Multimodal Inpatient Prehabilitation Prior to Heart or Lung Transplantation in a Latin American Transplant Reference Center

Franco Appiani[a*], Belen Abara[a], Ivan Ramirez[a], Christian Andrade[a], Joel Melo[a], Fernando Barra[a], Fernando Javier Verdugo[b], Victor Rossel[a], Jongsung Lim[a], Erika Donoso[a], Urania Arrué[a], and Maria Paz Riquelme[a]

[a]Cardiothoracic Transplant Program, Instituto Nacional del Tórax, Santiago, Chile; and [b]Hospital del Salvador, Santiago, Chile

ABSTRACT

Introduction. Whether the implementation of a multimodal prehabilitation program is effective and safe for high-risk heart or lung transplantation candidates, whose condition prevents hospital discharge, is unclear.

Methods. We conducted a retrospective study at a cardiothoracic transplant center in Chile. Two cohorts of hospitalized patients listed for heart or lung transplant were studied: the first underwent traditional (historical) and nonstructured prehabilitation, and the second underwent protocol-driven multimodal prehabilitation (MP). Adverse events and preoperative functional changes in the MP group were documented, as well as comparative postoperative outcomes between both cohorts.

Results. Between 2018 and 2023, 24 transplant recipients were analyzed. During the MP phase, significant improvement was observed in Medical Research Council scale (52.0 ± 7 to 58.7 ± 3; $P = .042$), sit-to-stand test (7.1 ± 7 to 15.9 ± 6; $P = .018$), and euthymic state (from 4 to 10 patients; P .036), without reported adverse events. Postoperatively, MP group demonstrated faster standing (1.9 ± 0.7 vs 1.3 ± 0.5 days; $P = .05$) and sitting times (2.0 ± 0.7 vs 1.2 ± 0.5 days; $P = .007$), with more early extubations (3 vs 11; $P = .003$) in comparison to the historical prehabilitation cohort.

Conclusion. In this small retrospective study, MP in hospitalized patients awaiting heart or lung transplantation appears to be safe and associated with improvements in pre- and postoperative outcomes.

SOLID organ transplantation (SOT) is the treatment of choice for patients diagnosed with end-stage organ failure. Several factors contribute to a greater likelihood of experiencing complications before, during, and after surgery, including older age, comorbidities, and frailty [1]. From this perspective, it is necessary for SOT candidates to be in an optimal state of health prior to transplantation to increase their resilience and mitigate postoperative complications.

Prehabilitation aims to optimize an individual's physiological response to a major stressor. This concept involves patient preparation through physical training, psychological support, and nutritional measures undertaken to improve their physical and mental well-being before major surgery [2,3].

This "fit to fight" concept has been well established in patients undergoing oncologic and abdominal surgery [4–6]. However, it has also been increasingly recognized as a strategy for improving perioperative outcomes in SOT [1]. Specifically, in candidates for heart and lung transplantation, participation in outpatient prehabilitation programs has proven effective in enhancing muscle strength, reducing frailty, and improving quality of life [3,5,7]. The feasibility of prehabilitation has been reported in critically ill patients, specifically those requiring mechanical circulatory support [4]. However, there is also a subset of patients whose conditions, while not critically severe, prevent hospital discharge. For this particular group, evidence on the efficacy and safety of implementing structured prehabilitation programs is notably lacking [8].

This research did not require external funding.

*Address correspondence to Franco Appiani, Jose Manuel Infante 717, Providencia, Santiago 7501117, Chile. E-mail: fappiani@gmail.com

0041-1345/20
https://doi.org/10.1016/j.transproceed.2024.11.034

Heart and lung transplants have been performed at our center since 2009. Historically, prehabilitation for patients who cannot be discharged before transplantation has occurred in isolated beds and has not been standardized. This approach has primarily emphasized physical conditioning, often neglecting nutritional and psychological aspects. During the SARS-CoV-2 pandemic, an area consisting of four beds was designated to isolate and protect transplant candidates. Coincidentally, the increase in human resources allowed for the intensification of prehabilitation for these patients and the addition of nutritional and psychological components in a protocolized manner.

The objective of this investigation was to describe our experience regarding the efficacy and safety of implementing a multimodal prehabilitation (MP) program in high-risk candidates for heart and lung transplantation whose condition prevents hospital discharge.

METHODS

This observational, retrospective study was conducted at a heart and lung transplant reference center in Chile. This study aimed to analyze the outcomes of two patient cohorts: those subjected to MP and those undergoing standard prehabilitation (historical group). The inclusion criteria for the study were as follows: Candidates for heart or lung transplantation who 1) were deemed by the transplant team to require hospitalization until the time of transplantation due to conditions such as respiratory failure or significant respiratory effort necessitating ventilatory support, or for heart transplant candidates, those categorized as INTERMACS 3 or presenting with incessant ventricular arrhythmias, and 2) had participated in a prehabilitation program for a minimum of 2 weeks prior to transplantation. The study excluded patients with diagnoses necessitating distinct prehabilitation approaches, like cystic fibrosis, and those in critical condition (eg, requiring invasive mechanical ventilation prior to transplantation or mechanical circulatory/respiratory support before or after transplantation).

MP was defined as a protocolized program incorporating physical, nutritional, and psychological components within a designated area for awaiting transplantation. The specifics of each domain of the MP are detailed in Table 1. Patients under the MP protocol were recruited from 2020 to 2023.

As a comparative group, a retrospective cohort of patients who underwent transplantation before the pandemic (between 2018 and 2020) and who were not subjected to MP (historical prehabilitation or HP) was included. Demographic variables were recorded before transplantation in both groups.

For the MP group, changes in functional variables before transplantation were recorded, including the Functional Status Score in the Intensive Care Unit (FSS-ICU), Sit-to-Stand, Medical Research Council scale, calf perimeter (CP), body mass index (BMI), weekly nitrogen balance (NB), and prevalence of depression, anxiety symptoms, or euthymia in the psychologist interviews. Adverse events related to the prehabilitation process were documented during this period.

Postoperative variables were recorded for both the MP and HP groups, including infections, acute kidney injury, early extubation (within the first 24 hours posttransplant), use of noninvasive ventilation or high-flow nasal cannula postoperatively, use of vasopressors, delirium, time to sit and stand, time in the intensive care unit, and total hospitalization time. All patients underwent postoperative rehabilitation following local guidelines (Fig 1).

Quantitative variables are expressed as mean ± standard deviation or median (quartile 1-3), qualitative variables as absolute number. Intergroup quantitative variables were compared through the Mann−Whitney *U* test. Intragroup comparisons were performed through Wilcoxon test. Prehabilitation duration, postoperative ICU length of stay, and hospital length of stay were compared through median analyses. Qualitative comparisons were performed using Fisher's exact test. Statistical analyses were performed on IBM SPSS 20.0. A P value $\leq .05$ was considered statistically significant. The protocol received approval from the ethics committee of the Servicio de Salud Metropolitano Oriente in Santiago, Chile (SSMOriente090424).

RESULTS

From November 2018 to June 2023, a total of 47 heart and lung transplants were performed, 24 of which met the inclusion criteria (12 in the MP group and 12 in the PH group). The average waiting time prior to transplantation (prehabilitation period) was 54 days. The mean age was 48.5 years, with the majority being male (79%). Diabetic patients were significantly more prevalent in the HP group (5 vs 0 patients; $P = .03$). Sixty-two percent of patients underwent lung transplantation. Among the variables specific to heart transplantation, 88% had a diagnosis of dilated cardiomyopathy, the average left ventricle ejection fraction was 18%, milrinone was the inotropic drug of choice at an average dose of 0.41 mcg/kg/min, and the average cold ischemia time was 166 minutes. Regarding lung transplantation, 80% of patients had been diagnosed with idiopathic pulmonary fibrosis. The average lung allocation score was 59 points. The patients had an average PaCO2 of 50.5 mm Hg and a systolic pulmonary artery pressure by echocardiogram of 61.3 mm Hg, with average ischemia times for the right and left lungs of 272 and 356 minutes, respectively. These clinical and demographic data did not show significant differences across the cohorts (Table 2).

Results in the MP group during the preoperative period: Data related to the physical, nutritional, and psychological MP domains were recorded, and their changes before transplantation were compared. Improvements were observed in sit-to-stand (7.1 ± 6.8 to 15.9 ± 5.8; $P = .018$), Medical Research Council-Sum score (52.0 ± 7.3 to 58.7 ± 3.4; P .042), and euthymia (4 vs 10 patients; $P = .036$); trends toward improvement were observed in FSS-ICU (26.3 ± 8.2 to 34.0 ± 2.6; P .059) and anxiety symptoms reported by patients (6 vs 1; P .067). No significant changes in depression were observed (2 vs 1; $P = 1.000$). No significant changes were observed in CP, BMI, or NB during the preoperative period. There were no recorded major events that hindered the continuation of the program. All included patients completed the scheduled prehabilitation sessions (Fig 2).

Table 1. Description of the Protocol Used in the Multimodal Prehabilitation (MP) Group Across Its Three Domains

Domain	Intervention	Frequency	Description
Physical	6-Minute Walk Test Test	Admission day and every 6-8 wk	Initial assessment and follow-up test of exercise tolerance. In patients able to ambulate, the time taken to walk and the distance covered over a 6-min period within a 30-meter distance are assessed. Dyspnea is recorded using the Borg scale, along with oxygen saturation, heart rate, and blood pressure. Training sessions are conducted with a dosage equivalent to 50%-60% of the Borg level achieved in this test.
	Sit-to-stand test	Admission day and every 2-4 wk	Initial assessment and follow-up test of exercise tolerance. This test measures the number of times a patient can sit and stand within 1 min. It assesses functional improvement in terms of exercise tolerance and allows for training dosage at 50%-60% of the achieved Borg scale.
	MRC (Medical Research Council)	Admission day and every 2-4 wk	Initial assessment and follow-up of muscle strength. This scale evaluates 6 separate movements, including 3 for the upper extremities and 3 for the lower extremities: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. The maximum score is 60 points (30 maximum points for each hemibody), and each muscle group is rated on a scale from 0 (muscular paralysis) to 5 (normal strength).
	Aerobic training session	3 sessions per week, interspersed with strength training sessions	Between 1 and 3 min of continuous loading at a constant speed (between 10 and 15 km/h) followed by 1-3 min of rest. This cycle is repeated for a total duration of 30-60 min. The load used is 50%-60% of the Borg obtained in the diagnostic test. Oxygen therapy is administered for StO2 > 90% (to avoid reflex vasoconstriction in patients with pulmonary hypertension). Exercise load is modulated based on the catabolic state. Depending on the weekly nitrogen balance—positive, neutral, or negative—the load is increased, maintained, or reduced, respectively.
	Upper extremity muscle strengthening	3 sessions per week	Each exercise targets a specific muscle group, with 3 sets of 6-15 repetitions based on Borg (between 3 and 5), heart rate (less than 120 bpm), and oxygen saturation (greater than 90%). Exercises include Pull (Unilateral Latissimus Dorsi, Unilateral Row), Push (Unilateral Pectoralis, Medial Deltoid), and Flexion and Extension of the elbow.
	Lower extremity muscle strengthening	3 weekly sessions that coincide with upper extremity strength training	Each exercise targets a specific muscle group, with 3 sets of 6-12 repetitions based on Borg (between 3 and 5), heart rate (less than 120 bpm), and oxygen saturation (greater than 90%). Exercises include Squats, Flexion and Extension of the knees, and Ankle Plantar Flexion. The load is adjusted based on the weekly Nitrogen Balance, and progress is assessed using the MRC score.
Nutritional	Nutritional assessment and management	Weekly nutritional assessment and daily monitoring	Includes the following components for evaluation: Nutritional diagnosis, Route of oral feeding, nasoenteral tube, or gastrostomy as needed; Energetic nutritional intake (35-40 kcal/kg/d in underweight and 12-15 kcal/kg/d in obesity); Protein intake based on pathology, training, and weekly nitrogen balance (usually 1.5-2 g/kg/d); Carbohydrates (40%-50% of the diet in 4-6 daily meals); Lipids (30%-35% of the diet); vitamins and trace elements as needed.
Psychological	Psychological Intervention	1-3 times per week	Psychological sessions or psychological support will always be conducted. Other interventions, either individually or collectively, will be carried out according to the patient's needs. These may include crisis interventions, problem-solving, psychoeducation, stress reduction techniques (stress management and relaxation techniques). The frequency of interventions will depend on the severity of symptoms. Additionally, they may receive group therapy and work with family members or caregivers.

Postoperative Results: Postoperative results were compared between the MP and HP groups, revealing a significant reduction in time to sit (2.0 ± 0.7 vs 1.2 ± 0.5 days; *P* .007) and a greater number of patients experienced early extubation (3 vs 11; *P* .002) in favor of the MP group, with a trend toward reducing Time to Stand (1.9 ± 0.7 vs 1.3 ± 0.5 days; *P* .05) and Infections (7 vs 2; *P* .089) in the MP group. No differences were observed in acute kidney injury, vasopressor need, delirium, postextubation noninvasive ventilation/high-flow nasal cannula, time in the intensive care unit, or hospitalization days (Table 3).

DISCUSSION

Prehabilitation prior to heart and lung transplantation has proven to be safe and effective in improving quality of life, functionality, and postoperative outcomes [1,3,9]. Currently, entry into ambulatory MP programs is recommended in international guidelines [3,10,11]. Transplant candidates whose condition prevents hospital discharge face elevated morbidity and mortality [10,12]. In this patient population, there is limited literature regarding the impact of prehabilitation programs [8]. Despite the small sample size in the present study, the

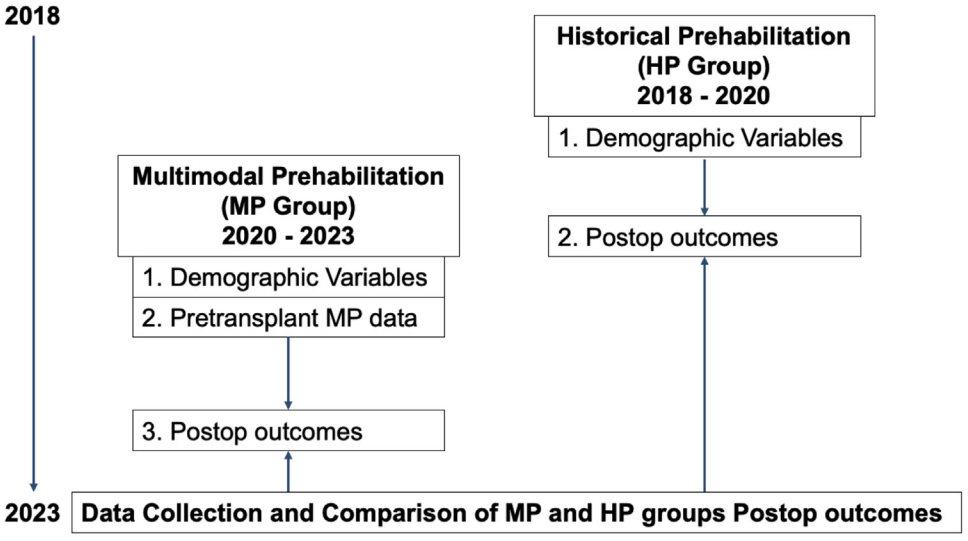

Fig 1. Data collection from MP and HP groups.

implementation of a protocolized MP program appeared to improve the preoperative functional parameters and postoperative outcomes without increasing the associated risk. In light of these results, several points are worth noting.

First, there are no international recommendations demonstrating the superiority of a particular protocol [11,13,14]. Our protocol was based on the experience and work formula of professionals in each area, serving as just one example among the many used in the literature [10].

Table 2. General Characteristics of the Studied Cohorts, Historical Prehabilitation (HP) Group and Multimodal Prehabilitation (MP) Group

Characteristics	HP (*n* = 12)	MP (*n* = 12)	*P*
Age—y	48 ± 12	49 ± 17	.67
Male sex—*n*	10	9	1.00
Comorbidity			
Hypertension—*n*	2	2	1.0
Diabetes—*n*	5	0	.03*
Dyslipidemia—*n*	0	1	1.00
Hypothyroidism—*n*	0	3	.21
Prehabilitation period (d)	50 (32-66)	52 (21-77)	1.00
Lung transplant group—*n*	9	6	.40
IPF—*n*	8	4	.52
LAS score	64 ± 17	60 ± 9	.68
PCO2 (mm Hg)	53 ± 10	61 ± 10	1.00
SPAP (mm Hg)	55 ± 17	57 ± 18	.66
Right Lung CIT (min)	268 ± 77	242 ± 80	.62
Left Lung CIT (min)	393 ± 73	368 ± 61	.62
Heart transplant group—*n*	3	6	.40
Dilated cardiomyopathy—*n*	3	5	.40
LVEF (%)	18 ± 2	18 ± 8	1.00
Milrinone dependent—*n*	3	5	.40
Milrinone dose (mcg/Kg/min)	0.45 ± 0.05	0.38 ± 0.13	1.00
CIT (min)	194 ± 61	166 ± 55	.38

Specific patient characteristics for lung transplant and heart transplant are provided. $P < .05$ is represented by (*).

CIT, cold ischemia time; IPF, idiopathic pulmonary fibrosis; LAS, lung allocation score; LVEF, left ventricular ejection fraction; PCO2, partial pressure of carbon dioxide; SPAP, systolic pulmonary artery pressure.

Second, demonstrating improvements in preoperative functional parameters is crucial for establishing a causal relationship between the intervention and improvements in postoperative variables. Throughout the training, we observed improvements in aerobic resistance and strength parameters, as well as improvements in psychological parameters. López-Baamonde et al [7] reported similar results in an outpatient pre−heart transplant group, with preoperative improvements in maximum oxygen consumption (VO2max 10.1-12.5 mL/kg/min, $P = .03$) and quality of life (MLHFQ score from 58 to 47 points, $P = .04$). Notably, the nutritional parameters, such as BMI, CP, and NB, remained unchanged. This may not necessarily be a negative outcome, considering that such patients maintain a highly catabolic metabolism, and subjecting them to increased physical exercise would be expected to significantly elevate catabolism (more negative NB) with greater clinical repercussions (more weight loss and lower CP) [15,16]. Perhaps the use of a protocol that incorporates the dosing of physical training and nutritional support according to the catabolic state allowed tolerance of the impact of prehabilitation without resulting in significant changes in these values.

Third, in the postoperative period, the reduction in mechanical ventilation time and the faster mobilization of patients observed in the MP group are similar to those reported by other authors and may reflect the effects of preoperative reconditioning [2,7]. Moreover, the observed trend toward a reduction in infections in the MP group is interesting; however, it should be studied in a larger cohort of patients and in a prospective manner. It is important to note that a higher number of diabetic patients were observed in the baseline demographic data of the HP group. While this could be considered a confounding variable, it is unlikely to have influenced the outcomes significantly,

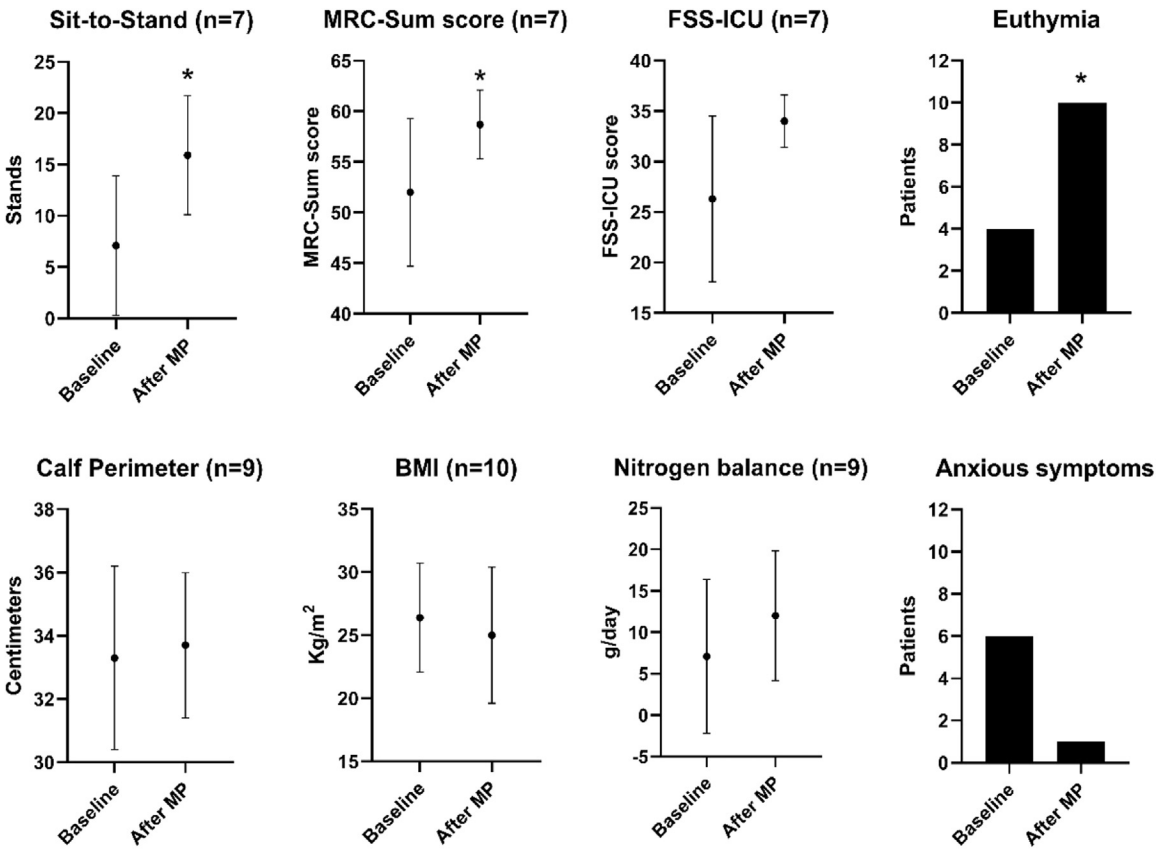

Fig 2. Evolution of preoperative functional parameters in the multimodal prehabilitation (MP) group. BMI, body mass index; FSS-ICU, Functional Status Score in the Intensive Care Unit; MRC, Medical Research Council scale. $P < .05$ is represented by (*).

as transplant candidates can only have uncomplicated diabetes, a condition that has not been shown to increase post-transplant complications [17].

Fourth, this study revealed that a greater proportion of patients achieved euthymia after receiving MP. Psychological interventions and follow-up have been reported to be effective in reducing anxiety and depression symptoms in patients before major surgery [9,10]. The use of screening methods (eg, Hospital Anxiety and Depression Scale), psychological support, group therapies, and mindfulness are strategies for addressing prehabilitation patients; however, there is limited evidence available for pretransplant patients [18,19]. Furthermore, although quality of life indices are frequently used as a metric to assess the effectiveness of psychological prehabilitation in outpatient settings, they have not been validated for in-hospital patients.

Table 3. Postoperative Outcomes According to the Studied Cohort, Historical Prehabilitation (HP) Group and Multimodal Prehabilitation (MP) Group

Postoperative Outcomes	HP ($n = 12$)	MP ($n = 12$)	P
Early extubation—*n*	3	11	.003*
Postextubation NIV/HFNC—*n*	3	4	1.00
Time to sit (d)	2.0 ± 0.7	1.2 ± 0.5	.007*
Time to stand (d)	1.9 ± 0.7	1.3 ± 0.5	.050
Vasopressor need (d)	1.4 ± 0.5	1.6 ± 0.8	.47
Infections—*n*	7	2	.08
Acute kidney injury—*n*	3	3	1.0
Delirium—*n*	1	1	1.0
ICU Length of stay (d)	11 (9-16)	13 (10-17)	1.0
Hospital Length of stay (d)	19 (12-21)	16 (13-18)	.684

$P < .05$ is represented by (*).
ICU, intensive care unit; NIV/HFNC, noninvasive ventilation/high-flow nasal cannula.

The limitations of this study include its retrospective design and a small sample size, which is characteristic of a low-frequency procedure and reflective of the reality in our country. Data entry for the historical prehabilitation group did not include preoperative functional parameters or minor complication events (eg, orthostatic hypotension). However, despite the severity of the condition, which includes patients with inotrope dependence, elevated lung allocation score scores, and pulmonary hypertension, there were no major complications that led to the discontinuation of the prehabilitation sessions. Last, the number of patients classified as frail was not analyzed because the diagnosis was not conducted using objective scoring systems and, therefore, would not be reliable data. Nevertheless, it is important to mention that frailty in other series has been described in 10% to 70% of lung transplant candidates and in one-third of cardiac transplant candidates, and it is associated with high postoperative morbidity and mortality. However, these patients could still benefit from a prehabilitation program [3,20,21].

Although the focus of this research was on evaluating prehabilitation, the advantages associated with a postoperative rehabilitation program are well known [22], and we believe that this component should consolidate the hospital trajectory for every transplanted patient. In our case, postoperative rehabilitation was provided in a standardized manner to all patients.

In conclusion, in this small retrospective study of high-risk, hospitalized patients awaiting lung or heart transplantation, the implementation of a protocolized MP program appears to be safe and correlated with improvements in pre- and postoperative parameters. Prospective studies are still needed to assess the effectiveness of such programs in similar populations.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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