

Cardiopulmonary Exercise Test With Comorbidity Index Before Allogeneic Hematopoietic Stem Cell Transplantation

Integrative Cancer Therapies
Volume 21: 1–8
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15347354221134249
journals.sagepub.com/home/ict



Sang Hoon Yeon, M.D.¹, Myung-Won Lee, M.D.¹, Pham Thi Thuy Duong, M.D.^{2,3}, Sora Kang, M.D.¹, Sungju Jee, M.D.¹, So-Young Ahn, M.D.¹, Hyewon Ryu, M.D.¹, Hyo-Jin Lee, M.D.¹, Jung Hye Kwon, M.D.¹, Hwan-Jung Yun, M.D.¹, Deog-Yeon Jo, M.D.¹, and Ik-Chan Song, M.D.^{1,2,3}

Abstract

Purpose: To evaluate the role of the cardiopulmonary exercise test (CPET) with comorbidity index as a predictor of overall survival (OS) and non-relapse mortality (NRM) in patients with hematological malignancies who undergo allogeneic hematopoietic stem cell transplantation (HSCT). **Methods:** We retrospectively analyzed consecutive adult patients with hematological malignancies who underwent HLA-matched donor-HSCT at Chungnam National University Hospital (Daejeon, South Korea) between January 2014 and December 2020. Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) was classified using the recommendations of the Mayo Clinic database. **Results:** Of 72 patients, 38 (52.8%) had $\text{VO}_{2\text{max}}$ values lower than the 25th percentile ($\text{VO}_{2\text{max}} \leq 25^{\text{th}}$) of an age- and sex-matched normal population. Patients with $\text{VO}_{2\text{max}} \leq 25^{\text{th}}$ had no significant differences both OS and NRM (30 month OS 29.8% vs 41%, $P = .328$; and 30 month NRM 16% vs 3.3%, $P = .222$), compared with other patients. $\text{VO}_{2\text{max}} \leq 25^{\text{th}}$ was assigned a weight of 1 when added to the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) to form a composite comorbidity/CPET index (HCT-CI/CPET). Patients with HCT-CI/CPET scores of 0 to 1 demonstrated significantly better OS and NRM than did patients with HCT-CI/CPET scores ≥ 2 [median OS not reached vs 6 months, $P < .001$ and 30 month NRM 7.4% vs 33.3%, $P = .006$]. An HCT-CI/CPET score ≥ 2 was the only adverse risk factor for NRM on multivariate analysis [hazard ratio (HR) of NRM 10.36 (95% CI 1.486–2.25, $P = .018$)]. **Conclusion:** The composite HCT-CI/CPET score can predict the survival and mortality of patients with hematological malignancies who undergo allogeneic HSCT.

Keywords

allogeneic hematopoietic stem cell transplantation, cardiopulmonary exercise test, comorbidity index, non-relapse mortality, overall survival

Submitted March 28, 2022; revised September 16, 2022; accepted October 5, 2022

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is essential for some patients with hematological malignancies, but it can be associated with substantial morbidity and mortality, particularly involving cardiopulmonary events.^{1,2} Although the mortality rate is improving with recent advances in HSCT, the mortality rate at 100 days after allogeneic HSCT is still about 10% for various reasons.³ Thus, it is important to identify patients at higher risk of transplantation-related complications. For example, the Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) is used to predict survival and non-relapse mortality (NRM) after allogeneic HSCT in patients with hematological

malignancies, based on their pre-transplant comorbidities and organ dysfunctions.⁴

¹Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Korea

²Department of Medical Science, College of Medicine, Chungnam National University, Daejeon, Korea

³Brain Korea 21 FOUR Project for Medical Science, Chungnam National University, Daejeon, Korea

Corresponding Author:

Ik-Chan Song, Department of Internal Medicine, College of Medicine, Chungnam National University, 282 Munwha-ro, Jung-gu, Daejeon 35015, South Korea.
Email: petrosong@cnu.ac.kr



We usually employ echocardiography, and a pulmonary function test featuring the diffusing capacity for carbon monoxide, to assess cardiopulmonary morbidity prior to HSCT.⁵ However, these measurements are conducted under resting conditions; thus, they do not provide a global measure of cardiopulmonary function or reserve capacity under stress conditions. Global cardiopulmonary function should reflect the integrative capacity of the cardiovascular and musculoskeletal systems in terms of oxygen transport and utilization. The incremental cardiopulmonary exercise test (CPET) that features a gas exchange measurement serves as the “gold standard” assessment of peak and submaximal parameters of exercise capacity.⁶ Recently, several studies have indicated that the CPET is a safe and feasible tool for objective assessment of the exercise capacities of patients with lung cancer, breast cancer, or leukemia.⁷⁻¹¹ Cancer patients exhibited significant reductions in peak and submaximal measures of cardiopulmonary function across the entire survivorship spectra. However, few studies have explored whether CPET combined with HCT-CI prior to allogeneic HSCT predicted the prognosis and mortality of patients with hematological malignancies.

Thus, we evaluated the role of the CPET combined with HCT-CI as a predictor of overall survival (OS) and NRM in patients with hematological malignancies who underwent allogeneic HSCT.

Materials and Methods

Patients and Treatments

We retrospectively analyzed consecutive adult patients (age >18 years) with hematological malignancies who underwent HLA-matched donor allogeneic HSCT in Chungnam National University Hospital (Daejeon, South Korea) between January 2014 and December 2020. We excluded patients receiving second transplantations and patients with refractory disease. Two conditioning regimens were used. The myeloablating conditioning regimen featured administration of 3.2 mg/kg busulfan for 4 days and 40 mg/m² fludarabine for 5 days. In the reduced intensity conditioning regimen, 3.2 mg/kg busulfan was administered for 2 days and 30 mg/m² fludarabine was administered for 6 days. No pharmacokinetic adjustment of busulfan dose was performed. Cyclosporine or tacrolimus was administered commencing on day -1, together with a short course of methotrexate for GVHD prophylaxis. Rabbit anti-thymocyte globulin (Sanofi-Aventis, Paris, France) was administered from days -3 to -1 at 1.5 mg/kg to prevent graft-versus-host disease. All patients received granulocyte colony-stimulating factor-mobilized peripheral blood stem cells (target CD34+ cell count, 5×10^6 /kg). Filgrastim 5 µg/kg was administered from day +5 until neutrophil recovery.

Incremental CPET

To determine the peak and sub-maximal markers of exercise capacity, CPET featuring 12-lead electrocardiogram monitoring (ST80i Stress Testing System; Philips Medical System, Andover, MA, USA) was performed by a specialist nurse prior to the delivery of conditioning therapy for allogeneic HSCT; this adhered to the CPET guidelines for clinical populations. All tests were performed using a respiratory desktop diagnostic suite, an automatic treadmill, and breath-by-breath expired gas analysis (Ultima Desktop Diagnostics; Medical Graphics Corp., Saint Paul, MN, USA). All patients with symptoms underwent limited exercise testing in accordance with the modified Bruce Protocol.^{12,13} When the respiratory exchange ratio exceeded 1.10, the participant was presumed to have achieved peak effort and the CPET was ended. The workloads were consecutively increased as follows (each lasted for 3 minutes). The first was 1.7 mph at a 0% grade, the second was 1.7 mph at a 5% grade, and the third was the first stage of the standard Bruce Test protocol. The maximal VO₂ (VO₂max) was defined as the highest VO₂ value over any 15 second interval within the last 60 seconds of exercise; the ventilatory threshold was calculated using standard methods.¹⁴ The reference standards for VO₂max measured via CPET were the standards of the Fitness Registry and the Importance of Exercise National Database of the United States.¹⁵

Outcomes and Statistical Analysis

The primary outcome was OS; secondary outcomes were NRM and clinical characteristics according to the values of VO₂max. NRM was defined as death from any cause other than relapse. Categorical variables were compared using the chi-squared test and logistic regression was employed to examine correlations. OS was assessed using the Kaplan-Meier method. Survival rates were compared using the log-rank test. Cumulative incidence functions were used to estimate NRM. Multivariate analyses of factors independently prognostic of OS and NRM were performed using a Cox proportional hazards regression model with 95% confidence interval (CIs). A *P*-value < .05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software ver. 26.0 (IBM Corporation, Armonk, NY, USA).

Statement of Ethics

The study protocol was approved by the Institutional Review Board of Chungnam National University Hospital (IRB no. CNUH 2018-02-032-011). All procedures followed were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration.

Table 1. Demographics and Clinical Characteristics of Patients According to VO₂max (N=72).

VO ₂ max	> 25 percentiles (N= 34)	≤25 percentiles (N= 38)	P-value
Age, median (range)	55 (30-70)	46 (18-64)	.002
Gender, M:F	16:18	31:7	.003
Disease			.578
AML	27 (79.4%)	26 (68.4%)	
ALL	5 (14.7%)	8 (21.1%)	
MDS	2 (5.9%)	2 (5.3%)	
Others	0 (0.0%)	2 (5.3%)	
Poor risk*	13 (38.2%)	24 (63.2%)	.058
Disease status			1.00
First CR	30 (88.2%)	33 (86.8%)	
Second CR	2 (5.9%)	3 (7.9%)	
MDS or others	2 (5.9%)	2 (5.3%)	
HCT-CI			.836
0	25 (73.5%)	28 (73.7%)	
1	9 (26.5%)	9 (23.7%)	
2	0 (0.0%)	0 (0.0%)	
3	0 (0.0%)	1 (2.6%)	
Conditioning			.164
MAC	23 (67.6%)	32 (84.2%)	
RIC	11 (32.4%)	6 (15.8%)	
Donor			.632
Sibling	22 (64.7%)	22 (57.9%)	
Unrelated	12 (35.3%)	16 (42.1%)	
GVHD prophylaxis	25 (73.5%)	26 (68.4%)	.392
CNI + MTX + ATG	4 (11.8%)	2 (5.3%)	
CNI + PTCy	5 (14.7%)	10 (26.3%)	
CNI + MTX			
Heart rate at CPET, median (range)	93 (63-123)	93 (61-143)	.970
F/U duration, month (range)	26 (3-67)	30 (3-82)	.402

Abbreviations: CR, complete remission; HCT-CI, Hematopoietic stem cell transplantation comorbidity index MAC, myeloablating conditioning; RIC, reduced intensity conditioning; GVHD, graft versus host disease; CNI, calcineurin inhibitor; MTX, methotrexate; ATG, anti-thymocyte globulin; PTCy, post-transplantation cyclophosphamide; F/U, follow up.

*Poor risk include sAML, tAML, AML with poor risk group in NCCN guideline, poor cytogenetics in ALL

The need for informed patient consent was waived because of the retrospective nature of the analysis.

Results

Patient Characteristics

From January 2014 to December 2020, 72 patients who met the inclusion criteria were enrolled. Patient characteristics are listed in Table 1. We divided all patients into 2 groups: patients with a VO₂max lower than the 25th percentile of an age- and sex-matched normal population, and other patients, in accordance with the reference standards of the Fitness Registry and the Importance of Exercise National Database. Of the 72 patients, 38 (52.8%) exhibited VO₂max values lower than the 25th percentile (VO₂max ≤ 25th); these were younger than other patients [median age (range) 46 years (18-64) vs 55 years (33-70), *P*=.002] and more were men [31 of 38 (81.5%) vs 16 of 34 (47.0%), *P*=.003]. The

median score of HCT-CI was 0 in both groups (0 score of HCT-CI in 53 patients, 1 in 18 patients, 3 in 1 patient). The most common disease was acute myeloid leukemia, followed by acute lymphoblastic leukemia and myelodysplastic syndrome (both groups). Poor-risk patients (ie, with secondary acute myeloid leukemia, therapy-related acute myeloid leukemia, or poor cytogenetics; scored using the National Comprehensive Cancer Network guidelines) were not significantly different between the 2 groups. Most patients were in their first complete remission at the time of HSCT. And, there were no significant differences in baseline heart rate at CPET before allogeneic HSCT and in any other characteristics between the 2 groups.

Survival Outcomes

Patients with VO₂max ≤ 25th had no statistically significant difference in OS, compared with other patients (OS at 30 months 59% vs 70.2%, *P*=.328, Figure 1A). They

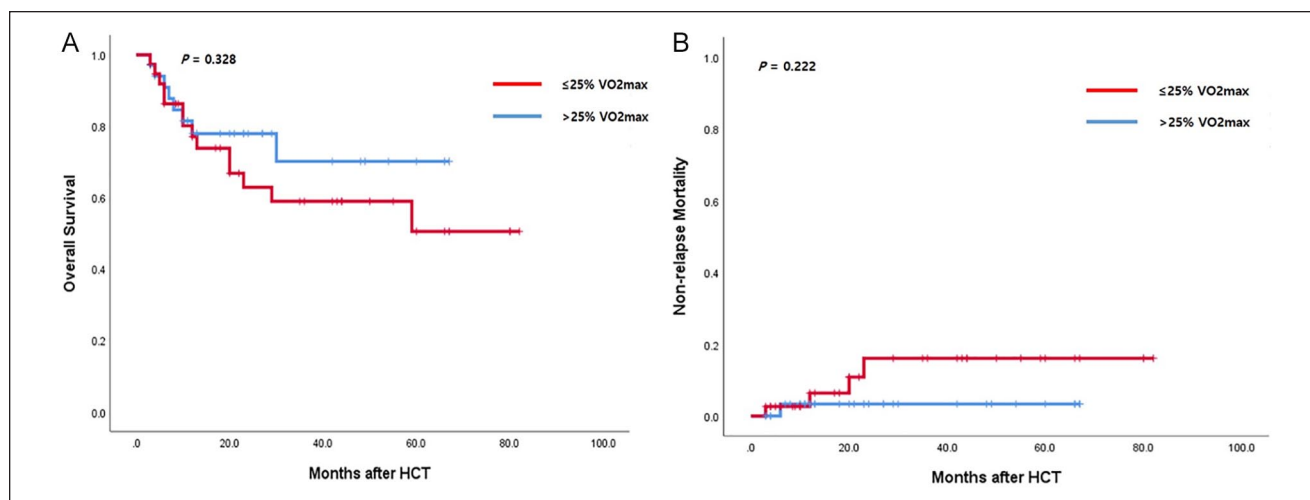


Figure 1. Overall survival (A) and non-relapse mortality (B) according to 25th percentile of VO₂max (N=72).

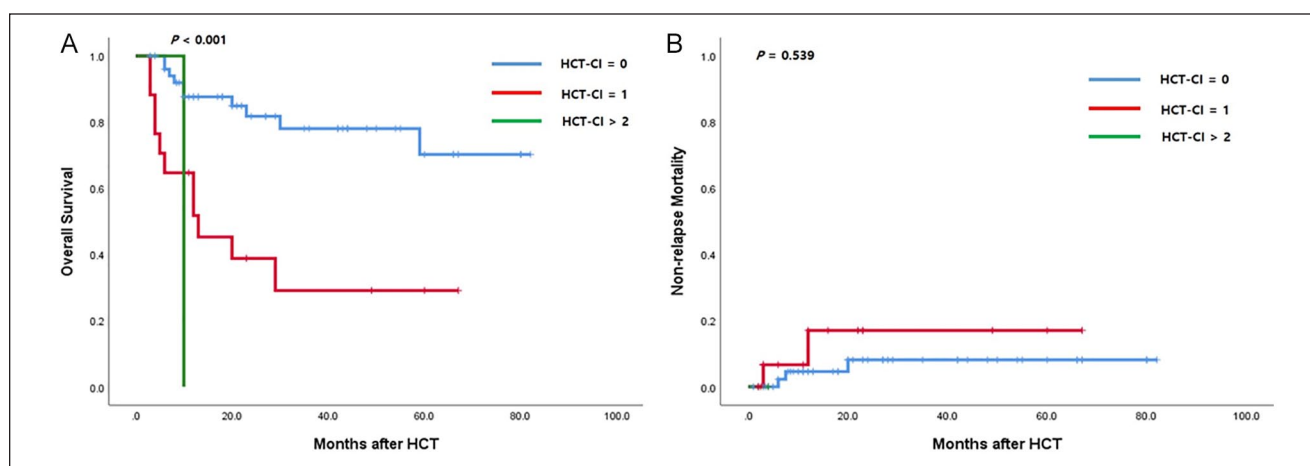


Figure 2. Overall survival (A) and non-relapse mortality (B) according to HCT-CI (N=72).

also demonstrated no difference of NRM, compared with other patients (NRM at 30 months 16.1% vs 3.5%, $P=.222$, Figure 1B). When survival outcomes were analyzed using the HCT-CI score, OS was strongly correlated with that score (median OS not reached in the group that scored 0, 12 months in the group that scored 1, and 10 months in the group that scored 2, $P<.001$, Figure 2A). However, statistical significance of the NRM calculated by HCT-CI score was lacking (NRM at 30 months 8.1% in the group that scored 0, 17% in the group that scored 1, and 0% in the group that scored 2, $P=.539$, Figure 2B). We added VO₂max $\leq 25^{\text{th}}$ (a value of 1) to the HCT-CI to create a composite comorbidity/CPET index (HCT-CI/CPET). Patients with HCT-CI/CPET scores of 0 to 1 exhibited significantly better OS than did patients with scores ≥ 2 (median OS not reached vs 12 months, $P<.001$, Figure 3A). Patients with HCT-CI/CPET scores of 0 to 1 demonstrated a significantly lower NRM than

did patients with HCT-CI/CPET scores ≥ 2 (NRM at 30 months 4.4% vs 33.3%, $P=.006$, Figure 3B). When we used multivariate Cox regression to evaluate risk factors for survival, older age (≥ 60 years) and an HCT-CI/CPET score > 2 were significant poor risk factors for OS [hazard ratio (HR) of 4.017 (95% CI 1.618-9.977), $P=.003$; and HR of 4.662 (95% CI 1.907-11.401), $P=.001$, respectively; Table 2]. An HCT-CI/CPET > 2 was the only adverse risk factor for NRM [HR 10.36 (95% CI 1.486-72.25), $P=.018$, Table 3].

Discussion

In this study, we showed that the CPET combined with HCT-CI score can predict overall survival (OS) and non-relapse mortality (NRM) in patients with hematological malignancies who undergo allogeneic HSCT. Patients with VO₂max $\leq 25^{\text{th}}$ had similar OS and NRM compared to the

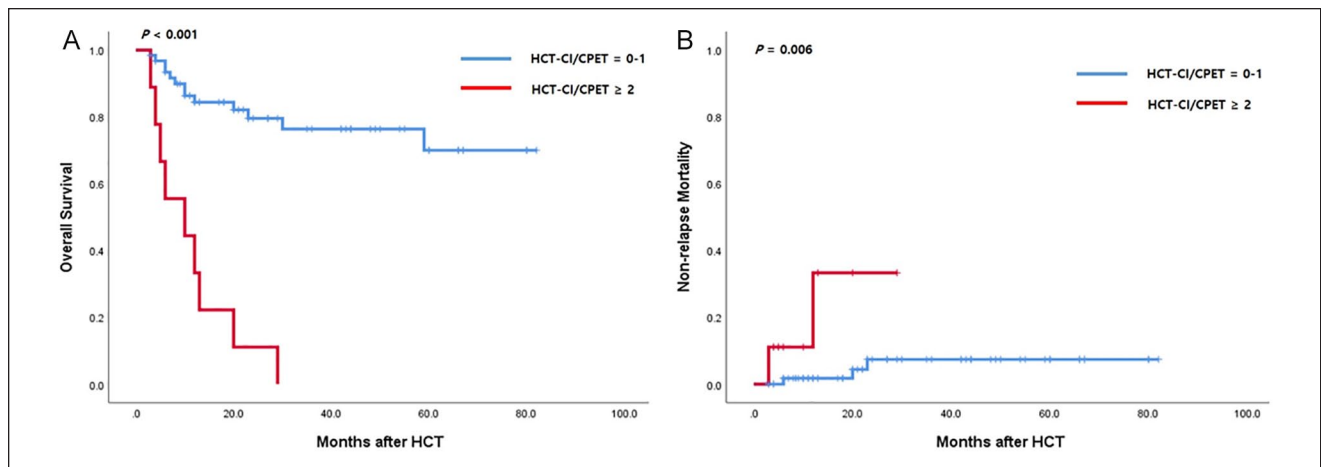


Figure 3. Overall survival (A) and non-relapse mortality (B) according to HCT-CI/CPET (N=72).

Table 2. Multivariate Cox Regression Models of Risk Factors for Overall Survival.

Parameters		HR	95% CI	P-value
Age, year	<60 (n=56)	1		
	≥60 (n=16)	4.017	1.618-9.977	.003
HCT-CI/CPET score	0-1 (n=63)	1		
	>2 (n=9)	4.662	1.907-11.401	.001
Risk status	Poor (n=37)	1		
	None (n=35)	0.556	0.188-1.648	.290
Conditioning regimen	MAC (n=55)	1		
	RIC (n=17)	1.238	0.425-1.618	.695

Abbreviations: HCT-CI, hematopoietic cell transplantation–comorbidity index; CPET, cardiopulmonary exercise test; HR, hazard ratio; MAC, myeloablating conditioning; RIC, reduced intensity conditioning.

Table 3. Multivariate Cox Regression Models of Risk Factors for Non-Relapse Mortality.

Parameters		HR	95% CI	P-Value
Age, year	<60 (n=56)	1		
	≥60 (n=16)	8.805	0.885-87.6	.064
HCT-CI/CPET score	0-1 (n=63)	1		
	>2 (n=9)	10.36	1.486-72.25	.018
Risk status	Poor (n=37)	1		
	None (n=35)	10.12	0.791-129.65	.075
Conditioning regimen	MAC (n=55)	1		
	RIC (n=17)	0.587	0.062-5.535	.642

HCT-CI, hematopoietic cell transplantation–comorbidity index; CPET, cardiopulmonary exercise test; HR, hazard ratio; MAC, myeloablating conditioning; RIC, reduced intensity conditioning.

other patients. And, HCT-CI score also did not show statistical difference of NRM in this patient cohort. However, when the CPET and HCT-CI scores were combined, the different survival outcomes of low-score (0-1) and high-score (≥2) groups became clearer.

Despite recent advances of allogeneic HSCT, NRM still serves as a major obstacle to performing HSCT.^{1,2} NRM is

mainly caused by infection or graft-versus-host disease (GVHD) or cardio-pulmonary complications in post-transplant period. The HCT-CI score was developed to predict the risk of death after allogeneic HSCT.⁴ Over the past few years, comorbidity assessment has improved allogeneic HSCT outcomes by providing important risk assessment information prior to HSCT.^{16,17} However, the HCT-CI

predicts prognosis using the forced expiratory volume in 1 s, diffusing capacity for carbon monoxide, and the left ventricular ejection fraction; functional capacity may not be adequately evaluated because the tests are performed at rest. The CPET is a non-invasive, integrated assessment of cardiovascular and pulmonary function in both resting and stressful states.¹⁸ Objective assessment of VO_2max is an important predictor of the health and survival of patients with several diseases, particularly cardiopulmonary diseases.¹⁹⁻²¹ Most studies examining the prognostic role of the CPET in cancer patients have focused on the VO_2max . Thus, we also used VO_2max as an exercise capacity parameter in patients with hematologic malignancies who underwent allogeneic HSCT. VO_2max is defined as the point at which oxygen uptake (VO_2) plateaus despite an increase in exercise rate during CPET. However, VO_2 plateaus are rarely observed in patients, suggesting that maximal exercise levels are not reached during CPET due to muscle fatigue and discomfort in patients.²² The highest VO_2 measured during a patient's CPET is often referred to as VO_2peak . In clinical practice, VO_2max and VO_2peak are often used interchangeably for practical purposes.²³

Several recent studies have indicated that the CPET is safe and reliable when used for an objective assessment of exercise capacity in patients with various cancers.^{7,24-26} Jones et al⁷ evaluated cardiopulmonary function across the breast cancer continuum and its prognostic significance in women with metastatic disease. Patients with breast cancer exhibited marked impairment in the VO_2peak across the entire survivorship continuum; the VO_2peak may thus serve as an independent predictor of survival in patients with metastatic disease.⁷ Jones et al⁸ investigated the prognostic importance of functional capacity and exercise behavior; they determined whether such parameters provided prognostic information beyond the insights afforded by traditional markers such as performance status, older age (>70 years), and sex (male) in patients with metastatic non-small cell lung cancer. Functional capacity was a strong independent predictor of survival in advanced non-small cell lung cancer patients; the information imparted added to the insights from existing risk factors, thus enhancing survival prediction.

However, few reports have explored the role of the CPET in patients undergoing allogeneic HSCT. Most such studies had small numbers of patients or were pilot works.^{24,27,28} For example, Wood et al evaluated 29 patients with hematological malignancies who underwent the CPET prior to HSCT; it was suggested that pre-HSCT VO_2max assessment was feasible and might predict symptom severity, the health-related quality-of-life, and mortality.²⁷ When comparing CPET data obtained prior to allogeneic HSCT to treat hematological malignancies, the VO_2max was significantly lower than in healthy controls. Dirou et al found that a high proportion (75.4%) of allogeneic HSCT survivors exhibited abnormal, cardiopulmonary exercise testing

parameters (compared with predicted normal values). Disability and fatigue were presumed to be strongly associated with decreased peak VO_2 values.²⁹ Similarly, in our study, the VO_2max of most patients (79.2%) was lower than the 50th percentile of healthy individual's reference of the Fitness Registry and the Importance of Exercise National Database of the United States (FRIEND); this was probably because most patients received high-intensity chemotherapy and had anemia before allogeneic HSCT, which has been associated with muscle weakness and/or a decline in cardiac function. For example, the anthracyclines frequently used to treat hematological malignancies can cause cardiomyopathy, a decreased ejection fraction.³⁰ In a previous study, we observed that HSCT patients exhibited a higher baseline heart rate and a significantly lower VO_2max , compared with normal controls.²⁴ In this study, the baseline heart rate at CPET before allogeneic HSCT was observed to be higher in both groups than in normal subjects. This high baseline heart rate can be a factor in lowering VO_2max in HSCT patients. The reference value of FRIEND is classified into 7 levels according to age and gender by VO_2max of CPET; 5th, 10th, 25th, 50th, 75th, 90th, 95th percentiles.¹⁵ As previously mentioned, when the VO_2max of HSCT patients were divided by 50th percentile of FRIEND reference, most of the patients in this study were less than 50th percentile, making it difficult to compare the 2 groups. So, we divided the patients into 2 groups using the 25th percentile threshold when comparing clinical outcomes, because that divided approximately half of the patients, allowing meaningful comparisons between the 2 groups.

In this study, younger and male patients more often exhibited VO_2max values below the 25th percentile, unexpectedly. We suggest that the intensity of modified BRUCE protocol, which is a tool developed for assessment of the cardiopulmonary function in cancer patients, mostly elderly, do not adequately measure VO_2max in young men undergoing allogeneic HSCT. In this study, relatively young patients with median age of 55 and 46 years in each group were enrolled. Given the toxicity and mortality of allogeneic HSCT, it is difficult to apply to the elderly patients.^{31,32} We thought that there was no significant difference in survival outcomes with VO_2max of CPET alone for this reason. Thus, the development of CPET protocol appropriate for patients with hematologic malignancies who will undergo allogeneic HSCT is required. For example, in younger patients, there may be a method to increase the exercise threshold to induce a higher VO_2max .

Several studies have reported a more sophisticated mortality-prediction model by combining HCT-CI with disease risk status or age, so we added HCT-CI score to the value of VO_2max for analysis of survival and mortality.^{16,17,33} In this study, age and HCT-CI/CPET and cytogenetic risk status were significant risk factors for OS and NRM in univariate analysis. However, the composite HCT-CI/CPET score was

the only adverse risk factor for OS and NRM in multivariate analysis. When the HCT-CI/CPET score was low, the patients showed statistically significant better OS and lower NRM in this study.

Although this study was retrospectively conducted at a single institute, selection bias was avoided because a comparatively large number of consecutive patients was enrolled. We suggest that the HCT-CI/CPET is useful tool for prediction of survival outcomes prior to allogeneic HSCT in patients with hematologic malignancies. It will be necessary to develop CPET protocol suitable for patients undergoing HSCT in the future. And because this study has a small number of patients to generalize the results, a multicenter study will be needed to validate the role of HCT-CI/CPET in a larger number of patients with hematologic malignancies.

Acknowledgments

We thank professor Deog Yeon Jo and Sungju Jee for revising the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors are salaried employees or graduate students of Chungnam National University or Chungnam National University hospital. All authors have no financial support from an industry source at this study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Chungnam National University Hospital Research Fund, 2021. (2021-CF-019)

ORCID iD

Ik-Chan Song  <https://orcid.org/0000-0002-6938-970X>

References

1. Patel SS, Rybicki LA, Corrigan D, et al. Prognostic factors for mortality among day +100 survivors after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:1029-1034.
2. Lucena CM, Torres A, Rovira M, et al. Pulmonary complications in hematopoietic SCT: a prospective study. *Bone Marrow Transplant*. 2014;49:1293-1299.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *New Engl J Med*. 2010;363:2091-2101.
4. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912-2919.
5. Enric C, Alessandro R. Evaluation and counseling of candidates. In: Carreras E, Dufour C, Mohty M, et al, eds. *The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]*. 7th ed. Springer; 2019;77-86. <http://www.ncbi.nlm.nih.gov/books/NBK553925>
6. Tran D. Cardiopulmonary exercise testing. *Methods Mol Biol*. 2018;1735:285-295.
7. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*. 2012;30:2530-2537.
8. Jones LW, Hornsby WE, Goetzinger A, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer*. 2012;76:248-252.
9. Ni HJ, Pudasaini B, Yuan XT, Li HF, Shi L, Yuan P. Exercise training for patients pre- and postsurgically treated for non-small cell lung cancer: a systematic review and meta-analysis. *Integr Cancer Ther*. 2017;16:63-73.
10. Dong X, Yi X, Gao D, et al. The effects of the combined exercise intervention based on internet and social media software (CEIBSMS) on quality of life, muscle strength and cardio-respiratory capacity in Chinese postoperative breast cancer patients: a randomized controlled trial. *Health Qual Life Outcomes*. 2019;17:109.
11. Kelsey CR, Scott JM, Lane A, et al. Cardiopulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study. *Bone Marrow Transplant*. 2014;49:1330-1336.
12. Bruce RA. Exercise testing for evaluation of ventricular function. *New Engl J Med*. 1977;296:671-675.
13. Kang DW, Fairey AS, Boulé NG, Field CJ, Wharton SA, Courneya KS. Effects of exercise on cardiorespiratory fitness and biochemical progression in men with localized prostate cancer under active surveillance: the ERASE randomized clinical trial. *JAMA Oncol*. 2021;7:1487-1495.
14. Rogers B, Giles D, Draper N, Mourot L, Gronwald T. Detection of the anaerobic threshold in endurance sports: validation of a new method using correlation properties of heart rate variability. *J Funct Morphol Kinesiol*. 2021;6:38.
15. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the importance of Exercise National Database. *Mayo Clin Proc*. 2015;90:1515-1523.
16. Ciurea SO, Kongtim P, Hasan O, et al. Validation of a hematopoietic cell transplant-composite risk (HCT-CR) model for post-transplant survival prediction in patients with hematologic malignancies. *Clin Cancer Res*. 2020;26:2404-2410.
17. Saeed H, Yalamanchi S, Liu M, et al. Age adjusted hematopoietic stem cell transplant comorbidity index predicts survival in a T-cell depleted cohort. *Hematol Oncol Stem Cell Ther*. 2018;11:90-95.
18. Stubbs DJ, Grimes LA, Ercole A. Performance of cardiopulmonary exercise testing for the prediction of post-operative complications in non cardiopulmonary surgery: a systematic review. *PLoS One*. 2020;15:e0226480.
19. Steffens D, Ismail H, Denehy L, et al. Preoperative cardiopulmonary exercise test associated with postoperative outcomes in patients undergoing cancer surgery: a systematic review and meta-analyses. *Ann Surg Oncol*. 2021;28:7120-7146.

20. Chae G, Ko EJ, Lee SW, et al. Stronger correlation of peak oxygen uptake with distance of incremental shuttle walk test than 6-min walk test in patients with COPD: a systematic review and meta-analysis. *BMC Pulm Med.* 2022;22:102.
21. Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. *Int J Cardiol.* 2013;167:1193-1198.
22. Dafoe W. Principles of exercise testing and interpretation. *Can J Cardiol.* 2007;23:274-274.
23. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol.* 2008;9:757-765.
24. Kim S, Song IC, Jee S. Cardiopulmonary exercise test in leukemia patients after chemotherapy: a feasibility study. *Ann Rehabil Med.* 2017;41:456-464.
25. Blanchon F, Grivaux M, Asselain B, et al. 4-year mortality in patients with non-small-cell lung cancer: development and validation of a prognostic index. *Lancet Oncol.* 2006;7:829-836.
26. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care.* 2005;4:7.
27. Wood WA, Deal AM, Reeve BB, et al. Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. *Bone Marrow Transplant.* 2013;48:1342-1349.
28. Vandekerckhove K, De Waele K, Minne A, et al. Evaluation of cardiopulmonary exercise testing, heart function, and quality of life in children after allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer.* 2019;66:e27499.
29. Dirou S, Chambellan A, Chevallier P, et al. Deconditioning, fatigue and impaired quality of life in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2018;53:281-290.
30. Bansal N, Adams MJ, Ganatra S, et al. Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors. *Cardiooncology.* 2019;5:18.
31. Wall SA, Devine S, Vasu S. The who, how and why: allogeneic transplant for acute myeloid leukemia in patients older than 60 years. *Blood Rev.* 2017;31:362-369.
32. Del Galy AS, Marouf A, Raffoux E, et al. Allogeneic hematopoietic stem cell transplantation in elderly patients with acute myeloid leukemia or myelodysplastic syndromes: myth and reality. *Leukemia.* 2021;35:225-228.
33. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2014;32:3249-3256.