Exercise limitations in pulmonary hypertension (PH) have a profound impact on the morbidity and mortality of patients with PH, for which various physiological systems are responsible. These exercise limitations are the result of a complex interaction between the cardiorespiratory and musculoskeletal systems. Considering these limitations and the ability of these dysfunctions to respond to exercise training, it was hypothesized that participation in exercise training would result in improvements in exercise capacity.

Exercise training in PH has gained popularity over the last two decades. Since the publication of the first randomized clinical trial by Mereles et al, there have been a growing number of published studies and on-going registered clinical trials. Recent systematic reviews and meta-analyses have shown demonstrable improvements in function after exercise training. However, many of the studies included in these reviews are limited by the generalizability of their findings and models of delivery. In addition, the use of a home-based model, which has been found to be equally effective as a supervised exercise program in cardiac rehabilitation, has not yet been studied extensively in PH. One study by Inagaki et al, which studied the effects of an unsupervised 12-week endurance and strength training program on eight patients with group IV PH, found a 33-m improvement in 6-min
walk distance (6MWD) along with improved quality of life (QoL). Lack of randomized trials with limited studies on heterogenous patients being studied creates the need for a more rigorous methodology with greater generalizability across various etiological groups of PH. This study was therefore aimed at assessing the effects of a 12-week, home-based exercise training program on functional capacity (i.e., 6MWD) and QoL in patients with PH.

2. Methodology

This was a prospective, nonblind, randomized clinical trial, which recruited patients with PH attending a tertiary care university teaching hospital between April 2012 and March 2016. Patients who were diagnosed to have PH (of either sex and any etiology and functional class), stable on medical therapy for three months, and having a tricuspid regurgitant velocity $>3.4\text{ m/s}$ with or without right ventricular dysfunction on transthoracic echocardiography were screened for inclusion. Patients with neuromuscular complications limiting rehabilitation, acute coronary events, and/or uncontrolled arrhythmias, undergoing long-term oxygen therapy, or who use home-based noninvasive ventilation were excluded from the study. Participants fulfilling criteria for inclusion and those consenting to participate were included into the study. The university ethics committee approved the study protocol, and all participants provided written informed consent.

A total of 84 patients were enrolled into the study and were randomly allocated to receive standard care (control group) or a structured, therapist-driven, home-based exercise program (experimental group), in addition to standard care, for 12 weeks. Details of these interventions are provided in the supplemental material. In addition to these interventions, both groups of patients also received a patient education manual – the Pulmonary Hypertension Manual (PulHMan), which has been shown to improve awareness on benefits of exercise in PH. The experimental group received a home-based exercise program that was modified from a program used for patients with heart failure. The allocation was performed by a person from an external source who is not involved in the study and using block randomization of varying block sizes to minimize bias. At entry into the study, a baseline evaluation of demographic parameters and outcomes was performed. Functional capacity was assessed using the 6-min walk test (6MWT) as per the standard recommendations, in which the participant was asked to walk as far as possible in 6 min on a 30-m walkway before assessment, vitals were assessed, and the patient was made to perform the test, after providing detailed instruction and demonstration. Vitals were monitored continuously during the test, and no change to prescribed medications was made. Considering the possibility of adverse events during the 6MWT, the test had a therapist walk behind the patient while continuously monitoring all vital signs. QoL and functional outcomes were assessed using the Medical Outcomes Survey Short Form – 36 (SF36) for both physical component score (PCS) and mental component score (MCS) and World Health Organization – functional class (WHO-FC), respectively. Right ventricular function, as determined from tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic function (RVSP), was assessed from transthoracic echocardiography using standard guidelines and using the GE Healthcare Vivid 7 ultrasound. All echocardiographic
readings were performed by the same cardiac technologist (>10 years of experience) who was unaware of the group allocation and details of outcome measures. Patients in the intervention arm were provided an exercise log book to ensure they remained adherent to the program (i.e., performed exercises on at least 3 days of the week) for the 12-week duration. All outcomes were reassessed at the end of 12 weeks.

Sample size was determined based on the study by Merles et al\(^5\) and a home-based study on heart failure\(^17\) in the same setting as this study. Because there was no difference between the adjusted and unadjusted means, only the unadjusted mean differences with their standard deviations and mean change from baseline for 6MWD, SF36, RVSP, and TAPSE are summarized in Table 2. The adjusted mean differences are reported in the Supplemental B (Tables).

An ANCOVA was run to determine the effect of home-based exercise training on postintervention outcomes (i.e., 6MWD, QOL, WHO-FC, RVSP, and TAPSE) after controlling for various preintervention covariates. For 6MWD, there was a statistically significant difference in postintervention 6MWD between the groups \((F(1,67) = 15.257, p < 0.001)\). The experimental group found an improvement of 48.5 m versus 13 m in the control group \((p < 0.001)\). For QOL, there was a statistically significant difference between the groups, with significant changes seen in the experimental group on the postintervention PCS and MCS scores \((F(1,67) = 19.219, p < 0.001\) and \(F(1,67) = 15.097, p < 0.001\), respectively). The difference in PCS and MCS between the groups improved by 5.5 and 4.2 units, respectively. In addition, the mean differences between the groups for the PCS and MCS along with the subdomains also showed significant differences, except for the subdomain of body pain (Table 2).

After exercise training, the postintervention WHO-FC showed a statistically significant improvement between the groups after controlling for various baseline covariates \((F(1,67) = 18.798, p < 0.001)\). There was however no change in the control group. A statistically significant reduction in median WHO-FC from class III to class II \((p < 0.001)\) was seen after exercise training (Table 3). Right heart function, in terms of RVSP and TAPSE, did not show a statistically \((p > 0.05)\) or clinically \((p > 0.05)\) significant change between the groups after exercise training (Table 2).

No adverse events or fatalities were observed during the study. Non—exercise-related adverse events were reported in both the groups and consisted of breathlessness (7/67; 10.4%), vertigo and hemoptysis (1/67; 1.4% each), and lower respiratory infection and warfarin-induced bleed (2/67; 2.9% each). One of the participants with the warfarin-induced bleed in the control group died. Among those who completed the 12-week intervention \((n = 34)\), adherence to the program was good (45.2% ± 13.9%) with most of the participants \((n = 26, 76.4%)\) completing between 40 and 60% of all exercise sessions. Only a small number \((3, 8.8%)\) completed <40% of all sessions, whereas five \((14.7%)\) were extremely compliant with the sessions, completing >60% of all sessions.

### 4. Discussion

This is the first home-based exercise training trial from India to demonstrate significant benefits in functional outcomes and QOL.
The mean improvement in 6MWD seen was 44 m, which was found to be more than the minimally clinically important difference of 33 m and similar to that observed in a recent clinical trial.26,28 and also in the sildenafil use in pulmonary arterial hypertension (SUPERS) trial that assessed the effects of sildenafil in PH.27 Considering the limited effect of exercise on the RV, the improvements in the 6MWD could be attributed to the impact of exercise on the peripheral muscles which resulted in the improved functional capacity.29 This thus improve functional capacity by improving peripheral oxygenation to the exercising muscles and could result in improved oxygenation to the exercising muscles and thereby improve functional capacity by improving peripheral oxygenation.30

Table 2

Unadjusted means between groups for all outcome measures after 12 weeks of home-based exercise training.

| Outcome | Control (n = 33) | Mean change from baseline | Experimental (n = 34) | Mean change from baseline |
|---------|------------------|---------------------------|----------------------|--------------------------|
| 6MWD (meters), mean ± SD | 275.3 ± 93.9 | 13 ± 39.8 NS | 334.1 ± 88.4 | 48.55 ± 44.98 NS |
| WHO-FC, median (IQR) NS | 2 (2.3) | –0.6 ± 0.3 NS | 2 (1.3) | –0.5 ± 0.5 NS |
| SF36-PCS, mean ± SD | 40.69 ± 8.51 | 0.07 ± 4.07 NS | 45.44 ± 8.42 | 4.59 ± 4.55 NS |
| SF36-MCS, mean ± SD | 42.23 ± 8.72 | 1.75 ± 5.75 NS | 48.68 ± 6.98 | 5.75 ± 5.91 NS |
| Physical function, mean ± SD | 38.65 ± 10.24 | 0.68 ± 3.48 NS | 42.3 ± 9.25 | 3.08 ± 8.67 NS |
| Role physical, mean ± SD | 38 ± 8.31 | 0.12 ± 4.92 NS | 44.85 ± 8.72 | 4.41 ± 8.24 NS |
| Body pain, mean ± SD NS | 56.53 ± 8.0 | –0.18 ± 8.43 NS | 56.29 ± 7.40 | –0.71 ± 11.41 NS |
| General health, mean ± SD | 33.71 ± 9.81 | –0.81 ± 5.63 NS | 42.23 ± 10.26 | 6.14 ± 7.19 NS |
| Vitality, mean ± SD | 44.43 ± 8.95 | 2.17 ± 5.78 NS | 51.33 ± 6.18 | 7.03 ± 10.28 NS |
| Social function, mean ± SD | 38.18 ± 9.51 | 1.41 ± 6.90 NS | 44.55 ± 7.71 | 4.79 ± 11.55 NS |
| Role emotional, mean ± SD | 38.86 ± 11.29 | 0.01 ± 6.71 NS | 45.54 ± 9.36 | 3.18 ± 9.03 NS |
| Mental health, mean ± SD | 44.06 ± 7.9 | 1.22 ± 4.66 NS | 44.68 ± 7.35 | 3.12 ± 9.83 NS |
| RVSP (mm Hg), mean ± SD NS | 83.75 ± 29.32 | –1.48 ± 4.91 NS | 75.76 ± 24.95 | –3.29 ± 8.03 NS |
| TAPSE (mm), mean ± SD NS | 14.8 ± 2.5 | 0.12 ± 1.47 NS | 15.03 ± 2.77 | 0.28 ± 0.56 NS |

Abbreviations: 6MWD, six-minute walk distance; MCS, mental component score; NS, not significant; PCS, physical component score; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization — functional class; SF36, Medical Outcomes Survey Short Form.

Table 3

Frequency distribution of change in WHO functional class for both groups after exercise training.

| WHO-FC | Control | Experimental |
|--------|---------|--------------|
|        | Baseline | Final | Baseline | Final |
| Class I, n (%) | 7 (16.7) | 7 (21.2) | 4 (9.5) | 11 (32.4) |
| Class II, n (%) | 17 (40.5) | 14 (42.4) | 16 (38.1) | 17 (50) |
| Class III, n (%) | 17 (40.5) | 11 (26.2) | 9 (21.0) | 6 (17.6) |
| Class IV, n (%) | 1 (2.4) | 1 (3) | 1 (2.4) | 0 (0) |

WHO-FC, World Health Organization — functional class.

The findings as patients in lower functional classes are important. A 71% reduction in the number of patients in WHO-FC III and a 175% increase in WHO-FC I with home-based exercise training are comparable with the improvements seen in previous studies.6,10,11,33

A 71% reduction in the number of patients in WHO-FC III and a 175% increase in WHO-FC I with home-based exercise training are important findings as patients in lower functional classes are known to have better outcomes in the long term. However, this study did not assess the long-term effects and therefore does not show how much higher the improvement was observed by Mereles et al5 with their 15-week exercise training program. RV dysfunction as measured by TAPSE did not improve after exercise training. This is contradictory to what has been seen in young healthy individuals and also in an animal model of chronic obstructive pulmonary disease-induced PH.38,39 However, the effects of exercise training on TAPSE in PH are yet to be explored.

The exercise program was found to be safe, with non–exercise-related adverse events being reported. Two fatalities that occurred were not the result of exercise. The safety profile of this study is similar to that reported in an earlier study40 and also in recent reviews.6,9 The testing of patients using the 6MWD was also safe. However, considering recent reports on adverse events during the 6MWT,41 it is advisable to ensure adequate supervision during the test and emphasize safety during exercise prescription.

In addition, the number of participants achieving the minimal clinically important difference (MCID) of 33 m on 6MWT was found to be greater in the experimental groups, with 27 of 34 achieving the MCID as against only 5 of 33 in the control group.

The study is limited by the lack of blinding for functional outcomes, which would influence the Hawthorne effect. Nevertheless, the study provides crucial data on the use of a simple inexpensive rehabilitation model of delivery for exercise training for individuals with PH. In addition, this study brings to light the importance of enrolling patients with PH into an exercise program using a home-based delivery model, especially in countries with limited resources and where geographical barriers prevent participation in supervised rehabilitation programs. Future studies need to assess the dose–response relationship for home-based delivery models and the impact of these programs on physical activity behaviors, dynamic cardiac function, and other biochemical parameters. Methods to improve adherence to home-based programs continue to be a major concern, and methodologies to improve this need to be considered in future trials.
5. Conclusion
A 12-week, home-based exercise training program improves functional capacity, functional class, and QoL in individuals with PH without any change in right heart function.

Conflict of interest
A.S.B. received the Tom Lantos Innovation in Community Service Award for development of the Pulmonary Hypertension Manual (PulHMan). The Pulmonary Hypertension Association’s Tom Lantos Innovation in Community Service Award is funded by Gilead. All other authors have no other conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhj.2019.03.002.

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