RESEARCH TOPIC CLI16
META-TWIN: Development of a Digital Twin Platform for Precision Medicine in Cardiovascular-Renal-Hepatic-Metabolic Syndrome

Research area
Medical area

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Abstract
Background: Cardiovascular-renal-hepatic-metabolic (CRHM) syndrome is an emerging clinical framework that captures the complex, multi-organ manifestations of metabolic dysfunction across the cardiovascular, renal, hepatic, and metabolic systems (1)(2). Rather than representing isolated organ diseases, these conditions are increasingly recognized as interconnected expressions of shared pathophysiological mechanisms, including insulin resistance, chronic inflammation, oxidative stress, neurohormonal activation, endothelial dysfunction, and fibrosis (1)(2). This integrated view is particularly relevant in contemporary clinical practice, where patients frequently present with overlapping metabolic, hepatic, renal, and cardiovascular abnormalities requiring coordinated assessment and management.
The therapeutic landscape of CRHM syndrome is rapidly evolving. Effective pharmacological therapies are now available across different components of the syndrome, including obesity, cardiovascular and renal disease, and MASH with significant fibrosis (F2-F3), offering new opportunities to modify multi-organ disease trajectories (3)(4). However, the growing availability of therapeutic options also highlights the urgent need for improved tools to identify patients at highest risk, predict disease progression across interconnected organ systems, and support personalized treatment strategies within a multidisciplinary care model (5)(6).
Digital twin models, computational representations of individual patients integrating multidimensional clinical data into predictive simulations, are emerging as promising tools to support precision medicine in complex diseases. These approaches have already been applied in several biomedical fields and have recently been explored in hepatology through a collaborative project between the Humanitas Hepatology Unit and the Humanitas AI Center focusing on hepatitis D virus infection. In addition, prior work within Humanitas has demonstrated the feasibility of artificial intelligence-based multimodal integration and synthetic data generation for precision medicine applications, further supporting the development of advanced digital twin frameworks (7)(8). Applying these approaches to CRHM

syndrome may enable a more integrated and dynamic understanding of multi-organ disease progression and therapeutic response.

Study objectives: The META-TWIN project aims to investigate whether the integration of multidimensional clinical, biochemical, metabolic, cardiovascular, renal, hepatic, and imaging-derived data into a digital twin framework can improve risk stratification and support precision medicine in patients with CRHM syndrome.
Specifically, the project seeks to determine whether digital twin models can identify clinically meaningful CRHM phenotypes, predict multi-organ disease trajectories, and support the selection of patients most likely to benefit from emerging pharmacological and non-pharmacological interventions within a multidisciplinary care pathway.

Study design: META-TWIN will be conducted as a prospective translational study enrolling adult patients referred to the Hepatology Unit, Nephrology Unit and to the Humanitas Center for Metabolic Diseases presenting with a CRHM phenotype. To ensure a structured characterization of disease burden, patients will be classified according to the systemic metabolic disorder (SMD) staging system, which stratifies individuals along a continuum from metabolic dysfunction to early and advanced multi-organ involvement (2).
Approximately 400 patients will be prospectively enrolled over the study period. The study will include individuals with metabolic dysfunction affecting one or more CRHM domains, including obesity or dysfunctional adiposity, dysglycaemia or type 2 diabetes, dyslipidaemia, hypertension, MASLD/MASH and liver fibrosis, chronic kidney disease or albuminuria, and cardiovascular disease. The cohort will be enriched for patients with early or established organ involvement, where integrated risk stratification and treatment selection are most clinically relevant.
At baseline, participants will undergo comprehensive phenotyping including anthropometric assessment, metabolic and biochemical profiling, cardiovascular risk evaluation, renal function assessment, and systematic characterization of hepatic involvement. Data collection will include body mass index, waist and hip circumference, blood pressure, glucose metabolism, lipid profile, liver enzymes, renal function parameters including serum creatinine and estimated glomerular filtration rate, albuminuria when available, and assessment of comorbidities and ongoing therapies. Lifestyle factors, including dietary habits and physical activity, will also be recorded.
Hepatic involvement will be assessed using standardized non-invasive approaches, including transient elastography for the evaluation of liver stiffness and steatosis, together with validated blood-based fibrosis scores such as FIB-4, MAF-5, and SAFE. When available, imaging-derived measures of liver fat and body fat distribution will be incorporated to better characterize adiposity phenotypes and ectopic fat deposition.
All clinical, biochemical, metabolic, cardiovascular, renal, hepatic, and imaging-derived data will be integrated into a structured analytical platform designed to support the development of patient-specific digital twin models. Advanced machine learning approaches will be applied to integrate multidimensional datasets and identify phenotypic clusters reflecting distinct CRHM profiles. Predictive modelling techniques will be used to simulate multi-organ disease

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trajectories, estimate the probability of clinically relevant outcomes, predict response to lifestyle or pharmacological interventions, and support clinical decision-making.
Participants will be followed longitudinally through routine clinical visits to capture changes in metabolic parameters, cardiovascular and renal risk profile, progression of hepatic disease, and response to therapeutic interventions. These longitudinal data will be used to iteratively refine and validate the predictive performance of the digital twin models.
To further assess the robustness and generalizability of the developed models, external validation analyses will be performed using large population-based datasets such as the UK Biobank, enabling evaluation of model performance across independent populations with multidimensional cardio–reno–hepato–metabolic phenotypes.

Sample size justification

The planned sample size of approximately 400 patients is considered adequate for the objectives of this prospective translational study. First, this sample size allows a robust characterization of heterogeneous CRHM phenotypes across multiple domains, ensuring sufficient representation of patients with varying degrees of metabolic dysfunction and organ involvement according to the SMD staging system. Second, from a statistical and machine learning perspective, a cohort of this size provides an appropriate balance between model complexity and overfitting risk. Given the high-dimensional nature of the collected data, the sample size is expected to support the development of predictive models using dimensionality reduction techniques and internal validation strategies. Assuming an event rate of approximately 10-15% for clinically relevant outcomes over follow-up, the study is expected to capture an adequate number of events to enable exploratory risk modelling and hypothesis generation. Finally, the availability of large external datasets, such as the UK Biobank, will allow independent validation of the developed models, mitigating limitations related to sample size and enhancing generalizability.

Conclusions

META-TWIN will establish a digital twin platform for precision medicine in CRHM syndrome. By integrating multidimensional patient data into predictive models, this approach may improve identification of patients at higher risk of multi-organ disease progression and enable more precise selection of candidates for emerging pharmacological and non-pharmacological therapies. In addition, the project will support a multidisciplinary, data-driven approach to patient management and contribute to the development of the Humanitas Center for Metabolic Diseases as a hub for integrated care and innovation

GCP statement

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki and applicable guidelines as well as all national legal and regulatory requirements.
To protect patient privacy, the videos obtained with patient consent will be anonymized.

The study will begin following ethics committee approval.

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