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Effects of tele-prehabilitation on clinical and muscular recovery in patients awaiting knee replacement: protocol of a randomised controlled trial

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ABSTRACT

Background The increasing prevalence of knee osteoarthritis and total knee arthroplasty (TKA) impose a significant socioeconomic burden in developed and developing countries. Prehabilitation (rehabilitation in the weeks immediately before surgery) may be crucial to prepare patients for surgery improving outcomes and reducing assistance costs. Moreover, considering the progress of telemedicine, candidates for TKA could potentially benefit from a tele-prehabilitation programme. We aim to evaluate the effects of a home-based tele-prehabilitation program for patients waiting for total knee replacement.

Methods and analysis Forty-eight male patients, aged 65–80, on a waiting list for TKA will be recruited and randomly assigned to the tele-prehabilitation intervention or control groups. Both groups will undergo the same 6-week exercise program (five sessions/week) and the same educational session (one per week). The tele-prehabilitation group will perform asynchronous sessions using a tablet, two accelerometers and a balance board (Khymeia, Padova, Italy), while the control group will use a booklet. The Western Ontario and McMaster Universities Osteoarthritis Index Questionnaire, at the end of the prehabilitation, will be the primary outcome. Secondary outcomes will include self-reported outcomes, performance tests and change in expressions of blood and muscle biomarkers. Ten healthy subjects, aged 18–30, will be also recruited for muscle and blood samples collection. They will not undergo any intervention and their data will be used as benchmarks for the intervention and control groups' analyses.

Ethics and dissemination This randomised controlled trial will be conducted in accordance with the ethical principles of the Declaration of Helsinki. This study has been approved by the Ethics Committee of Vita-Salute San Raffaele University (Milan, Italy. No. 50/INT/2022). The research results will be published in peer-reviewed publications.

Trial registration number NCT05668312.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial designed to investigate the effects of a completely asynchronous 6 weeks home-based tele-prehabilitation programme, delivered with advanced technologies to candidates for total knee arthroplasty.
⇒ The effects of tele-prehabilitation programme on biological markers of muscle and bone metabolism will also be evaluated in order to better describe the pathophysiology of these tissues in elderly with knee osteoarthritis.
⇒ Limitations are the recruitment limited to male subjects and not stratified for important prognostic variables, and the potential influence of postoperative rehabilitation on long-term follow-up.

INTRODUCTION

Background and rationale

Total knee arthroplasty (TKA) is the gold-standard procedure for treatment of end-stage knee osteoarthritis (OA) when conservative therapy has not produced satisfying results in reducing pain and improving function.[1] Risk factors of knee OA, such as population ageing, obesity and sedentary lifestyle, are constantly increasing. Therefore, the knee OA prevalence and the annual rates of knee replacement keep rising in all developed and developing countries, imposing a significant economic and organisational burden.[1–4] In 2019, in countries belonging to the Organisation for Economic Cooperation and Development (OECD), a mean of 137 surgeries for knee replacement per 100 000 people were performed (OECD Health Statistics 2021). In particular, 82 828 people underwent TKA in Italy, 18 135 in the only Lombardy.[5] In view of this, it is crucial developing care programmes aiming at optimising outcomes and reducing assistance costs.

Over the last decade, the systematic implementation of perioperative care protocols promoting patients' preparation to surgery and a reduced length of stay,[6] shown to guarantee enhanced postoperative recovery and costs reduction.[7] In particular, a minimum of 4–6 weeks of prehabilitation (or preoperative rehabilitation) in the weeks immediately before surgery, may reduce the risk of deteriorating functioning and global deconditioning while waiting for surgery and during early recovery after TKA, with significant improvements in patient-reported outcome measures (PROMs) before surgery and up to 3 months after.[8 9] A recent systematic review and meta-analysis[10] investigating the effects of prehabilitation before orthopaedic surgery, results in a higher improvement of preoperative function and health-related quality of life among patients undergoing all investigated procedures (TKA, THA, lumbar surgery), with moderate to low certainty of evidence.[10] However, the existing evidences on its effectiveness on postoperative outcomes remains controversial, especially for long-term outcomes.[11–13] It is well known that disuse and inactivity, occurring during illness and hospitalisation, result in rapid muscle atrophy and decreased muscle protein synthesis. Muscle stimulation in older individuals prior to disuse may prevent muscle deterioration ameliorating the recovery after surgery by improving protein synthesis, reducing proinflammatory released molecules, counteracting lipid oxidation and ectopic fat deposition thus preventing sarcopenia. Exercise promotes change in anabolic pathways such as muscular protein synthesis and lipid metabolism as metabolic fuel (via lipid droplets) during physical exercise. However, distance to healthcare providers, transport unviability or precarious financial situation represent a barrier to such services access.[14] In this prospective, remote home-based prehabilitation can optimise the delivery of care, especially by increasing the number of patients seen by a therapist in a single day, reducing the healthcare costs (both for healthcare system and for patients) and travel time. Moreover, the benefits for the patients are also better physical performance outcomes before surgery, higher knowledge on their own condition and preparation to surgery to undergo, as well as excellent satisfaction and compliance with the prehabilitation programme.[14 15]

After TKA, rehabilitation is fundamental to maximise patients' outcomes[16] and telerehabilitation has already proven, in several studies, to have effects comparable to face-to-face treatment in terms of pain relief, range of motion (ROM), quadriceps strength, physical function and satisfaction.[17 18] On the contrary, to date, there are only a few studies in literature evaluating the effectiveness of home-based prehabilitation programmes delivered using advanced technologies, with, moreover, heterogeneous rehabilitation systems, modalities and results.[8 14 19] In particular, in the musculoskeletal field, these studies investigate the effects of tele-prehabilitation delivered to patients affected by hip or knee OA, lumbar degenerative disease and primary meniscal tear. The delivery modality may be asynchronous, synchronous or both according to the prehabilitation programme. Asynchronous modality is normally used for educational sessions and mindfulness intervention, rarely for exercise, using video and/or slides that can be accessed via microsites created ad hoc.[20–22] Exercise therapy programmes, on the contrary, are usually delivered using a synchronous modality through video call systems.[8 15]

Considering the existing evidence on the effectiveness of preoperative rehabilitation and the established validity of telerehabilitation systems in guarantee outcomes similar to traditional rehabilitation, candidates for TKA could also deeply benefit from a tele-prehabilitation programme in terms of accessibility of care, costs and faster achievement of postoperative outcomes.

Objectives

We aim to evaluate the effects of a preoperative home-based rehabilitation programme delivered with an advanced technology system (Khymeia, Padova, Italy), for male patients waiting for total knee replacement. In particular, the primary objective of this study is to assess the superiority of a tele-prehabilitation programme compared to standard prehabilitation (remotely delivered with a booklet) in improving lower limb function. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[23] Questionnaire, at the end of prehabilitation, will be the primary outcome.

This study also aims at assessing at molecular level possible differences between groups in muscle function, pain, autonomy in the activity of daily living, adherence to treatment and patients' satisfaction with the prehabilitation modality. Through the analysis of fibre type distribution followed by differential muscle proteome evaluation and bioinformatic analysis in quadriceps protein muscle extracts and blood samples.[24] We will also evaluate possible changes in the expression of specific markers (Collagen 6a3, Matrix Metallopeptidase 2, Pprag coactivator 1alpha, AKT/pAKT, Miogenin, MURF, mTOR, fatty acids and ceramides) that the prehabilitation programme may be able to target.

Trial design

This trial protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials Statement.[25] The study is a monocentric, prospective, interventional, two-parallel groups, superiority randomised controlled trial.

METHODS

Study setting

This trial will be conducted from February 2023 at the IRCCS Galeazzi—Sant'Ambrogio Hospital in Milan (Italy). Subjects will be recruited and assessed at follow-up in an outpatient setting. The study protocol has been developed by the Laboratory of Movement and Sort Science and the data analysis will be conducted by an

independent Unit of Clinical Epidemiology of the IRCCS Galeazzi—Sant'Ambrogio Hospital. The trial (including the analyses) will be carried out from January 2023 to March 2025.

Eligibility criteria

Participants enrolled in the study will meet all the following inclusion criteria:

- Male sex of any ethnicity;
- Age between 65 and 80 years;
- Scheduled total knee arthroplasty according to the perioperative Fast-Track protocol;
- Preoperative criteria for home discharge (the surgeon assesses that the patient's clinical and functional preoperative conditions suggest that, after surgery, he would probably be discharged home and not to a facility).
- At least one cohabitating person, without known cognitive or severe motion impairments;
- Familiarity with tablet/computer usage and internet access;
- Informed consent signature.

Participants with one or more of the following criteria will be excluded:

- Scheduled revision of knee arthroplasty;
- Lower limb surgery or fractures within 6 months;
- Congenital or post-traumatic morphological alterations of the knee;
- Underwent rehabilitative programme within 6 months aiming at functional knee recovery;
- Neurological, muscular or oncological diseases;
- HIV, HCV, HBV, TPHA infection;
- Cognitive impairment reported in clinical anamnesis;
- Known allergic reactions to local anaesthetic;
- Non-suspendable anticoagulant drugs.

Ten healthy young subjects will be also recruited (Control-Young—Con-Y) only for discarded muscle and blood samples collection, which will be used as benchmarks for the intervention and control groups analyses. We will enrol males aged between 18 and 30, with a body mass index ≤30 kg/m^2, accessing the Galeazzi—Sant'Ambrogio Hospital for scheduled anterior cruciate ligament reconstruction. Subjects presenting neoplastic, muscular or neuromuscular diseases, infection of the sampling area, HIV, HCV, HBV and TPHA infections or taking non-suspendable anticoagulant drugs will not be included. These healthy young subjects will not undergo any prehabilitation programme.

All surgical activities will be performed by two different surgical teams.

Participants' timeline

As presented in figure 1, participants of both Tele-PRE and Con-O groups will be assessed at five time points: the day of the preadmission visit (T0), the day of surgery (T1), 7±2 days after surgery (T2), 15±2 days after surgery (T3), 90±7 days after surgery.

Further details on enrolment, interventions and assessments time points for Tele-PRE and Con-O groups are reported in appendix 1 in online supplemental file.[25]

Subjects in the Con-Y will only undergo biological material sampling, during surgery and demographic data collection, the day of surgery or during a presurgery visit.

Interventions

All subjects will undergo the same home-based, asynchronous, prehabilitation programme, with two different modalities according to their group allocation. Subjects allocated in the intervention group (Tele-prehabilitation—Tele-PRE) will perform the prehabilitative sessions using a virtual reality system, while subjects in the control group (Control-Older—Con-O) will follow the indications provided to them with a booklet. During the 6 weeks just before surgery, both Tele-PRE and Con-O groups will perform 5 sessions per week (30 sessions in total). Each session is planned as follows: 5 min of warm-up, approximately 30 min of work (including mobility, strengthening and balance exercises) and 5 min of cool-down. Subjects of both groups will also have to delve into a specific topic connected to their disease, surgery or recovery strategies, reading once a week an educational content (digital for the Tele-prehabilitation group, printed for the control one) dealing with:

- Information about knee OA and replacement

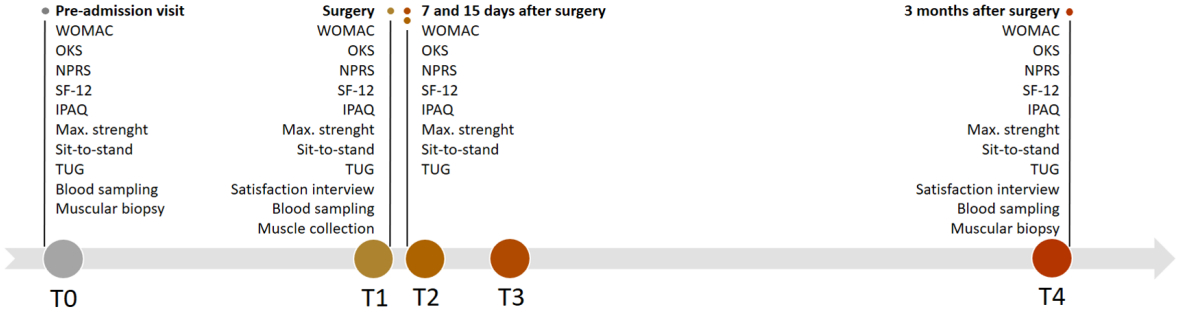

Figure 1 Participants' timeline. NPRS, Numeric Pain Rating Scale; OKS, Oxford Knee Score; TUG, Timed Up and Go test; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SF-12, Short Form-12; IPAQ, International Physical Activity Questionnaire.

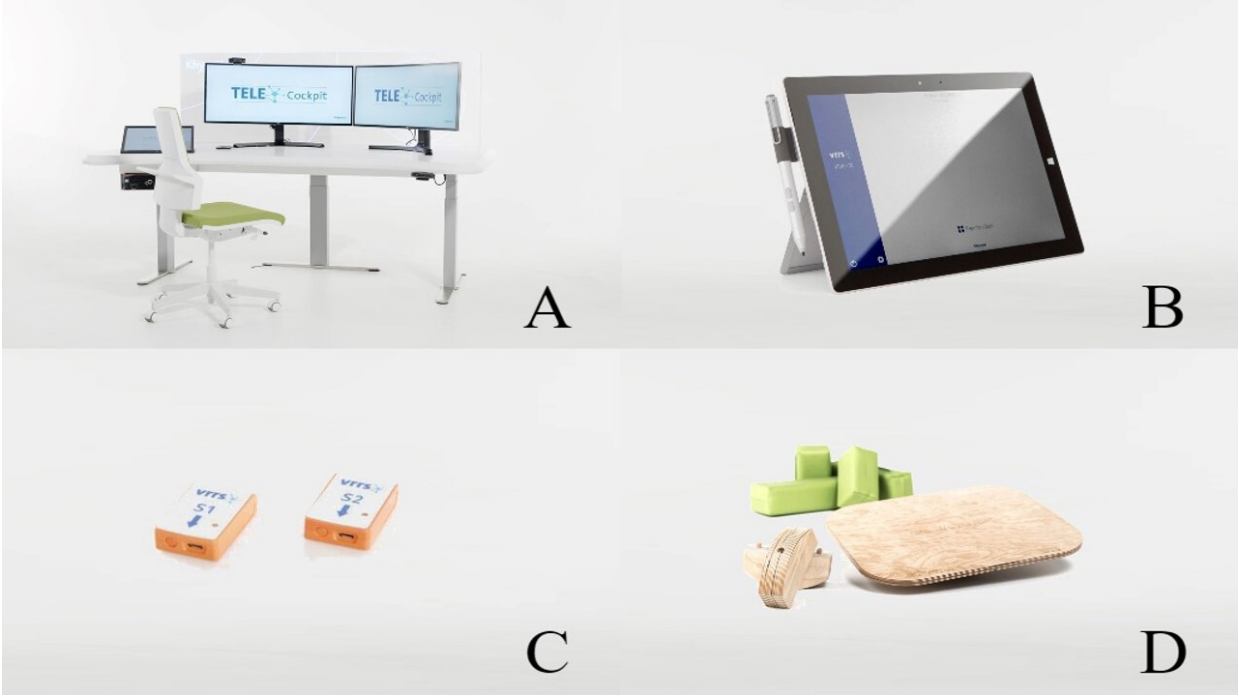

Figure 2 (A) TeleCockpit workstation, (B) VRRS Home Tablet, (C) VRRS Khymu and (D) VRRS Balance. VRRS, Virtual Reality Rehabilitation System.

- Postoperative symptoms, what to expect
- Advices for home organisation after surgery;
- Healthy life style: physical activity, nutrition and sleep;
- Advices for maintaining progresses;
- Motivational intervention.

Tele-prehabilitation

The tele-prehabilitation programme will be delivered using the following devices (Khymeia Health Innovation, Noventa Padovana, Padova, Italy):

- TeleCockpit, a workstation that the clinician can use to remotely manage a patient's home device, interact real-time or check the adherence to treatment (figure 2A). In particular, in this study the workstation will be used only to create the exercise prescriptions, to monitor adherence to treatment and to remotely manage exercise progression, if necessary. No prehabilitative activities will be addressed synchronously.
- Virtual Reality Rehabilitation System (VRRS) Home Tablet, with an uploaded mobile application for the exercises execution at home (figure 2B).
- VRRS Khymu, two accelerometers for patient's interaction with the virtual reality system during knee motion (figure 2C).
- VRRS Balance, a balance board for patient's interaction with the virtual reality system during centre-of-mass motion (figure 2D).

Subjects will be trained at T0 to use the devices they will bring home the same day (if belonging to the TELE-pre group) together with a printed reminder for device usage. They will be also provided with the following indications: performing sessions (1) when at least one cohabitating person is at home, (2) in a room that allows performing all movements safely and (3) respecting their pain and perceived effort.

Standard prehabilitation

Subjects in the control group will receive a booklet with printed descriptions and pictures of the exercises, containing also a 'prehabilitation diary' to be filled in at the end of each working session, to track the adherence to treatment.

Prehabilitation programme

The exercise volume of the 'work' section of the prehabilitative sessions will increase during the 6 weeks according to the patient's perceived effort. This progression will be based on the score, measured at the end of each workout, obtained at the Borg CR-10[26] scale self-administered by the patient at the end of each session. A score below 5 suggests increasing the workload in the next session. The progression of the working volume will be managed weekly by the clinician (a physiotherapist) in charge, for the intervention group connecting to the patient's device with the TeleCockpit workstation, and for the control group by communicating the changings in the prescription details during a phone call. In any case, all participants will receive a phone call once a week by the physiotherapist in charge, to promote retention and give them the opportunity to manifest any problem or difficulty related to their ongoing prehabilitation programme. After surgery, participants will receive phone calls only as reminders for the subsequent follow-up.

During each session, divided into warm-up, working phase and cool-down, subjects will perform the following exercises:

1. Warm-up (about 5 min)
   a. Knee bending and extension in lying position.
   b. Knee extensions while sitting.
   c. Get on tiptoes in standing position.
   d. March on site.
2. Working phase (about 30 min)
   a. Hip bending keeping the knee extended in lying position.
   b. Hip motion in space planes (imagining of drawing numbers with the tiptoe).
   c. Hip abduction keeping the knee extended side lying.
   d. Knee bending and hip extension in standing position.
   e. Half squat.
   f. Half lateral lunge.
   g. Monopodalic standing.
   h. Weight shifting (also on unstable surfaces) exercises.
3. Cool-down (about 5 min)
   a. Free walk.
   b. Leg swings while sitting.

Outcomes

Participants of the Tele-PRE and Con-O groups will be assessed for all the domains of the International Classification of Functioning. According to the timeline reported in figure 1, participants of the Tele-PRE and Con-O groups will undergo the following clinical assessments:

- WOMAC Questionnaire: a self-administered health status measure for pain, stiffness and function assessment in patients with hip or knee OA. It is composed of 24 items and uses a 5-point Likert scale (from 0 to 4). WOMAC Questionnaire has a minimal clinically important difference (MCID) is 12.5 points and an SEM of 5.1.[23 27]
- Oxford Knee Score (OKS) Questionnaire: a self-administrated questionnaire assessing symptoms and function in patients undergoing knee replacement. It is composed of 12 items and uses a 5-point Likert scale.[28] OKS has an MCID of 6 points and an SEM of 2.65 points.[29]
- Numeric Pain Rating Scale: an 11-point scale from 0 to 10 assessing pain. '0' is 'no pain', '10' is 'the most intense pain imaginable',[30] with an MCID of 1 point.[31]
- Short Form-12 Questionnaire: a questionnaire for health assessment, composed of 12 items, which can be self-administrated or completed through an interview. An algorithm is used to obtain the final composite score.[32] The SF-12 MCID is 1.8 for the physical component summary and 1.5 for the mental component summary.[33]
- International Physical Activity Questionnaire: a 9-item self-reported measure of physical activity. Adding up the week minutes of walking, moderate-intensity activity and vigorous-intense activity, multiplied per specific coefficients, the questionnaire estimates the overall Metabolic Equivalent of Task.[34]
- Passive and active knee Range Of Motion assessment: measured using a goniometer and expressed in degree.
- Sit-to-stand test: the subject is asked to stand-up and sit-down on a chair, standardised in size, for five consecutive times as much faster as he can. Time (in seconds) to complete the task is representative of the lower limb strength.[35] Normative data by age are provided by Bohannon.[35]
- Timed Up and Go test: the subject is asked, starting from seated on a chair, to stand-up, walk 3 m, go back to the chair and sit-down. Time (in seconds) to complete the task is representative of the subject's risk of fall.[36]
- Maximal knee extensors and flexors strength: measured using a dynamometer and expressed in kilograms.

At the end of the prehabilitation programme (T1), subjects in the Tele-PRE and Con-O groups will also:

- Fill in the 'Satisfaction interview', an ad hoc survey composed of 6-item 11-points scale (from 0 to 10). It investigates patient's satisfaction according to the modality of prehabilitation delivery (advanced technologies or printed booklet).
- Return the 'Prehabilitation diary' for the adherence assessment (only for the Con-O group).

Biological sampling and analyses

Quadriceps Muscle will be sampled by needle aspiration at time point T0 and T4 (only for participants belonging to Tele-PRE and Con-O groups) or discarded muscle material collection during surgical procedures (T1). Muscle sampling will be carried out by the surgeon in charge.

In collected muscle samples, myosin heavy chain isoform distribution will be assessed by Sodium Dodecyl Sulphate - PolyAcrylamide Gel Electrophoresis (SDS-PAGE), while levels of markers as PGC1alpha will be investigated by ELISA or western blot. Proteomics analysis will be conducted by Liquid Chromatography Mass Spectrometry (LC-MS), using TMT quantification, whereas lipidomics and sphingolipidomics analyses will be conducted by untargeted and targeted LC-MS.[37–42] Both the serum proteome and the biochemical characteristics of muscle present differences between men and women. Therefore, only men will be recruited so that varied proteins cannot be attributable to gender differences but to the intervention of patient.

Sample size

Based on the existing literature,[14] we expected to observe an effect size of 0.8 in WOMAC (primary outcome) between groups at the end of the tele-prehabilitation programme. Therefore, considering a test power of 80% and an alpha error of 5%, we have computed a sample size of 48 subjects, 24 for each group (taking into account

a possible drop-out rate of 15%–20%). The sample size calculation has been performed with the GPower software (Düsseldorf, Germany).

Recruitment

Candidates who comply with the inclusion and exclusion criteria will be asked to participate in the study by the surgeon involved and receive detailed information about the study protocol and objectives. If subjects agree to participate in the study, informed consent will be signed (appendices 2 and 3 in online supplemental file). Participants will not undergo any procedure included in the study protocol before the informed consent is given. After recruitment, subjects will be randomly allocated in the intervention (Tele-PRE) or in the control (Con-O) groups.

Allocation

In order to guarantee allocation concealment, a person not involved in the study will create a 1:1 ratio, computer-based, randomisation list. Recruited subjects will be allocated according to the randomisation list by a clinician involved in the study but extraneous to the participants' recruitment and assessment. Neither the surgeon, who is in charge of the subjects recruiting, nor the assessor will know the randomisation list.

Blinding

The assessor, who will carry out participant's clinical follow-up, the researchers in charge of the biological samples analyses and the statistician will be blinded to the allocation sequence. Subjects will be instructed not to reveal which group they belong to. Any deviation will be reported.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data collection, management and analysis

Data registered on source documents during participants' assessment will be entered in dedicated databases. Descriptive analyses of outcomes, study and patients characteristics will include means with SD, medians with ranges or frequencies with proportions, where appropriate. Shapiro-Wilk test will be used to assess the data distribution normality. T-test for independent data, or a non-parametric equivalent, will be used to study the differences between groups and within groups. The two-way analysis of variance will be used for all clinical data and for data related to muscle and blood samples. All analyses will be based on the intention-to-treat. When the follow-up of 25 participants is completed, the interim analysis will be conducted to evaluate the efficacy of the primary outcome. A $p<0.05$ will be considered statistically significant. All statistical analyses will be carried out using STATA MP V.16 software.[43]

Monitoring

Monitoring will be carried out by a certified external monitor. An ad hoc insurance policy is planned for the study. The principal investigator will allow monitoring by a Data Monitoring Committee, audits and inspections of the study by the ethics committee (EC), statutory bodies and quality assurance committees of all documents.

Any problem will be recorded by the researcher or his/her designee. If the problem is associated with an undesirable effect, it should be recorded in the appropriate section of the case report form (CRF).

If any adverse events related to the study are encountered, it is the responsibility of the sponsor to report them to the EC and competent authorities.

Ethics and dissemination

This trial will be conducted in accordance with the ethical principles of the Declaration of Helsinki, its recent enactments and good clinical practice guidelines, in compliance with regulatory and legal requirements. This protocol has been submitted to the EC in accordance with the legal requirements for formal approval of the study and approved on 14 October 2022. Any protocol modification will be discussed with the EC and applied only after formal approval.

Written informed consent is required for all subjects by the Principal Investigator or his/her designee.

Information related to subjects in the study will be kept confidential and managed in accordance with the relevant provisions (D.L.196/30 June 2003 as amended and EU Regulation 679/2016; Privacy Guarantor Guidelines of 24 July 2008). A signed written authorisation is required informing the subject about the personal health information collected by the subjects in the study, who will have access to this information and why, who will use or disclose this information, to whom the data will be disclosed and the reasons for this disclosure and, finally, the right of the study subjects to revoke the authorisation to use their personal health information. Essential documents and data resulting from the study will be kept at the principal investigators for at least 25 years after the study completion, while biological samples will be destroyed at the end of the study. If a subject withdraws or is excluded from the study for any of the aforementioned reasons, the reason and date of discontinuation will be recorded in the appropriate section of the CRF. In the event that a subject revokes authorisation to use personal health information, the principal investigator retains the ability to use all information collected before the subject's consent was revoked. Row data generated by our research will be made available as source document on reasonable request, while databases used for statistical analysis will be uploaded to an open access online repository. Databases will be made available at the end of the data analysis process. At the end of all follow-ups, participants will be provided with a brief Italian summary, reporting their clinical progresses through time points. Data collection

databases are available in the following data repository: https://osf.io/jwhc4/.

For the purposes of the research, anonymity will be guaranteed through the use of identification codes.

This study was approved by the EC of San Raffaele Hospital, Milano (Italy) (No. 50/INT/2022). The research results will be published in peer-reviewed publications.

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Contributors SGu, JV and LM conceived the study and designed the study protocol; CG and ET contributed to the design of the final study and provided the technical expertise for biological analysis; ES and DB contributed to the design of the final study and revised the manuscript; SGi and GC contributed to manuscript revision and provided biostatistical and epidemiological support. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

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