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The Geriatric Syndrome of Sarcopenia Impacts Allogeneic Hematopoietic Cell Transplantation Outcomes in Older Lymphoma Patients

Richard J. Lin, MD, PhD[1,2,*], **Laure Michaud, MD**[3,*], **Stephanie M. Lobaugh, MS**[4], **Reiko Nakajima, MD**[3], **Audrey Mauguen, PhD**[4], **Theresa A. Elko, MS**[1], **Josel D. Ruiz, MPH**[1], **Molly A. Maloy, MS**[1], **Craig S. Sauter, MD**[1,2], **Parastoo B. Dahi, MD**[1,2], **Miguel-Angel Perales, MD**[1,2], **Gunjan L. Shah, MD, MS**[1,2], **Nerea Castillo Flores, MD, PhD**[1], **Míriam Sanchez-Escamilla, MD**[5], **Ana Alarcón Tomas, MD**[6], **Lucrecia Yáñez San Segundo, MD, PhD**[5], **Christina Cho, MD**[1,2], **Ioannis Politikos, MD**[1,2], **Soo Jung Kim, NP**[8], **Beatriz Korc-Grodzicki, MD, PhD**[7,2], **Sean M. Devlin, PhD**[4], **Michael Scordo, MD**[1,2], **Heiko Schöder, MD, MBA**[3,2], **Sergio A. Giralt, MD**[1,2], **Paul A. Hamlin, MD**[8,2]

[1]Adult BMT Service, Memorial Sloan Kettering Cancer Center

[2]Weill Cornell Medical College

[3]Nuclear Medicine Service, Memorial Sloan Kettering Cancer Center

[4]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center

[5]University Hospital and Research Institute of Marqués de Valdecilla (IDIVAL), Santander, Spain

[6]Hospital Universitario Puerta de Hierro, Madrid, Spain

[7]Geriatrics Service, Memorial Sloan Kettering Cancer Center

[8]Lymphoma Service, Memorial Sloan Kettering Cancer Center

Abstract

Older patients with advanced hematologic malignancies are increasingly considered for allogeneic hematopoietic cell transplantation (allo-HCT) yet their survival outcomes remain suboptimal. We and others have previously shown that pre-HCT multi-morbidity and functional limitation and post-HCT geriatric syndromes significantly impact outcomes. Sarcopenia, an accelerated loss of muscle mass and function, has been increasingly recognized in older cancer patients. We identified 146 lymphoma patients 50 years or older who were allografted from 2008 to 2018 at our institution and found that before allo-HCT, 80 (55%) patients were sarcopenic. Pre-HCT sarcopenia was significantly associated with overall survival, progression-free survival, and non-relapse mortality independent of multi-morbidity and functional limitation. In 6-month landmark analysis, post-HCT sarcopenia remained significantly associated with survival. Our findings illustrate the high prevalence and profound impact of sarcopenia on survival. While requiring

Corresponding author: Richard J. Lin, MD, PhD, Adult BMT Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone : 646-499-1290 Fax : 888-727-9531, linr@mskcc.org.

*Equal contribution as co-first authors

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prospective confirmation, preemptive, longitudinal, and multidisciplinary interventions for sarcopenia are warranted to improve HCT outcomes for older patients.

Keywords

Sarcopenia; geriatric assessment; lymphoma; allogeneic hematopoietic cell transplantation

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) has been increasingly utilized in older adults with hematologic malignancies due to advances in supportive care measures, the development of reduced-intensity conditioning (RIC) regimens, and the improved patient selection [1–4]. Biological age, rather than the chronological age, is now routinely considered for allo-HCT eligibility [5,6]. Despite these advances, the mortality and morbidity of allo-HCT has remained high in older patients, with long-term overall survival (OS) in the 30–40% range and 2-year non-relapse mortality (NRM) of 20–30% [7–9]. These suboptimal outcomes suggest that there are additional, age-related aspects of allo-HCT that require investigation and optimization.

Geriatric syndromes are multifactorial clinical conditions that occur when accumulated effects of impairments in multiple organ systems render an older person vulnerable to situational challenges [10]. While clinically heterogeneous, these conditions often have multiple risk factors, involve multiple organ systems, and can complicate therapy and contribute to the frailty phenotype [11,12]. We have previously found that post-HCT delirium and falls, two common geriatric syndromes, significantly impacted long-term survival and had modifiable risk factors [13]. Geriatric syndromes are ideally recognized through comprehensive geriatric assessment (GA), defined as a multidisciplinary process to assess medical, psychosocial, and functional limitations of an older adult [14]. GA has emerged as an important risk stratification tool for survival in advanced hematologic malignancies, including allo-HCT [15–18].

Sarcopenia, loss of lean body muscle mass, is one of the most common geriatric syndromes and contributes to age-related functional decline and disability [19,20]. Several methods, including direct measurement of muscle mass through imaging or function through beside assessment, have been utilized to define sarcopenia in different patient populations [20]. Importantly, sarcopenia has been linked to treatment-related toxicities, healthcare resource utilization, and survival in multiple tumor types and transplant settings [21–26].

In patients with relapsed/refractory, aggressive or indolent lymphomas, RIC-based allo-HCT allows amplification of graft-versus-lymphoma effect and results in long-term disease control in a substantial portion of patients including those who are older [27,28]. Allo-HCT has been increasingly utilized at many institutions including ours for relapsed/refractory lymphoma even in the era of chimeric antigen receptor-based therapy [29]. Given that computerized tomography (CT) is a gold standard measure of body composition and sarcopenia [30,31], and that most lymphoma patients have staging scan prior to and following

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HCT, we examine the prevalence and impact of sarcopenia in older lymphoma allo-HCT patients.

MATERIAL AND METHODS

Patients, Geriatric Characteristics, and Transplant Care

This analysis included patients aged 50 years or older who underwent first allo-HCT for lymphoma using RIC-based regimen between 2008 and 2018 at our institution. We chose 50 years or older since this is the age when increased geriatric vulnerabilities are seen in patients undergoing transplant evaluation [15], and with available GA measures. A waiver of authorization for this retrospective review was obtained from the Institutional Review and Privacy Board. Pathologic diagnosis of lymphoma was confirmed at our institution. Pre-HCT assessment, transplant and post-transplant care, and disease monitoring followed standard institutional guidelines. Demographic data, disease and transplant characteristics, relapse/disease progression, cause of death, and survival were retrieved from our institutional database. Pre-transplant assessments of geriatric variables such as basic activities of daily living (Katz's ADL), IADL (Lawton's IADL), mood, nutrition, prior falls, weight loss (≥10 pounds in 3-month), and medication use were defined as previously [13]. Potentially inappropriate medication (PIM) use was defined by the updated Beers Criteria [32]. HCT-comorbidity index (HCT-CI) and revised disease risk index (DRI) were assigned according to published criteria [33,34].

Computerized Tomography (CT)-Based Identification of Sarcopenia

Cross-sectional images from a diagnostic CT or PET/CT images were assessed at 2-time points: baseline (up to 60-day before HCT) and within 180-day after HCT (closest to 100-day). Suboptimal images due to artefact were excluded. Evaluation of body composition was performed by two independent radiologists (LM and RN) using MIM software (supplemental method). Semiautomated threshold-based segmentation was used. Skeletal muscle and adipose tissue were defined by ranges of −29 to 150 HU and −190 to −30 HU, respectively. Radiologists were blinded to clinical information and independently identified lumbar vertebra and the following muscles; rectus abdominus, abdominal, psoas and paraspinal. Two adjacent axial images within the same series at the third lumbar vertebra were selected for the analysis of total muscle cross-sectional area (cm^2) and of total fat (subcutaneous and visceral adipose tissues) cross-sectional area (cm^2) and average of the results was calculated [30]. Skeletal muscle cross-sectional area was normalized for stature and reported as skeletal muscle index in cm^2/m^2. Sarcopenia was defined as a skeletal muscle index <41 in women, <43 in men with BMI <25, and <53 in men with BMI ≥25 [30]. Total lean body mass (TLBM) and total body fat mass (TBFM) were calculated as TLBM (Kg)=0.3 × [skeletal muscle at L3(cm^2)] +6.06 and TBFM (Kg)=0.042 × [fat tissue at L3(cm^2)] +11.2 [31].

Statistical Methods

Baseline characteristics in patients with and without pre-transplant sarcopenia were compared using Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous. Kaplan-Meier survival curves and cumulative incidence function were

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generated to examine the survival and incidence of NRM with relapse-related death and relapse as competing risks. The log rank test was used to compare OS and PFS between groups. The Gray's test was used to compare NRM between groups. Univariable Cox proportional hazards regression was used to analyze OS and PFS, and univariable Fine-Gray competing risks regression was used to analyze NRM. Multivariable models were built with all univariable covariates of $p < 0.1$. Wilcoxon signed rank tests were used to test for significant changes in anthropometric variables from pre-to-post-HCT time points and interobserver agreement was described using Cohen's Kappa coefficient. The correlation between measurements was described using Kendall's tau and graphed with Bland-Altman plots. All statistical computations were performed using SAS Software Version 9.4 (The SAS Institute, Cary, NC).

RESULTS

Patients Characteristics and Transplant Outcomes

Baseline characteristics of the cohort are listed in Table 1. The median age was 60.7 years (range, 50 −78.7 years). There was no significant difference in baseline HCT-CI, revised DRI, stem cell source, donor type, or CMV status except for slightly more females in the sarcopenic group (p=0.046). Ninety-seven percent of patients were Caucasian. Baseline geriatric deficits were common in domains of function, mobility, nutrition, mood, and medications and no significant difference was found among patients with and without sarcopenia (Table 1). With median follow-up of 4.12 years for survivors, the 5-year OS and PFS were 62% (95% Confidence Interval [CI] 53 – 71) and 56% (95% CI 47 – 65), respectively (Supplemental Figure A). The 3-year cumulative incidence of NRM and relapse/progression of disease were 21% (95% CI 14 – 28) and 18% (95% CI 12 – 24), respectively (Supplemental Figure B). Fifty-two patients died including 16 (31%) from relapse or disease progression; 25 (48%) from GVHD; 7 (13%) from organ failure; and 2 patients each (4%) from infection and others, respectively.

Changes in Body Composition and Factors associated with Sarcopenia

Based on CT definition, 55% (80/146) and 70% (90/128) of patients were sarcopenic prior to and following transplant, respectively. Among those 90 sarcopenic patients post-HCT, 65 patients were also sarcopenic pre-HCT. As shown in Table 1, neither age nor pre-transplant patient- or disease-related factors were associated with sarcopenia except for the female gender (p = 0.046). Moreover, sarcopenia was not associated with geriatric deficits including functional limitation measured by ADL/IADL deficit or prior fall, depression, comorbidities (HCT-CI), or PIM. Of 128 patients who had both pre- and post-HCT imaging, the changes in body composition were significant. The median change in TLBM was −2.86 kilogram (range, −16.7 – 9.87, and p<0.001) and the median change in TBFM was −2.23 kilogram (range −14.2 – 5.67, and p<0.001).

Impact of Pre-HCT Sarcopenia

As shown in Table 2, significant univariable covariates associated with NRM included pre-transplant sarcopenia and HCT-CI. On multivariable analysis, both pre-transplant sarcopenia (hazard ratio [HR] = 2.06, 95% CI: 1.02–4.19, p = 0.044) and HCT-CI ≥3 (HR = 2.6, 95%

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CI: 1.31–5.16, p = 0.006) remained significantly associated with NRM. For univariable analysis of OS, significant covariates included sarcopenia and HCT-CI. On multivariable analysis, pre-transplant sarcopenia (HR = 2.12, 95% CI: 1.18–3.8, p = 0.01) and HCT-CI ≥3 (HR = 2.38, 95% CI: 1.35–4.19, p = 0.003) remained significantly associated with inferior OS. For univariable analysis of PFS, significant covariates included sarcopenia, HCT-CI, and prior fall. On multivariable analysis, pre-transplant sarcopenia (HR = 1.78, 95% CI: 1.07–2.98, p = 0.03), HCT-CI ≥3 (HR = 2.21, 95% CI: 1.33–3.67, p = 0.002), and prior fall (HR = 1.92, 95% CI: 1.07–3.46, p = 0.03) remained significantly associated with inferior PFS. As shown in Figure 1, the combination of sarcopenia and HCT-CI effectively stratify OS (log rank p <0.001), PFS (log rank p <0.001), and NRM (Gray's p = 0.003). Patients with pre-HCT sarcopenia and HCT-CI ≥3 had the worst survival and highest incidence of NRM: 3-year OS of 41% (95% CI 24 – 57), PFS of 33% (95% CI 17 – 48), and NRM of 42% (95% CI 25 – 59), respectively.

Impact of Post-HCT Sarcopenia

One hundred twenty-one patients survived for at least 6-month post-HCT and were included in the landmark analysis of OS. Of these, one hundred ten patients survived or relapsed beyond 6-month post-HCT and were included in the landmark analysis of PFS and NRM. As shown in Table 3, the only significant covariate for NRM was HCT-CI. For univariate analysis of OS, significant covariates included sarcopenia and HCT-CI. On multivariable analysis, post-HCT sarcopenia (HR = 3.12, 95% CI: 1.1–8.89, p = 0.03) and HCT-CI ≥3 (HR = 2.94, 95% CI: 1.42–6.07, p = 0.004) remained significantly associated with inferior OS. For univariable analysis of PFS, significant covariates included post-HCT sarcopenia, HCT-CI, grade 2–4 aGVHD, and age. On multivariable analysis, post-HCT sarcopenia (HR = 4.2, 95% CI: 1.27–13.9, p = 0.02) and HCT-CI ≥3 (HR = 2.65, 95% CI: 1.28–5.49, p = 0.009) remained significantly associated with inferior PFS. As shown in Figure 2, the combination of post-HCT sarcopenia and HCT-CI effectively stratify OS (log rank p <0.001) and PFS (log rank p <0.001). Patients with post-HCT sarcopenia and HCT-CI ≥3 had the lowest survival: 3-year OS of 51% (95% CI 35 – 68) and PFS of 47% (95% CI 30 – 65), respectively.

DISCUSSION

In this study, we examined the incidence of sarcopenia prior to and following RIC allo-HCT for lymphoma and demonstrated its negative impact on allo-HCT outcomes independent of other geriatric vulnerabilities such as multi-morbidity or functional limitation. We found that the incidence of pre- and post-HCT sarcopenia defined radiographically was 55% and 70%, respectively, which is higher than what has been previously reported [24–26]. This is likely due to the older age of our cohort given the increasing incidence of sarcopenia in older adults [19,35]. Moreover, we did not identify an association of pre-HCT sarcopenia with any geriatric deficits or any disease-related factors except for gender, suggesting that sarcopenia is not a simple surrogate of disease burden, comorbidity, functional limitation, or nutritional status. This is consistent with previous findings in several geriatric oncology patient populations [23,35]. Finally, our method of sarcopenia detection is well-validated based on published literature [30, 36–38].

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Sarcopenia has profound negative impacts on the function, survival, and quality of life of general medical, surgical, and cancer patients [19,25,35,39]. We have demonstrated here that both pre- and post-HCT sarcopenia were associated with significantly increased NRM and worsened PFS and OS. Interestingly, two other significant variables, HCT-CI and prior fall, are surrogates of geriatric comorbidity and functional limitation, respectively [14,33]. We acknowledge that the mechanism by which sarcopenia directly contributes to mortality remains unclear and it is not related to body mass index (data not shown). It is possible that sarcopenia is the second "hit" that acts synergistically with multi-morbidity and functional limitation to amplify frailty and contribute to poor survival, consistent with the Rockwood deficit accumulation model [40]. Our results yield significant insights on geriatric factors contributing to inferior outcomes; namely, pre-HCT geriatric comorbidities, functional status, sarcopenia, as well as the development of sarcopenia post-HCT. There are likely other potential post-transplant contributors to OS and NRM in older patients including organ toxicities, infections, and graft-versus-host disease, and we are actively examining these factors in relation to comorbidities and geriatric syndromes.

Our study has several limitations. First, given its retrospective design and the timing of imaging, the causal relationship of sarcopenia with induction/salvage chemotherapy, aGVHD, and steroid use cannot be reliably established. Second, we lack grading and functional assessment of sarcopenia and its impact on quality of life. Third, the heterogeneity in donors, GVHD prophylaxis, and post-transplant complications including acute and chronic GVHD may confound our findings. Finally, this is a single institutional study with a predominantly Caucasian population which may not be applicable to other ethnic populations or institutional settings. We expect that the upcoming Blood and Marrow Transplant Clinical Trials Network (BMT CTN 1704) CHARM study will help address many of these issues (NCT03992352).

Nevertheless, our results have important implications for the selection of older patients for potential curative allo-HCT, and for management interventions in patients with sarcopenia. It is conceivable that the true impact of sarcopenia, multi-comorbidity, and functional limitation on transplant outcomes should be evaluated by a prospectively designed, GA-adapted, interventional trial, where non-transplant options are chosen for overly frail patients with combined deficits as demonstrated here, or to develop management strategies based on GA findings to improve outcomes. Potential GA-directed, multidisciplinary intervention on sarcopenia could include intensified rehabilitation, medication management, and nutritional support [14]. Such interventions have been shown to be feasible in small pilot trials [41,42]. In conclusion, our results add to the growing literature on the impact of geriatric vulnerabilities on HCT outcomes and provide an entry point for prospective, sarcopenia-directed, interventional trials for older allo-HCT patients to improve their outcomes and quality of life.

Supplementary Material

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DECLARATION OF INTEREST

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PAH—Research support and consulting fees from Portola Pharmaceuticals, Inc. Consultancy on advisory boards for: Astra-Zeneca, Celgene, Karyopharm.

CSS—Consultant on advisory boards for: Juno Therapeutics, Sanofi Genzyme, Spectrum Pharmaceuticals, Novartis, Precision Biosciences, Kite, a Gilead Company and GSK. Research funds for investigator-initiated trials from: Juno Therapeutics and Sanofi-Genzyme.

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IP – has received research support from Merck and serves on a Data and Safety Monitoring Board (DSMB) for ExCellThera.

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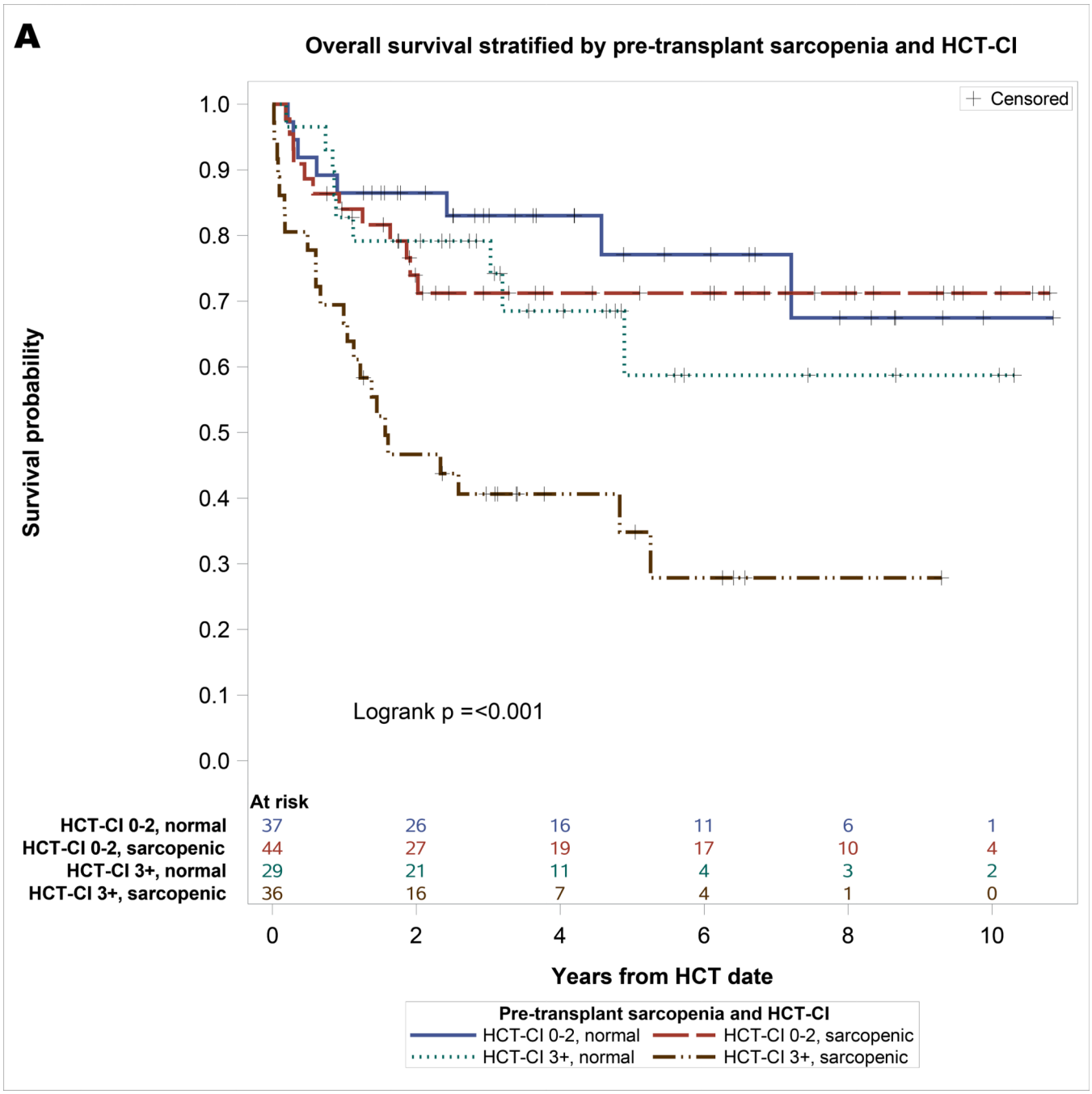

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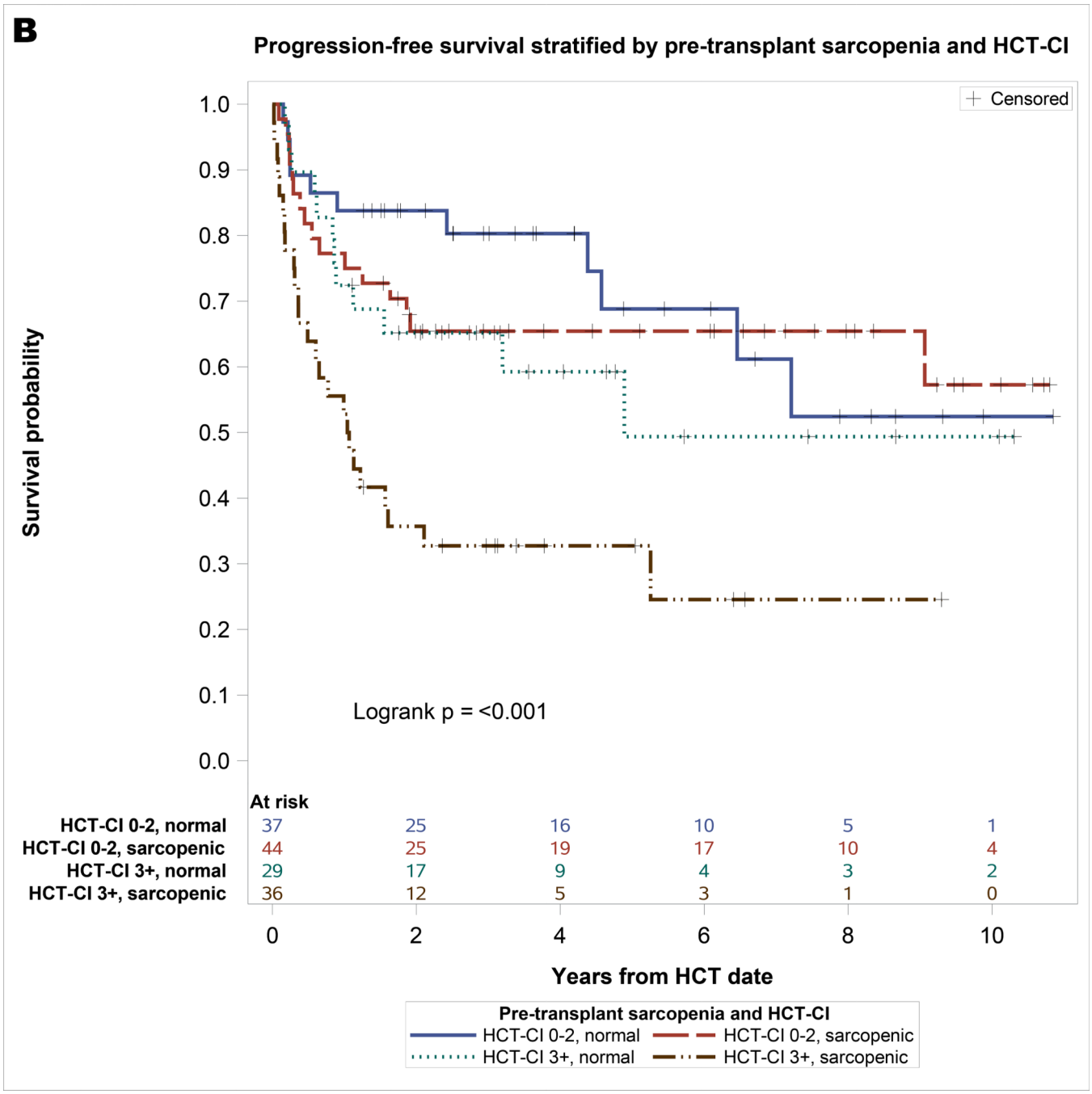

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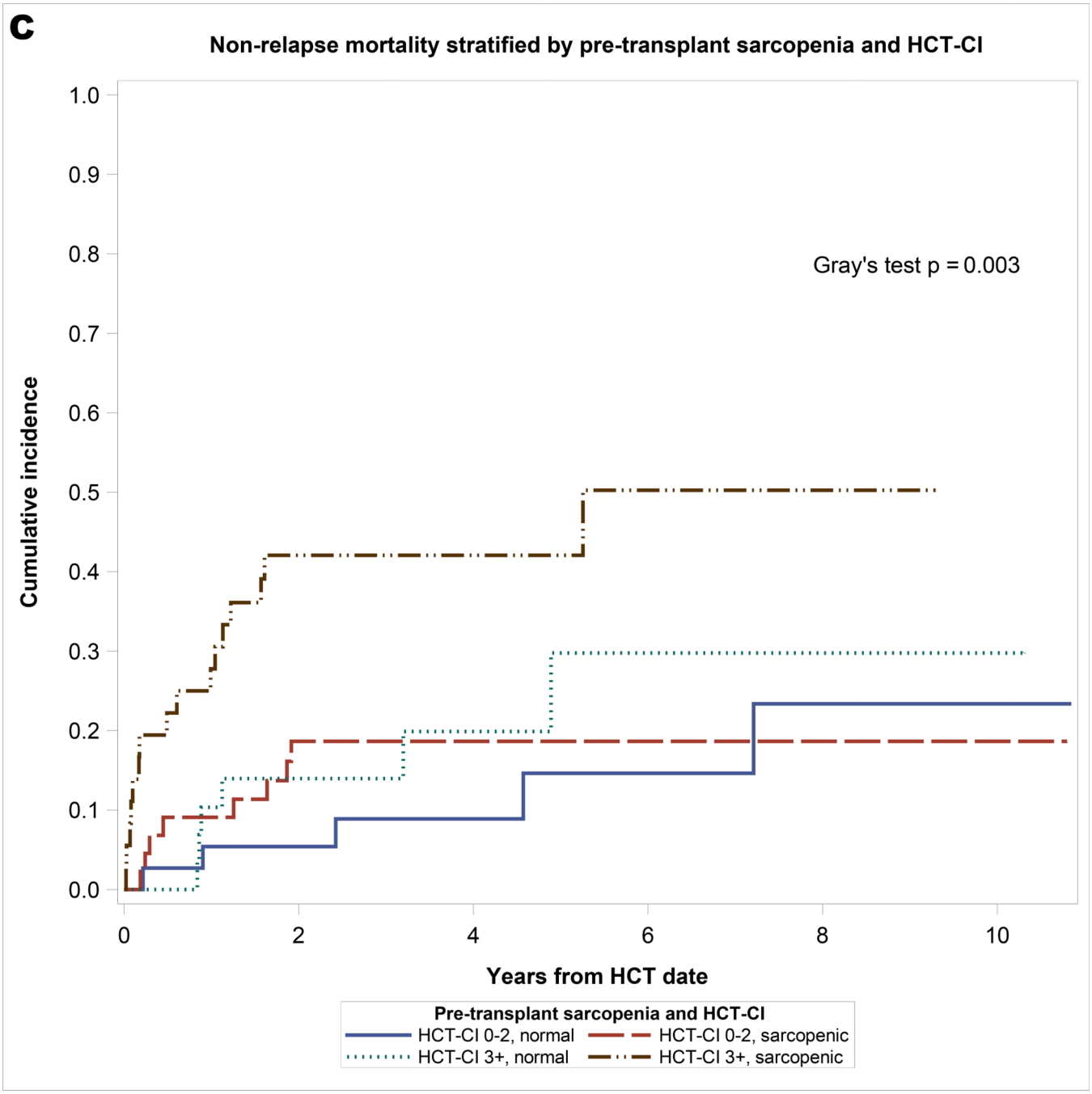

Figure 1.

A. Overall survival stratified by pre-transplant sarcopenia and HCT-CI with at-risk table. B. Progression-free survival stratified by pre-transplant sarcopenia and HCT-CI with at-risk table. C. Non-relapse mortality stratified by pre-transplant sarcopenia and HCT-CI.

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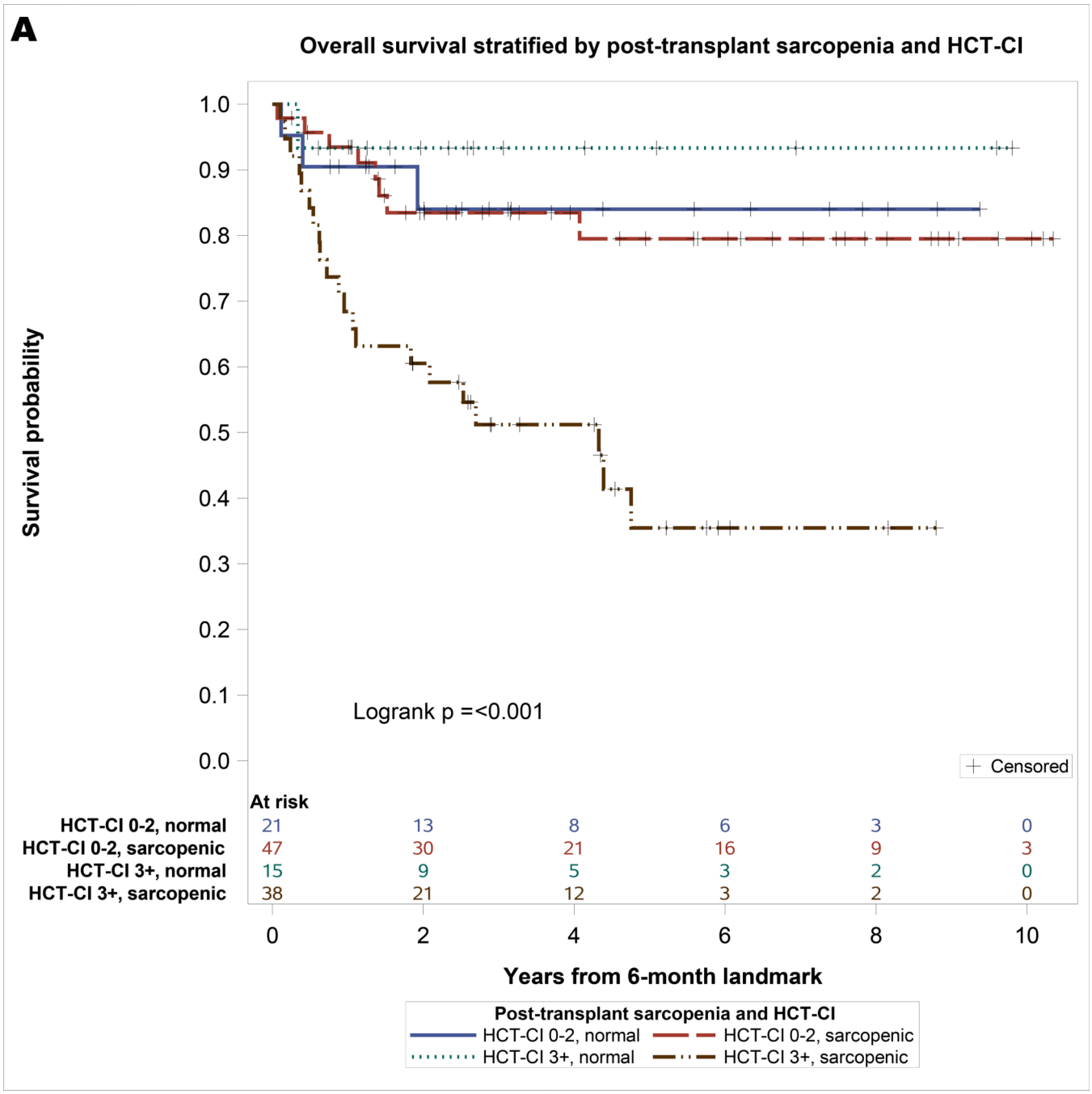

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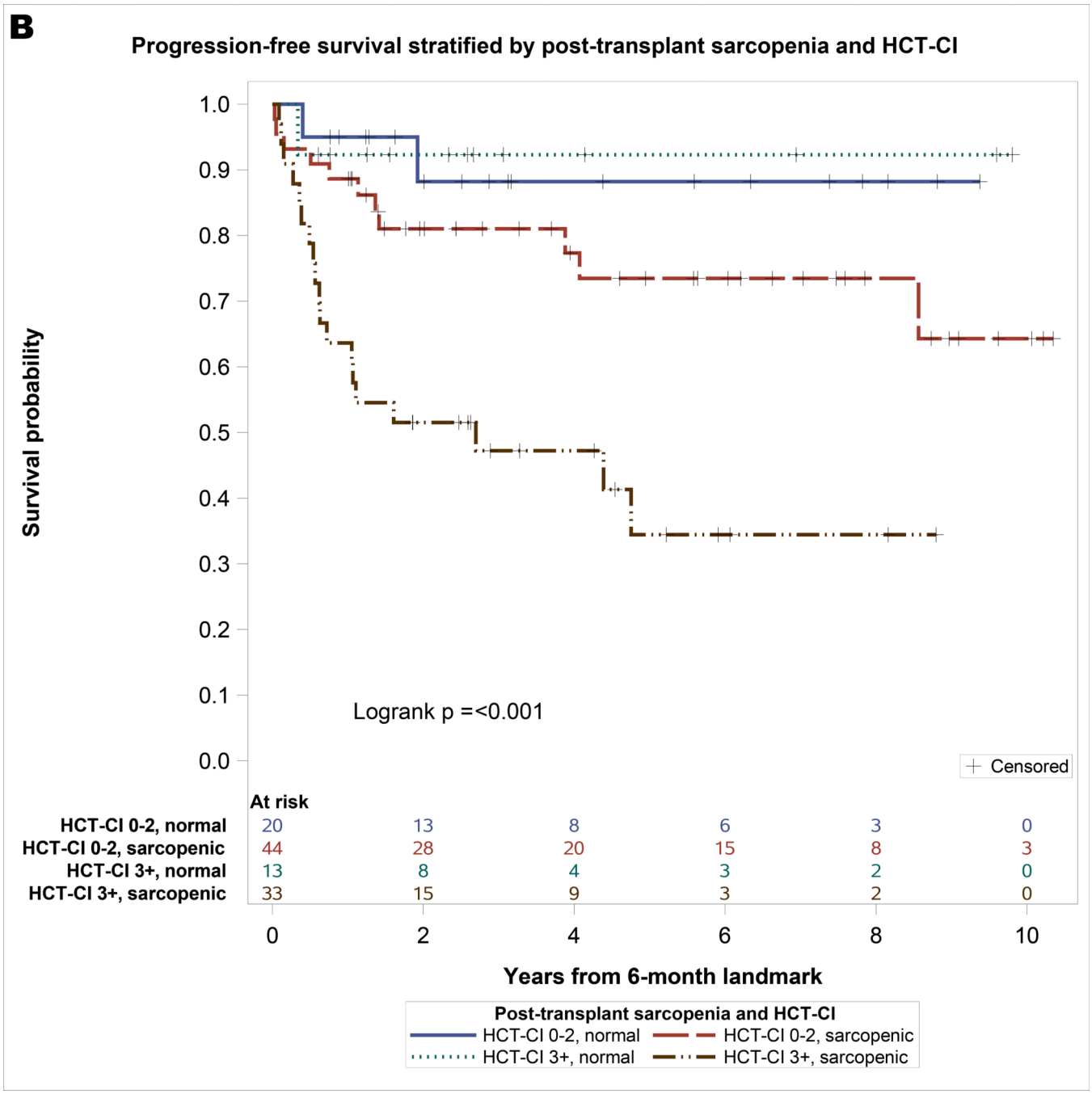

Figure 2.

A. Landmark Analysis of overall survival stratified by post-transplant sarcopenia and HCT-CI with at-risk table. B. Progression-free survival stratified by post-transplant sarcopenia and HCT-CI with at-risk table.

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Table 1.

Baseline characteristics by pre-transplant sarcopenia status.

	All patients (n=146)	Normal (n=66)	Sarcopenic (n=80)	p-value
Age (median, range)	60.7 (50–78.7)	58.9 (50–75.3)	61.5 (50.2–78.7)	0.09
Sex (n, %)				**0.046**
Male	102 (69.9)	52 (78.8)	50 (62.5)	
Female	44 (30.1)	14 (21.2)	30 (37.5)	
Lymphoma (n, %)				0.73
Hodgkin's	8 (5.5)	3 (4.6)	5 (6.3)	
Non-Hodgkin's	138 (94.5)	63 (95.5)	75 (93.8)	
Disease risk index (n, %)				>0.99
Low/intermediate	142 (97.3)	64 (97)	78 (92.5)	
High/very high	4 (2.7)	2 (3)	2 (2.5)	
HCT-CI (n, %)				>0.99
0–2	81 (55.5)	37 (56.1)	44 (55)	
≥3	65 (44.5)	29 (43.9)	36 (45)	
Stem cell source				>0.99
Peripheral blood	136 (93.2)	62 (93.9)	74 (92.5)	
Bone marrow	10 (6.8)	4 (6.1)	6 (7.5)	
Donor type				0.84
Matched	118 (80.8)	54 (81.8)	64 (80)	
Alternative	28 (19.2)	12 (18.2)	16 (20)	
Patient CMV				0.07
Positive	66 (45.2)	24 (36.4)	42 (52.5)	
Negative	80 (54.8)	42 (63.6)	38 (47.5)	
ADL/IADL				0.54
Impaired	11 (7.5)	5 (7.6)	6 (7.5)	

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	All patients (n=146)	Normal (n=66)	Sarcopenic (n=80)	p-value
Normal	89 (61)	37 (56.1)	52 (65)	
Missing	46 (31.5)	24 (36.4)	22 (27.5)	
PIM user				>0.99
Yes	70 (47.9)	32 (48.5)	38 (47.5)	
No	76 (52.1)	34 (51.5)	42 (52.5)	
Depression				0.66
Yes	24 (16.4)	12 (18.2)	12 (15)	
No	122 (83.6)	54 (81.8)	68 (85)	
Prior fall				0.66
Yes	24 (16.4)	12 (18.2)	12 (15)	
No	122 (83.6)	54 (81.8)	68 (85)	
Weight loss				0.09
Yes	14 (9.6)	3 (4.5)	11 (13.8)	
No	132 (90.4)	63 (95.5)	69 (86.3)	

Abbreviations: HCT-CI, Hematopoietic cell transplantation-comorbidity index; CMV, Cytomegalovirus; ADL, Activities of daily living; IADL, Instrumental activities of daily living; PIM, Potentially inappropriate medication.

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Table 2.

Univariable and multivariable analyses of pre-transplant factors associated with OS, PFS, and NRM.

	Univariable Analysis						Multivariable Analysis					
	OS		PFS		NRM		OS		PFS		NRM	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Sarcopenia		0.03		0.05		0.06		**0.01**		**0.03**		**0.044**
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Yes	1.93 (1.08–3.45)		1.67 (1.00–2.79)		1.97 (0.98–3.97)		2.12 (1.18–3.80)		1.78 (1.07–2.98)		2.06 (1.02–4.19)	
HCT-CI		0.003		0.002		0.008		**0.003**		**0.002**		**0.006**
0–2	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
≥3	2.38 (1.35–4.17)		2.22 (1.35–3.67)		2.51 (1.28–4.94)		2.38 (1.35–4.19)		2.21 (1.33–3.67)		2.60 (1.31–5.16)	
Prior fall		0.10		0.02		0.23		0.12		**0.03**	-	-
No	Ref.		Ref.		Ref.		Ref.		Ref.			
Yes	1.72 (0.90–3.29)		2.04 (1.14–3.65)		1.61 (0.74–3.49)		1.69 (0.88–3.25)		1.92 (1.07–3.46)			

Abbreviations: OS, Overall survival; PFS, Progression free survival; NRM, Non-relapse mortality; HR, Hazard ratio; CI, Confidence interval; HCT-CI, Hematopoietic cell transplantation-comorbidity index; Ref., Reference.

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Table 3.

Univariable and multivariable 6-month landmark analyses of factors associated with OS, PFS, and NRM.

	Univariable Analysis						Multivariable Analysis					
	OS (n=121)		PFS (n=110)		NRM (n=110)		OS (n=121)		PFS (n=110)		NRM (n=110)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Sarcopenia		0.03		0.01		0.19		**0.03**		**0.02**	-	-
No	Ref.		Ref.		Ref.		Ref.		Ref.			
Yes	3.12 (1.10–8.86)		4.57 (1.40–15.0)		2.27 (0.66–7.78)		3.12 (1.10–8.89)		4.20 (1.27–13.9)			
HCT-CI		0.004		0.006		0.002		**0.004**		**0.009**		**0.002**
0–2	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
≥3	2.93 (1.42–6.05)		2.68 (1.33–5.40)		3.04 (1.22–7.55)		2.94 (1.42–6.07)		2.65 (1.28–5.49)		3.04 (1.22–7.55)	
aGVHD		0.14		0.03		0.37	-	-		0.11	-	-
Grade 0–1	Ref.		Ref.		Ref.				Ref.			
Grade 2–4	1.69 (0.84–3.37)		2.13 (1.07–4.24)		1.50 (0.62–3.63)				1.76 (0.88–3.52)			
Age (per 10 years)	1.04 (0.99–1.09)	0.17	1.04 (0.99–1.09)	0.10	1.03 (0.97–1.10)	0.36	-	-	1.01 (0.96–1.06)	0.75	-	-

Abbreviations: OS, Overall survival; PFS, Progression free survival; NRM, Non-relapse mortality; HR, Hazard ratio; CI, Confidence interval; HCT-CI, Hematopoietic cell transplantation-comorbidity index; Ref., Reference; aGVHD, Acute graft-versus-host disease.