate selection and peri-transplant management.[5]

Frailty assessment has emerged as a valuable tool for risk stratification and clinical decision-making.[6] Although initially described in geriatric populations, frailty is now recognized as a multidimensional and dynamic condition that can affect adults with haematological malignancies regardless of chronological age.[7] More specifically, in patients with LPS undergoing auto-HSCT, frailty has been associated with inferior survival and increased transplant-related complications,[8] supporting its systematic assessment in clinical practice regardless of baseline characteristics.[9,10]

Recognizing the potential impact of frailty on transplant-related toxicity and outcomes, the Spanish Group for Hematopoietic Transplantation and Cell Therapy (GETH-TC) launched a prospective, multicentre initiative to investigate frailty in adults undergoing HSCT.[11] Following a systematic review, the haematopoietic cell transplantation (HCT) frailty scale (HCT-FS), originally developed at the Princess Margaret Cancer Center (PMCC) (Toronto, Canada), for allogeneic HSCT candidates,[12] was implemented across 15 transplant centres in January 2022.

The present study evaluates the applicability of the HCT-FS in patients undergoing auto-HSCT for LPS, assessing frailty longitudinally from the first consultation to day +100, and its association with clinical outcomes.

METHODS

Study design, multicentre participation and patient selection

Fifteen GETH-TC centres prospectively assessed frailty in candidates for auto-HSCT between January 2022 and September 2023, irrespective of age or diagnosis, after obtaining informed consent. The implementation of the HCT-FS was conducted in an observational manner, and frailty results did not influence transplant eligibility or procedural planning. Data were prospectively collected using REDCap, a secure electronic data capture platform hosted by GETH-TC, and were updated in March 2025. The study protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona and the GETH-TC Board and was conducted in accordance with the Declaration of Helsinki.

Frailty and quality of life (QoL) assessments

The frailty evaluation protocol was standardized across participating sites. Frailty was assessed using the HCT-FS, as illustrated in Figure 1. To ensure consistency, all investigators and nursing staff completed centralized remote training sessions led by the principal investigator, who had prior experience with the Canadian protocol.

Frailty was measured at the first HSCT consultation, at HSCT admission and on day +100. Patients were classified as fit, pre-frail or frail based on the evaluation of the eight components of the HCT-FS (Figures S1 and S2). Cognitive function was additionally evaluated using the Mini-Cog test. From January 2023, QoL was also assessed at hospital admission and on day +100 using the EQ-5D-5L questionnaire.

Frailty assessments were integrated into clinical practice and completed in a median time of 15 min. Evaluations were conducted by haematologists or qualified nurses using existing institutional resources, without additional staffing, funding or extra patient appointments.

Auto-HSCT procedures and main definitions

Eligibility for auto-HSCT and transplant-related decisions followed standard institutional protocols. Peripheral blood stem cells were mobilized with standard-dose granulocyte colony-stimulating factor (G-CSF), with plerixafor administered selectively based on CD34+ cell counts. Conditioning regimens and supportive care were defined according to local practice. Most patients received carmustine, etoposide, cytarabine and melphalan (BEAM) as conditioning. Disease response was classified according to established international criteria.

Statistical analysis

Frailty category (fit, pre-frail, frail) was considered the main explanatory variable. Associations between frailty status and clinical outcomes were analysed, including duration of hospitalization, overall survival (OS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM). Categorical variables were summarized as counts and percentages, and continuous variables as medians with ranges or interquartile ranges. Comparisons were performed using appropriate statistical tests. Predictors of frailty were evaluated using binary logistic regression (frail vs. fit/pre-frail). A two-sided p-value <0.05 was considered statistically significant. Analyses were conducted using EZRv2.8 software.

HCT Frailty Scale
Clinical Frailty Scale (CFS) ≥ 3 (Frail) *vs.* 1-2 (Not-Frail)
Instrumental Activities of Daily Living (IADL) Scale ≥ 1 Limitation *vs.* No Limitations
Timed Up and Go Test (TUGT) Abnormal > 10 seconds *vs.* Normal
Grip Strength (GS) Test Abnormal *vs.* Normal If female < 16 kg If male < 26 kg
Self-Rated Health Question (SRH-Q) Fair, Poor *vs.* Excellent, Very Good, Good
Fall in last 6 months Yes *vs.* No
Albumin Serum Level Abnormal (< 38 g/L) *vs.* Normal
C-reactive Protein (CRP) Abnormal (≥ 11 mg/L) *vs.* Normal
Mini-Cog Test Abnormal if 0-2 *vs.* Normal if 3-6

HCT Frailty Scoring System	Normal	Abnormal
CFS: ≥ 3 (*vs.* 1-2)	0	1.5
IADL: ≥ 1 Limitation (*vs.* No Limitation)	0	1
TUGT: Abnormal (*vs.* Normal)	0	1.5
GS: Abnormal (*vs.* Normal)	0	1
SRH-Q: Fair, Poor (*vs.* Excellent, Very Good, Good)	0	1
Fall in last 6 months: Yes (*vs.* No)	0	1
Albumin level: Abnormal (*vs.* Normal)	0	1.5
CRP: Abnormal (*vs.* Normal)	0	2
Total Score	0	10.5
Patient classification	**Fit** **Pre-Frail** **Frail**	**≤ 1** **>1 - <5.5** **≥ 5.5**

FIGURE 1 Haematopoietic cell transplant (HCT) frailty scale.

TABLE 1 Baseline characteristics of patients according to frailty at first consultation.

Baseline characteristics of patients	All patients *N* = 156	Fit *N* = 45 (28.8)	Pre-frail *N* = 93 (59.6)	Frail *N* = 18 (11.6)	*p*-value
Median age (range)	56 (19–75)	55 (25–71)	56 (24–72)	62 (19–75)	**0.013**
Older 60 years (%)	64 (41)	14 (31.1)	38 (40.8)	12 (66.6)	**0.035**
Sex					
Male, *n* (%)	101 (64.7)	27 (60)	62 (66.7)	12 (66.7)	0.732
Female, *n* (%)	55 (35.3)	18 (40)	31 (33.3)	6 (33.3)	
Type of lymphoproliferative disease, *n* (%)					
B-NHL	90 (57.6)	29 (64.4)	53 (57)	8 (44.4)	0.326
T-NHL	14 (9)	4 (8.9)	10 (10.8)	0 (0)	
Primary CNS lymphoma	19 (12.2)	3 (6.7)	12 (12.9)	4 (22.2)	
Hodgkin lymphoma	33 (21.2)	9 (20)	18 (19.3)	6 (33.4)	
Line of treatment, *n* (%)					
First line	64 (43.5)	20 (48.8)	37 (41.1)	7 (43.8)	0.364
Second line	65 (44.2)	14 (34.2)	45 (50)	6 (37.5)	
Third or more	18 (12.3)	7 (17)	8 (8.9)	3 (18.8)	
Missing data	9	4	3	2	
KPS < 90%, *n* (%)	51 (35.7)	6 (14.6)	36 (41.4)	9 (60)	**<0.001**
Missing data	13	4	6	3	
HCT-CI > 3, *n* (%)	6 (4.4)	0	5 (6.2)	1 (7.1)	0.263
Missing data	21	5	12	4	
Abnormal Mini-Cog test (<3), *n* (%)	19 (12.2)	0 (0)	12 (12.9)	7 (38.9)	**<0.001**

Note: *p*-values that are statistically significant ($p < 0.05$) are shown in bold.

Abbreviations: CNS, central nervous system; HCT-CI, haematopoietic cell transplant-comorbidity index; KPS, Karnofsky performance status; NHL, non-Hodgkin lymphoma.

RESULTS

Multicentre implementation of the HCT-FS

Between January 2022 and November 2023, 15 HSCT units prospectively implemented the HCT-FS in routine clinical practice. During this period, 156 adults with LPS who underwent auto-HSCT and had complete frailty assessments at the first consultation and at hospital admission were included.

Frailty assessment and predictors of frailty at first consultation

Baseline patient characteristics are summarized in Table 1. Median age was 56 years (range 19–75), with 64 (41%) patients aged >60 years. Male patients accounted for 101 (64.7%) cases and female patients for 55 (35.2%). At the first consultation, 51 (35.7%) patients had a Karnofsky performance status (KPS) <90%, and 6 (4.4%) had an HCT-Comorbidity Index (HCT-CI) >3.

At the first consultation, 45 (28.8%) patients were classified as fit, 93 (59.6%) as pre-frail and 18 (11.6%) as frail. First consultations were generally performed before the stem cell collection, at a median of 43 days (interquartile range [IQR] 20–90 days) before HSCT admission. Frailty was more prevalent in older adults (median age: frail, 62 years vs. pre-frail and fit, 56 and 55 years, respectively; $p = 0.03$), in those with KPS <90% (frail 60.0% vs. pre-frail 41.4% vs. fit 14.6%; $p < 0.001$) and in those with abnormal Mini-Cog scores (frail 38.9% vs. pre-frail 12.9% vs. fit 0%, $p = 0.001$).

Complementary multivariate binary logistic regression analysis reported in Table 2 confirmed that frail patients at the first consultation were more likely to have an abnormal Mini-Cog test (OR 7.6, $p = 0.004$). Nevertheless, no significant association was observed between frailty and older age ($p = 0.13$), sex ($p = 0.28$) or HCT-CI >3 ($p = 0.38$).

Frailty dynamics before transplant

As shown in Figure 2, between the first consultation and hospital admission, transitions between frailty states were documented. At HSCT admission, 48 (30.8%) patients were classified as fit, 84 (53.8%) as pre-frail and 24 (15.4%) as frail; however, these changes did not significantly affect the overall distribution of frailty among patients between these two time points ($p = 0.235$).

Nevertheless, individual-level transitions were observed (Figure S3A), with 56 (35.9%) patients changing frailty category during this period. Improvement was observed in 27 (17.3%) patients, including 44.4% of those initially classified as frail. Conversely, deterioration occurred in 29 (18.6%) patients, highlighting the dynamic nature of frailty during pretransplant evaluation.

TABLE 2 Predictors for frailty at first consultation.

Univariate	Frail (vs. fit and pre-frail) odds ratio (95% CI)	*p*-value
Median age (continuous variable)	1.05 (0.99–1.10)	0.055
Older 60 years (vs. younger)	7.69 (2.75–21.46)	**<0.001**
Type of lymphoproliferative disease		
T-NHL (vs. B-NHL)	0	0.999
HL (vs. B-NHL)	2.27 (0.75–7.15)	0.159
PCNSL (vs. B-NHL)	2.72 (0.73–10.23)	0.139
Type of lymphoproliferative disease		
PCNSL (vs. other)	4.51 (1.32–15.48)	**0.016**
Sex		
Female (vs. male)	0.90 (0.32–2.57)	0.856
HCT-CI		
>3 (vs. 0–3)	1.78 (0.19–16.48)	0.609
KPS		
<90% (vs. 90%–100%)	3.07 (1.02–9.19)	**0.045**
Mini-Cog		
Abnormal (vs. normal)	6.68 (2.18–20.42)	**0.001**
Disease status prior to HSCT		
Active disease (vs. CR)	0.39 (0.04–3.15)	0.379
Multivariate	**Frail (vs. fit and pre-frail) odds ratio (95% CI)**	***p*-value**
Age > 60 (vs. younger)	2.85 (0.74–11.04)	0.13
PCNSL (vs. others)	2.23 (0.43–11.59)	0.34
Sex—female (vs. male)	0.42 (0.08–2.05)	0.28
HCT-CI > 3 (vs. 0–3)	3.02 (0.25–36.13)	0.38
KPS < 90% (vs. 90%–100%)	2.16 (0.53–8.77)	0.28
Mini-Cog—abnormal (vs. Normal)	7.65 (1.88–31.11)	**0.004**

Note: *p*-values that are statistically significant ($p < 0.05$) are shown in bold.

Abbreviations: HCT-CI, haematopoietic cell transplant-comorbidity index; HL, Hodgkin lymphoma; KPS, Karnofsky performance status; NHL, non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma.

Impact of frailty on transplant outcomes and QoL

Because frailty status did not significantly differ between the first consultation and hospital admission, frailty assessed at the first consultation was used to evaluate its association with transplant outcomes, maximizing its early predictive value.

Among patients undergoing inpatient HSCT, the median length of hospitalization was 15 days, with no significant differences across frailty groups ($p = 0.48$), although fit individuals had a numerically shorter median stay (13 vs. 15 and 15 days). Readmission within 6 months occurred in 20 (12.8%) patients and was similar across fit, pre-frail and frail patients (6.7%, 15% and 16.7%; $p = 0.337$).

After a median follow-up of 23.2 months (IQR 18.3–28.4), 45 (28.8%) patients relapsed and 19 (12.2%) died. Most deaths were attributable to relapse ($n = 13$, 8.3%), while NRM occurred in 6 (3.8%) patients. Early mortality within 6 months was documented in 5 (3.2%) patients, due to disease progression ($n = 2$) and infectious complications ($n = 3$), and did not differ by frailty status (fit: 0 cases, pre-frail 4 cases and 1 frail patient; $p = 0.284$). As shown in Table 3 and Figure 3A, 1-year OS was high across all groups: 97.6% (84.3–99.7) in fit, 92.3% (84.5–96.3) in pre-frail and 88.5% (61.4–97.0) in frail patients, with no statistically significant differences between groups ($p = 0.322$). One-year CIR was 13.5% (5.4–23.5), 21.4% (13.5–30.6) and 4.8% (0.3–20.2) ($p = 0.311$), while 1-year NRM was 0%, 2.2% (0.4–6.9) and 11.5% (1.8–31.3) respectively ($p = 0.199$).

QoL was assessed at HSCT admission in 65 patients transplanted after 2023. As reported in Table S1, frail patients reported consistently worse QoL compared with fit and pre-frail patients, with significantly greater impairment in self-care ($p = 0.010$) and usual activities ($p = 0.023$).

Frailty evolution at day +100 after auto-HSCT

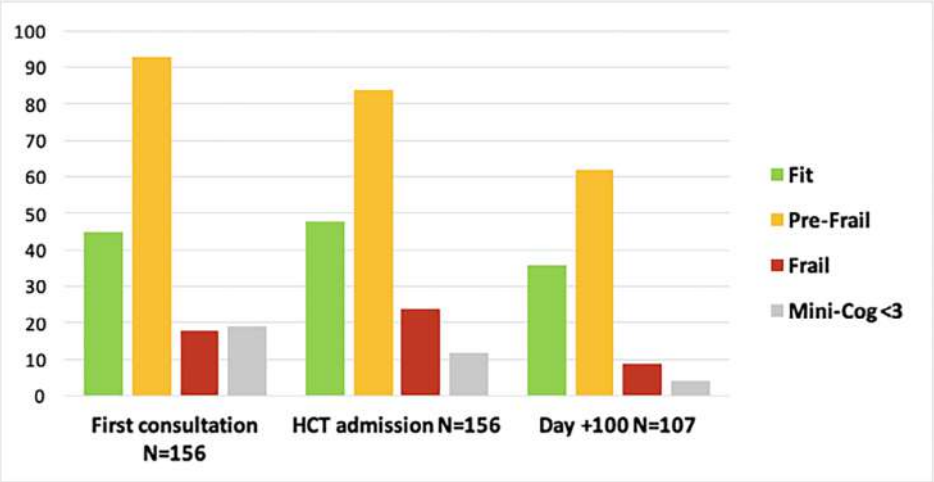
A third frailty assessment at day +100 was available in 107 patients who remained under follow-up at the transplant centre. At this time point, 36 (33.6%) patients were classified as fit, 62 (57.9%) as pre-frail and 9 (8.5%) as frail. As summarized in Figure 2 and Figure S3B, frailty status changed significantly, confirming that frailty is a dynamic condition during the post-transplant period ($p = 0.001$).

As detailed in Table 4, frail patients were older (61 vs. 50 and 55 years; $p = 0.004$) and had experienced significantly longer hospital stays during transplantation (21 vs. 14 and 15 days; $p = 0.005$) than fit and pre-frail patients. Moreover, frail patients had a higher prevalence of reduced KPS (<90%) before auto-HSCT (66.7% vs. 16.7% and 41.9%, $p < 0.001$). Post-transplant outcomes were additionally estimated using landmark analysis, showing a trend towards inferior survival among frail patients, with 1-year OS of 100% in fit patients, 96.6% (87.2–99.1) in pre-frail patients and 77.8% (36.5–93.9) in frail ones, although differences did not reach statistical significance ($p = 0.166$). Additionally, as shown in Figure 3B, 1-year NRM and CIR of fit, pre-frail and frail patients were 0%, 0% and 11.1% (0.4–41.2) ($p = 0.083$) and 14.7% (5.3–28.7), 16.5% (8.4–26.9) and 35.6% (6.5–67.6) ($p = 0.338$) respectively.

Lastly, QoL assessed at day +100 further emphasized differences between frail patients and fit and pre-frail ones, with frail patients reporting significantly lower perceived health status, with a median score of 55% compared with 90% among fit patients ($p = 0.002$).

Frailty evolution according to lymphoma subtype

Frailty evolution differed significantly according to baseline lymphoma subtype ($p < 0.001$). As detailed in Table S2 and Figure S4, patients with B-cell and T-cell non-Hodgkin lymphoma were more frequently classified as fit (33.3% and



	First Consultation N=156	HCT Admission N=156	P value	Day 100 N=107	P value
Fit	45 (28.8)	48 (30.8)		36 (33.6)	
Pre-Frail	93 (59.6)	84 (53.8)	0.235	62 (57.9)	0.001
Frail	18 (11.6)	24 (15.4)		9 (8.5)	
Mini-Cog <3	19 (12.2)	12 (7.7)		4 (3.7)	

FIGURE 2 Dynamic of frailty from first consultation to day +100.

62.5%, respectively) or pre-frail (59.1% and 37.5%) at day +100, with only 7.6% and 0% of patients remaining frail at this time point. In contrast, patients with primary central nervous system (CNS) lymphoma showed less favourable frailty trajectories: only a minority were classified as fit at day +100 (15.4%), while this group exhibited the highest proportion of frail patients (23.1%), likely reflecting ongoing neurological and functional impairment. Patients with Hodgkin lymphoma showed the most favourable evolution, with a progressive reduction in frailty prevalence across assessments, decreasing from 18.2% at first consultation to 5% at day +100, indicating substantial recovery following transplantation.

DISCUSSION

This multicentre, prospective study demonstrates that frailty is prevalent, dynamic and clinically relevant in patients with LPS undergoing auto-HSCT. Using the HCT-FS in a real-world setting, we show that frailty can be systematically assessed without additional resources and provides meaningful information beyond conventional eligibility criteria.

Although the therapeutic landscape of LPS has evolved with the introduction of chimeric antigen receptor T-cell (CAR-T-cell) therapies,[13,14] auto-HSCT remains a key consolidative strategy for patients with immunochemotherapy-sensitive disease.[2] However, patient selection continues to rely largely on performance status and comorbidity indices, which fail to capture multidimensional vulnerability. In contrast, evidence supporting frailty assessment in auto-HSCT remains limited and has largely focused on multiple myeloma, where frailty has similarly been associated with poorer tolerance and outcomes.[15]

In our cohort, approximately 15% of patients were frail and nearly 60% pre-frail at the first consultation, despite being considered eligible for auto-HSCT. This observation highlights that biological vulnerability is common even in carefully selected candidates and supports the concept that frailty reflects disease-related, treatment-related and functional factors not adequately captured by traditional metrics.[16]

Consistent with prior studies, frailty was associated with impaired performance status and cognitive dysfunction.[17,18] Notably, patients with primary CNS lymphoma exhibited higher frailty rates, reflecting the impact of neurological impairment and cognitive deficits frequently present at diagnosis, which compromise functional reserve and autonomy independently of systemic disease burden.[19,20] Although achieving disease control prior to auto-HSCT is essential in this subgroup, persistent neurological sequelae may continue to contribute to frailty despite adequate tumour response.[21] In contrast, the prognosis for Hodgkin lymphoma is more favourable, as these patients are generally younger, have fewer comorbidities and recover well. For B-cell and T-cell non-Hodgkin lymphomas, we found no significant differences, as similar chemotherapy and immunotherapy regimens are used. Importantly, frailty was not limited to older adults and was also observed in younger patients, highlighting that frailty is also driven by disease-related factors, cumulative treatment exposure and therapy-associated toxicity[22] and underscoring the need for systematic frailty assessment across all patient subgroups and ages.[23,24]

TABLE 3 Correlation between frailty at first consultation and HSCT characteristics and results.

Impact of frailty on outcomes	All patients $N=156$	Fit $N=45$ (28.8)	Pre-frail $N=93$ (59.6)	Frail $N=18$ (11.6)	p value
Disease status prior to HSCT, *n* (%)					
Complete response	127 (86.4)	35 (85.4)	77 (85.5)	15 (93.7)	0.865
Partial response	18 (12.3)	5 (12.2)	12 (13.3)	1 (6.3)	
Stable disease/progression	2 (1.3)	1 (2.4)	1 (1.2)	0	
Missing data	9	4	3	2	
Conditioning regimen, *n* (%)					
Myeloablative	151 (96.8)	44 (97.8)	90 (96.8)	17 (94.4)	0.794
BEAM	127	37	78	12	
BCNU+Tiothepa	18	4	11	3	
MEL200	4	3	1	0	
CBV	2	0	0	2	
Dose-adjusted	5 (3.2)	1 (2.2)	3 (3.2)	1 (5.6)	
Adjusted BEAM	4	1	3	0	
Adjusted BCNU+Tiothepa	1	0	0	1	
HSCT modality, *n* (%)					
Inpatient	121 (77.6)	31 (68.9)	74 (79.6)	16 (88.9)	0.175
Outpatient	35 (22.4)	14 (31.1)	19 (20.4)	2 (11.1)	
Median days HSCT admission[a] (from day 0)	15 (13–18)	13 (13–17)	15 (13–19)	15 (12–16)	0.480
Readmission during first 6 months[b]	20 (12.8)	3 (6.7)	14 (15.0)	3 (16.0)	0.337
Median follow-up (months) (IQR)	23.2 (18.3–28.4)	25.3 (20.3–31.8)	22.9 (17.3–27.5)	22 (9.9–28.1)	0.446
Relapse, *n* (%)	45 (28.8)	11 (24.4)	30 (32.3)	4 (22.2)	0.387
Death, *n* (%)	19 (12.2)	3 (6.7)	13 (14)	3 (16.7)	0.512
Non-relapse mortality (overall)	6 (3.8)	1 (2.2)	3 (3.2)	2 (11.1)	0.225
Early mortality rate (6 months), *n* (%)	5 (3.2)	0 (0)	4 (2.6)	1 (0.6)	0.338
Overall survival					
1 year	94.0 (88.8–96.8)	97.6 (84.3–99.7)	92.3 (84.5–96.3)	88.5 (61.4–97.0)	0.322
Relapse-free survival					
1 year	77.3 (69.6–83.2)	85.8 (71.1–93.4)	72.3 (61.8–80.4)	83.0 (55.9–94.2)	0.534
Non-relapse mortality					
1 year	2.6 (0.9–6.2)	0	2.2 (0.4–6.9)	11.5 (1.8–31.3)	0.199
Cumulative incidence of relapse					
1 year	20.1 (14.1–26.9)	13.5 (5.4–23.5)	21.4 (13.5–30.6)	4.8 (0.3–20.2)	0.311

Abbreviations: BCNU, carmustine; BEAM, carmustine+etoposide+cytarabine+melphalan; CBV, cyclophosphamide+carmustine+etoposide; HSCT, haematopoietic stem cell transplantation; IQR, interquartile range; MEL200, Melphalan 200 mg/m^2.

[a]Estimated on inpatient HSCT.

[b]Readmissions occurring during first 6 months and not related with disease relapse.

Frailty assessed at the first consultation showed a consistent association with worse QoL, particularly in self-care and usual activities, and a numerical increase in NRM, although statistical significance was not reached. These results are consistent with prior observations in allogeneic HSCT and in studies conducted in patients with LPS. Specifically, Ramdany et al. conducted a prospective study implementing frailty assessment in 52 patients with LPS using the Haemato-Oncology frailty scale.[25] A total of 19.2% were classified as frail at the start of chemotherapy, predicting lower PFS compared to fit patients ($p=0.03$). Aligned with our results, they also demonstrated the greater relevance of cognitive impairment in frailty compared to other components. All these findings support the importance of early identification of frailty, offering a potential window for timely supportive interventions.[26]

A key strength of this study is the longitudinal assessment of frailty, revealing frequent bidirectional transitions before transplantation and significant changes by day +100.[27] At this time point, frailty was associated with older age and longer hospital stays, reflecting that the HSCT procedure strongly impacts the fitness of older adults.[28,29] Moreover, post-transplant outcomes based on frailty at day +100 revealed that frail patients had numerically inferior OS and

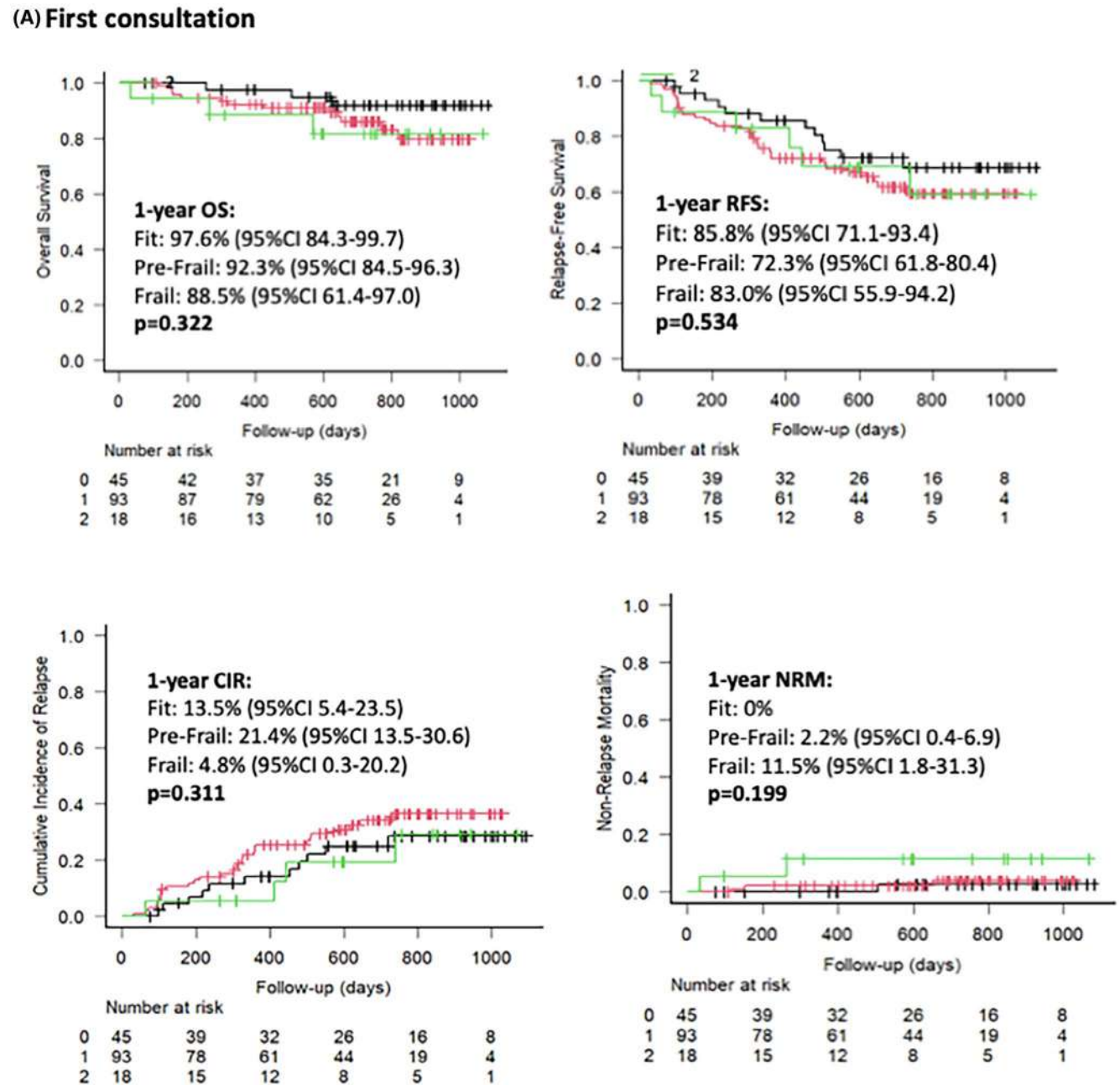


FIGURE 3 Impact of frailty on outcomes (overall survival [OS], release-free survival [RFS], cumulative incidence of relapse [CIR] and non-relapse mortality [NRM]) at first consultation (A) and day +100 (B).

higher NRM, indicating that persistent frailty limits recovery capacity and exacerbates functional impairment.

Our results emphasize the value of repeated frailty assessment and support frailty as a potentially modifiable target through complementary supportive interventions.[30,31] Emerging evidence favours prehabilitation strategies, particularly those centred on physical activity, to enhance patient readiness for auto-HSCT. Supporting this, prior studies have also shown that greater muscle strength correlates with reduced transplant-related complications.[32] Similarly, Cornago et al. recently reported that better muscle strength at auto-HSCT admission is associated with lower requirements for parenteral nutrition and red blood cell transfusions, reduced incidence of mucositis, fewer intensive care unit admissions, shorter hospitalization and improved outcomes.[33]

At the same time, deterioration observed in some initially fit patients emphasizes that intensive therapy may precipitate or exacerbate frailty.[34] Frail patients at first evaluation demonstrated physical improvement by day +100. These bidirectional changes reinforce the need for longitudinal monitoring and support the integration of structured prehabilitation and rehabilitation programmes to mitigate treatment-related decline and optimize transplant

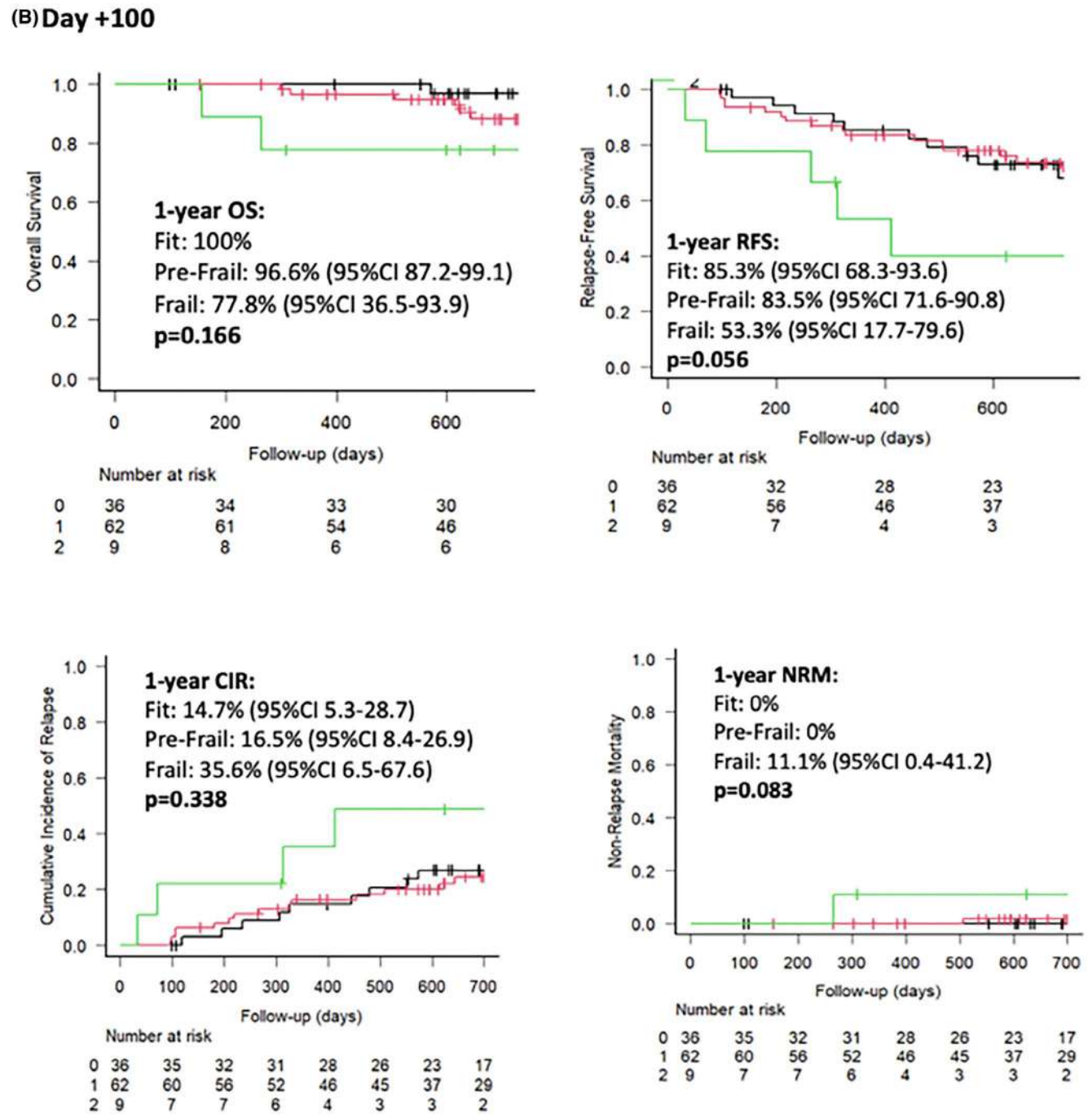


FIGURE 3 (Continued)

outcomes.[35–37] Disease-specific frailty trajectories further underscore the interaction between lymphoma biology and functional reserve. Persistent frailty in primary CNS lymphoma contrasts with the favourable evolution observed in Hodgkin lymphoma, where most patients recovered functional status by day +100.[38]

Finally, this study demonstrates that the HCT-FS is a feasible, pragmatic and generalizable tool for frailty assessment in auto-HSCT. Its short completion time, straightforward training requirements and seamless integration into routine workflows reinforce its potential role as a standardized instrument for frailty assessment in transplant programmes irrespective of baseline diagnosis, patient chronological age or transplant type.

While our study provides valuable insights, several limitations should be acknowledged. Frailty was not assessed at diagnosis, there was heterogeneity in lymphoma subtypes and a proportion of patients were lost to follow up at day +100 because they had returned to their referral centres. Furthermore, only 18 patients were classified as frail at first

TABLE 4 Baseline characteristics of patients and outcomes based on frailty assessments at day +100.

	Fit *N* = 36	Pre-frail *N* = 62	Frail *N* = 9	*p*-value
Median age, (range)	50 (24–71)	55 (27–75)	61 (56–69)	**0.004**
Male, *n* (%)	24 (66.7)	36 (58.1)	4 (44.0)	0.434
Female, *n* (%)	12 (33.3)	26 (41.9)	5 (55.6)	
Type of lymphoproliferative disease, *n* (%)				
B-NHL	22 (61.1)	39 (62.9)	6 (66.7)	0.221
T-NHL	5 (13.9)	3 (4.8)	0 (0)	
Primary CNS lymphoma	2 (5.5)	8 (12.9)	3 (33.3)	
Hodgkin disease	7 (19.4)	12 (19.4)	0 (0)	
HCT-CI > 3, *n* (%)				0.812
Missing data	1 (2.8)	3 (4.8)	2 (22.2)	
KPS < 90% before auto-HSCT, *n* (%)	6 (16.7)	26 (41.9)	6 (66.7)	**<0.001**
Disease status prior to HSCT, *n* (%)				
Complete response	30 (83.3)	50 (80.7)	6 (66.7)	0.231
Partial response	1 (2.8)	9 (14.5)	2 (22.2)	
Stable disease/progression	3 (8.3)	1 (1.6)	0 (0)	
Missing data	2	2	1	
Median days HSCT admission (from day 0)	14 (13–17)	15 (13–18)	21 (16–71)	**0.005**
Readmission				
Frailty at first consultation, *n* (%)				
Fit	18 (50.0)	15 (24.2)	0 (0)	**<0.001**
Pre-frail	17 (47.2)	41 (66.1)	5 (55.6)	
Frail	1 (2.8)	6 (9.7)	4 (44.4)	
Frailty at admission, *n* (%)				
Fit	22 (61.1)	13 (21)	0 (0)	**<0.001**
Pre-frail	12 (33.3)	42 (67.7)	3 (33.3)	
Frail	2 (5.5)	7 (11.3)	6 (66.7)	
Impact of frailty on outcomes (+100 days landmark)				
Median follow-up, months (IQR)	22.2 (17.5–31.4)	21.4 (16.5–26.4)	17.5 (6.2–21.8)	0.472
Relapse, *n* (%)	10 (27.8)	16 (25.8)	4 (44.4)	0.508
Death, *n* (%)	2 (5.5)	6 (9.7)	2 (22.2)	0.399
Overall survival				
1 year	100	96.6 (87.2–99.1)	77.8 (36.5–93.9)	0.166
Relapse-free survival				
1 year	85.3 (68.3–93.6)	83.5 (71.6–90.8)	53.3 (17.7–79.6)	**0.056**
Non-relapse mortality				
1 year	0	0	11.1 (0.4–41.2)	0.083
Cumulative incidence of relapse				
1 year	14.7 (5.3–28.7)	16.5 (8.4–26.9)	35.6 (6.5–67.6)	0.338
Impact of frailty on quality of life (QoL)	***N* = 15** **Missing data: 21**	***N* = 30** **Missing data: 32**	***N* = 6** **Missing data: 3**	
Mobility, *n* (%)				
1	15 (100)	25 (83.3)	3 (50)	**0.036**
2	0 (0)	5 (16.7)	3 (50)	
3	0 (0)	0 (0)	0 (0)	
Self-care, *n* (%)				
1	15 (100)	29 (96.7)	5 (83.3)	0.080
2	0 (0)	1 (3.3)	0 (0)	
3	0 (0)	0 (0)	1 (16.7)	

TABLE 4 (Continued)

Impact of frailty on quality of life (QoL)	*N* = 15 Missing data: 21	*N* = 30 Missing data: 32	*N* = 6 Missing data: 3	
Daily activities, *n* (%)				
1	13 (86.7)	23 (76.7)	2 (33.3)	**0.020**
2	2 (13.3)	7 (23.3)	3 (50)	
3	0 (0)	0 (0)	1 (16.7)	
Pain/discomfort, *n* (%)				
1	12 (80)	20 (66.7)	3 (50)	0.068
2	3 (20)	10 (33.3)	2 (33.3)	
3	0 (0)	0 (0)	1 (16.7)	
Anxiety/depression, *n* (%)				
1	10 (66.7)	24 (80)	2 (33.3)	**0.018**
2	5 (33.3)	5 (16.7)	2 (33.3)	
3	0 (0)	1 (3.3)	2 (33.3)	
Current health status perception (%) (range)	90 (60–100)	70 (40–100)	55 (30–70)	**0.002**

Note: *p*-values that are statistically significant ($p < 0.05$) are shown in bold.

Abbreviations: CNS, central nervous system; HCT-CI, haematopoietic cell transplantation-comorbidity index; KPS, Karnofsky performance status; IQR, interquartile range; NHL, non-Hodgkin lymphoma.

consultation, which may limit the statistical power to detect significant differences in survival. Additionally, these results apply to patients deemed eligible for auto-HSCT and may not be generalizable to non-transplanted populations.

In conclusion, this study demonstrates that frailty is prevalent, dynamic and clinically meaningful in patients with LPS undergoing auto-HSCT. Systematic and longitudinal frailty assessment using the HCT-FS may improve risk stratification, guide supportive care and identify opportunities for targeted interventions aimed at optimizing both survival and QoL.

AUTHOR CONTRIBUTIONS

Laura Fox: Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Mónica Baile:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Marina Acera:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **María del Mar Pérez-Artigas:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Joaquina M. Salmerón:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Verónica Illana:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Andrés Sánchez-Salinas:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Javier Cornago:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration; data curation; supervision; software; resources. **Zahra Abdallahi-Lefdil:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Laura Pardo:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **José Luis López-Lorenzo:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Sara Villar:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Mónica Molina:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Sara Fernández-Luis:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Patricia Beorlegui-Murillo:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Laura Solán:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Leddy Patricia Vega:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Olga Alda:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Javier López-Marín:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Albert Esquirol:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Alberto Mussetti:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Leyre Bento:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **Julia Ribes:** Conceptualization; investigation; validation; visualization; writing – review and editing; data curation. **María Queralt Salas:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; data curation; supervision; resources; project

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to report.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona and the GETH-TC board and conducted in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

All patients who took part in the study signed two copies of an informed consent form after being informed of the nature of the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

We applied to the geriatric medicine research team (gmru@dal.ca) for permission to use the Clinical Frailty Scale (application number: 2602021144), which was granted on 2 February 2026. Similarly, we submitted a request to Geriatric Nursing at NYU Rory Myers College of Nursing (nursing.hign@nyu.edu) to use the IADL, and our request was granted.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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