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ENIGMA-shock: protocol for a study framEwork for aN InteGrated assessMent of cArdiac rehabilitation programmes in patients acutely managed for cardiogenic shock

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ABSTRACT

Introduction The treatment of patients with cardiogenic shock (CS) has been focused historically on single interventions (medical treatments, percutaneous and surgical interventions and, more recently, various temporary mechanical circulatory supports). However, none of these interventions has significantly changed the short-term prognosis of CS. Moreover, considerable interest in interventions applied in the acute setting has not been matched with comprehensive assessment of patients' long-term follow-up, not only for survival and rehospitalisation but also for quality of life and functional status, recovery from critical illness and its destructive sequelae, and a global evaluation of the overall sustainability of pathways of care. To fill this knowledge gap, the ENIGMA study will be conducted.

Methods and analysis This is a prospective and retrospective multicentre registry conducted under the scientific coordination of the IRCCS Fondazione Don Gnocchi and funded by the Italian Ministry of Health (PNRR-MCNT2-2023-12377767). Data referring to 2000 patients included in the Altshock registry, the largest multicentre CS registry in Italy, will be analysed. A standardised protocol of high-intensity cardiac rehabilitation has been defined and will be followed by the involved institutions after the inclusion of the first 1000 patients. Where feasible, this new pathway will be implemented in every institution. All the patients enrolled will be evaluated according to the Long-Term Conditions Questionnaire, the Kansas City Cardiomyopathy Questionnaire and a questionnaire on the patient experience at 6-month follow-up, to evaluate real-life comparative effects on patient outcomes and experiences. In conclusion, a health technology assessment (HTA) analysis, grounded in the EUnetHTA Core Model, will be conducted to define the potential multidimensional benefits and effects with regard to the overall economic, organisational and social sustainability of the innovative dedicated pathway. Various data sources will be used to conduct the HTA: (1) literature evidence, to define the evidence-based comparative indicators considering both surgical approaches; (2) real-world anonymised data from the hospitals included in the study, to enable costing of the rehabilitative pathways; and (3) healthcare professionals' perceptions, defining the perceived added value of the innovative pathway versus the historical one, based on an evaluation scale ranging from −3 to +3.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is an observational multicentre study that will evaluate, for the first time, the patient's complete journey through all stages of care, from admission for cardiogenic shock to recovery, promoting a model of collaborative research.
⇒ The standardisation of a high-intensity cardiac rehabilitation programme that integrates the acute and postacute care will complete the epidemiological picture and improve diagnosis and treatment in the postcritical stage.
⇒ The multidimensional assessment of the innovative rehabilitative pathway will provide a holistic evaluation, encompassing clinical outcomes, economic feasibility, organisational and social efficiency, and patient-reported measures, thus ensuring a robust understanding of the pathway's impact on patient recovery and on the overall sustainability of healthcare services.
⇒ Conducting a multidimensional assessment is resource-intensive, requiring extensive data collection, coordination among multiple stakeholders and integration of diverse evaluation tools (eg, structured literature review, economic analyses and patient surveys), thus posing challenges in ensuring timely and accurate assessments.
⇒ A structured telephonic interview has been defined for the retrospective cohort, and the possibility of recall bias and missing reports cannot be excluded.

Ethics and dissemination The study was approved by the ethical committee (EC) of Lombardy Region (CET 44/24), on 28 May 2024, and is under evaluation by the EC of three other centres. The study protocol will be evaluated for ethics by 10 more centres in January 2025. Study results will be published in peer-reviewed publications and disseminated through conference presentations. The Associazione Nazionale Scompensati Cardiaci (AISC; 'National Association of Patients with Heart Failure'), the Progetto Vita initiative and the non-profit organisation 'Heart Helps Heart' have endorsed the project and will be involved in disseminating information about the project and its outcomes to the general public.
Clinical trial registration number The ENIGMA-shock study has been registered at ClincialTrials.gov: NCT06572826.

INTRODUCTION

Cardiogenic shock (CS) is a life-threatening, heterogenous syndrome of end-organ hypoperfusion potentially leading to multiorgan failure. Its in-hospital mortality is around 50% and this has remained substantially unchanged, despite the development of advanced treatment strategies.[1] Native heart recovery is not always achieved, and timely access to heart replacement therapies (HRTs: permanent left ventricle assist device and heart transplantation) dramatically affects prognosis.[2–5] Invasive procedures and temporary mechanical circulatory support (tMCS) imply prolonged bed rest in the intensive care unit (ICU), which brings about a syndrome of skeletal muscle wasting owing to critical illness, named ICU-acquired weakness (ICUAW).[6] ICUAW significantly affects morbidity and mortality. It can involve muscles alone—critical illness myopathy (CIM)—and neurons alone—critical illness polyneuropathy—or be associated with both muscular and neuronal involvement—critical illness polyneuromyopathy. ICUAW incidence ranges from 25% to 31% and its treatment requires significant healthcare system resources. Patients staying longer than 8 days in ICU have a 50% likelihood of developing ICUAW.[7] Female and elderly patients are more prone to developing ICUAW; indeed, muscle volume begins to decline by about 8% per decade from approximately 50 years of age, with ensuing significant decline in muscle strength.[8–10] Notwithstanding, severe deconditioning jeopardises candidacy for HRTs and their results.

Although cardiac rehabilitation is well documented for other heart conditions, there is a notable paucity of literature specifically addressing its implementation for CS survivors. Research has consistently shown that specific rehabilitation programmes can reduce mortality and morbidity in patients with coronary artery disease and heart failure.[11] For CS survivors, tailored programmes may facilitate enhanced recovery through structured physical activity, medical evaluation and psychosocial support, addressing the unique challenges posed by the severe myocardial injury and subsequent multifunctional impairments associated with CS.[12] However, standardised pathways for patients discharged alive but with several forms of disability are still lacking. In this context, data from randomised studies, along with updated inclusion criteria and a national network for postacute care, are urgently needed. This gap underscores the strategic importance of developing and evaluating these programmes tailored to this unique patient population.

In 2020, we instituted an all-comers CS registry with 23 participating centres in Italy, in which almost 1000 patients have been included and are currently registered (NCT04295252). Primary aims of the study described in this article are to increase the number of clinical centres involved in the registry and support the creation of dedicated pathways of care based on the registry, covering the major gap in postacute care integration. Once the new pathways are designed, the aims of the ENIGMA project will be to validate their economic and organisational sustainability and provide a holistic picture of other potential benefits, including improved clinical outcomes and better healthcare accessibility owing to reduced fragmentation of services and a seamless transition through care.

Although a changing paradigm has been advocated in CS treatment,[13] comprehensive therapeutic courses have never been defined and diagnostic–therapeutic pathways do not exist after the acute management phase. In the ENIGMA-shock study, interconnected care among operators working in different settings and shared knowledge; close collaboration with the Associazione Nazionale Pazienti Scompensati; the collection of patient-reported experiences (PREMs) and patient-reported outcomes measures (PROMs); and the involvement of the non-profit legal entities Progetto Vita and 'Heart Helps Heart' will facilitate patient-centred care and promote the link between the research community and the general public.

Study aims

The ENIGMA project has the three specific aims. The first aim is to provide a granular assessment of the postacute phase programme for CS, patients' functional disability, and their return to work and quality of life, specifically considering gender. A brief survey conducted among the centres involved in the Altshock programme confirmed that no standardised pathways of care for CS exist in the postdischarge setting. However, owing to a lack of dedicated resources, granular assessment of follow-up is not available. We aim to provide a more comprehensive epidemiological picture by the inclusion of regions of Italy that do not currently have dedicated centres available and pathways in use for the postacute care of this group of patients. This will enable the definition of a 'hub and spoke' model for acute–postacute interconnected care for CS patients, which is the second aim of the project. The concepts of 'hub' and 'spoke' have been defined for CS acute settings and have contributed to improving outcomes in patients with time-dependent disorders simply by creating an efficient network. However, no prior experiences have expanded this approach to the postacute phase, despite CS patients being the most compromised patients in the setting of acute heart failure. Moreover, there are no studies investigating the association between the Society for Cardiovascular Angiography

and Intervention (SCAI) classification (recognised as a powerful and independent predictor of outcome) and functional disability, and evidence on the numbers and proportions of patients who can return to work and the degree and type of disability they are left with does not exist. Thus, third and in conclusion, we will attempt to provide a comprehensive picture of the potential benefits of a pathway with acute–postacute connections with respect to the current standard of care, in which a new pathway considers systematic referral to high-intensity cardiac rehabilitation for CS patients. Specific validation of an innovative pathway for patients acutely managed for CS is multifaceted and is imperative for ensuring the safety, efficacy and cost-effectiveness of this potential new intervention.

All these aspects need to be evaluated using a multidimensional approach, as required by both Italian law and EU regulations on health technology assessment (HTA). Implementation of the EUnetHTA Core Model is important in this case, as it plays a crucial role in informing policy decisions and clinical guidelines, thereby shaping the quality of healthcare delivery.[14] HTA advocates evidence-based and multidisciplinary approaches to the evaluation process in which different technologies are compared against several criteria that deal with their economic, social, clinical, ethical and organisational implications; among the various alternatives, the technology with better 'added value' is chosen.

METHODS AND ANALYSIS

The ENIGMA-shock is a prospective observational study. It will include:

1. A retrospective cohort of CS patients who did not follow a standardised longitudinal, interprofessional and multidimensional care pathway for recovery.
2. A prospective cohort that, after a standardisation of a high-intensity cardiac rehabilitation plan, will follow the new pathway.
3. An HTA analysis, grounded in the EUnetHTA Core Model and conducted to compare the historical pathways with the new standardised pathways.

Study population

All consecutive patients with CS enrolled in the Altshock registry will be included. The primary study endpoint is all-cause death and readmission-free survival in the CS survivor cohort, at 6-month and 1-year follow-up from discharge from the ICU.

The secondary endpoint will be functional recovery, evaluated as follows:

- By the severity of critical illness polyneuropathy, using clinical evaluation (using the Medical Research Council Scale for Muscle Strength), with electromyography and nerve conduction if required, at 6-month follow-up;
- Using a disease-specific PROM, the Kansas City Cardiomyopathy Questionnaire, at 6-month follow-up;
- Using a chronic-condition PROM, standardised by the Food and Drug Administration and the Oxford Patient-Reported Outcomes Group's Long-Term Conditions Questionnaire, at 6-month follow-up;
- According to PREMs—eight indicators will guide the measurement of PREMs according to the National Standards. These indicators will include respect for patient-centred values, preferences and expressed needs; coordination and integration of care; information, communication and education; physical comfort; emotional support; welcoming and involvement of family and friends; transition and continuity; and access to care.

Sample size

Sufficient sample size is required to estimate the effect of postacute care services on death rate and hospital readmission rate. We estimated an overall cohort of CS patients of about 2000. Data from the Altshock registry have highlighted that 38% of CS patients die in hospital. Therefore, we have estimated that the survivor cohort will include approximately 1240 patients. A sample size of approximately 620 patients included in the new pathway and 620 following historical pathways was calculated as being adequate to show a 10% difference in all-cause death/readmission-free survival probability.

A sample of this size will allow us to estimate, with a level of significance ≤5% and power of 80%, a 10% difference in all-cause death and readmission-free survival probability between patients who receive postacute care services and those who do not. The log-rank test will be used to compare the survival curves, with the following three assumptions: (1) a similar sample size for the two groups; (2) a probability of death or readmission-free survival of 42%, at 6-month follow-up in the latter, according to the Altshock registry figures; and (3) a percentage of loss to follow-up not exceeding 20% for each group.

Validation and assessment of the innovative pathways

From a methodological perspective, a mixed method approach[15] will be used to validate the innovative model, thus defining its advantages and integrating scientific evidence, health economics tools and healthcare professionals' perceptions. This will provide a holistic perspective of the changes that will have occurred in implementing the pathway. Figure 1 provides an infographic that summarises key comparisons between the standard model of care and the innovative pathway.

Clinical factors affecting the pathways will be in terms of efficacy and safety outcomes, derived from real-life data collected by the Altshock registry. In addition, managerial aspects will be evaluated and implemented. A Responsible, Accountable, Consulted, Informed (RACI) matrix[16] will be proposed and adapted for the two groups of patients: those receiving postacute care and those not receiving postacute care. In forming the RACI matrix, healthcare professionals' roles and responsibilities will be

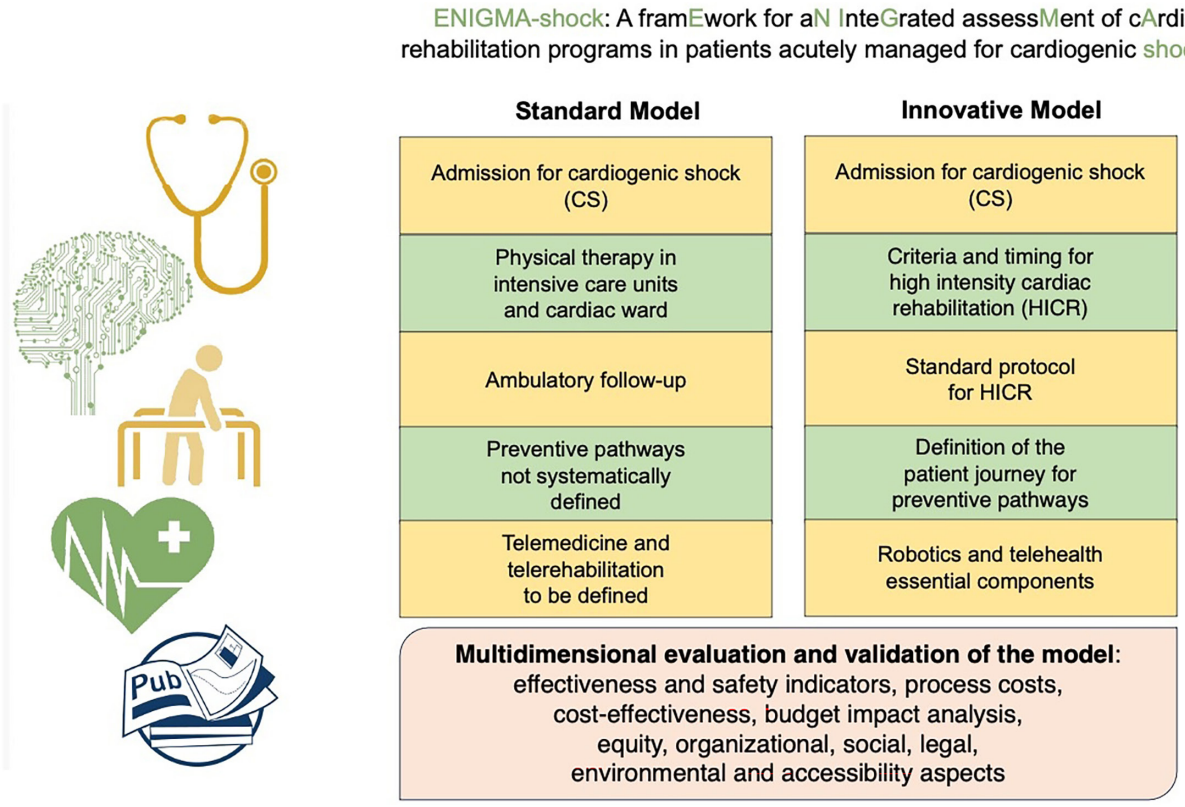

Figure 1 Infographic summarising key comparisons between the standard model of care and the innovative pathway for the ENIGMA-shock study.

defined for each pathway for postacute care, considering the pathway's process and activity.

Key performance indicators for the processes, outcomes and performance results for the two pathways will be identified. This will define the potential for increased accessibility, owing to the decrease in the number of services needed after the introduction of the new pathways.

Organisational issues will be addressed, considering short-term (12-month) and long-term (24-month) time horizons. These will include the evaluation of training courses, hospital meetings, learning time, productivity losses and other investments, comparing the two pathways. The multidimensional assessment will also consider qualitative aspects that could provide perceptions and perspectives of the healthcare professionals involved, with reference to the level of acceptability of the new pathway devoted to patients discharged alive, in comparison with the standard procedures.

An evaluation of economic benefits, analysis of cost-effectiveness, assessment of the economic dimensions and analysis of the impact on budget will be conducted. Three economic evaluation tools will be used. First, an activity-based costing analysis will be performed[17 18] to determine the total cost, with a focus on projected costs. After definition of the process costs, a cost–efficacy analysis will be conducted to define the pathway that presents the best trade-off between costs incurred and efficacy. The economic dimension evaluation will be completed with a budget impact analysis,[19 20] to assess the sustainability and feasibility of the introduction of the new pathway.

Data analysis

The quantitative variables will be described using mean and SD in the case of Gaussian distribution, or median and IQR in the case of non-Gaussian distribution. For the categorical variables, absolute frequencies and percentages will be reported. Two-sided statistical tests will be applied and a p value<0.05 will be considered statistically significant.

Statistical analyses will be performed using SAS software, V.9.4. A time-to-event survival analysis, with all-cause death or readmission as the event, will be performed to estimate the change in survival probability over time. Subjects without one of these two events at the last observation will be censored. Kaplan–Meier survival curves and 50th percentile (median) will be calculated for each group (ie, with and without postacute care services), reported with two-sided 95% CI. The survival curves will be compared using log-rank test. Multivariable Cox proportional hazard models will be applied to estimate the relationship between the use of postacute care services and the study endpoint, after adjustment for potential confounders (sex, age, comorbidity, length of stay in ICU, non-invasive ventilation, invasive mechanical ventilation, mechanical circulatory support, SCAI stage). The results will be expressed as HRs with 95% CIs. The assumption

of hazard proportionality will be verified both graphically and by adding time-dependent covariates to the model.

Focusing on the statistical analysis required to achieve the three aims, quantitative and qualitative data will be first analysed considering descriptive statistics, frequencies and distributions. Economic results will be presented as average value ± SE or median value and will be compared among pathways with parametric or non-parametric methods, depending on the nature of the results. Further analysis will define the potential statistical differences between the various cost drivers, based on patient gender, using independent sample t-tests and one-way analysis of variance. Bayesian statistics will be used in the comparison of clinical pathways, as Bayesian methods provide a complete paradigm for both statistical inference and decision-making under uncertainty. Beta and gamma distributions will be developed accordingly.

Qualitative information will be presented by considering the average value of the perceptions declared, divided per domain or dimension of reference, of the HTA framework. Inferential analyses will be conducted to compare the different scenarios under assessment, identifying statistically significant differences between the modalities used to manage patient care, to establish any advantages. To identify factors predicting an adequate rehabilitative pathway, a hierarchical sequential linear regression model will be implemented that examines adjusted R statistic. These analyses will be performed using the Statistical Package for Social Science (SPSS Statistics Viewer, V.27, IBM), and a significance level of 0.05 will be assumed.

Data will be acquired using a dedicated software package (REDCap, https://www.project-redcap.org/) that enables quality checks and prevents out-of-range data entries. The software will also generate alerts in the case of missing data and incomplete acquisitions. Data quality will be periodically verified by preliminary data analyses to avoid the risk of missing information or outliers related to incorrect data entry process.

Rehabilitation intervention

We cannot ignore that the acute care is most important in the patient's journey, but without postacute assessment, care, rehabilitation and prevention, patients are at risk of complications and rehospitalisation. The aim of cardiac rehabilitation is to maximise clinical stability and recovery possibilities in cardiac patients, thereby minimising residual disability. The rehabilitation pathway for post-CS patients depends on their clinical condition and the timing of multidisciplinary team intervention. The clinical–functional picture that emerges involves two components that determine the patient's rehabilitative complexity: cardiological and neuromotor.

Rehabilitation programme

The rehabilitation of post-CS patients involves a multifaceted approach designed to address various aspects of recovery.[21 22] Respiratory physiotherapy is fundamental, focusing on techniques to improve lung function and enhance oxygenation. Muscle strengthening is another crucial component, involving exercises that target multiple muscle groups using resistance bands, weights and body-weight exercises to rebuild muscle mass and strength. Endurance training tailored to the patient's capabilities is essential, incorporating activities such as walking, treadmill exercises and cycling. Cardiovascular training involves both interval training and continuous aerobic exercises to improve heart function and circulation.[23–25]

The neuromotor rehabilitation programme for post-CS patients is a critical component of the recovery process, with the aims of restoring functional independence and enhancing quality of life. Neuromotor rehabilitation is important in addressing sarcopenia and in managing the sequelae of polyneuropathies.[26 27] These conditions often result in significant motor deficits and sensory impairments, further contributing to muscle atrophy and functional limitations.

In addition, secondary prevention strategies are integral to the rehabilitation programme. These strategies include lifestyle modifications such as dietary changes, smoking cessation and stress management, to reduce the risk of recurrent cardiovascular events.[25]

To guarantee standardised procedures among multiple different facilities in the first months of the study (September–December 2024), a multidisciplinary team has established the following (figure 2):

1. Rehabilitative care in the acute phase that includes ventilatory support management, training of both the patient and staff in positioning and early, frequent mobilisation. It is essential to establish an alliance between the patient and the multidisciplinary team in order to increase the volume of activity the patient performs throughout the day, minimising inactivity.
2. Three stages of rehabilitation in the postacute phase (after the patient is transferred to high-intensity cardiological rehabilitation):
    i. **Initial phase with fragile haemodynamic stability**. The goal is to enable the start of physical training while unloading the cardiovascular system and preventing complications related to inactivity. The patient performs resistance training with continuous positive airway pressure, provided with a total daily volume of at least 90 min, divided into a number of sessions appropriate to the patient's tolerance and stability (an average of ten 10 min sessions per day). The intensity of effort is calibrated using the Borg scale corresponding to a low intensity (≤10), and the haemodynamic impact of the activities is minimal or none. In patients with critical illness syndrome, an electrophysiological assessment is carried out to identify the type and extent of the problem, whether neuropathic and/or myopathic, and, when deemed necessary, a specific treatment plan is initiated, including speech therapy and neuromotor rehabilitation, delivered

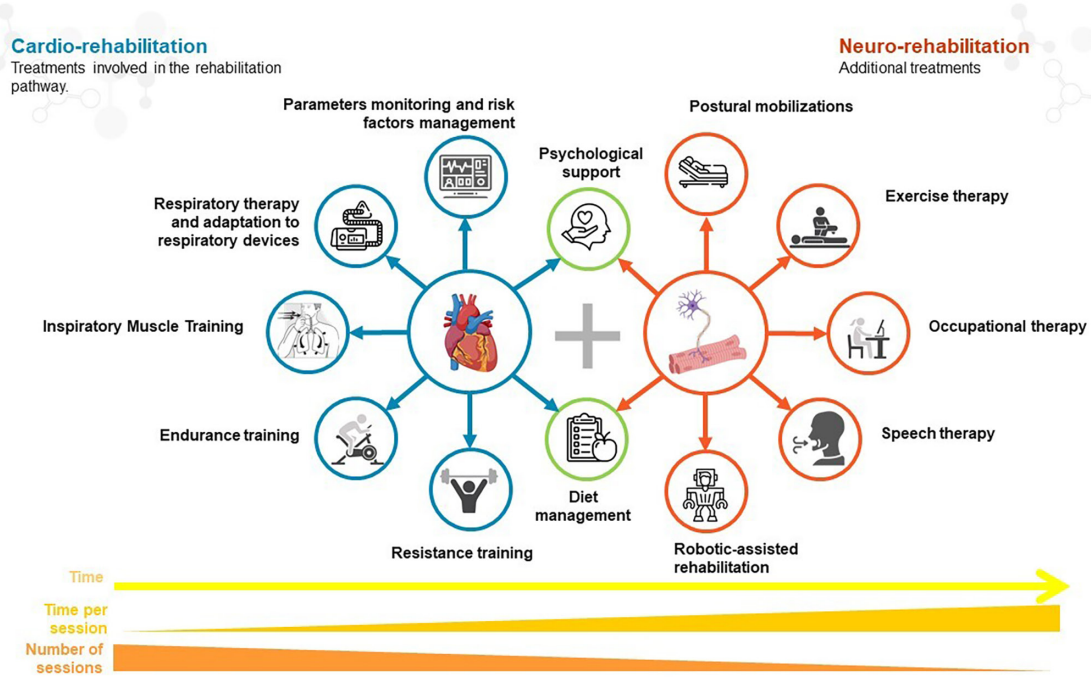

Figure 2 Rehabilitation programme.

according to the local facilities. When feasible, functional electrical stimulation may be implemented for treatment. Logopedic screening and nutritional assessment are crucial to this phase, along with treatment of dysphagia and speech disorders, and nutritional integration.

ii. **Intermediate phase, with improved clinical stability**. The goal is to perform a reconditioning programme that prepares the patient for a cardiopulmonary exercise test. The patient follows a comprehensive endurance and resistance training programme, integrated with inspiratory muscle training (IMT) where necessary. Activities are performed with a minimum daily volume of 90 min, optimised to 120 min when allowed, by reducing the number of sessions and increasing the duration of individual interventions. The patient engages in activities at mild to moderate intensity, monitored using the Borg scale (12/13). Endurance activities are performed using a stationary bike, treadmill or walking training. Resistance training includes natural load exercises and exercises with additional weights to adjust the required intensity. When available, strength training machines such as leg press are used. The patient is trained to perform part of the activity programme independently, to increase the total amount of daily activity. The patient is trained in IMT, adjusted for time and intensity according to international guidelines,[28] based on the maximal inspiratory pressure evaluation conducted upon admission. For patients with ICUAW, this treatment integrates both endurance and resistance training with neuromuscular facilitation exercises, neurodynamic manoeuvres and perceptual stimulation to promote recruitment and strengthening of sarcopenic muscles. Targeted exercises to regain antigravitational control are also included, using robotic devices when available. These reduce the operator's workload by alleviating weight and intensifying treatment, allowing for highly repetitive, progressively intensive and programmable exercises enhanced by virtual and augmented reality tools.[29–32] The robotic devices used at the Don Gnocchi Foundation are G-EO and C-MILL. G-EO is a system for lower limb treatment and gait retraining that allows the execution of lower limb movements with a programmable weight suspension system. Stair simulation is also enabled.[33] C-MILL helps in learning to stand, walk and pay attention. The advanced C-MILL system is essential for daily functional therapy, improving balance distribution and gait, and reducing the risk of falls. The expansion of training with the C-MILL treadmill also improves balance distribution.

iii. **Final phase**. The goal in this phase is to optimise the patient's endurance and strength training levels, based on the cardiopulmonary exercise test, when available. The patient performs endurance training with diversified activities in a daily session lasting at least 50 min, at an intensity corresponding to oxygen consumption between the first and second ventilatory thresholds, identified through CPET (Cardiopulmonary exercise test) or based on values equivalent to a Borg scale score of 12–14 (moderate/high). For resistance training, a standardised group of 10 exercises for the upper and lower limbs is performed, with 12–15 repetitions

per set, for at least three sets, with intensity regulated by additional loads beyond the natural load, aiming to work at an OMNI RES (OMNI-Resistance Exercise Scale) value of 4/5. Patients with complex neuromotor problems may perform this phase with the support of advanced robotic systems, when available, to optimise both the time and quality of the results, reducing the number of professional resources required.

Return to home is facilitated through occupational therapy and psychological support, laying the foundations for disease management in the community, within a chronic care pathway aimed at reducing the need for specialised care.

Expected outcomes

In general terms, the ENIGMA project may have the potential to transform the delivery of care of CS patients, contributing to the overall improvement and reorganisation of important pathways for healthcare systems. This will have positive impacts on clinical and health outcomes, as well as patient acceptance and adherence, improving access to care and the equitable distribution and appropriate allocation of healthcare, human and economic resources. Relevant gaps both in the literature and in clinical practice will be addressed.

Stemming from an 'acute' programme (the Altshock registry), the ENIGMA project will immediately create an acute–postacute linkage, as suggested by international experiences in heart failure and coronary artery disease (Get with the Guidelines and TAKEheart) based on the concept that the first step to decreasing mortality and readmission is a structured postdischarge programme.

From a clinical perspective, the ENIGMA project will generate data and insights that will foster the implementation of specialised cardiac rehabilitation pathways aimed at improving patient CS management, treatment and outcomes, including reduced mortality and rehospitalisation rates, as well as quality of life and social determinants of health. By facilitating a structured and personalised approach to postacute care, the ENIGMA project is expected to enhance functional recovery and return-to-work rates among CS survivors. These anticipated effects are grounded in the robust evidence supporting the efficacy of cardiac care programmes in other cardiac populations, which suggests similar benefits can be extended to CS patients.[34 35] Improving the efficacy and safety profile will lead to enhanced patient engagement and adherence. Comprehensive psychosocial support including counselling and peer support, which are integral to addressing mental health issues, will be offered. This holistic approach will not only improve psychological well-being but also enhance overall cardiac outcomes by promoting adherence to treatment and lifestyle changes, as part of providing patients with personalised care pathways based on the severity and impact of their clinical condition.

From an economic and organisational perspective, the ENIGMA project seeks to establish the cost-effectiveness and sustainability of such innovative interventions, validating the feasibility and sustainability of new pathways within diverse healthcare settings, thus generating increased efficiency and improved accessibility to care.

Based on the above, the ENIGMA project is expected to yield a multifaceted set of outcomes that collectively aim to transform the postacute care landscape for CS survivors. By demonstrating the clinical efficacy, economic efficiency and organisational feasibility of innovative pathways, the project will provide a robust evidence base to inform policy decisions, clinical guidelines and best practices in cardiac rehabilitation.

Risk analysis

Immortal time bias can arise when the period between entry into a study (T0) and the date of treatment initiation is not accounted for in the analysis.[36] This time lag is referred to as 'immortal' because the subjects who end up in the treatment group must survive until the start of treatment; otherwise, they would fall into the untreated group, and this can distort the observed effects and generate an illusion of treatment effectiveness. In the ENIGMA study, the selection of the with and without postacute care groups will be based on postacute care that can begin after the starting date for survival analysis (T0: discharge from the ICU). In cases where there is a time lag between T0 and the start of postacute care, analyses with postacute care as a time-dependent variable will be performed.

To ensure that the study data will be managed according to good clinical practice principles and to maintain the privacy of the participants across regions, data management strategies will be defined. Protection of patients' personal data will be guaranteed by the involvement of a data protection officer at the leading centre.

To ensure overall strategic coordination of the ENIGMA project, project management will be used to continuously monitor the advancement of the various aspects of the project, so that priorities and activities can be modified to achieve the main objectives. Workflow management software (Trello, Atlassian Corporation) will be structured and used to align role players in the project with the project milestones and timing; coordinate activities and facilitate communication among role players; and anticipate potential criticisms or conflicts, avoiding or mitigating potential risks.

Patient and public involvement

The Associazione Nazionale Pazienti Scompensati Cardiaci will be involved in guaranteeing patient participation in all the study phases and ensuring patient empowerment in the study processes. The same organisation, along with the Progetto Vita initiative and 'Heart Helps Heart', will be involved in disseminating information about the project and its outcomes to the general public and relevant stakeholders.

ETHICS AND DISSEMINATION

The study was approved by the ethical committee (EC) of Lombardy Region (CET 44/24), on 28 May 2024 and is under evaluation by the EC of three other centres. Six more centres will be evaluated in January 2025. The study will follow generally accepted research practices described by good clinical practice principles. Patients will be actively enrolled as part of the research activities and will sign an informed consent for their participation. Results will be reported through peer-reviewed scientific publications and presentations at international conferences. The Associazione Nazionale Pazienti Scompensati Cardiaci, the Progetto Vita initiative and 'Heart Helps Heart' will be involved in disseminating information about the project and its outcomes to the general public and relevant stakeholders.

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Contributors NM, FP and EF developed the initial study concept. NM, FP, PP, MC, AR, EF and LF were responsible for the design of the study, including the methodology, and wrote the original draft of the protocol. AS, LG, SF, MP, AG, FO, GT, IC, DA and AT contributed to critical revisions of the manuscript. NM and FP are the scientific coordinators of the study and bear overall responsibility for all aspects of the study design, protocol and study conduct. NM acquired funding for the study. All authors contributed to reviewing and editing the protocol and have read and approved this manuscript. NM acted as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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