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An outpatient hospital-based exercise training programme for patients with cirrhotic liver disease awaiting transplantation: a feasibility trial

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Abbreviations page:

List of abbreviations:

AT	anaerobic threshold
CPET	cardiopulmonary exercise testing
DASI	Duke activity status index
ESLD	end-stage liver disease
HVPG	hepatic venous pressure gradient
LT	liver transplant
MAC	mid-arm circumference
MAMC	mid-arm muscle circumference
MELD	model for end-stage liver disease
TSF	triceps skinfold thickness
UKELD	united kingdom model for end-stage liver disease
VE/VCO_2	ratio of ventilation to carbon dioxide output
VO_2peak	peak oxygen consumption

Abstract:

Background: Time spent on the waiting list prior to liver transplantation (LT) provides an opportunity to optimise recipient fitness through prehabilitation; potentially reducing the physiological impact of major surgery. We assessed the feasibility and effectiveness of a six-week exercise programme in patients with cirrhotic liver disease awaiting LT.

Methods: This single centre, prospective cohort, feasibility study, enrolled patients awaiting LT to a six week period of thrice weekly, supervised exercise on a static bike. Cardiopulmonary exercise testing (CPET) was used to objectively assess cardiopulmonary fitness at baseline and after six weeks of exercise. A follow-up CPET was performed at 12 weeks. CPET-derived measures were used to guide prescription of the training programme. A non-randomised control cohort of LT patients were selected to match the exercise group based on specific demographic data. Allocation to study arms was primarily based on the distance participants lived from the hospital where training occurred. Both groups received structured nutritional advice.

Results: The exercise programme was feasible, with 9/16 (56%) patients completing the full programme of six weeks. Peak oxygen consumption (VO_2peak) in the exercise group rose from a mean (SD) of 16.2 (± 3.4) ml/kg/min at baseline to 18.5 (±4.6) ml/kg/min at week 6 (p=0.02). In the control group VO_2peak decreased from a mean (SD) of 19.0 (± 6.1) ml/kg/min to 17.1 (±6.0) at week 6 (p=0.03).

Conclusion: We have demonstrated that it is feasible to engage patients awaiting LT in an intensive aerobic exercise programme with a signal of improvement in fitness being detected.

Background:

Liver transplantation (LT) is the only curative treatment for end-stage liver disease (ESLD), with a one- and five-year survival of 93.8% and 81.3% respectively across UK liver transplant centres.[1] Malnutrition is a frequent burden in ESLD; reported in more than 50% of patients with decompensated liver disease and long recognised as a prognostic and therapeutic determinant in ESLD.[2] Physical deconditioning and sarcopenia result from the combined effects of impaired dietary intake, altered macronutrient and micronutrient metabolism, chronic inflammation and low physical activity.[3] Frailty is the end result of prolonged sarcopenia and physical deconditioning. The frailty syndrome is itself associated with a higher rate of complications in the perioperative period, including susceptibility to infection, hepatic encephalopathy, ascites and is an independent predictor of lower survival in cirrhosis and in patients undergoing liver transplantation.[4,5] Measures should be taken to address poor physical fitness and frailty in this cohort. Attention is turning towards the development of effective exercise/lifestyle intervention programmes known as 'prehabilitation' for patients awaiting LT, where involvement of a liver multidisciplinary team is essential, particularly in respect to tailored physical and nutritional intervention.

Recent studies have shown a beneficial impact of preoperative exercise for patients with colon and rectal cancer[6–8] in terms of cardiorespiratory fitness,[7] respiratory muscle endurance,[6] fatigue and physical health perceptions.[8] A reduction in postoperative hospital length of stay in the intervention group has been demonstrated when prehabilitation has been used in both cardiac and major vascular surgery.[9]

There is currently limited data available to determine the effects of exercise in the complex cohort of patients with ESLD awaiting LT. A 2018 meta-analysis sought to assess the effects of exercise on patients with cirrhosis,[10] revealing only four small studies with 81 patients included. A limited range of clinical conditions were studied and heterogenous outcome

measures reported. Associations with improvement in peak oxygen consumption (VO_2peak),[11] exercise capacity[11–13] quality of life,[13] reduced fatigue[11] and hepatic venous pressure gradient (HVPG)[14] were found.

Knowledge pertaining to the field of exercise training prior to LT is still at an early stage; indeed, there is no existing evidence that patients with decompensated liver disease awaiting transplantation would simply comply with a prehabilitation programme. There is considerable scope for further evaluation to define the optimal prehabilitation programme to keep patients well on the liver transplant waiting list. This single-centre study was designed to address the issue of feasibility and it forms the first stage in a larger programme of work to investigate the impact of perioperative exercise training on patients awaiting LT.

We wanted to know whether it would be possible to engage patients in a programme of intense supervised aerobic exercise, in a hospital setting over a period of six weeks. We designed a simple feasibility study to determine this, to understand fitness levels in patients awaiting LT and to see if there were any signals of fitness improvement when compared to a group of matched patients not involved in an exercise programme.

Methods:

Study design

This single centre cohort study assessed the feasibility of a six-week, structured, prehabilitation programme in patients awaiting LT. It also compared levels of fitness before and after the programme to a demographically matched control group awaiting LT who did not undergo exercise training. Ethical approval for this study was granted by London Bromley Research Ethics Committee (16/LO/0762). Local NHS permission was granted by the Royal Free London NHS Trust. Written consent was obtained for all patients. Trial registration was not considered necessary for this non-randomised internal feasibility study.

Study setting / participants:

Patients aged 18 years and over with a diagnosis of cirrhotic liver disease awaiting LT at the Royal Free Hospital were invited to join a six-week exercise training programme. The study ran from June 2016 to December 2017. Patients were eligible for inclusion once they were formally listed for LT. Invitation to the exercise programme was based on the distance potential participants lived from the hospital as the exercise intervention was delivered within the hospital in an outpatient clinic. It was assumed that those patients living a long distance from the hospital would be unable to make this journey three times a week for six weeks. The study was limited to cirrhotic patients given the high prevalence of physical inactivity, compounded by multiple other factors including malnutrition, decreased hepatic protein synthesis, hypermetabolism, low testosterone and an increase in inflammatory cytokines, alongside cardiac and skeletal muscle deconditioning and the potential for an exercise intervention to limit decline.

Specific exclusion criteria were: non-cirrhotic liver disease, an oncological diagnosis as the primary reason for transplantation and a contraindication to exercise training or testing (according to the American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP) guidelines.[15] Given that the primary aim of this study was feasibility, formal randomisation was not considered necessary and the study was not designed to detect differences in outcomes. The 'standard care' cohort of patients (no exercise programme) were matched to those in the exercise group according to specific demographic criteria: age, sex and disease severity (model for end-stage liver disease (MELD) score). Once patients were matched, allocation to study arms was a function of geographical location and logistical ability to commit to attending hospital three times per week.

Assessment of fitness:

Self-reported activity status was assessed at baseline using the Duke activity status index (DASI) score.[16] Serial CPET was used to objectively assess change in cardiopulmonary fitness at the following time points: baseline (week 0), at the midpoint of the exercise training to guide the subsequent exercise prescription (week 3; exercise group only), at the end of the 6 week exercise programme and a final CPET at week 12. All CPETs were performed using an electromagnetically-braked cycle ergometer (Corival, Lode, Gronigen, the Netherlands) and a breath-by-breath analysis system (Cortex, Leipzig, Germany). The CPET testing protocol involved patients resting for 3 minutes, undergoing 3 minutes unloaded exercise on a static bike, then between 6-10 minutes of appropriate incrementally ramped exercise (dependent on patient fitness), during which cycling intensity was gradually increased. Patients were fitted with a facemask to enable continuous measurement of respiratory variables. Finger prick haemoglobin concentration was routinely measured prior to each CPET test (Hemocue, Ängelholm, Sweden). CPET data were analysed by the same two trained practitioners (one was blinded to patient identification). Anaerobic threshold (AT) and VO_2peak were used to assess changes in fitness. Where disagreement in AT interpretation of > 10% occurred, a third blinded expert was asked to interpret AT position.

Exercise programme:

Following the baseline CPET, patients were asked to attend thrice weekly exercise training sessions for 6 weeks. Outpatient sessions were held at the Royal Free Hospital, London, UK and patients travelled from home for each appointment. Each training session consisted of 40 minutes (including 5 min warm-up and 5 min cool-down) of interval training on an electromagnetically braked cycle ergometer (Optibike Ergoselect 200; Ergoline, GmbH, Bitz, Germany). The exercise training intensities were formulated according to an individual's CPET data at weeks 0 and 3, and altered according to measured work rates at VO_2 for AT

and VO_2peak. The interval training protocol consisted of alternating moderate (80% of work rate at VO_2 at AT: 4 x 3 minute intervals) to severe (50% of the difference in work rates between VO_2 at peak exercise and VO_2 at AT: 4 x by 2 minute intervals) intensities (total 20 min) for the first two sessions. This was then increased to 40 minutes (6 x 3 minute intervals at moderate intensity and 6 x 2 minute intervals at severe intensity).

Power intervals were calculated for each subject as follows:

Moderate-intensity exercise: (work load at VO_2 and AT −2/3 of work ramp) × 80 %

Severe-intensity exercise: ((Work load at VO_2 Peak- work load at AT −2/3 of work ramp) × 50 %) + work load at AT

Comparison (control) group:

A comparator 'usual care' group was created by selecting patients matched to those in the exercise group according to age, sex and MELD (model of end-stage liver disease) score. These patients underwent CPET at 0, 6 and 12 weeks but no exercise programme was initiated. Once patients were demographically matched, allocation to study groups was based on geography and logistics; the patient living furthest from the hospital was allocated to the control group to avoid any logistical issues in thrice weekly hospital visits.

Nutritional assessment:

Both the groups received standardised nutritional assessment and advice, at baseline and at 6 weeks. Difficulties in the accurate assessment of nutritional status in patients with cirrhosis are widely recognised, given that many of the markers associated with malnutrition are intrinsically affected in liver disease (e.g. albumin and lymphopenia). Therefore skeletal muscle evaluation provides an objective means to determine nutritional status.[3,17]

Assessment was made and nutritional advice given by the same specialist liver transplant dietitian at baseline (prior to first CPET) and again prior to the week six CPET for all patients in both the exercise and comparator groups. The RFH Global Assessment Data Collection

Form was used which encompasses measures of body mass index (BMI), mid-arm muscle circumference (MAMC), triceps skinfold thickness (TSF), hand-grip strength combined with details of dietary intake[18] (see supplementary material). The Royal Free Hospital (RFH) Global Assessment Data Collection Form has been validated as a nutritional assessment method specifically for this patient population.[18]

Usual recent dietary intake was assessed using a self-reported diet history. Details of any dietary restrictions and nutritional support supplements were recorded. These data were used to provide an overall impression of the adequacy of the diet in relation to estimated daily requirements, for energy (35-40 kcal/kgBW/d) and protein (1.2-1.5 g/kgBW/d).[19–22] Intakes were categorised as *adequate* if they met estimated requirements, *inadequate* if they did not meet estimated requirements but exceeded 500 kcal/d, or *negligible* if they provided fewer than 500 kcal/d.[18]

Anthropometric assessment:

An estimated dry weight was determined using clinical assessment, previously documented weights, ascitic volumes removed at paracentesis, and published guidelines. BMI was calculated from the estimated dry weight and height[18] Mid-arm circumference (MAC) and triceps skinfold thickness (TSF) were measured on the nondominant arm using Holtain/Tanner Whitehouse skinfold callipers (Holtain, Crymych, UK) and a tape measure. Mid-arm muscle circumference (MAMC) was then calculated as per the formula:

$$MAMC = MAC - (TSF \times 0.3142)$$[23]

MAMC and TSF measurements were compared with published standards[24] and MAMC expressed in relation to the 5th percentile, for the appropriate age and gender category.[18]

Follow up assessment:

All participants were invited to a follow up CPET at 12 weeks after baseline if they were still awaiting LT. The purpose of this was to determine any alteration in level of fitness from week 6 to 12.

Statistics:

Data were examined for normality using the Shapiro-Wilk test. Continuous data were presented as median with interquartile range (IQR), or mean with standard deviation (SD) for normally distributed data and categorical data as number (percentage). Paired data were compared using Mann-Whitney analyses (continuous, non-normal distribution) or *t* test analyses (continuous, normal distribution). All tests were two tailed, and significance was taken as $p < 0.05$. Statistics were calculated using IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM Corp.

Results

A total of 16 patients were recruited to the exercise group and 17 to the standard care group (a total of 33 patients); there were no differences in demographic data between groups (table 1). There were no differences in self-reported activity status between groups at baseline as reflected in the DASI score. Baseline mean haemoglobin concentration was lower in the exercise group at 108.6 (20.8) g/l versus 117.6 (19.8) g/l in controls (p=0.21). Nine of the 16 patients in the exercise group completed the 6-week exercise programme (56%). In the control group, 11 out of 17 patients (65%) completed CPET tests at week six. Transplantation and clinical deterioration were the predominant reasons for patient drop-out (see figure 1 for study flow diagram); no patient dropped out of the intervention group due to an inability to complete the exercise prescribed to them. Deterioration was largely the result of obstructive cholangiopathy and need for hospitalisation.

Of the 20 patients (61%) completing the 6 week study period (9 in the exercise arm and 11 in the control group), a further 5 (25%) did not complete the 12 week follow-up CPET (4 were in the control group); transplantation being the primary reason for this with 3 patients receiving a liver. One patient withdrew from the control arm as they did not want to do a third CPET test and another control arm patient deteriorated due to profound decompensation of cirrhotic liver disease necessitating hospitalisation.

There were no incidents of worsening cirrhotic decompensation as a result of the exercise and no adverse incidents related to exercise training were reported. Compliance with the prescribed exercise training was high with 127 out of the overall total of 135 exercise sessions (94%) completed by the 9 patients finishing the exercise intervention.

CPET measures at baseline and at weeks 6 and 12 are displayed in table 2. There was an increase in VO_2peak in the exercise group from a mean (SD) of 16.2 (± 3.4) ml/kg/min at baseline rising to 18.5 (±4.6) ml/kg/min at week 6 (p=0.02). By week 12 (6 weeks after exercise cessation) the mean VO_2peak reduced to 17.4 (±3.0) ml/kg/min. In the control group, VO_2peak decreased from a mean of 19.0 (± 6.1) ml/kg/min to 17.1 (±6.0) at week 6 (p=0.03). Figure 2 illustrates VO_2 at AT and peak across both exercise and comparator groups at baseline, weeks 6 and 12. There was a significant increase in mean VE/VCO_2 (ratio of ventilation to carbon dioxide output) at AT in the control group, rising from a baseline value of 30.9 (4.0) to 33.6 (4.5) at week 6.

The anthropometric measures (as per the RFH global assessment tool) at baseline and week 6 assessments, are displayed in table 3. There was no overall change in BMI (dry weight) in either group across the study period; patients in the exercise group had a higher BMI than controls at baseline. An increase in mean handgrip strength from 26.4 (±7.5) kg at baseline to 29.4 (±6.4) kg at week 6 was observed in the exercise group (p=0.05), whilst handgrip in the control group was 29.1 (±10.7) kg at baseline and 30.5 (±13) kg at week 6 (p=0.80). There

was no change in MAC over the six-week study period in either group. The mean MAMC in the exercise group was 28.6 (±4.6) cm at baseline and 29.9 (±5.7) cm after 6 weeks of training (p=0.22), indicating an increase in muscle mass, whereas, the mean MAMC in the control group was 24.2 (±3.3) cm at baseline and 23.5 (±3.7) cm at week 6 (p=0.16).

Of the 20 patients that completed the six-week study period, 16 had received their liver transplants with one patient still on the waiting list one year after the end of the study. Two patients (one in the exercise and one in the control group) were delisted as they clinically improved hence no longer met transplantation criteria and one control patient went on to be delisted due to profound decompensation and deterioration. The mean time to transplant with respect to completion of the six-week exercise training period was 165 (118) days in the exercise group and 192 (211) days in the controls.

There were no deaths in the postoperative period until hospital discharge in either group. Post-transplant outcome data is presented in table 4. The median (IQR) hospital length of stay for the index transplant admission in the exercise group was 13 (6) days and 30 (13) days in the control group, a difference of 13 days (p=0.02).

Discussion

This study demonstrated that it was safe and feasible to engage patients with cirrhotic liver disease awaiting LT surgery in an intense, supervised exercise programme comprised of three sessions a week in a hospital outpatient clinic for a total of for six-weeks. Whilst the study was not designed or powered to detect differences in secondary outcomes we observed an increase in VO_2peak in patients who underwent the exercise programme, which declined six weeks after cessation of the programme. This suggests exercise has the potential to improve aerobic fitness but that this gain is lost and deconditioning occurs once exercise stops. In contrast, a decline in VO_2peak was observed in a matched control group, suggesting that this patient group becomes progressively more unfit over time, probably as a result of their

underlying disease and lack of exercise. In addition, handgrip strength improved in the exercise group, suggesting that lower limb exercise may have a more systemic impact.

This study demonstrated that it was feasible to motivate patients to attend hospital three times a week and participate in an aerobic exercise training programme whilst awaiting LT. We observed a high rate of compliance with exercise sessions in our centre in those selected based on the distance they lived from the hospital. It is perfectly reasonable to assume that compliance would be far less were patients to have lived further away, as was the case in the comparator group of this study. Given that many patients awaiting LT nationally live a substantial distance from their transplant centre, such an intense method of exercise intervention may not be appropriate for all of them due to the logistics of travel. A modified approach to training patients in their local hospital, a local gymnasium or within their own home could be viable alternatives. Future research should seek to address this area and involve patients with the design of studies to optimise what will work best for them in this regard.

This study has a number of limitations. Due to the feasibility design, participants were not randomised, there was no observer blinding and the sample size was not powered to detect differences in physiological or postoperative outcomes. All these factors increase the chance of confounding and a type 2 error in the presented data. The purpose of collecting these data, however, were to determine the level of fitness in patients awaiting LT in our centre, the heterogeneity in that measure and whether there was a signal of improvement in fitness in the exercised group versus the non-exercised group. All of this information will be essential for the design of a more comprehensive study aimed at evaluating the efficacy of an exercise intervention. A further limitation of this study was the notable drop out rate of participants, with 13 patients (39.4%) in total (7 in exercise and 6 in control) failing to complete the six week study period. This information is also crucial for the design of future studies. Five of

these patients were transplanted shortly after recruitment, which is an inherent, unpredictable risk specific to the study population. Likewise, attrition due to patient medical deterioration is also not an unexpected finding given the comorbid nature of the cohort. What is important to note, however, is that no patients in the exercise cohort dropped out because they were physically or logistically unable to complete the programme. This demonstrates that the amount of exercise prescribed was tolerable by all patients. Postoperative outcomes following LT are highly multifactorial and attributing the significant reduction in hospital length of stay to preoperative exercise in the context of an inadequately powered trial would be but inappropriate, particularly given the lag time from completion of exercise to transplantation. However, it is an association that merits further research.

Existing LT literature demonstrates consistently that malnutrition adversely impacts upon post transplant morbidity and mortality[20,25–27]; likewise, an association between low cardiopulmonary reserve and 90-day post-transplant mortality has been shown.[28] We have demonstrated that a preoperative exercise training programme alongside structured nutritional advice, may aid in maintaining muscle mass and strength. It follows that close attention to nutrition and physical optimisation on the liver transplant waiting is essential and is indeed an emerging research target.

Having demonstrated that intense aerobic exercise training is feasible in patients with cirrhosis awaiting LT and that there may be measurable improvements in fitness, urgent follow up research is required in this area. Modification of our design with the input of patients could result in a deliverable intervention that will have a tangible effect on the long-term outcomes of this patient population. A greater understanding of the dose-response relationship of exercise and outcomes is required, along with a more detailed understanding of factors that determine ongoing patient engagement with complex interventions such as this. Our collaborative interdisciplinary approach sets a precedent for future studies to build

upon and a multi-centre study to assess efficacy is now required. Exercise has been shown to be effective in improving the health and well being of almost every patient group it has been applied to[29] and it is highly likely this could be the case for patients with end-stage liver disease who are awaiting transplantation surgery.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Cardiopulmonary exercise testing measures throughout the study

Timepoints: 1 = baseline, 2 = week 6, 3 = week 12.

a) *Exercise programme group:* serial mean (SD) VO_2 at AT and peak exercise (ml/kg/min) at baseline, week 6 week and 12

b) *Control group:* serial mean (SD) VO_2 at AT and peak (ml/kg/min) at baseline, weeks 6 and week 12

Table 1: Baseline demographic, clinical and physiological data of the two patient cohorts

	Exercise (n=16)	**Usual care (n=17)**	p value
Age (years) Mean (SD)	**55.6** (7.8)	**55.6** (7.8)	0.99
Sex No. (%) female	**2** (12.5)	**3** (17.6)	
MELD Mean (SD)	**13.7** (4.6)	**13.2** (3.7)	0.73
UKELD Mean (SD)	**52.9** (2.7)	**52.2** (3)	0.45
DASI Median (IQR)	**43.5** (32)	**36.7** (23)	0.76
METS Median (IQR)	**8.1** (3.9)	**7.3** (2.8)	0.76
Haemoglobin (g/L) Mean (SD)	**108.6** (20.8)	**117.6** (19.8)	0.21
Aetiology: • **Alcohol related** No. (%)	**6** (37.5)	**6** (35.3)	
• **Hepatitis** No. (%)	**5** (31.3)	**1** (5.9%)	
• **NASH** No. (%)	**2** (12.5)	**3** (17.6)	
• **Cholestasis** No. (%)	**3** (18.7)	**6** (35.3)	
• **Autoimmune hepatitis** No. (%)	**0**	**1** (5.9)	

Table 2: CPET measures at baseline, week 6 and week 12 in both cohorts.

	Exercise programme (n=9)			**Usual care (n=11)**		
	Wk 0	**Wk 6**	**Wk 12**	**Wk 0**	**Wk 6**	**Wk 12**
VO_2peak (ml/kg/min) ♯ Mean (SD)	**16.2** (3.4)	**18.5** (4.6) *	**17.4** (3.0)	**19.0** (6.1)	**17.1** (6.0) *	**18.4** (7.4)
AT (ml/kg/min) ♯ Mean (SD)	**10.9** (2.6)	**11.4** (2.1)	**10.5** (2.4)	**13.0** (3.5)	**11.8** (3.2)	**12.6** (2.7)
VE/VCO_2 at AT Mean (SD)	**32.8** (4.5)	**34.2** (4.4)	**34.5** (4.0)	**30.9** (4.0)	**33.6** (4.5) *****	**32.9** (4.1)
Maximum heart rate (bpm) Mean (SD)	**124** (24)	**128** (20)	**131** (10)	**121** (19)	**114** (23)	**122** (12)
Peak workload (W) Mean (SD)	**117** (26)	**134** (26) *****	**134** (25)	**142** (43)	**128** (49)	**143** (44)
Haemoglobin (g/L) Mean (SD)	**114.6** (19.5)	**112.3** (13.7)	**108** (14.4)	**125.1** (19.9)	**117.7** (24.4)	**125.0** (22.0)

AT = anaerobic threshold, VO_2peak = peak oxygen consumption, VE/VCO_2= ratio of ventilation to carbon dioxide output.

***** Denotes a significant difference from baseline values (p= <0.05).

♯ dry body weight was used for ascitic patients

Table 3: anthropometric measures at baseline and week 6 in both cohorts.

	Exercise (n=9)			**Usual care (n=11)**		
	Wk 0	**Wk 6**	p value	**Wk 0**	**Wk 6**	p value
BMI (dry weight) Mean (SD)	**30.9** (5.6)	**31.1** (5.5)	0.38	**27** (4.6)	**26.9** (3.8)	0.86
Handgrip (kg) Mean (SD)	**26.4** (7.5)	**29.4** (6.4)	0.05	**29.1** (10.7)	**30.5** (13)	0.80
MAC (cm) Mean (SD)	**35.4** (7)	**35.7** (6.9)	0.59	**30.2** (3.7)	**30** (3.5)	0.75
MAMC (cm) Mean (SD)	**28.6** (4.6)	**29.9** (5.7)	0.22	**24.2** (3.3)	**23.5** (3.7)	0.16

BMI = body mass index, MAC = mid-arm circumference, MAMC = mid-arm muscle circumference.

Table 4: Post-transplant clinical data

	Exercise (n=7)	**Usual care (n=9)**	p value
Donor risk index Mean (SD)	1.5 (0.34)	1.62 (0.26)	0.24
Duration of ICU stay (days) Median (IQR)	2 (4)	4 (5.5)	0.77
Hospital length of stay (days) Median (IQR)	13 (6)	30 (13)	0.02
6 month survival Number (%)	7 (100)	9 (100)	

Figure 1

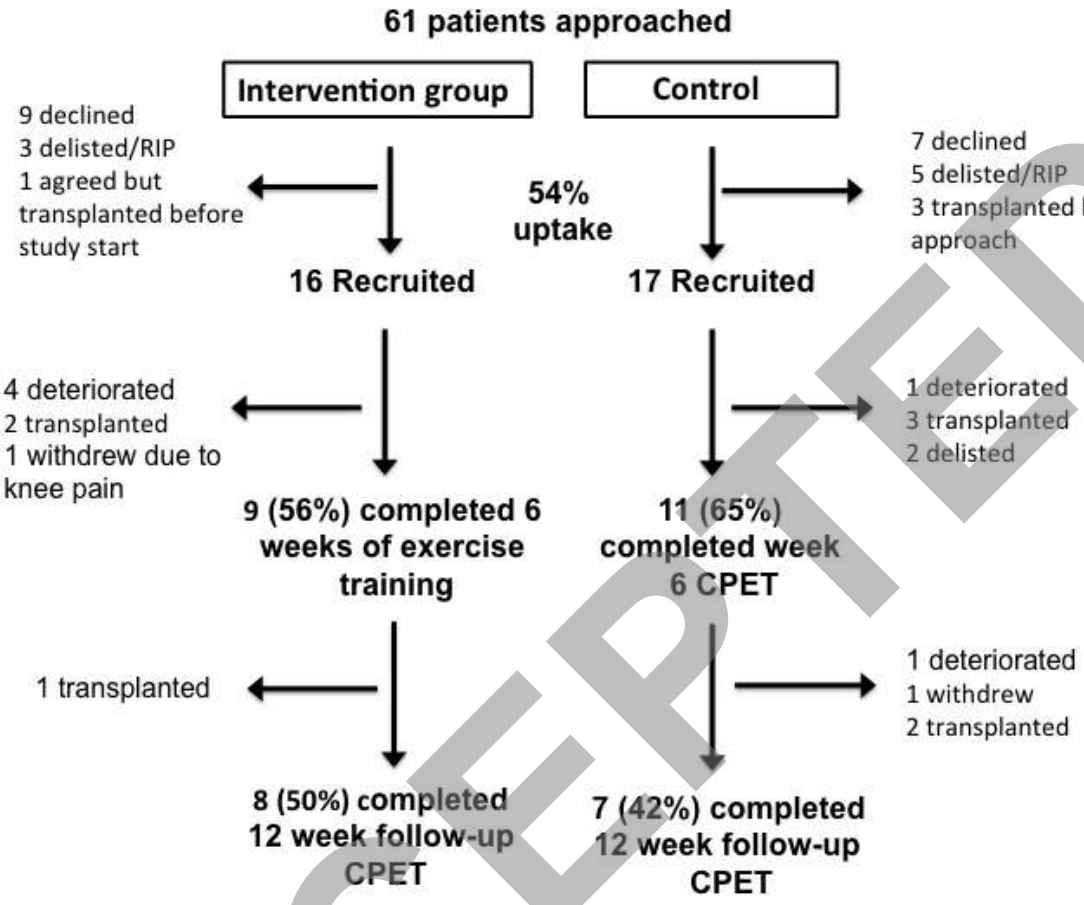

Figure 2A

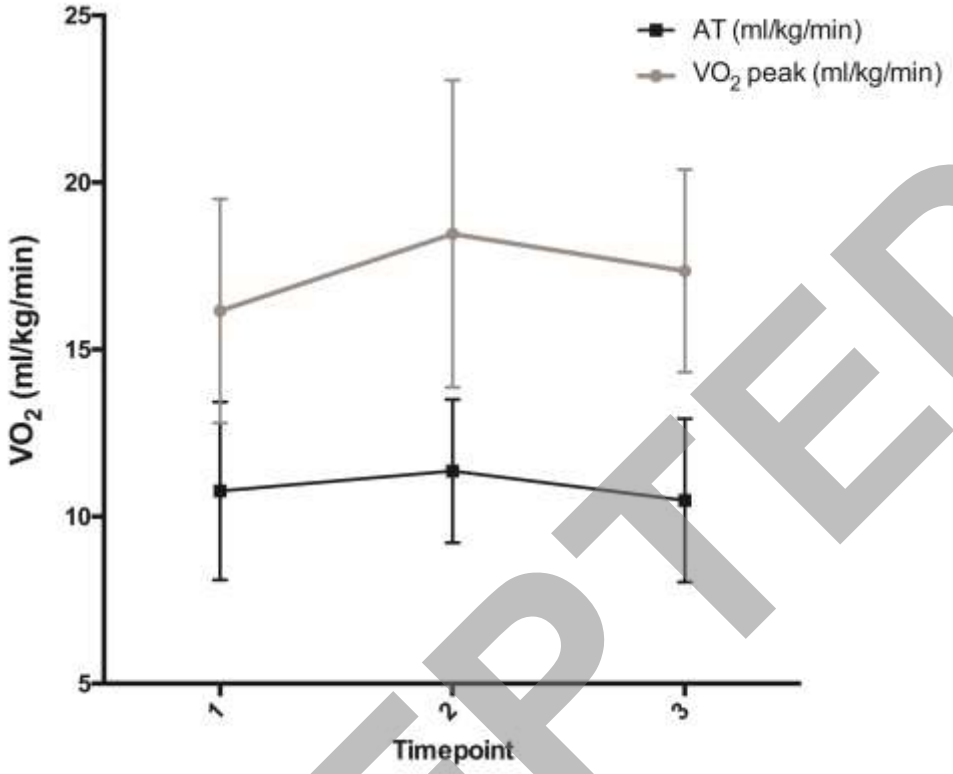

Figure 2B