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Research article

# PRE-STAR: Multidimensional Pre-Habilitation in Patients with Aortic Stenosis Undergoing Surgical Valve Replacement

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## Abstract

**Background:** Evidence suggests that patients with aortic stenosis awaiting AVR are mostly characterized by a 'fragile phenotype', which strongly influences post-operative outcomes. Studies in the literature allow us to define frailty as a dynamic risk factor, modifiable through a Pre-Habilitation program in different dimensions such as respiratory, functional, nutritional and psychological but no study has yet proposed a preoperative rehabilitation program that acts simultaneously on all these dimensions.

**Objective:** To evaluate the impact of Multidimensional Pre-habilitation in patients with aortic stenosis undergoing AVR (CAVR/MIAVR) and to assess the social and health impact that such a program may have on the hospital management of patients.

**Methods:** Single-blind, single-center study, comparing patients undergoing Pre-Habilitation (PRE-STAR) with control patients in 'Usual Care' (UC). Primary outcome measure was C-POMS (Cardiac Post-Operative Morbidity Score). Secondary outcome measures were: specific batteries of assessments in the different dimensions examined in the study (respiratory, functional, nutritional, psychological and clinical), quality of recovery (15-QoR), total length of hospital stay and TICCH length of stay. Measures were collected at baseline, the day before surgery (at the end of the Pre-Habilitation period), the fifth post-operative day and on the 60th post-operative day. The PRE-STAR group attended three sessions/week of respiratory muscle training and functional exercise training (aerobic exercise, resistance and balance training) for at least a four-week period. Furthermore, in order to impact on the nutritional dimension, the PRE-STAR TEAM provided patients in the experimental group with a brochure with standard nutritional advice to decrease cardiovascular risk. Concerning the psychological dimension, daily psychological support has been given to patients in the pre- operative period. The control group received the usual routine care (no Pre-habilitation). Considering the high susceptibility to SARS-CoV-2 infection of patients with CVD, the PRE-STAR program was realized remotely, exploiting the non-inferiority of "Home-based" telemedicine versus "Center-based" programs.

**Results:** 40 patients were randomized to the PRE-STAR experimental group, 40 to the control group. Results shows that Multidimensional Pre-Habilitation can significantly reduce the burden of total morbidity after AVR [total C-POMS score – PRE-STAR group: 1.8 ± 1.2 vs. Control: 2.6 ± 1.5, p = 0.02], can significantly increase all functional assessments (SPPB, Hand Grip and Gait Speed) with a p value never exceeding 0.03, can significantly increase lung volumes and capacities (Voldyne spirometric device), can decrease risk of malnutrition (MNA), can reduce depression and anxiety levels (BDI, BAI) and improve general cognitive functioning (MMSE). The study protocol has been shown to succeed in shortening the total length of hospital stay in the experimental group in a statistically significant proportion (p = 0.02).

**Conclusions:** Multidimensional Pre-Habilitation program is feasible, safe and effective to reduced total morbidity burden after AVR and to improve pre, peri and post-operative functional capacity, lung volumes, nutritional condition, general cognitive functioning, anxiety and depressive symptoms. Furthermore, the study has demonstrated an improvement in experience of pain, perceived quality of life, quality of recovery and total length of hospital stay. Moreover, telemedicine has been a key tool for the feasibility of the PRE-STAR program. However, the sample size is not large enough to make generalizable conclusions, thus more data is required.

**Keywords:** Pre-Habilitation; Cardiac Surgery; Aortic Stenosis; Aortic Valve Replacement; Telemedicine; Morbidity Outcome; C-POMS

## Background

Italy is currently one of the longest-living countries in the world: with almost 14 million people over-65, our country has the oldest population in Europe. Compared to 2010 the over-65s have grown by about 1.8 million and will increase by two and a half times between 2021 and 2100 [1]. These data define a scenario of widespread vulnerability, since chronic diseases such as heart failure are more frequent in this age group. As a matter of fact heart failure is the first causes of hospitalization after the age of 65, and can be read as "the price to pay for success", since the expansion of therapeutic options with innovative techniques and procedures in interventional cardiology and cardiac surgery has reduced mortality due to acute pathologies such as IMA, placing doctors in front of elderly patients with heart disease who are candidates for the later onset of heart failure.

The elderly patient presents significant complexity related to deterioration of organs and systems and to the progressive reduction of physical and cognitive functions, as well as by high comorbidity [2]. Therefore, definition of frailty appears to be an important element in the context of cardiac surgery, since it represents a marker of adverse events in heart failure [2-6] and it's associated with increased susceptibility to perioperative stress.

Frailty is a geriatric syndrome that affects approximately 10 per cent of people over-65, with prevalence reaching 60 per cent in patients with cardiovascular disease. It is characterized by decreased physiological and functional reserve and reduced ability to cope with stressful factors, resulting in increased risk of disability and death from minor external stresses [7]. Specifically, according to the conceptualization of Fried, et al. [8], the *fragile phenotype* includes reduced muscle strength, fatigue, reduced walking speed, weight loss and reduced physical activity. There is strong evidence to support the close relationship between frailty and cardiovascular disease morbidity and mortality [9-15]. Indeed, cardiovascular disease and frailty share common pathophysiological bases, such as chronic low- grade inflammation, as evidenced by increased levels of C-reactive protein and inflammatory cytokines [16]. In addition to sharing pathogenetic mechanisms, it has been shown how cardiovascular pathology in turn contributes to the frail phenotype, leading to alterations in multiple systems and apparatuses of the body [17,18].

In light of this background, the CVD that most draws our attention is aortic stenosis: it's a degenerative pathology of the aortic valve, characterized by high incidence and prevalence in elderly people. Thus, the presence of aortic stenosis is frequently associated with geriatric syndromes that strongly influence these patients' prognosis [19].

Aortic Valve Replacement (AVR) approaches include conventional aortic valve replacement with median longitudinal sternotomy (CAVR) and minimally invasive aortic valve replacement with mini-sternotomy (MIAVR). Frailty is increasingly recognized as a predictor of outcomes in patients with aortic stenosis undergoing both surgical techniques [9], and this is the reason why frailty has been added as an assessment parameter to traditional risk scores (such as EuroSCORE II) used in cardiac surgery, improving the overall prediction of post-operative mortality and morbidity [19-21]. As a matter of fact, nowadays the importance of placing patients with Valvular Heart Disease (VHD) within a Heart Valve Center is increasingly well known: patients with VHD are dominated by the elderly, with degenerative disease and multiple comorbidities, thus a centre of excellence its needed to provide all the diagnostic and therapeutic possibilities to the patient. This is made possible by the Heart Team, composed of multi-specialists and including cardiologists, interventional cardiologists and cardiac surgeons, but also physiatrists and

physiotherapists, capable of performing a multidimensional assessment able to break down individual department's walls which, in certain situations, represent limits that do not allow the patient to receive the best treatment possible.

**Pre-habilitation in the frail cardiac surgical patient**

For patients awaiting cardiac surgery, Pre- Habilitation is an evidence-based, cost-effective, multidisciplinary pre-operative program of optimizing physical functionality to enable the individual to maintain a normal level of functionduring and after surgery. It provides the establishment of integrated strategies to reduce the incidence of postoperative complications, accelerate the rehabilitation process, decrease the length of hospitalization, and increase the quality of life before and after surgery [22-24].

Studies in literature allow us to define frailty as a dynamic risk factor of adverse outcomes, modifiable through a Pre-Habilitation program in four different dimensions: respiratory, functional, nutritional and psychological.

**Respiratory dimension**

Considering that patients with lack of respiratory muscle strength have a higher risk of post- operative complications [25,26], the feasibility [54] and effectiveness of pre-operative inspiratory muscle training (IMT) on the reduction of post- operative pulmonary complications (atelectasis, pneumonia), improvement of inspiratory muscle strength and reduction of hospitalization in patients undergoing cardiac surgery has been widely demonstrated [27-29,30-33].

**Functional dimension**

Exercise improves outcomes in elderly, frail and HF patients [34-36], through decreasing circulating levels of inflammatory markers [36], production of free radical scavengers [37] and improving insulin resistance [38]. As demonstrated in the HF-ACTION study (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) [39-41], exercise is associated with improved exercise capacity, quality of life and reduced mortality and hospitalization, and is recommended in this class of patients [42-45].

Worldwide mainly sectoral studies have been carried out which consider either only respiratory rehabilitation intervention or only aerobic recovery. Protocols do not include programs to improve strength, which is generally correlated with an overall recovery of the person [46,47]. Specifically, available data shows that a Pre-Habilitation program in patients awaiting cardiac surgery is to be considered effective if carried out for sixty minutes a day, twice a week for at least four weeks [48].

**Nutritional dimension**

It is widely documented that nutritional support can be a strategy to prevent or delay sarcopenia, a biological substrate of frailty that worsens muscle function and physical performance in heart failure patients, increasing the risk of complications in post-operative care [3]. Malnutrition-related markers are hypoalbuminemia [49-51], hyposideremia [52,53], anaemia [54-56] and serum creatinine levels [57,58].

**Psychological dimension**

Pre-operative waiting time is associated with high levels of stress, anxiety and reactive depression, which affect baseline disease and post-operative outcomes [59,60]. The American Heart Association (AHA) recommends psychopathological screening in all patients with CVD to identify those who may require further evaluation and treatment [61].

**Objective**

In view of scientific evidence currently available, we have proposed a standardized Pre-Habilitation program aimed to optimizing the condition of the frail patient candidate for AVR, through a synergic action on respiratory and functional dimensions and a careful assessment of nutritional and psychological dimensions.

Primary objective was to demonstrate the effectiveness of a Pre-Habilitation multidimensional program by using an innovative scale as the Cardiac Post-Operative Morbidity Score (C-POMS) [62], comparing data collected with the two different surgical techniques of AVR (CAVR and MIAVR) to assess the social and health impact that such a program may have on the hospital management of patients. As reported by Sanders, et al., the C-POMS is a simple, validated score (0-13) by which to identify and quantify total morbidity burden after adult cardiac surgery on post-operative days.

Secondary objectives were to demonstrate that this kind of program can improve respiratory function, aerobic capacity, muscle strength, physical function, nutritional status, psychological condition, quality of life, quality of post-operative recovery and reduce length of intensive and ordinary care [63].

**Material and methods**

**Study design**

Single-blind, single-center, two-arm (arm A and arm B) study, comprising patients undergoing Pre- Habilitation (PRE-STAR) and control patients in usual care (UC).

### Patients

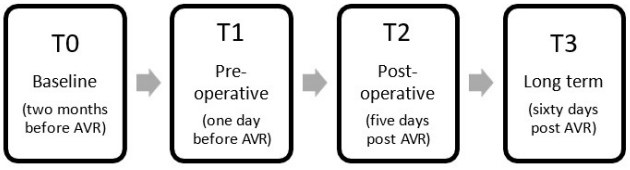
From April 2021 to April 2022, 40 subjects per arm were enrolled (total 80), identified among patients of the Complex Operational Unit (UOC) of Cardiac surgery at the Cardiovascular Sciences Department in Agostino Gemelli IRCCS University Hospital Foundation (Rome).

Eligible patients were identified, enrolled and followed by the PRE-STAR TEAM, made up of cardiac surgeons, cardiologists, physiatrists, geriatricians and physiotherapists.

Inclusion criteria included SVA patients undergoing elective AVR, both with conventional (CAVR) and minimally invasive (MIAVR) technique. Exclusion criteria included patients with a clinical history of SCA; sustained ventricular tachycardia; physical conditions that preclude rehabilitation program such as severe walking disability; mental conditions that preclude rehabilitation program such as moderate-severe cognitive impairment (MMSE<22) or psychiatric illness; severe COPD; previous cardiac surgery; inability to perform exercises and inability to sign the consent form.

### Assessments and materials

Eligible patients were assessed on pre-operative ambulatory visit and, once enrolled, they were submitted to four assessments at different timepoints: at time 0 of the study (T0), i.e. about two months prior to scheduled cardiac surgery, first assessments targeted at taking charge of the patient were carried out; at time 1 (T1), i.e. the day before surgery, assessments at the end of the Pre-Habilitation period were carried out; at time 2 (T2), i.e. on the fifth post-operative day, post-operative assessments were carried out; finally at time 3 (T3), i.e. on the 60th post-operative day, long-term assessments after surgery were carried out.




Considering the high susceptibility to SARS-CoV-2 infection of HF patients, PRE-STAR Pre- Habilitation program was realized remotely, exploiting the non-inferiority of "Home-based" telemedicine versus "Center-based" programs, widely demonstrated in literature [64-68]: telemedicine was exploited to carry out Pre-Habilitation meetings and to monitor patient's general condition during the preparation period for cardiac surgery. In particular, patients were treated in group video calls according to the scores obtained in physical assessments.

### T0: Baseline assessment

In the first phase of the study, the PRE-STAR TEAM summoned eligible patients to the Agostino Gemelli Hospital's Ambulatorio Valvole to verify inclusion and exclusion criteria and allocated enrolled patients to the two arms of the study with a computerized stratified block randomization procedure of varying lengths.

A questionnaire aimed at estimating adherence to the PRE-STAR Telemedicine program was submitted to enrolled patients and specific batteries of assessments in the different dimensions examined in the study: respiratory, functional, nutritional, psychological and clinical (Table 1).

| DIMENSION | ASSESSMENTS |
|---|---|
| **Respiratory** | Incentive Spirometer (Voldyne spirometric device) |
| **Functional** | Short Physical Performance Battery (SPPB) |
| | Gait-Speed Test |
| | Hand-Grip Test |
| | 36-item Short Form Health Survey (SF-36) |
| **Nutritional** | Mini Nutritional Assessment (MNA) |
| | Body Mass Index (BMI) |
| | Malnutrition-related markers: albumin, hemoglobin, iron, creatinine |
| **Psychological** | Mini-Mental State Examination (MMSE) |
| | Beck's Anxiety Inventory (BAI) |
| | Beck's Depression Inventory (BDI) |
| **Clinical** | Medical history: diagnosis, surgical technique, medications, risk factors, medical history of HF |
| | Visual Analogue Scale (VAS) |
| | EURO-Score II |
| | NYHA Class |
| | ECO Parameters: EF, TAPSE, Gmax, Gmed, PAPs, Aortic Bulb diameter, Ascending Aorta diameter, Bicuspid Aortic valve |
| | Inflammatory markers: PCR, IL-6 |
| | HF biomarkers: NT-pro-BNP, sST2, hs- TnT/ hs-TnI, eGFR |

**Table 1:** PRE-STAR Multidimensional Assessment.

### T1: Pre-operative assessment

Patients were assessed by the team the day before the scheduled cardiac surgery at the end of PRE- STAR Pre-Habilitation.

The primary objective of this phase was to demonstrate patient's adherence to Pre- Habilitation and telemedicine programs, by means of a questionnaire to check the appropriateness of this intervention.

Furthermore, the same information investigated at T0 (Table 1) were collected to show improvement in the four dimensions as a result of the PRE- STAR program.

### T2: Post-operative assessment

Patients were assessed on the fifth post-operative day, before hospital discharge. The primary objective of this phase was to demonstrate an improvement in post-operative clinical and physical condition in the PRE-STAR group VS the control group, by collecting the same information investigated at T0 and T1 (Table 1).

The primary endpoint of the study (C- POMS) was assessed (Table 2) and the PRE-STAR TEAM has gathered the following additional data: 15-item Quality of Recovery Scale score [69], total length of hospital stay and cardiac intensive care unit (TICCH) length of stay. We aimed to demonstrate that a Pre-Habilitation program such as the one proposed by this study could reduce AVR patients' post-operative complications and length of hospital stay, with a positive social and health impact on hospital management.

| **MORBIDITY** | **C-POMS** |
|---|---|
| **TYPE** | **CRITERIA** |
| **Pulmonary** | Presence of one or more of the following: |
| | New requirement for oxygen or respiratory support (including nebuliser therapy or request for chest physiotherapy on or after D5) |
| | Pleural effusion requiring drainage |
| **Infectious** | Presence of one or more of the following: |
| | Currently on antibiotics |
| | Has had a temperature of >38 ˚C in the last 24 h |
| | Has a white cell count/CRP level requiring in- hospital review or treatment |
| **Renal** | Presence of one or more of the following: |
| | Presence of decreased urine output requiring intervention (including IV furosemide) |
| | Increased serum creatinine (>30% from pre- operative level) |
| | Urinary catheter in situ |
| | New urinary incontinence |
| | Serum potassium abnormalities requiring treatment |

| | |
|---|---|
| **Gastrointestinal** | Presence of one or more of the following: |
| | Unable to tolerate an enteral diet for any reason including nausea, vomiting and abdominal distension |
| | Nasogastric tube |
| | Diagnosis of a gastrointestinal bleed |
| | Diarrhoea |
| **Cardiovascular** | Presence of one or more of the following: |
| | The use of inotropic therapy for any cardiovascular cause |
| | Pacing wires (on or after D5) and/or requiring temporary or new permanent pacing |
| | Diagnostic tests or therapy within the last 24 h for any of the following: (1) new MI or ischaemia, (2) hypotension (requiring fluid therapy, pharmacological therapy or omission of pharmacological therapy, (3) atrial or ventricular arrhythmias, (4) cardiogenic pulmonary oedema, thrombotic event (requiring anticoagulation), (5) hypertension (pharmacological therapy or |
| | omission of pharmacological therapy) |
| **Neurological** | New neurological deficit (including confusion, delirium, coma, lack of coordination, drowsy/slow to wake, poor swallow, blurred vision, sedated, changing loss of |
| | consciousness) |
| **Haematological** | Presence of one or more of the following: |
| | - Untherapeutic INR requiring pharmacological therapy or omission of pharmacological therapy |
| | - Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, |
| | fresh-frozen plasma, or cryoprecipitate |
| **Wound** | Presence of one or more of the following: |
| | Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms |
| | Chest drains |
| | Wound pain significant enough to require continuing or escalating analgesic intervention |
| **Pain** | Postoperative pain significant enough to require parenteral opioids and/or continuing or additional analgesia |
| **Endocrine** | New or additional requirements for blood sugar management |
| **Electrolyte** | Electrolyte (including sodium, urea, phosphate) imbalance requiring oral or intravenous intervention (not including potassium as included in renal category) |
| **Review** | Remaining in hospital for further review, investigation and/or procedure |

| | |
|---|---|
| **Assisted Ambulation** | A new or escalated post-operative requirement for mobility assistance (including wheelchair, crutches, zimmer frame, walking sticks or assistance) |

**Table 2:** The Cardiac Post-Operative Morbidity Score (C-POMS) as reported in Sanders et al. 2012.

**T3: Long-term assessment**

Patients were assessed 60 days after surgery, during the medical examination scheduled by the cardiac surgeons.

The same information investigated at T0, T1 and T2 (Table 1) were collected in both control and PRE-STAR groups, to evaluate a better postoperative recovery in who have gone through the Pre-Habilitation program.

**PRE-STAR program**

After being enrolled, PRE-STAR group patients were divided into groups of four according to the scores of the baseline assessment (T0), in order to plan Pre-Habilitation sessions tailored on individual patients' needs and abilities.

Each patient was supported and treated by synergism in the four dimensions for at least a four- week period:

- **Respiratory dimension**

Inspiratory muscle training, diaphragmatic training and increase in lung volumes by the Voldyne spirometric device.

- **Functional dimension**

Administration of aerobic workout at progressive intensity and length, both in continuous mode and in "aerobic interval training" with warm-up and cool-down phases; active limb and trunk kinesiotherapy by introduction of external loads from the second week (0.5kg dumbbells and 2kg elastic bands), performed in a seated position for the first two weeks and in a static standing position from the third week; proprioceptive exercises on static and dynamic balance performed firstly in bipodal and later in monopodal stance in gradual instability: full hand stance on the chair

- stance of two fingers per hand - stance of no more than one finger per hand - no stance. These exercises were performed with the mentorship of a physiotherapist three times a week in group sessions. Each session lasted forty-five minutes and the last one was no later than two days before surgery. Exercises were also promoted outside the sessions with the physiotherapist, i.e. on a stand-alone basis by sending weekly reminders (via WhatsApp). Exercises were prescribed following a gradual criteria and referring to an "Exercise Brochure" that was emailed to all patients. The intensity was adjusted to the patient's tolerance.

- **Nutritional dimension**

Sensitization of enrolled patients to follow the traditional Mediterranean diet characterized by a high consumption of fresh fruit and vegetables, legumes, nuts and unprocessed cereals; low consumption of meat and meat products and low consumption of dairy products (with the exception of the long-preservable cheeses). To help patients keep in mind the key nutritional instructions to follow, the PRE-STAR TEAM handed them an explicative brochure.

- **Psychological dimension**

The PRE-STAR TEAM has provided reassurance, enlightenment and day-to-day support, with the aim of accompanying and making the patient feel accompanied to surgery.

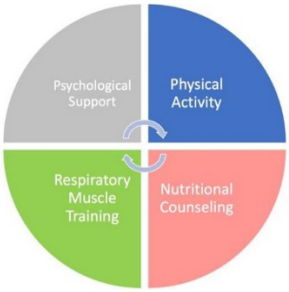



**Figure 1:** The PRE-STAR program, based on personalized and synergical improvement of four dimensions: Respiratory, Functional, Nutritional and Psychological.

**Statistical analysis**

As the primary endpoint of this study was the identification and quantification of total morbidity burden after adult cardiac surgery on post- operative days (C-POMS), the sample size was calculated taking a previous study as a reference [41]: Sanders et al. in "Predictors of total morbidity burden on days 3, 5, and 8 after cardiac surgery" used the C-POMS reference scale and identified mean scores associated with complications due to surgery in relation to post- operative days.

Power 0.80, alpha 0.05, n=66 per group; 10% increase for drop-outs; 10% increase for incomplete protocol.

Data is presented with descriptive tables and summary graphs.

Continuous variables are presented as mean ± standard deviation if normally distributed and as median (interquartile range) if non normally distributed. Categorial variables are presented with absolute and relative frequencies. The Kolmogorov-Smirnov test was used to determine whether the continuous variables were

Normally distributed. Two groups comparisons were performed using Fisher's exact test for categorical variables. On the other hand, continuous variables were compared with Student's t test or Mann Whitney's U test, as appropriate.

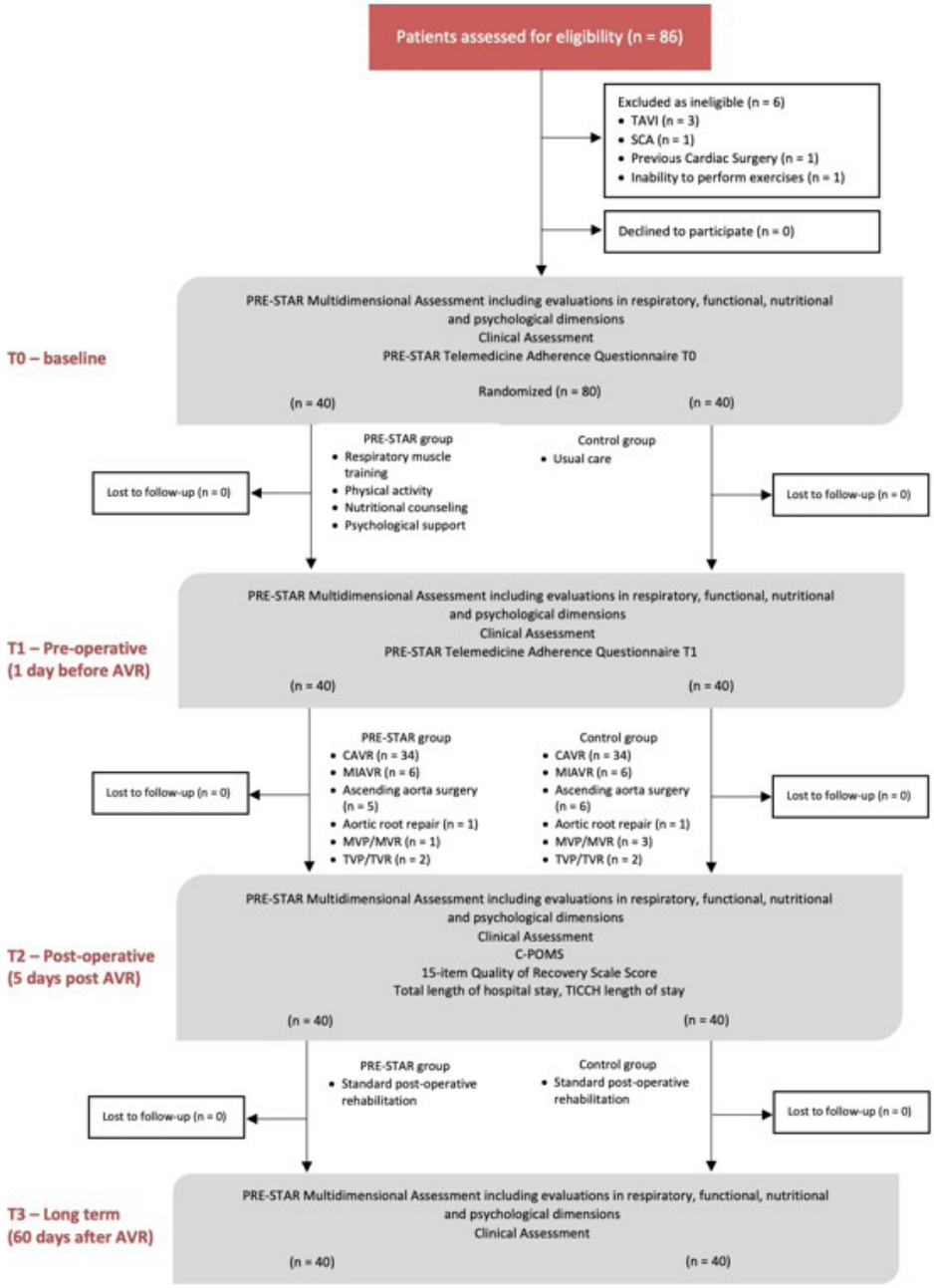



**Figure 2:** Design and flow of participants through the PRE-STAR study.

All tests were "two-tailed," and a type I error of 0.05 was accepted. Missing data was handled by replacing them with the mean value of the variable of interest, but only if their percentage was below 5 percent. Otherwise, the variable in question was not considered in the analysis. ANOVA analysis for repeated-measures variables at the indicated timepoints (T0, T1, T2, T3) was required for comparison.

Sphericity of the model was assessed by Greenhouse-Geisser epsilon.

All of these analyses were performed with MedCalc software version 15.8.

## Results

### Baseline participant characteristics

A total of 80 patients were considered eligible for inclusion and randomized into the PRE-STAR group (n = 40) or control group (n = 40). After randomization no patients withdrew their consent to participate in the PRE-STAR program and no patients were lost to follow-up. Of the 80 patients enrolled in the study at baseline, all completed the study.

Baseline characteristics of the entire cohort are summarized in Table 3.

| | ***Entire Cohort (n = 80)*** | | |
|---|---|---|---|
| | **Control PRE-STAR** | | |
| | **Group (n=40)** | **Group (n=40)** | **p value** |
| Age, years | 69.5 (62 – 75) | 72 (67 – 74) | 0.5 |
| Male, n (%) | 23 (57.5) | 21 (52.5) | 0.82 |
| BMI, kg/m2 | 28 ± 3.4 | 28 ± 4.9 | 0.96 |
| BMI > 30 kg/m2, n (%) | 18 (45) | 16 (40) | 0.82 |
| EF, % | 57.6 ± 6.8 | 58.8 ± 9.3 | 0.51 |
| Hypertension, n (%) | 32 (80) | 32 (80) | 1 |
| Dyslipidemia, n (%) | 26 (65) | 26 (65) | 1 |
| Current smoker, n (%) | 15 (37.5) | 16 (40) | 1 |
| Diabetes mellitus, n (%) | 11 (27.5) | 9 (22.5) | 0.8 |
| Family history of CVD, n (%) | 21 (52.5) | 22 (55) | 1 |
| Prior cardiac surgery, n (%) | 2 (5) | 1 (2.5) | 1 |
| Prior cardiovascular disease, n (%) | 11 (27.5) | 11 (27.5) | 1 |
| Bicuspid aortic valve, n (%) | 20 (50) | 18 (45) | 0.82 |
| Antiplatelet therapy, n (%) | 16 (40) | 15 (37.5) | 1 |
| Anticoagulant therapy, n (%) | 4 (10) | 5 (12.5) | 1 |
| EuroSCORE II, % | 1.26 ± 0.6 | 1.3 ± 0.6 | 0.76 |
| Isolated MIAVR | 6 (15) | 6 (15) | 1 |
| Isolated CAVR | 25 (62.5) | 26 (65) | 1 |
| CAVR + Aortic Root | 1 (2.5) | 1 (2.5) | 1 |
| CAVR + Ascending Aorta | 5 (12.5) | 4 (10) | 1 |
| CAVR + Mitral Valve | 1 (2.5) | 1 (2.5) | 1 |
| CAVR + Tricuspid Valve | 1 (2.5) | 2 (5) | 1 |
| CAVR + Mitral and tricuspid Valve | 1 (2.5) | - | 1 |

**Table 3:** Baseline Characteristics of the Entire Cohort.

Patient age was slightly higher in the PRE-STAR group than in the control group [69.5 (62 – 75) vs. 72 (67 – 74), p = 0.50]. The number of males was higher in the control group than in the PRE-STAR group [23 (57.5%) vs. 21 (52.5%), p = 0.82]. There was no s14zignificant difference in BMI between the control and PRE-STAR groups [28.0 ± 3.4 vs. 28.0 ± 4.9 kg/m$^2$, p = 0.96], but values of BMI >30 were higher in the control group than in the PRE-STAR group [18 (45%) vs. 16 (40%) kg/m$^2$, p = 0.82].

Ejection Fraction (EF) was slightly superior in the PRE-STAR group than in the control group, but with nonsignificant difference [58.8 ± 9.3 vs. 57.6± 6.8, p = 0.51].

Regarding cardiovascular risk factors (hypertension, dyslipidemia, smoking, diabetes mellitus, family history of CVD), CV medical history (prior cardiac surgery, prior CV disease, bicuspid aortic valve) and antiplatelet/anticoagulant therapy, there were no significant differences between the groups. The EuroSCORE II was not significantly different between the PRE-STAR group and the control group [1.30 ± 0.6 vs. 1.26 ± 0.6, p = 0.76].

Concerning the distribution of the two groups in the surgical procedure type, no significant difference was shown.

BMI= Body Mass Index; CAVR= Conventional Aortic Valve Replacement; CVD= Cardiovascular disease; MIAVR= Minimally Invasive Aortic Valve Replacement; MVR= Mitral Valve Replacement; MVP= Mitral Valve Repair; n= number of patients; NYHA= New York Heart Association; TVR= Tricuspid Valve Replacement; TVP= Tricuspid Valvuloplasty; VAS= Visual Analogue Scale.

**Intraoperative and postoperative data**

**Primary endpoint**

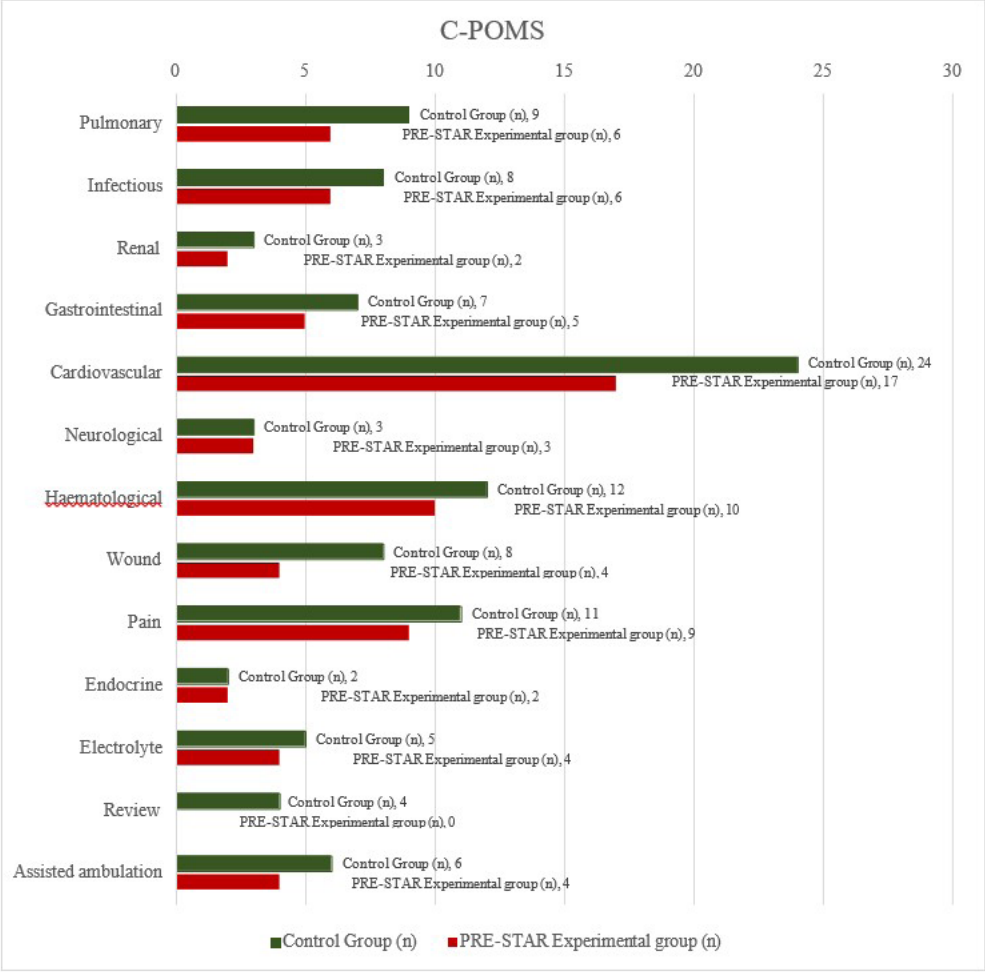
In patients who underwent PRE-STAR program C- POMS total score was significantly lower than in the control group [1.8 ± 1.2 vs. 2.6 ± 1.5, p =0.02]. Differences in single items were not statistically significant.

C-POMS extended results are reported in Table 4 and Graph 1.

| | Entire Cohort (n = 80) | | |
|---|---|---|---|
| | Control Group (n = 40) | PRE-STAR Group (n = 40) | P Value |
| Pulmonary, n (%) | 9 (22.5) | 6 (15) | 0.57 |
| Infectious, n (%) | 8 (20) | 6 (15) | 0.77 |
| Renal, n (%) | 3 (7.5) | 2 (5) | 1 |
| Gastrointestinal, n (%) | 7 (17.5) | 5 (12.5) | 0.76 |
| Cardiovascular, n (%) | 24 (60) | 17 (42.5) | 0.18 |
| Neurological, n (%) | 3 (7.5) | 3 (7.5) | 1 |
| Haematological, n (%) | 12 (30) | 10 (25) | 0.8 |
| Wound, n (%) | 8 (20) | 4 (10) | 0.35 |
| Pain, n (%) | 11 (27.5) | 9 (22.5) | 0.8 |
| Endocrine, n (%) | 2 (5) | 2 (5) | 1 |
| Electrolyte, n (%) | 5 (12.5) | 4 (10) | 1 |
| Review, n (%) | 4 (10) | 0 (0) | 0.12 |
| Assisted ambulation, n (%) | 6 (15) | 4 (10) | 0.74 |
| TOT, n (%) | 2.6 ± 1.5 | 1.8 ± 1.2 | 0.02 |

**Table 4:** C-POMS results in control group and PRE-STAR experimental group.

C-POMS= Cardiac Post-Operative Morbidity Score.




**Graph 1:** C-POMS outcomes after AVR.

**Functional dimension**

Table 5 shows the detailed results of functional dimension assessments. The baseline characteristics related to functional measurements showed no significant differences between the two groups.

At the end of the PRE-STAR Pre-Habilitation program (T1), all functional assessments are improved significantly in the experimental group.

The Short Physical Performance Battery (SPPB) gave us an overview of patients' ability/disability. Starting from exactly overlapping conditions between the two groups, at T1 there was a statistically significant difference in favor of the PRE-STAR group compared with the control group, which was maintained at T2 and T3 [T1: 11.0 ± 1.0 vs. 9.2 ± 1.4, $p < 0.001$; T2: 8.6 ± 1.6 vs. 6.0 ± 1.2, $p < 0.001$; T3: 10.8 ± 1.4 vs. 9.6 ± 1.6, $p < 0.001$]. SPPB trend in the four timepoints is summarized in Graph 2.

Regarding Handgrip, Table 5 and Graphs 3-4 show the highest value of three measurements for each hand and the strength was significant greater in the PRE-STAR group compared to the control group in both hands in all the analyzed timepoints [T1 – *right*: 30.6 ± 10.2 vs. 25.6 ± 7.4, $p = 0.01$; T2 – *right*: 27.0 ± 8.4 vs. 22.6 ± 5.9, $p = 0.01$; T3 – *right*: 10.8 ± 1.4 vs. 9.6 ± 1.6, $p = 0.01$; T1 – *left*: 28.2 ± 10.7 vs. 23.6 ± 6.9, $p = 0.001$; T2 – *left*: 24.7 ± 8.5 vs. 20.5 ± 6.0, $p = 0.001$; T3 – *left*: 27.8 ± 9.7 vs. 23.6 ± 7.3, = 0.001].

A better performance in the PRE-STAR group than in the control group was also demonstrated in Gait Speed Test at T1 and T2 in all four different speeds (*static*, *dynamic*, *semi-static*, *semi-dynamic*) [T1 – *static*: 4.2 ± 1.2 vs. 5.0 ± 1.4, p = 0.03; T1 – *dynamic*: 3.8 ± 0.9 vs. 4.8 ± 1.2, p = 0.01; T1 – *semi-static*: 3.8 ± 1.0 vs. 4.6 ± 1.2, p = 0.01; T1 – *semi-dynamic*: 3.9 ± 1.0 vs. 4.8 ± 1.0, p = 0.002; T2 – *static*: 4.9 ± 1.2 vs. 6.3 ± 1.8, p = 0.03; T2 – *dynamic*: 4.6 ± 1.1 vs. 5.9 ± 1.6, p = 0.01; T2 – *semi-static*: 4.5 ± 1.1 vs. 5.9 ± 1.6, p = 0.01; T2 – *semi-dynamic*: 4.5 ± 1.0 vs. 6.0 ± 1.6, p = 0.002], while at T3 significant difference was demonstrated only in the *static speed* [4.0 ± 1.1 vs. 4.6 ± 1.1, p = 0.03]. Gait Speed Test trend is pointed out in Graphs 5 to 8.

Significant differences were also observed in all SF-36 items except for *social functioning*, with improved findings in the PRE-STAR group compared with the control group: *physical functioning* [T1: 2.5 ± 0.4 vs. 2.1 ± 0.5, p = 0.001; T2: 2.2 ± 0.5 vs. 1.8 ± 0.4, p = 0.001; T3: 2.7 ± 0.2 vs. 2.4 ± 0.4, p = 0.001]; *role limitations due to physical health* [T1: 1.8 ± 0.5 vs. 1.6 ± 0.5, p = 0.02; T2: 1.5 ± 0.5 vs. 1.1 ± 0.2, p = 0.02; T3: 1.6 ± 0.3 vs. 1.5 ± 0.4, p = 0.02]; r*ole limitations due to emotional problems* [T1: 2.0 ± 0.5 vs. 1.5 ± 0.5, p = 0.001; T2: 1.5 ± 0.5 vs. 1.2 ± 0.3, p = 0.001; T3: 1.9 ± 0.2 vs. 1.6 ± 0.4, p = 0.001]; *energy/fatigue* [T1: 3.9 ± 0.4 vs. 3.6 ± 0.5, p = 0.001; T2: 4.1 ± 0.5 vs. 3.2 ± 0.7, p = 0.001; T3: 3.6 ± 0.4 vs. 3.6 ± 0.5]; *emotional well-being* [T1: 4.1 ± 0.4 vs. 3.5 ± 0.4, p< 0.001; T2: 4.0 ± 0.4 vs. 3.3 ± 0.5, p < 0.001; T3: 4.0 ± 0.4 vs. 3.7 ± 0.4, p < 0.001]; *pain* [T1: 1.3 ± 0.5 vs. 2.4 ± 0.7, p < 0.001; T2: 3.0 ± 0.6 vs. 3.7 ± 0.7, p < 0.001; T3: 1.3 ± 0.5 vs. 1.4 ± 0.5, p < 0.001]; *general health* [3.2 ± 0.3 vs. 2.9 ± 0.4, p < 0.001; T2: 3.3 ± 0.4 vs. 2.8 ± 0.5, p < 0.001; T3: 3.3 ± 0.4 vs. 3.1 ± 0.3, p < 0.001]. As foretold, the results gained on *social functioning* were not significant [T1: 2.9 ± 0.5 vs. 3.1 ± 0.4, p = 0.78; T2: 3.1 ± 0.5 vs. 3.0 ± 0.4, p = 0.78; T3: 3.0 ± 0.2 vs. 2.9 ± 0.4, p = 0.78]. Trend of the SF-36 items are shown separately in Graphs 9 to 16.

| | | | ***Entire Cohort (n = 80)*** | |
|---|---|---|---|---|
| | | **Control Group (n = 40)** | **PRE-STAR Group (n = 40)** | ***p value*** |
| ***SPPB*** | | | | |
| | T0 | 9.2 ± 1.6 | 9.0 ± 1.6 | |
| | T1 | 9.2 ± 1.4 | 11.0 ± 1.0 | *Between < 0.001* |
| | T2 | 6.0 ± 1.2 | 8.6 ± 1.6 | *Within < 0.001* |
| | T3 | 9.6 ± 1.6 | 10.8 ± 1.4 | *Interaction < 0.001* |
| ***HANDGRIP KG*** | | | | |
| **Right** | | | | |
| | T0 | 26.0 ± 7.5 | 25.6 ± 10.6 | *Between 0.01* |
| | T1 | 25.6 ± 7.4 | 30.6 ± 10.2 | *Within < 0.001* |
| | T2 | 22.6 ± 5.9 | 27.0 ± 8.4 | *Interaction < 0.001* |
| | T3 | 25.9 ± 7.4 | 29.9 ± 9.8 | |
| **Left** | | | | |
| | T0 | 23.6 ± 6.9 | 23.4 ± 9.7 | *Between 0.001* |
| | T1 | 23.4 ± 6.7 | 28.2 ± 10.7 | *Within < 0.001* |
| | T2 | 20.5 ± 6.0 | 24.7 ± 8.5 | *Interaction < 0.001* |
| | T3 | 23.6 ± 7.3 | 27.8 ± 9.7 | |
| ***GAIT SPEED*** | | | | |

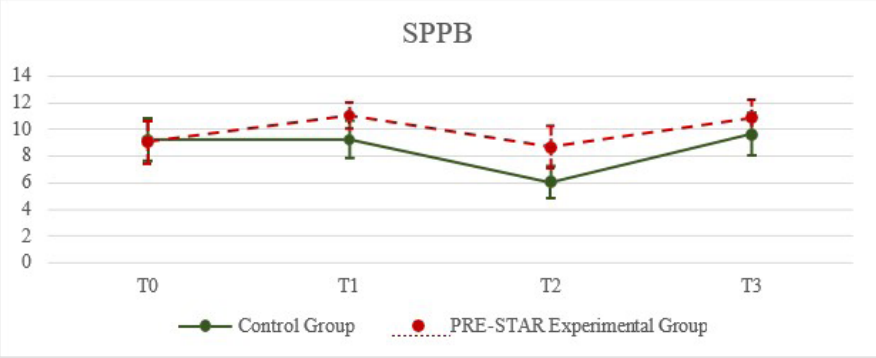
| | | | | |
|---|---|---|---|---|
| **Static** | | | | |
| | T0 | 5.0 ± 1.4 | 5.1 ± 1.8 | *Between 0.03* |
| | T1 | 5.0 ± 1.4 | 4.2 ± 1.2 | *Within < 0.001* |
| | T2 | 6.3 ± 1.8 | 4.9 ± 1.2 | *Interaction < 0.001* |
| | T3 | 4.6 ± 1.1 | 4.0 ± 1.1 | |
| **Dynamic** | | | | |
| | T0 | 4.4 ± 1.1 | 4.5 ± 1.4 | *Between 0.01* |
| | T1 | 4.8 ± 1.2 | 3.8 ± 0.9 | *Within < 0.001* |
| | T2 | 5.9 ± 1.6 | 4.6 ± 1.1 | *Interaction < 0.001* |
| | T3 | - | - | |
| **Semi-static** | | | | |
| | T0 | 4.4 ± 1.1 | 4.5 ± 1.3 | *Between 0.01* |
| | T1 | 4.6 ± 1.2 | 3.8 ± 1.0 | *Within < 0.001* |
| | T2 | 5.9 ± 1.6 | 4.5 ± 1.1 | *Interaction < 0.001* |
| | T3 | - | - | |
| **Semi-dynamic** | | | | |
| | T0 | 4.4 ± 1.0 | 4.6 ± 1.4 | *Between 0.002* |
| | T1 | 4.8 ± 1.0 | 3.9 ± 1.0 | *Within < 0.001* |
| | T2 | 6.0 ± 1.6 | 4.5 ± 1.0 | *Interaction < 0.001* |
| | T3 | - | - | |
| ***SF-36*** | | | | |
| **Physical Functioning** | | | | |
| | T0 | 2.2 ± 0.4 | 2.2 ± 0.5 | *Between 0.001* |
| | T1 | 2.1 ± 0.5 | 2.5 ± 0.4 | *Within < 0.001* |
| | T2 | 1.8 ± 0.4 | 2.2 ± 0.5 | *Interaction < 0.001* |
| | T3 | 2.4 ± 0.4 | 2.7 ± 0.2 | |
| **Role limitations due to physical** | | | | |
| **health** | | | | |
| | T0 | 1.7 ± 0.6 | 1.7 ± 0.8 | *Between 0.02* |
| | T1 | 1.6 ± 0.5 | 1.8 ± 0.5 | *Within < 0.001* |

| | | | | |
|---|---|---|---|---|
| | T2 | 1.1 ± 0.2 | 1.5 ± 0.5 | *Interaction < 0.001* |
| | T3 | 1.5 ± 0.4 | 1.6 ± 0.3 | |
| **Role limitations due to emotional** | | | | |
| **problems** | | | | |
| | T0 | 1.8 ± 0.6 | 1.8 ± 0.8 | *Between 0.001* |
| | T1 | 1.5 ± 0.5 | 2.0 ± 0.5 | *Within < 0.001* |
| | T2 | 1.2 ± 0.3 | 1.5 ± 0.5 | *Interaction 0.002* |
| | T3 | 1.6 ± 0.4 | 1.9 ± 0.2 | |
| **Energy/Fatigue** | | | | |
| | T0 | 3.9 ± 0.6 | 3.8 ± 0.5 | *Between 0.001* |
| | T1 | 3.6 ± 0.5 | 3.9 ± 0.4 | *Within < 0.001* |
| | T2 | 3.2 ± 0.7 | 4.1 ± 0.5 | *Interaction < 0.001* |
| | T3 | 3.6 ± 0.5 | 3.6 ± 0.4 | |
| **Emotional well-being** | | | | |
| | T0 | 3.8 ± 0.4 | 3.8 ± 0.4 | *Between < 0.001* |
| | T1 | 3.5 ± 0.4 | 4.1 ± 0.4 | *Within < 0.001* |
| | T2 | 3.3 ± 0.5 | 4.0 ± 0.4 | *Interaction < 0.001* |
| | T3 | 3.7 ± 0.4 | 4.0 ± 0.4 | |
| **Social functioning** | | | | |
| | T0 | 3.1 ± 0.4 | 3.1 ± 0.4 | *Between 0.78* |
| | T1 | 3.1 ± 0.4 | 2.9 ± 0.5 | *Within 0.38* |
| | T2 | 3.0 ± 0.4 | 3.1 ± 0.5 | |
| | T3 | 2.9 ± 0.4 | 3.0 ± 0.2 | |
| **Pain** | | | | |
| | T0 | 2.1 ± 0.8 | 2.2 ± 0.8 | *Between < 0.001* |
| | T1 | 2.4 ± 0.7 | 1.3 ± 0.5 | *Within < 0.001* |
| | T2 | 3.7 ± 0.7 | 3.0 ± 0.6 | *Interaction < 0.001* |
| | T3 | 1.4 ± 0.5 | 1.3 ± 0.5 | |
| **General health** | | | | |

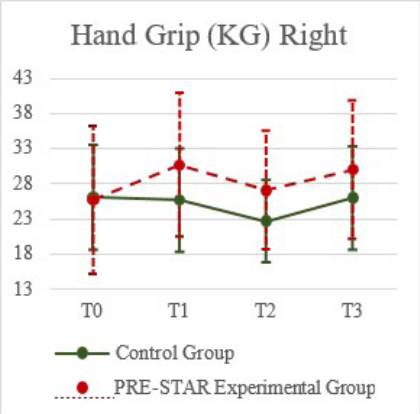
| | | | | |
|---|---|---|---|---|
| | T0 | 3.1 ± 0.4 | 3.2 ± 0.3 | *Between < 0.001* |
| | T1 | 2.9 ± 0.4 | 3.2 ± 0.3 | *Within 0.02* |
| | T2 | 2.8 ± 0.5 | 3.3 ± 0.4 | *Interaction 0.01* |
| | T3 | 3.1 ± 0.3 | 3.3 ± 0.4 | |

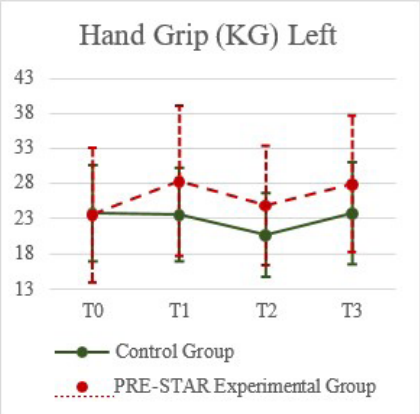
**Table 5:** Functional dimension test results in control group and PRE-STAR experimental group.

SF-36= 36-Item Short Form Health Survey; SPPB= Short Physical Performance Battery.

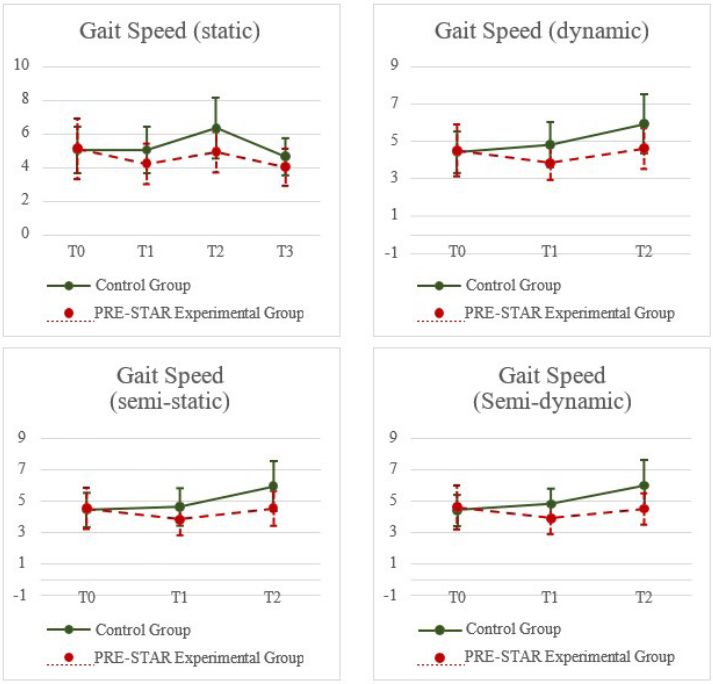



**Graph 2:** Trend of SPPB in the four timepoints.



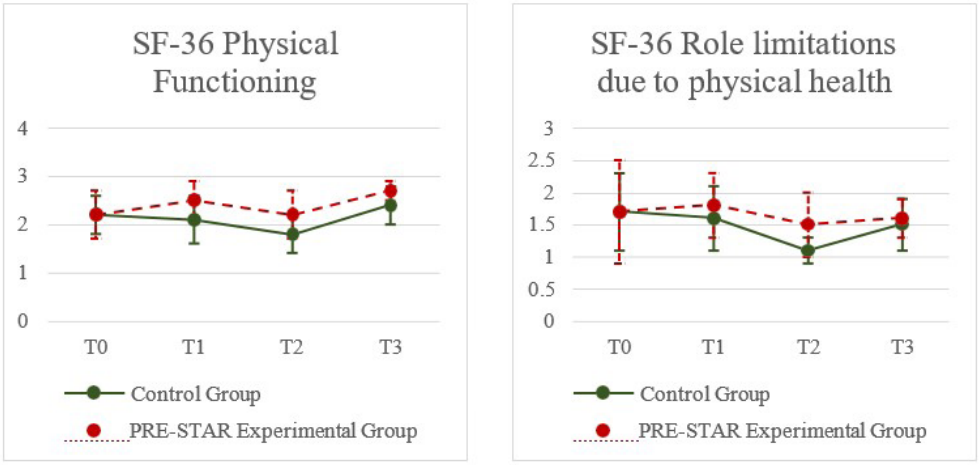



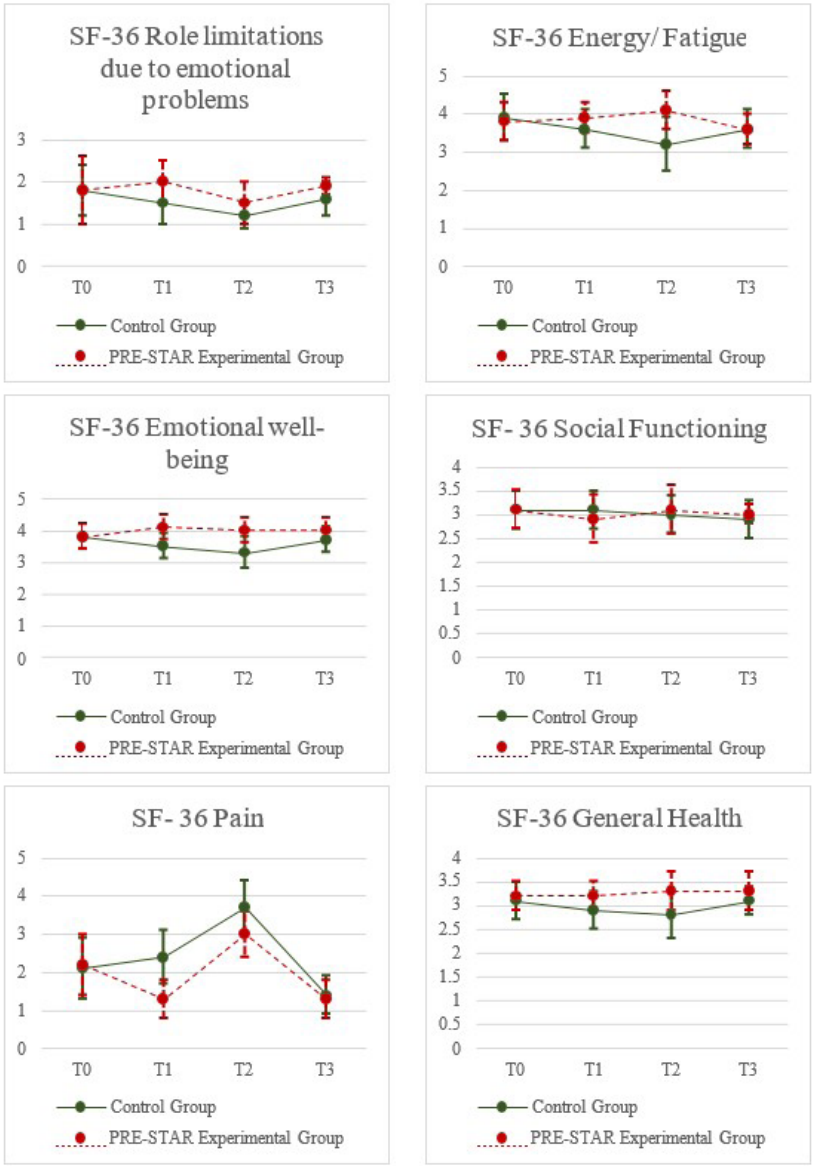

**Graph 3-4:** Trend of Hand Grip in the four timepoints.




**Graph 5:** Trend of Gait Speed (static) in the four timepoints.

**Graph 6 to 8:** Trend of Gait Speed (dynamic, semi-static and semi-dynamic) in T0, T1 and T2.





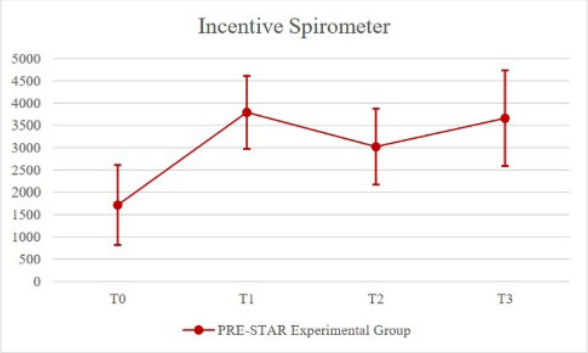

**Graph 9 to 16:** Trend of SF-36 in the four timepoints.

**Respiratory dimension**

Respiratory dimension assessmentwas performed only in the PRE-STAR group, showing a significant increase in terms of liters (Vital Capacity) in the utilization of incentive spirometry at the four different timepoints [T0: $1714 \pm 899$, $p < 0.001$; T1: $3794 \pm 818$, $p < 0.001$; T2: $3025 \pm 852$, $p < 0.001$; T3: $3662 \pm 1072$, $p < 0.001$]. In more detail, vital capacity showed a significant increase in maximum mobilizable air volume at T1 for the PRE-STAR group, with a slight inflection at T2. Values still remain largely above baseline even at T2. This data can be observed in Table 6 and Graph 17.

| | *PRE-STAR Group (n = 40)* | *p value* |
|---|---|---|
| ***Incentive*** | | |
| ***Spirometer*** | | |
| T0 | 1714 ± 899 | *< 0.001* |
| T1 | 3794 ± 818 | |
| T2 | 3025 ± 852 | |
| T3 | 3662 ± 1072 | |

**Table 6:** Respiratory dimension test results in the PRE-STAR group.




**Graph 17:** Trend of Incentive spirometer in the four timepoints in the PRE-STAR group.

### Nutritional dimension

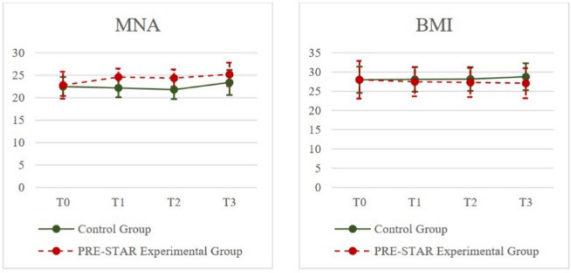
Nutritional dimension assessment results are shown in Table 7. The baseline characteristics related to these measurements showed no significant differences between the two groups.

It's pointed out that there was a significant difference in MNA score between the PRE-STAR group and the control group in T1, T2 and T3 [T1: 24.6 ± 1.9 vs. 22.2 ± 2.1, p < 0.001; T2: 24.4 ± 1.9 vs. 21.8 ± 2.1, p < 0.001; T3: 25.2 ± 2.6 vs. 23.4 ± 2.8, p < 0.001] – Graph 18, while this was not so much evidenced in the BMI score [T1: PRE-STAR group 27.5 ± 3.8 vs. control group 28.1 ± 3.2, p = 0.31; T2: 27.3 ± 3.8 vs. 28.2 ± 3.1, p = 0.31; T3: 27.1 ± 3.9 vs. 28.8 ± 3.5, p = 0.31] – Graph 19.

| | | *Entire Cohort (n = 80)* | |
|---|---|---|---|
| | **Control Group (n = 40)** | **PRE-STAR Group (n = 40)** | **p value** |
| ***MNA*** | | | |
| T0 | 22.5 ± 2.1 | 22.8 ± 3.0 | *Between < 0.001* |
| T1 | 22.2 ± 2.1 | 24.6 ± 1.9 | *Within < 0.001* |
| T2 | 21.8 ± 2.1 | 24.4 ± 1.9 | *Interaction < 0.001* |
| T3 | 23.4 ± 2.8 | 25.2 ± 2.6 | |
| ***BMI*** | | | |
| T0 | 28.0 ± 3.4 | 28.0 ± 4.9 | *Between 0.31* |
| T1 | 28.1 ± 3.2 | 27.5 ± 3.8 | *Within 0.45* |
| T2 | 28.2 ± 3.1 | 27.3 ± 3.8 | |
| T3 | 28.8 ± 3.5 | 27.1 ± 3.9 | |

**Table 7:** Nutritional dimension test results in control group and PRE-STAR group.

BMI= Body Mass Index; MNA= Mini Nutritional Assessment.




**Graph 18-19:** Trend of MNA and BMI in the four timepoints.

### Psychological dimension

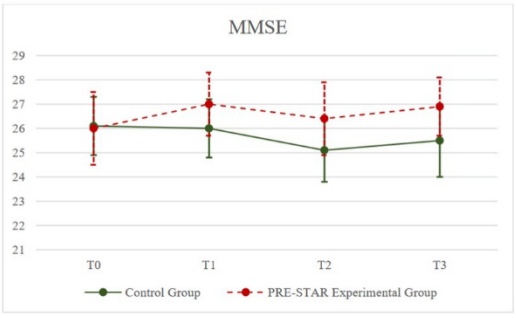
Psychological dimension assessment results are shown in Table 8. The baseline characteristics related to these measurements showed no significant differences between the two groups.

MMSE, BAI and BDI scales have highlighted a statistically significant difference between the PRE- STAR group and the control group in T1, T2 and T3: MMSE [T1: 27.0 ± 1.3 vs. 26.0 ± 1.2, $p < 0.001$; T2: 26.4 ± 1.5 vs. 25.1 ± 1.3, $p < 0.001$; T3: 26.9 ± 1.2 vs. 25.5 ± 1.5,$p < 0.001$]; BAI [T1: 14.1 ± 8.9 vs. 23.3 ± 8.3, $p < 0.001$; T2: 14.1 ± 8.1 vs. 23.9 ± 8.3, $p < 0.001$; T3: 5.2 ± 3.0 vs. 7.4 ± 3.2, $p < 0.001$]; BDI [T1: 9.5 ± 6.1 vs. 16.5 ± 6.5, $p < 0.001$; T2: 9.4 ± 5.5 vs. 17.1 ± 6.9, $p < 0.001$; T3: 5.4 ± 3.4 vs. 7.1 ± 3.8, $p < 0.001$] – Graphs 20 to 22.

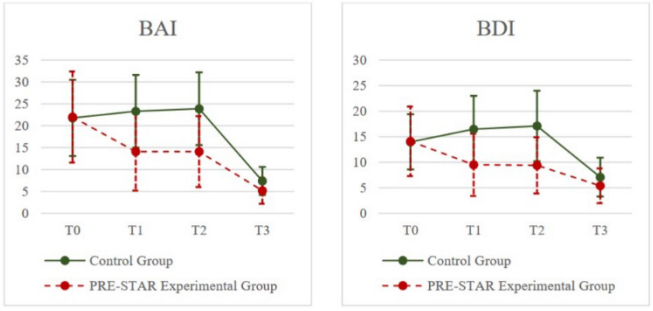
| | | *Entire Cohort (n = 80)* | |
|---|---|---|---|
| | **Control Group (n = 40)** | **PRE-STAR Group (n = 40)** | **p value** |
| ***MMSE*** | | | |
| T0 | 26.1 ± 1.2 | 26.0 ± 1.5 | *Between < 0.001* |
| T1 | 26.0 ± 1.2 | 27.0 ± 1.3 | *Within < 0.001* |
| T2 | 25.1 ± 1.3 | 26.4 ± 1.5 | *Interaction < 0.001* |
| T3 | 25.5 ± 1.5 | 26.9 ± 1.2 | |
| ***BAI*** | | | |
| T0 | 21.8 ± 8.7 | 22.0 ± 10.4 | *Between < 0.001* |
| T1 | 23.3 ± 8.3 | 14.1 ± 8.9 | *Within < 0.001* |
| T2 | 23.9 ± 8.3 | 14.1 ± 8.1 | *Interaction < 0.001* |
| T3 | 7.4 ± 3.2 | 5.2 ± 3.0 | |
| ***BDI*** | | | |
| T0 | 14.0 ± 5.4 | 14.1 ± 6.8 | *Between < 0.001* |
| T1 | 16.5 ± 6.5 | 9.5 ± 6.1 | *Within < 0.001* |
| T2 | 17.1 ± 6.9 | 9.4 ± 5.5 | *Interaction < 0.001* |
| T3 | 7.1 ± 3.8 | 5.4 ± 3.4 | |

**Table 8:** Psychological dimension test results in control group and PRE-STAR experimental group.

BAI= Beck's Anxiety Inventory; BDI= Beck's Depression Inventory; MMSE= Mini-Mental State Examination.




**Graph 20:** Trend of MMSE in the four timepoints.




**Graph 21-22:** Trend of BAI and BDI in the four timepoints.

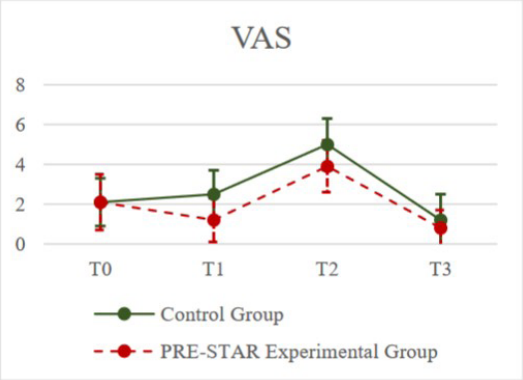
### Other data

Concerning VAS, at T1 there was a statistically significant difference in terms of experience of pain between the PRE-STAR group and the control group, which was maintained at T2 and T3 [T1: 2.1 ± 1.4 vs. 2.1 ± 1.4, $p = 0.002$; T2: 1.2 ± 1.1 vs. 2.5 ± 1.2, $p = 0.002$; T3: 0.8 ± 0.9 vs. 1.2 ± 1.3, $p = 0.002$] – Table 9 and Graph 23.

| | | **Entire Cohort (n = 80)** | |
|---|---|---|---|
| | **Control Group (n = 40)** | **PRE-STAR Group (n = 40)** | **p value** |
| **VAS** | | | |
| T0 | 2.1 ± 1.2 | 2.1 ± 1.4 | Between 0.002 |
| T1 | 2.5 ± 1.2 | 1.2 ± 1.1 | Within < 0.001 |
| T2 | 5.0 ± 1.3 | 3.9 ± 1.3 | Interaction < 0.001 |
| T3 | 1.2 ± 1.3 | 0.8 ± 0.9 | |

**Table 9:** Trend of VAS in the four timepoints.

VAS= Visual analogue scale.




**Graph 23:** Trend of patient's perception of pain as measured by VAS in the four timepoints.

At T2, i.e. on the fifth postoperative day, 15-QoR data, hospital and TICCH length of stay were also collected, as shown in Table 10 and Graphs 24 to 26.

Findings regarding the total length of hospital stay have shown a significant difference in the study group that participated in the PRE-STAR program compared with the control group [7.5 ± 1.4 vs. 8.3 ± 1.5, p = 0.02]. The same can be said for some of the 15-QoR's items: *been able to enjoy food* [6.3 ± 1.7 vs. 5.4 ± 1.6, p = 0.02]; *feeling rested* [6.6 ± 1.2 vs. 6.0 ± 1.4, p = 0.04]; *able to look after personal toilet and hygiene unaided* [8.7 ± 1.2 vs. 7.4 ± 1.9, p < 0.001]; *able to communicate with family or friend* [8.9 ± 0.9 vs. 8.4 ± 1.2, p < 0.04]; *able to return to work or usual home activities* [7.2 ± 1.3 vs. 6.5 ± 1.3, p = 0.02]; *feeling comfortable and in control* [6.6 ± 1.4 vs. 5.9 ± 1.1, p = 0.02]; *moderate pain* [5.3 ± 1.6 vs. 3.4 ± 1.2, p < 0.001]; *severe pain* [7.4 ± 1.7 vs. 5.4 ± 2.0, p < 0.001]; *feeling worried or anxious* [5.7 ± 1.8 vs. 4.6 ± 1.7, p = 0.01]; *feeling sad or depressed* [7.1 ± 1.8 vs. 6.2 ± 1.5, p = 0.02]. Other 15-QoR's items were not shown to be significant: *able to breathe easily* [PRE-STAR group 6.5 ± 1.6 vs. control group 6.0 ± 1.4, p = 0.14]; *have a good sleep* [6.8 ± 1.5 vs. 6.4 ± 1.3, p = 0.20]; *giving support from hospital doctors and nurses* [8.3 ± 1.0 vs. 8.2 ± 1.0, p = 0.66]; *having a feeling of general well-being* [5.7 ± 1.6 vs. ] 5.6 ± 1.0, p = 0.74; *nausea or vomiting* [5.6 ± 1.7 vs. 5.0 ± 1.5, p = 0.42].

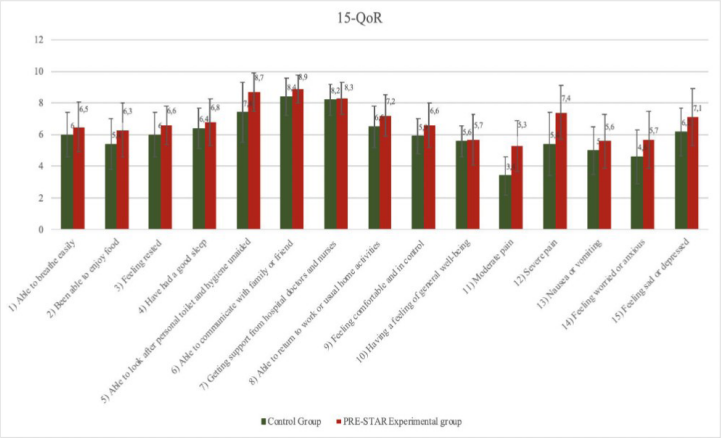
Not even data on TICCH length of stay showed statistically significant differences between PRE- STAR group and control group [2.2 ± 0.5 vs. 2.4 ± 0.6, p = 0.23].

| | | Entire Cohort (n = 80) | |
|---|---|---|---|
| | Control Group (n = 40) | PRE-STAR Group (n = 40) | p value |
| Total Length of hospital stay | 8.3 ± 1.5 | 7.5 ± 1.4 | 0.02 |
| TICCH Length of stay | 2.4 ± 0.6 | 2.2 ± 0.5 | 0.23 |
| 15-QoR | | | |
| 1) Able to breathe easily | 6.0 ± 1.4 | 6.5 ± 1.6 | 0.14 |
| 2) Been able to enjoy food | 5.4 ± 1.6 | 6.3 ± 1.7 | 0.02 |
| 3) Feeling rested | 6.0 ± 1.4 | 6.6 ± 1.2 | 0.04 |
| 4) Have had a good sleep | 6.4 ± 1.3 | 6.8 ± 1.5 | 0.2 |
| 5) Able to look after personal toilet and | 7.4 ± 1.9 | 8.7 ± 1.2 | < 0.001 |
| hygiene unaided | | | |
| 6) Able to communicate with family or | 8.4 ± 1.2 | 8.9 ± 0.9 | 0.04 |
| friend | | | |
| 7) Getting support from hospital doctors | 8.2 ± 1.0 | 8.3 ± 1.0 | 0.66 |
| and nurses | | | |
| 8) Able to return to work or usual home | 6.5 ± 1.3 | 7.2 ± 1.3 | 0.02 |
| activities | | | |

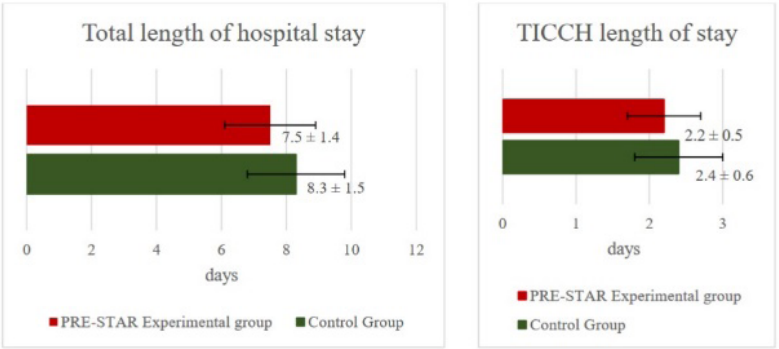
| | | | |
|---|---|---|---|
| 9) Feeling comfortable and in control | 5.9 ± 1.1 | 6.6 ± 1.4 | 0.02 |
| 10) Having a feeling of general well-being | 5.6 ± 1.0 | 5.7 ± 1.6 | 0.74 |
| 11) Moderate pain | 3.4 ± 1.2 | 5.3 ± 1.6 | < 0.001 |
| 12) Severe pain | 5.4 ± 2.0 | 7.4 ± 1.7 | < 0.001 |
| 13) Nausea or vomiting | 5.0 ± 1.5 | 5.6 ± 1.7 | 0.1 |
| 14) Feeling worried or anxious | 4.6 ± 1.7 | 5.7 ± 1.8 | 0.01 |
| 15) Feeling sad or depressed | 6.2 ± 1.5 | 7.1 ± 1.8 | 0.02 |
| TOT | 90.2 ± 9.5 | 102.6 ± 9.6 | 0.42 |

**Table 10:** Postoperative Outcomes in control group and PRE-STAR study group.

15-QoR= 15 item - Quality of Recovery Scale; TICCH= Cardiac Surgery Intensive Care Unit.




**Graph 24:** 15 item - Quality of Recovery Scale**.**




**Graph 25-26.** Total and TICCH length of stay.

**The impact of telemedicine on cardiac Pre-habilitation**

This study is one of the first to have declined in telematic form cardiac Pre-Habilitation available in traditional settings. Since the present Italian health care provision lacks pre-habilitation services, our study is designed as an effort to shape a tool that can fill this gap with low-cost and simple resources. Our protocol has planned to assess adherence at the beginning and at the end of the PRE-STAR program, demonstrating high scores in all patients enrolled in the study. This finding had different meanings in the two timepoints (T0, T1): at the beginning of the program (T0) it confirmed the high receptivity of patients in the period leading up to the surgery, while at the end (T1) it was suggestive of the satisfaction and ease with which patients participated in the tele-intervention.

This window of high adherence allowed the promotion of a lifestyle change that was radical in some ways. To appreciate what has just been outlined, it is enough to consider the total training volume that was offered to inactive patients with an average age of 72 (67 – 74).

## Discussion

The present study shows that Multidimensional Pre-Habilitation can reduce the burden of total morbidity after aortic valve replacement, both CAVR and MIAVR, on post-operative days. What has just been stated can be observed in the results of the study's primary endpoint, i.e. the Cardiac Post-Operative Morbidity Score (C-POMS). The data in Table 4 and Graph 1 shows that C-POMStotal score was significantly lower in the PRE- STAR group than in the control group [1.8 ± 1.2 vs. 2.6 ± 1.5, p = 0.02], even if single items were not statistically significant. Nevertheless, the Graph shows a clear trend in favor of the experimental group in the following items: *pulmonary* [PRE-STAR: 6 (15) vs. control: 9 (22.5), p = 0.57], *infectious* [6 (15) vs. 8 (20), P = 0.77], *gastrointestinal* [5 (12.5) vs. 7 (17.5), p = 0.76], *cardiovascular* [17 (42.5) vs. 24 (60), p = 0.18], *haematological* [10 (25) vs. 12 (30), p = 0.80], *wound* [4 (10) vs. 8 (20), p = 0.35], *pain* [9 (22.5) vs. 11 (27.5), p = 0.80], *review* [0 (0) vs. 4 (10), p = 0.12] and *assisted ambulation* [4 (10) vs. 6 (15), p = 0.74]. The statistical non-significance value at this time is justified by taking into account the fact that the proper sample size has not yet been attained, and we expect that as the study goes on, the items just cited will also show a significant difference between the two groups. Furthermore, PRE-STAR study reveals that such a Pre-Habilitation program can empower the patient with a greater reserve to face the physical, metabolic, and psychological stresses given by the aortic valve replacement. Results in all the four dimensions analyzed confirm this assumption and *Graphs* presented in the previous chapter clearly demonstrate this. As a matter of fact, the "advantage" gained during the PRE-STAR Pre-Habilitation program (measured at T1) is exploited in the post-operative period to cope with recovery after surgery. Thus, at T2 the measurements do not fall below those at baseline (T0).

Specifically, the PRE-STAR protocol confirms that patients awaiting elective surgery, if left to fend for themselves will wait in anxiety and fear and worsen their physical status by becoming less active. This can be observed in the functional dimension results: data and Graphs 2 to 8 show how patients who have underwent the PRE-STAR program before AVR achieved a statistically significant increase in all functional assessments (SPPB, Hand Grip and Gait Speed), with a p value never exceeding 0.03. Concerning the SPPB, while the PRE-STAR group never falls below the baseline level (T0), the control group experienced a continuous and progressive deterioration in performance, reaching levels of the scale that could be ascribed to mild/moderate disability. Moreover, as expected, the advantage over the control group obtained in the pre-operative (T1) was preserved in the short-term post-operative (T2). As for the long-term post-operative assessments (T3), an advantage over the control group was maintained as well, but to a minor extent compared to what was shown at T2, and this can be rationally justified by the fact that in the postoperative period both groups underwent the same standard postoperative rehabilitation. The same results can be evinced in Hand Grip and Gait Speed tests, in which patients in the control group at T1 performed equal or worse than their own performance at T0, while patients in the experimental group improved in both strength and speed.

Assessments regarding respiratory dimension were gathered only in the experimental group, because only these patients were provided with the Voldyne spirometric device required for respiratory exercises. Whereas logically the patients in the control group who did not have to do Pre- Habilitation were not provided with it. The PRE-STAR Pre-Habilitation program has increased lung volumes and capacities to significant proportions: the improvement is mostly evident at T1 with an increase of more than two liters [T0: 1714 ± 899; T1: 3794 ± 818, p < 0.001], but the results and Graph 17 show that it is preserved even in the postoperative period (T2, T3), never falling below the baseline value [T2: 3025 ± 852, p < 0.001; T3: 3662 ± 1072, p < 0.001]. This, in accordance with the literature, implies the reduction of postoperative pulmonary complications, length of stay, morbidity, mortality and costs [41-44,48-51].

Moving forward in the discussion of the dimensions under consideration, it can be claimed to have achieved remarkable results also in the optimization of the nutritional status of patients in the experimental group. In this protocol there was no actual counseling with a nutritionist, but only the delivery of a brochure with standard nutritional advice to decrease cardiovascular risk. In addition to this, the PRE-STAR TEAM worked to raise the patient's awareness of a healthy diet and lifestyle, and this effort has eventually been shown to be sufficient to have an improvement in the MNA score: the two groups started at baseline from about the same score [PRE-STAR 22.8 ± 3.0 vs. control 22.5 ± 2.1], then in the PRE-STAR group after the Pre-Habilitation time period there was evidence of decreased risk of malnutrition with increased test score [24.6 ± 1.9], which remained unchanged in the following post-operative assessments [T2: 24.4 ± 1.9; T3: 25.2 ± 2.6]; on the other hand, in the control group the score remained unchanged at T1, then decreased at T2 [21.8 ± 2.1] and increased at T3 [23.4 ± 2.8] but still remained at a lower value than the PRE-STAR group. In contrast, the protocol did not lead to appreciable changes in body mass index. All the while, it should be pointed out that other values such as abdominal circumference and body composition were not measured. Therefore, the conclusions that can be drawn in this regard are reduced.

Regarding the psychological dimension, just as mentioned above for the nutritional dimension, it was not possible to offer patients of the experimental group an effective psychological counseling with a specialist. Instead, what was done was to give daily psychological support to patients in the pre-operative period: the PRE- STAR TEAM made themselves completely available to patients, made any doubts clear and reassured when necessary. It must be added that each patient among the experimental group performed physiotherapy sessions in groups with 3 other people in the same clinical and psychological condition, making the sessions become an opportunity for dialogue, sharing and support among patients and with physical therapists. Patients have referred to feeling "accompanied" to the cardiac surgery, which is often a cause of stress, anxiety and depression especially in elderly patients with a chronic history of HF. 5t6yi9Having made that assumption, what the PRE- STAR study showed was actually a reduction in stress and anxiety levels at T1 in patients in the experimental group both in comparison with their condition at baseline [BAI - T0: 22.0 ± 10.4 vs. T1: 14.1 ± 8.9; BDI - T0: 14.1 ± 6.8 vs. T1: 9.5 ± 6.1] and in comparison with the control group, in which anxiety and depression in contrast increased [BAI - T0: 21.8 ± 8.7 vs. T1: 23.3 ± 8.3; BDI - T0: 14.0 ± 5.4 vs. T1: 16.5 ± 6.5]. This trend was maintained in the immediate post-operative period (T2), while in the long term (T3) the scores of both BAI and BDI of the two groups strongly decreased and almost equalized. The finding that at T3 the psychological results in the two groups were equal can be reasonably explained by the fact that both groups underwent standard rehabilitation and would have received the same care and attentions from the medical staff. In the PRE-STAR protocol, we also planned to assess general cognitive functioning with the MMSE, assuming that it could be affected by pre- and post-operative psychological stress. Our assumption was clearly supported by concrete data that can be visualized in Graph 20: the experimental group achieved a significant score improvement at T1 compared to baseline [T0: 26.0 ± 1.5 vs. T1: 27.0 ± 1.3] and compared to the control group in which, on the other hand, the MMSE score remained unchanged during the period of awaiting surgery [T0: 26.1 ± 1.2 vs. T1: 26.0 ± 1.2]. The difference in scores between the two groups remained unchanged in the assessments at T2 and T3, as if to emphasize that the improvement in scores in the preoperative period occurred as a result of less influence of an impaired psychological status on cognitive function.

Another scale that deserves comment is the SF-36: widespread improvement on all domains concerning physical health (*Physical Functioning, Role limitations due to physical health, Energy/ Fatigue, Pain, and General Health*) and psychological status (*Role limitations due to emotional problems, Emotional well-being*) was shown (Graphs 9 to 16), to reinforce what was previously reported about the impact that the PRE- STAR program had on these dimensions. Comparison with the control group shows that the improvement is significant on all domains at all timepoints of the study. Only the *Social Functioning* domain returns similar means between the two groups, with values not statistically significant ($p = 0.78$). We cannot give a precise explanation on this finding, but we suppose that the patients' social function was probably affected by the SARS-CoV2- related restrictions such as lockdowns, forbidden relative visits during hospitalization and during postoperative rehabilitation. Larger-scale data notlimited to this historical period at the height of the pandemic is needed to find a clear rationale.

To confirm one of the domains of the SF-36 (*Pain*) concerning patients' perception of pain, the VAS might be helpful: as can be seen from Graph 23, either at T1 or T2, the group undergoing Pre-Habilitation experienced significantly less pain than the control group [T1: 1.2 ± 1.1 vs. 2.5 ± 1.2; T2: 3.9 ± 1.3 vs. 5.0 ± 1.3, $p = 0.002$]. In the long-term follow-up (T3), the gap between the two groups decreased, reaching similar but still smaller values in the PRE-STAR group [0.8 ± 0.9 vs. 1.2 ± 1.3], as if to demonstrate that standard rehabilitation in the post-operative period is a relevant factor to consider.

To what has been discussed up to this point, it needs to be added that the PRE-STAR protocol has been shown to succeed in shortening the total length of hospital stay (Graph 25) in the experimental group in a statistically significant proportion ($p = 0.02$). On the other hand, TICCH length of stay was non significantly reduced ($p = 0.23$), but as can be evaluated in Graph 26, a positive trend is present even for this measure in the PRE-STAR group compared to the control group.

We hope that as the study continues and the number of patients enrolled increases, this finding will also become statistically significant.

Last but not least outcome that needs to be mentioned is the 15-item Quality of Recovery Scale that was assessed at T2, before hospital discharge. It did not show significant improvement in all its items but, as well as for TICCH length of stay, a positive trend in favor of the PRE-STAR group is clear, as it can be seen in Graph 24.

**Study limitations**

The study did not reach the sample size suggested by the power analysis, and therefore it has to keep on going in order to make the primary endpoint(C- POMS) statistically significant.

The significant differences between the two groups did not maintain the same in the postoperative period in all the measurements and this is understandable as all patients that underwent cardiac surgery received standard postoperative rehabilitation.

## Conclusions

The main results of the study demonstrate that a Multidimensional Pre-Habilitation program is feasible, safe and effective to reduced total morbidity burden after aortic valve replacement and to improve pre, peri and post-operative functional capacity (SPPB, Hand Grip, Gait Speed and SF-36), lung volumes by the Voldyne spirometric device, nutritional condition (MNA), general cognitive functioning, anxiety and depressive symptoms (MMSE, BAI and BDI). Furthermore, PRE-STAR study has demonstrated an improvement in experience of pain (VAS), perceived quality of life (SF-36), quality of recovery (15-QoR) and total length of hospital stay.

This data, taken with existing literature results, strongly highlights the need to develop standardized multidimensional Pre-Habilitation protocols for patients with aortic valve stenosis and to extend the studies to a wider range of cardiac surgical patients.

Moreover, attention must also be placed on telemedicine, which has been a key tool for the feasibility of our Pre-Habilitation program by reducing costs and risks associated with the high susceptibility of these patients to SARS-CoV-2 and other nosocomial infections.

However, the sample size is not enough large to make generalizable conclusions. Thus, more data is required to reveal the concrete beneficial effects of the PRE-STAR study in the patient population.

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## Competing interests

Authors have no conflict of interest to disclose.

## Author contributions

LL and BM: were responsible for data collection and wrote the manuscript. MA and FF: performed pre-habilitation sessions. FC: was responsible for statistical analysis. AR and MM: supervised the scientific content of the paper.

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