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Cardiorespiratory Fitness From Cardiopulmonary Exercise Testing Is a Comprehensive Risk-stratifying Tool in Liver Transplant Candidates

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Background. Cardiovascular disease and physical decline are prevalent and associated with morbidity/mortality in liver transplant (LT) patients. Cardiopulmonary exercise testing (CPX) provides comprehensive cardiopulmonary and exercise response assessments. We investigated cardiorespiratory fitness (CRF) and cardiac stress generated during CPX in LT candidates. **Methods.** LT candidates at 2 centers underwent CPX. Standard-of-care cardiac stress testing (dobutamine stress echocardiography, DSE) results were recorded. Physical function was assessed with liver frailty index and 6-min walk test. CPX/DSE double products were calculated to quantify cardiac stress. To better study the association of CPX-derived metrics with physical function, the cohort was divided into 2 groups based on 6-min walk test median (372 m). **Results.** Fifty-four participants (62 ± 8 y; 65% men, Model for End-Stage Liver Disease-Na 14 [10–18]) underwent CPX. Peak oxygen consumption was 14.1 mL/kg/min for an anerobic threshold of 10.2 mL/kg/min, with further CRF decline in the lower 6MWT cohort despite lack of liver frailty index-frailty in 90%. DSE was nondiagnostic in 18% versus 4% of CPX ($P = 0.058$). All CPX were negative for ischemia. A double product of ≥25 000 was observed in 32% of CPX and 11% of DSE ($P = 0.020$). Respiratory function testing was normal. No patient presented major cardiovascular events at 30 d post-LT. **Conclusions.** CPX provided efficient and effective combined cardiopulmonary risk and frailty assessments of LT candidates in a 1-stop test. The CRF was found to be very low despite preserved physical function or lack of frailty.

(*Transplantation Direct* 2024;10: e1725; doi: 10.1097/TXD.0000000000001725.)

Successful selection of liver transplant (LT) recipients requires a thorough assessment of medical and physical fitness in a time-sensitive manner to promote candidate survival. Chief among the myriad clinical conditions that inform recipient selection is the determination of perioperative cardiopulmonary risk and functional capacity. Cardiovascular disease is a leading cause of perioperative and post-LT morbidity and mortality, and reduced functional capacity (physiological reserve) among LT candidates is associated with negative outcomes.[1-3] Cardiorespiratory fitness (CRF) has been shown to predict transplant outcomes,[4-7] and apart from quantifying physiological reserve, it is a clinical vital sign and strongest predictor of overall and cardiovascular mortality.[8] Despite the well-recognized importance of assessment of both cardiovascular risk and CRF required for effective LT evaluation, methods for such screening are highly variable across LT centers and, particularly in the case of cardiac risk assessment, multicenter data to designate superior screening strategies are

Received 3 September 2024. Revision received.

Accepted 9 September 2024.

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The study was funded by NIH-NIDDK P30DK120531 Pilot and Feasibility Program, Cycle 2020.

The authors declare no conflicts of interest.

D.L.H., B.L.-M., C.M.W.-G., P.M.R., C.W., E.J.C., H.E.V., D.E.F., and A.D.R. contributed in study concept and design, critical revision of article, important intellectual content, and final approval of the version to be published. D.L.H., A.D.R., B.L.-M., P.M.B., C.M.W.-G., and W.C. contributed in recruitment and data acquisition. A.D.R., B.L.-M., C.M.W.-G., C.W., and D.E.F. contributed in monitoring of CPX. D.L.H., C.M.W.-G., and A.D.R. contributed in analysis and interpretation of data/drafting of the article. A.D.R. contributed in study supervision.

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Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001725

lacking.[9-12] In addition to variable screening methods, the time required to complete LT evaluation testing can contribute to a high burden of clinical appointments for candidates with associated costly demands.[13] Furthermore, prolonged evaluation periods delay LT recipient selection, which can prove irreparable if candidates experience interval acute clinical deterioration prohibiting them from further consideration for LT.[14,15]

Cardiopulmonary exercise testing (CPX) is a noninvasive multimodal tool of longstanding clinical utility in the fields of cardiology and pulmonary medicine, where it serves as a reference standard for CRF assessment with particular clinical utility among heart and lung transplant candidates.[16-19] Data demonstrating the use of CPX among LT candidates are limited and primarily consist of single-center studies showing the association of peak oxygen consumption (VO_{2peak}) with all-cause mortality and post-LT morbidity in LT candidates.[4,7] To the best of our knowledge, no studies have been performed demonstrating the prognostic utility of CPX among LT candidates with respect to the incidence of post-LT major adverse cardiac events (MACEs). Data demonstrating agreement between CPX-generated CRF metrics and conventional methods of physical function and frailty assessment in LT candidates are also limited.[20]

Given the ever-increasing prevalence of older age, cardiovascular disease burden, and frailty among LT candidates, we sought to better determine the clinical utility of CPX among LT candidates at 2 academic transplant centers. Specifically, we aimed to (1) prospectively determine the agreement of CPX parameters of cardiac risk to standard-of-care cardiac stress testing (dobutamine stress echocardiography [DSE]), including the incidence of post-LT 30-d MACEs, (2) prospectively determine the agreement of CPX determinants of CRF to conventional frailty metrics in LT candidates, and (3) describe the potential utility of CPX to assess pulmonary function.

PATIENTS AND METHODS

Patient Population and Study Design

We conducted a multicenter, prospective analysis of consecutive adult LT candidates at the University of Pittsburgh and Mayo Clinic Arizona from September 2020 to March 2022. Participants completed CPX during LT evaluation or while waitlisted for LT, along with the following physical function tests: 6-min walk test (6MWT), liver frailty index (LFI) (both centers), and gait speed test (GST; University of Pittsburgh only) within 30 d of CPX. Per protocol, candidates underwent DSE at the time of LT evaluation except when contraindicated/unavailable; for these cases, another form of cardiac stress test or coronary angiogram was requested on a case-by-case basis.

Exclusion criteria consisted of patient younger than 40 y or older than 75 y, platelets <30 000/μL, international normalized ratio >3, chronic kidney disease (CKD) grades 3–5 (glomerular filtration rate <30 mL/min/1.73 m^2), and standard medical contraindications to LT, such as documented history of left main coronary artery stenosis, moderate to severe aortic stenosis, reduced systolic function (left ventricular ejection fraction <50%), severe atrioventricular arrhythmias, and severe chronic obstructive pulmonary disease (COPD). Additional exclusion criteria included contraindications to exercise, such as orthopedic limitation, overt hepatic encephalopathy at the time of consent or CPX, and portopulmonary hypertension. Written informed consent was obtained from all study participants. The study was conducted in accordance with both the Declaration of Helsinki and the Declaration of Istanbul. The study was approved by institutional review boards at the University of Pittsburgh and Mayo Clinic.

Cardiopulmonary Exercise Testing

CPX was performed at both LT centers using a semirecumbent cycle-ergometer (Medtronic, Minneapolis, MN). All CPX were administered by trained exercise physiologists in accordance with recommendations from the American Heart Association and American College of Chest Physicians.[21,22] Patients were seated on the ergometer and connected to 12-lead electrocardiography (ECG) for continuous collection of heart rate [HR]/rhythm and dynamic stress-induced changes. They were also fitted with a facemask to record gas exchange (oxygen consumption [VO_2], carbon dioxide production [VCO_2], breathing pattern, minute ventilation, inspiratory timing, etc). Please see **Supplemental Methods** (**SDC**, http://links.lww.com/TXD/A717s for further details.

Pulmonary function testing (PFT), specifically spirometry, was performed according to the American Thoracic Society guidelines to determine forced vital capacity (FVC), forced expiratory volume in 1 s of the FVC (FEV_1), slow vital capacity, and inspiratory capacity. Predicted values for all pulmonary function measures were based on predicted equations from NHANES III at rest in all patients.[23]

Hemodynamic, gas exchange, and PFT parameters were further used to determine indicators of cardiopulmonary function and CRF, specifically:

- Peak oxygen uptake (VO_{2peak}; expected values, 38 ± 8 mL/kg/min for men and 29 ± 7 mL/kg/min for women).[24]
- Anaerobic threshold (AT; VO_2 determined by equivalents method).
- Respiratory exchange ratio (marker of cardiometabolic stress in CPX).
- Ventilatory efficiency (VE/VCO_2).
- Breathing reserve.
- Expiratory flow limitation (Mayo Clinic only).

To assess expiratory flow limitation, first, a stable end-of-expiration or end-expiratory lung volume was obtained during tidal breathing, during resting gas exchange, and while seated on the cyclo-ergometer. Then, participants were instructed to perform a slow vital capacity maneuver by specifically taking a maximal inhalation and exhalation until completely emptying their lungs (ie, residual volume) to calculate the inspiratory capacity. This allowed for the placement of the tidal breaths within the maximal flow volume loop (FVC). Then, at least 6 tidal breaths flow loops were recorded during the final stages of exercise. Expiratory flow limitation was present if tidal breaths encroached on the maximal flow volume loop. The percentage of the loop that touched or exceeded the FVC was calculated and reported as the percentage of expiratory flow limitation.[25]

Any patient on beta-blocker therapy was instructed to remain off beta-blockers for a minimum of 48 h before CPX. Three days he scheduled CPX, patients were contacted by LT program administrative staff to confirm instructions for

discontinuation of beta-blocker therapy to preserve the accuracy of CPX.

Data Collection

We collected data on patient demographics as well as medical history (hypertension, hyperlipidemia, diabetes mellitus, CKD, atrial fibrillation), family history of coronary artery disease (CAD), and history of smoking. The causes of liver disease and manifestations of portal hypertension were recorded. The severity of liver disease was further accounted for by the calculated Model for End-Stage Liver Disease (MELD-Na) score. Recorded data from CPX included hemodynamics, CRF metrics, and PFT, as mentioned earlier.

The presence of CAD on CPX was determined by the presence of new-onset ischemic change on ECG (ST segment elevation, ST segment depression ≥1.0 mm, T-wave inversion, Q-wave formation), and/or symptoms consistent with exercise-induced angina.[16,21] CPX results were compared against the standard of care for cardiac ischemia assessment per DSE and frailty (LFI ≥4.5, GST <0.9 m/s, and 6MWT <250 m).[5,9] DSE variables collected included hemodynamics (HR and blood pressure), ejection fraction, presence of wall motion abnormalities, or ischemic changes on ECG. DSE findings suggestive of ischemia were identified by an interpreting cardiologist. A DSE was considered nondiagnostic when peak HR was <85% of the age-predicted maximum, whereas the CPX was considered nondiagnostic when the respiratory exchange ratio at VO_{2peak} was <1.0 in the presence of a VE/VCO_2 at VO_{2peak} ≥36.[16] The double product, which results from multiplying the HR times the systolic blood at peak stress, was calculated for both CPX and DSE as an index of myocardial oxygen consumption to quantify maximal cardiovascular stress achieved during the tests. A double product ≥25 000 is reflective of a high cardiac workload and associated with improved CAD diagnostic performance.[26] A previously described chronotropic index formula, consisting of a ratio of HR reserve to metabolic reserve at peak exercise [(HR at peak − HR at rest)/([220 − age] − hear rate at rest) × 100] was used, and chronotropic incompetence was defined as chronotropic index <0.8.[27,28]

Study Endpoints

Patients were followed prospectively until the following clinical outcome: delisting for LT, death, or 30 d post-LT, whichever occurred first. MACE was defined as a composite of acute coronary syndrome, new-onset arrhythmia (atrial fibrillation/flutter, ventricular tachycardia/fibrillation, supraventricular tachycardia refractory to cardioversion or symptomatic atrioventricular block; all confirmed on electrocardiography), new-onset heart failure (collective objective evidence of hypoxia, pulmonary or lower extremity edema, new systolic or diastolic dysfunction on echocardiography), stroke, or cardiac arrest within first 30 d of LT.[29,30] Assessment for MACE was performed by 2 physicians via electronic medical record review.

Statistical Analysis

For the purpose of analysis, we divided our cohort into 2 balanced groups depending on their physical function: those <50th percentile and those ≥50th percentile of the 6MWT distance (372 m). The comparison between patients in the lower versus upper spectrum of 6MWT allowed us to better understand how functional capacity, as measured in the clinic through a readily available test, corresponded to CRF from CPX, and whether there was a relationship with a particular clinical phenotype.

Continuous variables were expressed as median with percentiles 25th–75th or mean with SD, and they were compared with either the *t* test (normally distributed data) or the Mann-Whitney *U* test (nonnormally distributed data). Categorical data were compared with chi-square testing. McNemar testing was used for the examination of paired dichotomous data, including CPX and DSE for cardiac risk stratification, and CPX and 6MWT for physical fitness assessment. Correlations between CPX, 6MWT, and LFI were assessed using Spearman's rank correlation coefficient. *P* values of <0.05 were considered statistically significant.

RESULTS

A total of 54 LT candidates completed CPX (41 from the University of Pittsburgh and 13 from Mayo Clinic), and clinical characteristics of participants are summarized in Table 1. The mean age was 62 ± 8 y, 65% of participants were men, and 94% were of White race. Leading causes of liver disease were chronic hepatitis C (28%) and metabolic-associated dysfunction steatohepatitis (MASH) (28%), and a majority had decompensated cirrhosis (89%); median MELD-Na was 14 and Child-Turcotte-Pugh was 8 (class B/C: 56%/31%). For the entire cohort, the median 6MWT was 372 m and 7 participants (13%) walked <250 m. Within the total cohort, 42 participants had a calculated LFI, and 4 (10%) were frail per LFI. At University of Pittsburgh, 40 of 41 participants underwent GST, and 9 (23%) were frail per GST.

Among the physical function cohorts, the lower 6MWT cohort had a higher mean age (64 versus 59 y, $P = 0.019$). The lower 6MWT cohort also had significantly higher rates of decompensated disease, specifically hepatic encephalopathy (41% versus 15%; $P = 0.033$) and a history of variceal bleeding (78% versus 44%; $P = 0.012$), although there was no significant difference in MELD-Na between the 2 cohorts (14 versus 15; $P = 0.98$). There was a higher prevalence of anemia in the lower 6MWT cohort (median hemoglobin 11 versus 13 g/dL, $P = 0.002$). There was no significant difference in rates of metabolic comorbidities, CKD, or COPD between the 2 cohorts. As expected, frailty metrics (LFI and GST) were compatible with functional decline for participants in the lower 6MWT cohort.

Cardiorespiratory Fitness Assessment and Dynamics per Physical Function Cohort

For the total cohort, the workload was 86 W (65–110) with a CPX duration of 9 ± 3 min and time to AT of 6 ± 3 min. The median peak oxygen consumption (VO_{2peak}) was 14.1 mL/kg/min for an AT of 10.2 mL/kg/min at VO_{2peak}. VO_{2peak} showed a nonsignificant trend for higher values in men compared with women, a difference driven by the upper 6MWT cohort (Figure 1). VO_{2peak} strongly correlated with 6MWT ($\rho = 0.75$; $P < 0.001$), LFI ($\rho = -0.73$; $P < 0.001$), and GST ($\rho = 0.699$; $P < 0.001$). The VO_{2peak} association with 6MWT and GST was preserved when participants were categorized as having functional decline or frailty (Figure 2), although it was lost with LFI. The loss of discriminatory capacity of LFI was explained by the overlap between prefrail and frail patients, as shown

TABLE 1.

Cohort clinical characteristics per 6MWT subcohorts

Characteristics	Total (N = 54)	6MWT <372 (N = 27)	6MWT≥372 (N = 27)	*P*
Age, y	62 (8)	64 (7)	59 (7)	**0.019**
Sex				
Male	35 (65%)	16 (59%)	19 (70%)	0.39
Ethnicity				
Not Hispanic/Latino	36 (67%)	19 (70%)	17 (63%)	0.16
Hispanic/Latino	7 (13%)	5 (19%)	2 (7%)	
Not reported	11 (20%)	3 (11%)	8 (30%)	
Race				
White	51 (94%)	27 (100%)	24 (89%)	0.20
Black	1 (2%)	0 (0%)	1 (4%)	
Not reported	2 (4%)	0 (0%)	2 (7%)	
Cause				
MASH	15 (28%)	8 (30%)	7 (26%)	0.27
HCV	15 (28%)	10 (37%)	5 (19%)	
Alcohol	12 (22%)	3 (11%)	9 (33%)	
Cryptogenic	6 (11%)	4 (15%)	2 (7%)	
Autoimmune	5 (9%)	1 (4%)	4 (15%)	
Other	1 (2%)	1 (4%)	0 (0%)	
HCC	24 (44%)	12 (44%)	12 (44%)	1.00
Variceal bleed	15 (28%)	11 (41%)	4 (15%)	**0.033**
Nonselective beta-blocker	10 (19%)	6 (22%)	4 (15%)	0.48
History of HE	33 (61%)	21 (78%)	12 (44%)	**0.012**
Ascites	40 (74%)	22 (81%)	18 (67%)	0.21
Diuretics	40 (74%)	23 (85%)	17 (63%)	0.062
History of LVP	29 (54%)	16 (59%)	13 (48%)	0.41
History of SBP	5 (9%)	2 (7%)	3 (11%)	0.64
Total bilirubin	1.7 (1.1–2.6)	1.7 (1.1–2.6)	1.6 (1.1–2.8)	0.76
ALT	26 (20–39)	23 (19–34)	30 (20–51)	0.18
AST	43 (30–58)	40 (29–53)	46 (36–66)	0.19
ALP	112 (96–155)	112 (106–155)	111 (82–150)	0.47
Albumin	3.4 (3.0–3.7)	3.3 (2.8–3.6)	3.5 (3.2–3.9)	0.058
Hemoglobin	12 (11–14)	11 (10–12)	13 (12–14)	**0.002**
Platelets	90 (64–123)	82 (60–123)	91 (66–123)	0.97
INR	1.3 (1.2–1.5)	1.3 (1.2–1.4)	1.4 (1.2–1.5)	0.76
Creatinine	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	0.41
Sodium	137 (133–139)	137 (131–140)	137 (133–139)	0.84
MELD-Na	14 (10–18)	14 (10–18)	15 (10–17)	0.98
Child-Turcotte-Pugh	8 (8–10)	9 (9–10)	8 (7–10)	0.083
BMI	29.2 (6.2)	28.6 (6.6)	29.9 (5.8)	0.42
Obese	19 (35%)	7 (26%)	12 (44%)	0.15
Smoking	3 (6%)	1 (4%)	2 (7%)	0.75
Family history of CAD	25 (46%)	13 (48%)	12 (44%)	0.20
CAD	3 (6%)	2 (7%)	1 (4%)	0.55
Dyslipidemia	17 (31%)	10 (37%)	7 (26%)	0.37
Diabetes mellitus	26 (48%)	16 (59%)	10 (37%)	0.10
Hypertension	27 (50%)	13 (48%)	14 (52%)	0.79
Atrial fibrillation	1 (2%)	1 (4%)	0 (0%)	0.31
CKD	2 (4%)	1 (4%)	1 (4%)	0.60
COPD	2 (4%)	1 (4%)	1 (4%)	1.00
LFI	3.4 (0.8)	4.0 (0.6)	2.8 (0.7)	**<0.001**
6MWT	363.7 (134.4)	266.0 (106.5)	457.5 (80.9)	**<0.001**
GST	1.1 (0.3)	0.9 (0.2)	1.3 (0.3)	**<0.001**

Data are presented as mean (SD) or median (IQR) for continuous measures and n (%) for categorical measures.

ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GST, gait speed test; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; LFI, liver frailty index; IQR, interquartile range; INR, international normalized ratio; LVP, large volume paracentesis; MELD, Model for End-Stage Liver Disease - Sodium; 6MWT, 6-min walk test; SBP, systolic blood pressure.Bolded results highlight statistically significant differences between groups.

in **Figure S1** (**SDC,** http://links.lww.com/TXD/A717). A sensitivity analysis using an LFI threshold of 4.2 for frailty did not change results (data not shown). Although VO_{2peak} weakly correlated with the Child-Turcotte-Pugh score (ρ = –0.27; P = 0.04), it did not correlate with MELD-Na (ρ = –0.14; P = 0.29).

When divided among the 6MWT cohorts, patients in the reduced 6MWT cohort had significantly shorter duration of CPX (7 ± 2 versus 11 ± 3 min; $P < 0.001$) and maintained markedly lower workloads compared with patients in the higher 6MWT cohort (68 [56–84] versus 109 [93–132] watts; $P < 0.001$; Table 2). Patients in the reduced 6MWT cohort also demonstrated shorter time to AT (5 ± 2 versus 7 ± 3 min; $P < 0.001$), lower AT (10.0 [8.1–11.3] versus 11.6 [8.7–15.3] mL/kg/min; $P = 0.010$), and lower VO_{2peak} overall compared with the higher performing 6MWT cohort (11.8 [10.6–13.0] versus 17.3 [14.5–20.6] mL/kg/min; $P < 0.001$). Additionally, significant differences in CPX hemodynamics were identified at the time of VO_{2peak} between the 2 6MWT cohorts. Specifically, the reduced 6MWT cohort had lower HR at VO_{2peak} (109 [97–127] versus 132 [122–140] bpm; $P < 0.001$) and lower respiratory rate at VO_{2peak} (31 [26–35] versus 36 [31–43] rpm; $P = 0.016$). A significantly lower HR drop (from maximum) was observed at 3 min postexercise in the reduced 6MWT cohort (15.5 [11.0–25.0] versus 35.5 [28.0–46.0]), denoting a prolonged recovery phase. Chronotropic incompetence, based on a calculated chronotropic index from CPX HR reserve, was observed in 87% of patients, with no differences between the 6MWT cohorts ($P = 0.36$).

Cardiac Risk Assessment

All participants completed 2-dimensional transthoracic echocardiography, which was negative for systolic dysfunction or clinically significant valvular heart disease. Two participants had a right ventricular systolic pressure >40 mm Hg, but their right heart catheterization failed to demonstrate pulmonary arterial hypertension.

Among the total cohort, 41 participants also completed standard-of-care DSE per purposes of transplant evaluation. There were 7 participants (18%) who had nondiagnostic DSE, which contrasted with only 2 (4%) of nondiagnostic CPX results ($P = 0.058$). All cases with nondiagnostic DSE underwent nuclear medicine myocardial perfusion imaging or coronary angiography to rule out ischemic or obstructive CAD. Notably, there were demographic or clinically meaningful differences between the 41 participants who underwent DSE and the 13 who did not (**Table S1, SDC,** http://links.lww.com/TXD/A717).

For all 54 participants who completed CPX, none developed ischemic changes on ECG or onset of angina during CPX to suggest clinically significant CAD. The double product was numerically higher in CPX than in DSE but significantly higher for participants in the upper 6MWT cohort (Figure 3).

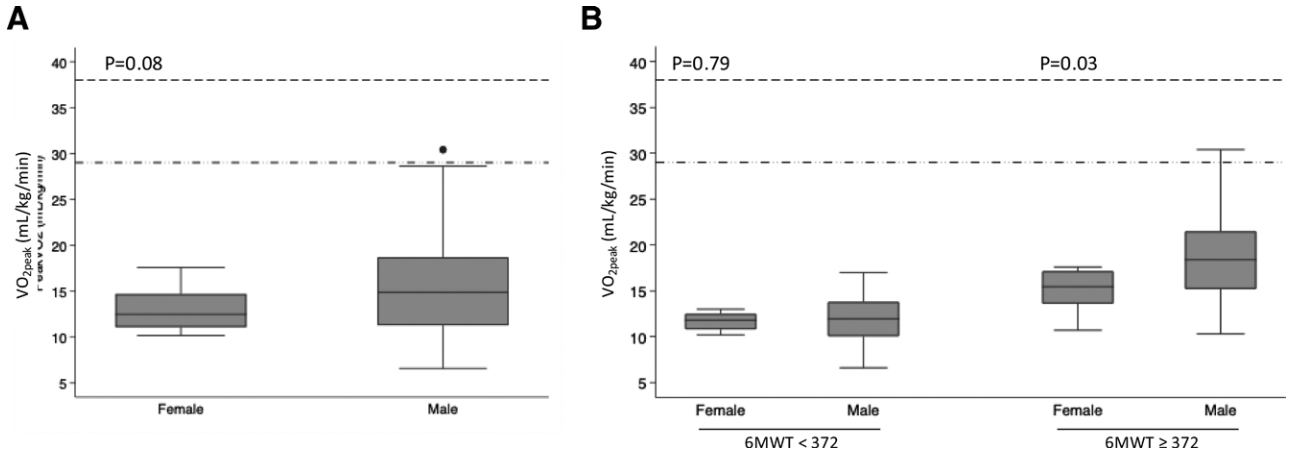

FIGURE 1. Cardiorespiratory fitness (VO_{2peak}) according to sex and the 6MWT cohort stratification. A, The VO_{2peak} shows a nonsignificant trend for lower values in women (12.5 [11.5–14.4] mL/kg/min) compared with men (14.9 [13.8–17.2] mL/kg/min). B, The cohort splits by upper and lower 6MWT cohorts, demonstrating that the difference between women and men is driven by the upper cohort with no difference in VO_{2peak} for the lower 6MWT cohort. For reference, VO_{2peak} expected values are 38 ± 8 mL/kg/min for men and 29 ± 7 mL/kg/min for women. 6MWT, 6-min walk test; VO_{2peak}, peak oxygen consumption.

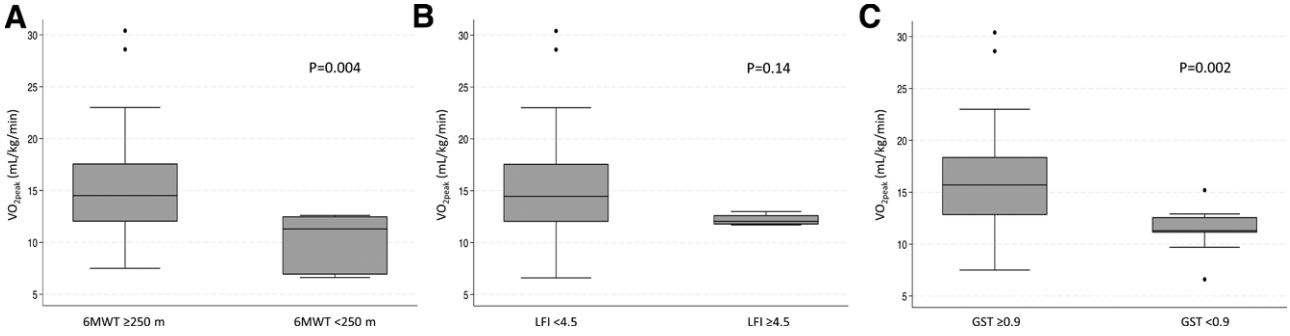

FIGURE 2. Cardiorespiratory fitness (VO_{2peak}) according to physical function (frailty) tests. Participants with a physical decline or frailty had a significantly lower VO_{2peak} when assessed with the 6MWT (A) or with the GST (C), but not when frailty was assessed with the LFI (B). Standard cutoff values were used to identify physical decline or frailty, as follows: 6MWT <250 m, LFI ≥4.5, and GST <0.9 m/s. For reference, VO_{2peak} expected values are 38 ± 8 mL/kg/min for men and 29 ± 7 mL/kg/min for women. GST, gait speed test; LFI, liver frailty index; 6MWT, 6-min walk test; VO_{2peak}, peak oxygen consumption.

TABLE 2.

Cardiopulmonary exercise testing per 6MWT cohorts

	Total (N = 54)	6MWT <372 (N = 27)	6MWT ≥372 (N = 27)	*P*
Workload, W	86 (65–110)	68 (56–84)	109 (93–132)	**<0.001**
Maximum Borg PE	18 (17–19)	17 (16–18)	18 (17–19)	**0.019**
Total CPX time, min	9 (3)	7 (2)	11 (3)	**<0.001**
Time to AT, min	6 (3)	5 (2)	7 (3)	**<0.001**
Resting HR, bpm	73 (64–81)	75.0 (67–84)	73 (62–77)	0.090
HR at VO_{2peak}, bpm	126 (107–135)	109 (97–127)	132 (122–140)	**<0.001**
HR reserve	0.59 (0.40–0.74)	0.39 (0.29–0.60)	0.67 (0.58–0.75)	**<0.001**
Resting O_2Sat, %	97 (95–99)	97 (95–100)	97 (94–99)	0.52
O_2Sat at VO_{2peak}, %	96 (93–98)	96 (93–98)	96 (93–98)	0.75
Resting RR, rpm	16 (13–19)	15 (13–19)	16 (14–19)	0.53
RR at VO_{2peak}, rpm	33 (28–39)	31 (26–35)	36 (31–43)	**0.016**
MAP rest	86.7 (81.3–92.7)	86.0 (79.3–88.0)	88.0 (83.3–94.7)	0.18
VO_{2peak}, mL/kg/min	14.1 (11.3–17.3)	11.8 (10.6–13.0)	17.3 (14.5–20.6)	**<0.001**
VO_{2peak} <60% predicted	29 (54%)	20 (74%)	9 (27%)	**0.003**
AT, mL/kg/min	10.2 (8.6–12.5)	10.0 (8.1–11.3)	11.6 (8.7–15.3)	**0.010**
RER at VO_{2peak}	1.2 (1.1–1.3)	1.1 (1.0–1.3)	1.2 (1.2–1.3)	**0.011**
VE at VO_{2peak}	57.6 ± 16.5	44.1 ± 11.3	68.1 ± 16.1	**<0.001**
VE/VCO_2 at VO_{2peak}	37.5 (32.1–44.3)	38.1 (33.7–45.3)	37.2 (31.9–40.5)	0.10
3-min HR recovery	27.0 (16.5–37.0)	15.5 (11.0–25.0)	35.5 (28.0–46.0)	**<0.001**
Breathing reserve	0.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.2	0.37

Data are presented as mean (SD) or median (IQR) for continuous measures.

AT, anaerobic threshold; CPX, cardiorespiratory exercise testing; HR, heart rate; IQR, interquartile range; MAP, mean arterial pressure; O2Sat, oxygen saturation; RER, respiratory exchange ratio; RR, respiratory rate; VE, minute ventilation; VE/VCO2, ventilatory efficiency; VO_{2peak}, peak oxygen consumption. Bolded results highlight statistically significant differences between groups.

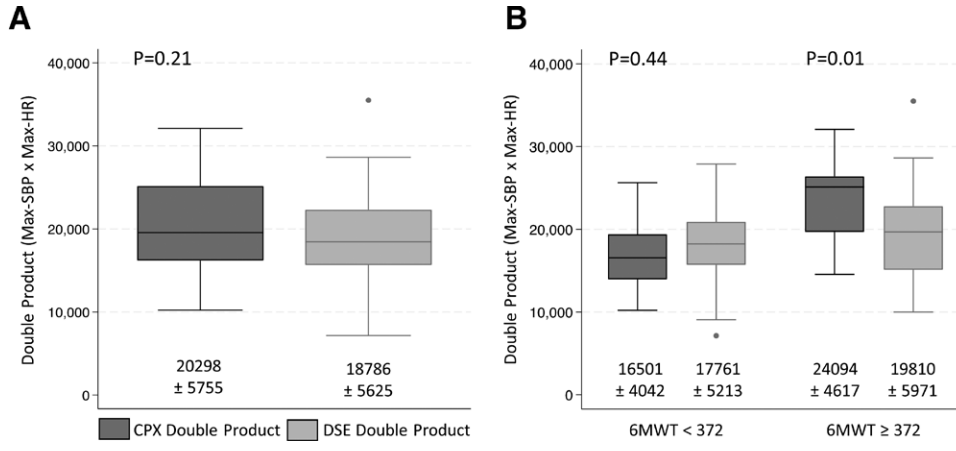

FIGURE 3. Comparison between double product from CPX and DSE. A, The comparison for all patients. B, The comparison according to the physical function cohorts. Although no differences were identified for the whole cohort (despite the elimination of the 1 outlier [*P* = 0.13]), the upper 6MWT cohort with more preserved physical conditioning showed a higher double product for CPX when compared with DSE. CPX, cardiorespiratory exercise testing; DSE, dobutamine stress echocardiogram; HR, heart rate; SBP, systolic blood pressure; 6MWT, 6-min walk test.

On average, a higher rate of double product of ≥25 000 was observed in CPX compared with DSE (32% versus 11%; *P* = 0.020). We then compared maximum HR and blood pressure responses for both CPX and DSE, finding that the former was higher in DSE (138 ± 11 versus 122 ± 19 bpm; *P* < 0.001), whereas the latter was higher in CPX (systolic: 166 ± 28 versus 135 ± 36 mm Hg; *P* < 0.001).

Pulmonary Function Assessment

All patients in the cohort completed resting PFT immediately before CPX, although data were only captured in 43 patients (Table 3). Median FEV_1/FVC for the cohort was 81% (69–86), with no significant differences in FVC, FEV_1, or FEV_1/FVC between the 6MWT cohorts. **Figure S2 (SDC,** http://links.lww.com/TXD/A717) shows results for expiratory flow limitation.

Clinical Outcomes

Among the total cohort, 7 patients (13%) were delisted and 20 (37%) underwent LT. Reasons for delisting included acute clinical deterioration followed by patient death (N = 4; 57%), pursuit of transplant at a different center (N = 1; 14%), relapse of substance use (N = 1; 14%), and transplant contraindicated (N = 1; 14%). One patient died after LT from aspiration on postoperative day 5. VO_{2peak} showed a nonsignificant trend for lower CRF among the 5 participants who died either before LT or during the perioperative period (11.3 ± 3.3 mL/kg/min)

TABLE 3.

Baseline pulmonary function tests per 6MWT cohorts

	Total (N = 43)	6MWT <372 (N = 17)	6MWT ≥372 (N = 23)	*P*
FVC, L	3.31 (2.5–3.8)	2.8 (2.5–3.5)	3.4 (2.8–3.9)	0.15
FEV_1, L	2.35 (2.0–3.0)	2.1 (2.0–2.6)	2.5 (1.9–3.1)	0.14
FEV_1/FVC, %	81 (69–86)	83 (77–86)	79 (67–85)	0.87

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; 6MWT, 6-min walk test.

when compared with the rest of the cohort (15.1 ± 4.8 mL/kg/min; $P = 0.08$); however, no such difference could be observed for 6MWT (367 ± 127 versus 328 ± 203 m; $P = 0.54$), LFI (3.3 ± 0.8 versus 3.4 ± 0.6; $P = 0.94$), or GST (0.99 ± 0.24 versus 1.13 ± 0.24 m/s; $P = 0.24$). No MACE occurred within the first 30 d posttransplant.

DISCUSSION

As the present study demonstrates, CPX is a single noninvasive test that was well tolerated in our cohort of LT candidates with decompensated cirrhosis, including a large proportion of patients with refractory ascites and Child-Turcotte-Pugh C. CPX is uniquely capable of providing a wealth of clinically valuable data to transplant providers in a markedly efficient manner. Although CPX is previously best known in this population for providing prognostic value from VO_{2peak} pertaining to pre- and post-LT outcomes,[7,20,31,32] our study provides novel data showing that CPX can also inform appropriate recipient selection. Furthermore, our study provides a direct comparison of CPX-derived metrics of physiologic reserve to other physical function assessment tools (LFI, 6MWT, and GST) for which there is a paucity of data in the hepatology literature.

The study demonstrated the utility of CPX as an effective screening method for advanced cardiopulmonary disease among LT candidates. We prospectively demonstrated that CPX was at least comparable with DSE in screening for clinically significant ischemia through continuous ECG monitoring. CPX showed a tendency for less nondiagnostic or indeterminate results than DSE. Additionally, CPX-generated cardiac hemodynamics during stress produced a higher double product, particularly in patients with preserved physical function (ie, 6MWT ≥372 m). The double product, also known as the maximum rate pressure product, has a very high sensitivity to rule out MACE when ≥25 000, even in patients with nondiagnostic DSE, and such a degree of hemodynamic stress was more frequently achieved with CPX versus DSE. Moreover, the accuracy of the double product for prognosticating incidental MACE outperforms that of the age-predicted maximum HR.[26]

For the identification of CAD-related manifestations, exercise-induced cardiac stress is superior to its pharmacologically induced counterpart, and it is also safer and better tolerated.[33] Although such comparison has not been previously reported in LT candidates, patients with decompensated cirrhosis show suboptimal cardiac stress induction with dobutamine due to their characteristic chronotropic incompetence and systemic vasodilatation. Considering prior experience,[34,35] our study improved exercise stress performance and tolerance by using a semirecumbent cyclo-ergometer, which was also key to eliminating a potential risk for falls in frail participants. Thus, when considering CPX for LT candidates, a semirecumbent cyclo-ergometer is recommended. However, because stress echocardiography increases the sensitivity for the identification of CAD, it would be ideal to combine CPX with baseline and stress echocardiography.[36] In fact, coupling CPX with echocardiography would enable comprehensive screening for all relevant cardiac conditions directly contributing to substantially increased perioperative risk and post-LT MACE (ie, ischemia, ventricular dysfunction, advanced valvulopathy, portopulmonary vascular disorders), along with CRF and dynamic systemic and pulmonary physiologic responses.

We further evaluated for cardiac risk through CPX-generated HR reserve, finding an almost universal prevalence of chronotropic incompetence (87%) despite beta-blockers being held before testing. Chronotropic incompetence is a cardiac metric that accounts for the effects of age, CRF, and resting HR and is associated with the prediction of cardiac and all-cause mortality.[27,37] Because exercise-induced rise in HR is a major contributor to the VO_{2peak}, chronotropic incompetence is likely the main explanation for the low VO_{2peak} observed in our cohort. However, sarcopenia, a highly prevalent condition and cause of morbidity and mortality, is tightly linked to the VO_{2peak} in end-stage liver disease. Skeletal muscle is the main organ responsible for oxygen extraction kinetics during exercise, and as such, sarcopenia could be a major culprit behind a reduced arteriovenous oxygen difference and an additional explanation for a low VO_{2peak} in LT candidates.[22,38] This finding promotes the importance of identifying sarcopenia during LT evaluation and having nutrition and exercise programs to mitigate associated risks derived from sarcopenic-associated reduced physical function.[22,39,40] Novel studies assessing CPX-generated hemodynamics and skeletal muscle oxygen extraction are warranted to enhance our understanding of exercise tolerance, dyspnea on exertion, and cirrhotic cardiomyopathy in LT candidates.

Expectedly, the VO_{2peak} strongly correlated with all metrics of functional decline or frailty. Frailty, a construct of decreased physiologic reserve, is highly prevalent in patients with advanced liver disease and is strongly associated with increased morbidity and mortality before and after LT.[41-43] As such, frailty assessment has become an integral component of LT candidate evaluation. The 6MWT is a submaximal exercise stress test that is highly practical given the overall low barriers to use and it has been studied as a CPX surrogate for perioperative risk stratification.[44] We found CPX markers of reduced exercise tolerance in the lower 6MWT cohort, including a shorter time to reach AT and lower VO_2 at AT. These findings speak of less efficient anaerobic systems that can result in premature metabolic acidosis, and such low cardiorespiratory fitness markers (including VO_{2peak}) are associated with increased post-LT mortality, as well as post-LT complications such as longer overall/ICU hospital stay.[4,45,46] Not surprisingly, participants who did not reach LT had the lowest VO_{2peak} at 11 mL/kg/min.

Participants in the upper 6MWT cohort were not exempt from a low CRF phenotype per CPX despite acceptable 6MWT distances, low MELD-Na, and absence of cardiopulmonary comorbidities. To give some context, the VO_{2peak} identified in our cohort is similar to that reported for heart transplant candidates (13 mL/kg/min) and less than half of that expected for healthy volunteers of the same sex and similar age range (29 mL/kg/min for women and 38 mL/kg/min for men).[47,48] Even when eliminating the most deconditioned patients (ie, 6MWT <250 M), the average VO_{2peak} for

the whole cohort continued to be low at 16 ± 5 mL/kg/min because values ≤17.6 mL/kg/min are associated with poor short-term waitlist survival in LT candidates.[31] Nonfrail participants per LFI or GST also showed a low VO_{2peak} at ≈15 mL/kg/min, providing proof of concept that clinically meaningful CRF derangement precedes the development of frailty. Such low VO_{2peak} is below the threshold required for full and independent living and thus could be used for timely referral to prehabilitation.[49-51]

The importance of efficiency in LT evaluation cannot be overemphasized, as this can impact patient mortality. In this regard, CPX constitutes an efficient test that is able to provide ischemic risk estimation, a dynamic assessment of cardiopulmonary function, and a surrogate of physical decline to determine the need for prehabilitation. When linked to echocardiography (baseline and stress), CPX with echocardiography has the potential to provide the most comprehensive assessments in one test, making it particularly attractive to expedite LT evaluation (Figure 4), a time-sensitive endeavor.[14] The pulmonary assessment in our cohort was normal and in agreement with the absence of a pathological source of severe exercise limitation, including advanced COPD. Unfortunately, only 1 center was able to calculate the expiratory flow limitation, which is an important metric of exercise intolerance that further characterizes breathing mechanics and helps disclose subclinical chronic pulmonary disease.[25] Expiratory flow limitation can be a cause of dyspnea even when resting pulmonary function tests are normal, and because it is dictated by an individual's operational lung volumes, it can be improved with training and coaching. As such, prehabilitation addressing the expiratory flow limitation is an attractive way to prevent immediate post-LT respiratory complications, including hypostatic pneumonias.[52]

Our study has a few limitations. First, the cohort was underpowered with respect to the association of CPX metrics and clinical outcomes, especially given that post-LT outcomes were limited to the first 30 d. Second, recruitment occurred throughout the peaks of the COVID pandemic (July 2020 to February 2022), which generated multiple challenges and could have potentially introduced selection bias, resulting in fewer frail patients than expected for our LT centers.[53,54] Containment strategies at our medical centers promoted telemedicine, limited access to patient's caregivers, and prolonged waiting time for CPX due to its potential for aerosolization, thus dissuading many frail patients from consenting. Third, anemia (which can affect VO_{2peak}) was more prevalent in the reduced 6MWT cohort. However, only 4 participants showed anemia of sufficient severity to impact VO_{2peak} (<9.5 g/dL), and they were evenly split between the lower and upper 6MWT cohorts.[55] Fourth, although the median MELD-Na in our cohort was 14 and fell in the lower range reported in similar publications at the time of LT evaluation (ie, 14–18),[4,56,57] it fell within the range described in our evaluations/waitlisted population.[53,58] Moreover, almost all of our participants had decompensated cirrhosis, were Child-Turcotte-Pugh classes B/C, and half of them were undergoing repeated large-volume paracentesis, corresponding to a largely underrepresented profile on prior CPX studies. Finally, we recognize that CPX has limited availability to larger academic medical centers and is dependent on the presence of specially trained staff, conditions affecting external validation of our results.

The use of CPX in LT candidates can provide an array of clinically valuable data to transplant providers. Our study demonstrates the effective use of CPX to screen for advanced cardiopulmonary disease and promote appropriate recipient selection. CPX can also help elucidate physiologic causes and metrics of reduced CRF, which are of high value in this patient population where frailty is strongly associated with poorer clinical outcomes. CPX allows for the efficient capture of such comprehensive data that can benefit LT candidate waitlist and

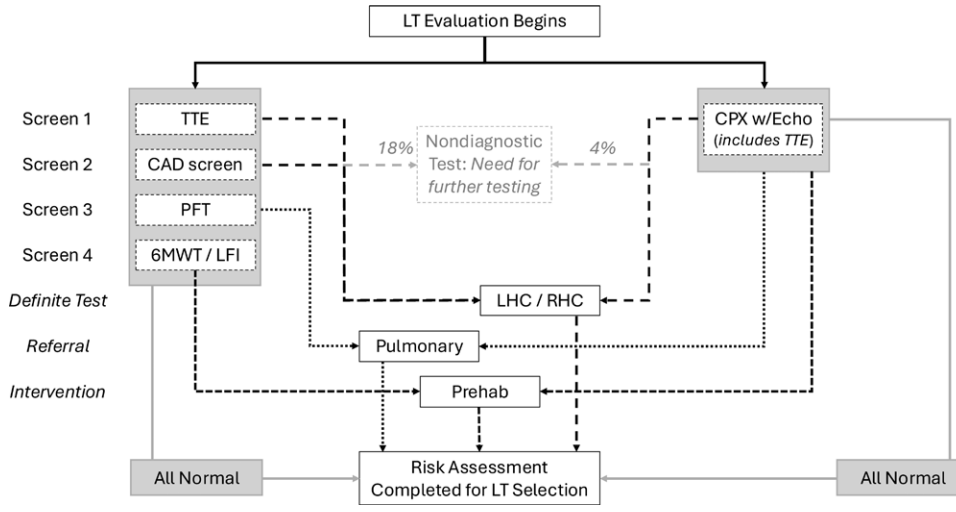

FIGURE 4. Potential role for CPX during LT evaluation. Based on our findings and existing literature, we propose a new paradigm for LT evaluation incorporating the invaluable data yielded by CPX. To the left is the current model where four assessments are needed for cardiac anatomy and heart failure (screen 1) with a TTE, CAD risk estimation (screen 2) with any form of cardiac stress testing or cardiac computed tomography angiogram, pulmonary disease (screen 3) with PFT, and physical fitness/function or physiologic reserve (screen 4) with the 6MWT or LFI. On the right side, CPX—particularly when linked to on-site echocardiography—can provide more comprehensive information while simplifying the clinical workflow to 1 screening test, from which patients with a normal CPX can be sent directly to LT. Abnormal results from either side of screening would be dealt with more definite testing (eg, LHC/RHC), consultation referral (such as pulmonary), or an intervention (eg, prehabilitation). CAD, coronary artery disease; CPX, cardiopulmonary exercise testing; LFI, liver frailty index; LHC, left heart catheterization; LT, liver transplant; PFT, pulmonary function test; RHC, right heart catheterization; 6MWT, 6-min walk test; TTE, transthoracic echocardiogram.

post-LT survival.[8,59] Our study provides the foundation to further study the role that CPX can play toward simplifying and making LT evaluation more efficient and to better determine the prognostic utility of its metrics in the context of prehabilitation and post-LT outcomes.

ACKNOWLEDGMENTS

The authors thank Rachel K. Grubbs and Steven J. Anthony for their technical support.

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