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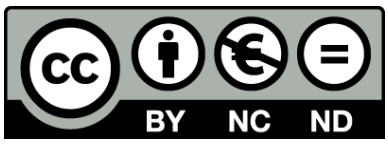
Predictive Modelling for Personalised Multimorbidity Management

Rubèn González Colom



DOCTORAL PROGRAM IN MEDICINE AND TRANSLATIONAL RESEARCH
School of Medicine and Health Sciences. University of Barcelona.

UNIVERSITAT DE BARCELONA

DOCTORAL THESIS

Predictive Modelling for Personalised Multimorbidity Management

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Rubèn Gonzalez Colom

Supervised by:

Dr. Isaac Cano Franco and **Prof. Josep Roca Torrent**

Doctoral thesis dissertation presented by **Rubèn González Colom** to apply for the degree of doctor at the University of Barcelona.

Directed by **Dr. Isaac Cano Franco** (University of Barcelona)

Tutorised by **Prof. Josep Roca Torrent** (University of Barcelona)

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ABBREVIATIONS AND ACRONYMS

ACG - Adjusted Clinical Groups

AI - Artificial Intelligence

AMG - Adjusted Morbidity Groups

API – Application Programming Interface

APR-DRG - All Patient Refined Diagnosis Related Groups

BDMM - Bayesian Direct Multimorbidity Maps

CCI - Charlson Comorbidity Index

CDISC - Clinical Data Interchange Standards Consortium

CDSS - Clinical Decision Support System

CDM - Common Data Model

CHSS - Catalan Health Surveillance System

COPD - Chronic Obstructive Pulmonary Disease

CRG - Clinical Risk Groups

DHF - Digital Health Framework

DW - Disability Weight

EHR - electronic Health Record

EI - Elixhauser index

EHDS - European Health Data Space

FAIR - Findable, Accessible, Interoperable, Reusable

FHIR - Fast Healthcare Interoperability Resources

GDPR - General Data Protection Regulation

HCB - Hospital Clínic de Barcelona

HaH - Hospital at Home

HRA - Health Risk Assessment

HRIC - Health Research and Innovation Cloud

IS - Implementation Science

LHS - Learning Healthcare System

LIME - Local Interpretable Model-agnostic Explanations

MDA - Mean Decrease in Accuracy

MDCG - Medical Device Coordination Group

MCPM - Multisource Clinical Predictive Modelling

MDD - Major Depressive Disorder

MDR - Medical Device Regulation

NA - Next Adopter

NCD - Non-Communicable Diseases

oGP - original Good Practice

OMOP - Observational Medical Outcomes Partnership

P4 Medicine - Predictive, Preventive, Personalized, and Participatory Medicine

PREM - Patient Reported Experience Measures

PROM - Patient Reported Outcome Measures

RCT - Randomized Controlled Trial

SHAP - SHapley Additive Explanations

XAI - Explainable Artificial Intelligence

LIST OF ARTICLES

Article 1: Mireia Calvo, **Rubèn González-Colom**, Núria Seijas, Emili Vela, Carme Hernández, Guillem Batiste, Felip Miralles, Josep Roca, Isaac Cano, Raimon Jané. 2020. *Health Outcomes from Home Hospitalization: Multisource Predictive Modelling*. Journal of Medical Internet Research (JMIR). (Published, IF: 7.4, Q1, Health Informatics)

Article 2: Rubèn González-Colom, Carmen Herranz, Emili Vela, David Monterde, Joan Carles Contel, Antoni Sisó-Almirall, Jordi Piera-Jiménez, Josep Roca, Isaac Cano. 2023. *Prevention of Unplanned Hospital Admissions in Multimorbid Patients Using Computational Modelling: Observational Retrospective Cohort Study*. Journal of Medical Internet Research (JMIR). (Published, IF: 7.4, Q1, Health Informatics)

Article 3: Rubèn González-Colom, Gerard Carot-Sans, Emili Vela, Mireia Espallargues, Carme Hernández, Francesc Xavier Jiménez, David Nicolás, Montserrat Suárez, Elvira Torné, Eulalia Villegas-Bruguera, Fernando Ozores, Isaac Cano, Jordi Piera-Jiménez, Josep Roca. 2023. *Five years of Hospital at Home adoption in Catalonia: impact and challenges*. BMC Health Services Research. (In review, IF: 2.8, Q1, Health policy)

Article 4: Rubèn González-Colom, David Monterde, Roberta Papa, Mart Kull, Andres Anier, Francesco Balducci, Isaac Cano, Marc Coca, Marco De Marco, Giulia Franceschini, Saima Hinno, Marco Pompili, Emili Vela, Jordi Piera-Jiménez, Pol Pérez, Josep Roca. 2023. *Toward adoption of health risk assessment in population-based and clinical scenarios*. International Journal of Integrated Care (IJIC). (In review, IF: 2.4, Q2, Health policy)

Article 5: Rubèn González-Colom, Kangkana Mitra, Emili Vela, Andras Gezsi, Teemu Paajanen, Zsofia Gal, Gabor Hullam, Hannu Mäkinen, Tamas Nagy, Mikko Kuokkanen, Jordi Piera-Jiménez, Josep Roca, Peter Antal, Gabriella Juhasz, Isaac Cano. 2023. *Multicentric validation of a Multimorbidity Adjusted Disability Score to stratify depression-related risks using temporal disease maps*. Journal of Medical Internet Research (JMIR). (In review, IF: 7.4, Q1, Health Informatics)

Appendix: **Rubèn González-Colom**, Isaac Cano, Jordi Piera-Jiménez, Josep Roca. 2023. *Personalized Medicine meets Artificial Intelligence; Chapter 10: Multilevel Modelling with AI: The Synergy-COPD Endeavour*. Springer books. (Published)

THESIS SUMMARY

Predictive Modelling for Personalised Multimorbidity Management

Multimorbidity affects equally individuals and healthcare systems. Multimorbidity is associated with poor prognosis, functional impairment, and reduced quality of life, leading to increased healthcare resource utilisation and costs. Considering the rising incidence of multimorbidity, the long-term viability of health institutions is under threat. Research on disease mechanisms and health data analytics agree that, beyond the primary diagnostic, the overall disease burden is an important determinant of health outcomes, suggesting that a disease-centred approach is not optimal for management of patients with multiple chronic conditions. This resulted in the development of tools to measure multimorbidity, such as the Adjusted Morbidity Groups (AMG) or the Queralt indices. These tools have fostered Health Risk Assessment (HRA) strategies when aligned with integrated care programs. HRA adjusted to multimorbidity represents a fundamental cornerstone for comprehending the impacts of the phenomenon, allowing it to inform health policies and better allocate healthcare resources. As well as HRA enables the implementation of personalised healthcare strategies through patient stratification, facilitating the identification of at-risk individuals and advising the development of targeted interventions to optimise health outcomes. Nevertheless, despite the promising prospects offered by HRA, a noticeable disparity persists between its potential and its current implementation, particularly within the clinical domain.

To this end, the thesis investigated three major HRA challenges through specific use cases.

The first use case (**Articles 1-3**) was centred on creating clinical predictive modelling, using machine learning tools, to refine service selection upon patients' hospital admission and to enhance transitional care after discharge. Key findings highlighted multimorbidity's role as a major risk for adverse health events. The use case addressed technical challenges in modelling, such as feature selection, data accessibility, model

design, evaluation, and explainability. However, areas like application in real world settings remained out of the scope of the studies.

The second use case (**Article 4**) involved transferring the AMG tool to Marche region (IT) and Viljandi Hospital (EE). Both enablers and barriers for transference and adoption of such tool, in clinical and public health contexts, were assessed employing robust methodological approaches grounded in established implementation frameworks. The dual perspectives offered by Marche and Viljandi, this is, a regional healthcare organisation and a county hospital, respectively, facilitated tailored AMG adoption guidelines and generalisable recommendations for addressing data requirements, GDPR nuances, and data exploitation through dashboards and KPIs. Additional research is proposed within this thesis to grasp each EU member state's context seeking to create a harmonised HRA strategy for the future, avoiding inefficiencies and potential pitfalls.

The last piece of the research (**Article 5**) investigated new strategies to incorporate disease trajectory insights, and enhanced analysis of disease clustering, into morbidity groupers. This integration aimed to improve the ability to adjust the morbidity burden assessment to an index disease and its comorbid conditions while enhancing the prediction of the progression of multimorbidity. The study utilised depression as a use case to create a new morbidity grouper, the so-called MADS – Multimorbidity Adjusted Disability Score. In the analysis of the MADS distribution, a connection was observed between its risk levels and adverse health events; in this regard, the associations were stronger in outcomes related to mental health. After validation with patients' cohorts in Catalonia, the UK, and Finland, the approach hinted at a deeper integration between psychiatric and somatic medicine, aiming to better address depression-linked multimorbidity. While the results were promising, discussions continue on refining the method and its potential to improve the efficiency of existing tools, like the AMG algorithm.

The research for this thesis was conducted within the framework of two European projects from 2020 to 2023:

1. The Joint Action on implementation of digitally enabled integrated person-centred care (JADECARE) project.

2. Temporal disease map-based stratification of depression-related multimorbidities: towards quantitative investigations of patient trajectories and predictions of multi-target drug candidates (TRAJECTOME).

RESUM EN CATALÀ

Modelatge Predictiu per la Gestió Personalitzada de la Multimorbiditat

La multimorbiditat suposa una càrrega tant per la població com pels sistemes de salut. La concurrència de múltiples condicions cròniques està associada amb un pronòstic desfavorable, a un deteriorament funcional i una disminució de la qualitat de vida, aquest fet està estretament lligat a un augment de l'ús de recursos i costos sanitaris. Considerant l'augment de la incidència de la multimorbiditat, la viabilitat a llarg termini dels sistemes de salut està en risc. La investigació sobre els mecanismes de la malaltia i l'anàlisi de bases de dades administratives de l'àmbit de la salut concorden que, més enllà del diagnòstic primari, la càrrega de comorbiditats és determinant en els resultats de salut, suggerint que un enfocament centrat en la malaltia no és òptim per a la gestió de pacients amb múltiples condicions cròniques. El reconeixement de la importància de la multimorbiditat ha resultat en el desenvolupament d'eines per mesurar-la, com els Grups de Morbiditat Ajustats (GMA) o els sistema de Queralt. Alineades amb programes de atenció integrada aquestes eines han impulsat estratègies d'Avaluació del Risc en la Salut (ARS). L'ARS ajustada per càrrega de morbiditat representa una pedra angular fonamental per comprendre l'impacte de la multimorbiditat, informar les polítiques de salut i millorar la distribució dels recursos sanitaris. En entorns d'atenció sanitària, l'ARS permet la implementació d'estratègies de salut personalitzades a través de l'estratificació del pacient, facilitant la identificació d'individus en risc i assessorant el desenvolupament d'intervencions dirigides per optimitzar els resultats de salut. No obstant això, malgrat les perspectives prometedores ofertes per l'ARS, persisteix una disparitat notable entre el seu potencial i la seva implementació, particularment dins del domini clínic.

Aquesta tesi doctoral investiga tres grans reptes de la HRA a través de casos d'ús específics.

El primer cas d'us (**Articles 1-3**) es va centrar en la creació de modelatge predictiu en l'entorn clínic, utilitzant eines d'aprenentatge automàtic, per millorar la selecció de serveis a l'ingrés hospitalari i per millorar l'atenció transicional després de l'alta. Les

principals troballes van destacar el paper de la multimorbiditat com al principal determinant de risc principal per a esdeveniments de salut adversos. El cas d'ús va abordar reptes tècnics en modelatge, com la selecció de variables predictores, l'accessibilitat de dades, el disseny i l'avaluació del model i l'explicabilitat de les prediccions. No obstant això, àrees com l'aplicació en el món real i el manteniment continu del model van quedar fora de l'àmbit dels estudis.

El segon cas d'ús (**Article 4**) va implicar la transferència del GMA a la regió de Marche (IT) i a l'Hospital de Viljandi (EE). Tant els facilitadors com les barreres per a la transferència i adopció d'aquesta eina, en contextos clínics i de salut pública, van ser avaluats utilitzant enfocaments metodològics robustos basats en marcs d'implementació establerts. Les perspectives duals ofertes per Marche i Viljandi, des d'una organització sanitària regional fins a un hospital provincial, van facilitar pautes d'adopció d'GMA a mida i recomanacions generalitzables per abordar l'accés al conjunt mínim a dades, les interpretacions de la legislació vigent en ètica de l'investigació i protecció de dades, i l'explotació dels resultats a través de quadres de comandament i indicadors clau de rendiment. L'estudi delimita una recerca addicional per comprendre el context de cada estat membre de la UE, buscant crear una estratègia d'HRA harmonitzada per al futur, evitant ineficiències i possibles esculls.

L'últim cas d'us (**Article 5**) es va enfocar a la recerca de noves estratègies per incorporar competències derivades de l'anàlisi de les trajectòries de malaltia i l'anàlisi millorada de l'agrupació de malalties, als agrupadors de morbiditat. Aquesta integració tenia com a objectiu millorar la capacitat d'ajustar l'avaluació de la càrrega de morbiditat a una malaltia índex i les seves condicions comòrbides, alhora que millorava la predicció de la progressió de la multimorbiditat. L'estudi va utilitzar la depressió com a malaltia objectiu per crear un nou grup de morbiditat, el denominat MADS. En l'anàlisi de la distribució del MADS es va observar una connexió entre els seus nivells de risc i esdeveniments adversos de salut, al respecte, les associacions eren més fortes en resultats relacionats amb la salut mental. Després de la validació a Catalunya, el Regne Unit i Finlàndia, els resultats van suggerir una integració més profunda entre la medicina psiquiàtrica i somàtica, amb l'objectiu de tractar millor la multimorbiditat lligada a la depressió. Encara que els resultats van ser prometedors, el debat sobre la

refinació del mètode i el seu potencial per potenciar l'eficiència d'eines existents, com l'algoritme AMG segueix vigent.

Els estudis que integren aquesta tesi es van realitzar dins el marc de dos projectes europeus contemporanis, en el període comprès entre 2020 i 2023:

1. The Joint Action on implementation of digitally enabled integrated person-centred care (JADECARE) project.

2. Temporal disease map-based stratification of depression-related multimorbidities: towards quantitative investigations of patient trajectories and predictions of multi-target drug candidates (TRAJECTOME).

INTRODUCTION

1. THE PROBLEM OF MULTIMORBIDITY

In modern ageing societies, one of the pressing healthcare challenges to address is the co-occurrence of multiple chronic diseases, also known as multimorbidity(1–3). Multimorbidity significantly strains individuals and healthcare systems due to its association with poor prognosis, functional impairment, and reduced quality of life(4,5). This is particularly relevant in multimorbid patients afflicted by depression or other mental disorders who may face extra challenges in maintaining their overall health, impeding their capacity for disease self-management, reducing adherence to treatment plans, and elevating the probability of adopting unhealthy behaviours (6,7).

In addition, the complex clinical situations arising from multimorbidity can lead to increased healthcare resource utilization, including encounters with healthcare professionals, hospitalizations, and pharmacological prescriptions, resulting in a substantial rise in healthcare costs(8,9). Multimorbidity incurs significant global costs contingent on disease combinations, country, and care expenses, and these costs are projected to escalate rapidly due to population ageing and the increasing prevalence of chronic diseases. This trend makes multimorbidity the primary catalyst for healthcare cost escalation, posing a substantial threat to the sustainability of healthcare systems(10).

The emergence of multimorbidity is not arbitrary and frequently aligns with shared risk factors and/or underlying pathophysiological mechanisms(11–13). Multimorbidity has a complex biological basis that results from intricate interactions between genetic and environmental factors throughout the lifespan(14). Common biological mechanisms, including chronic inflammation, oxidative stress, and cellular ageing, seem to underpin the development of multimorbidity(15–17). Furthermore, these mechanisms are influenced and modulated by exposure to various environmental stressors, such as physical inactivity, inadequate nutrition, and psychological stress(18).

This vision has significantly transformed the perception of diseases and their interactions, involving a paradigm shift towards network medicine(19,20). Network medicine offers a comprehensive view of health and disease, by focusing on the interactions between biological systems at the molecular, cellular, organismal, and environmental levels, in contrast to the traditional reductionist view of medicine, which focuses on the analysis of individual components of biological systems, such as genes, proteins, or pathways. It is widely acknowledged that clinical phenotypes rarely stem from a single gene anomaly but rather arise from the interplay of multiple molecular processes(19,20). Therefore, the key focus of network medicine is to identify the fundamental molecular elements and processes underlying disease. This change from clinical phenotypes to endotypes, offers the potential for a more nuanced disease classification and a novel perspective on the relationship between comorbid conditions.

Far away from laboratory settings and through the analysis of large clinical datasets, the practical implementation of the concept, that multiple diseases share common genetic, environmental, and molecular mechanisms, has propelled the exploration of the diseasome(21,22). The diseasome is a network-medicine approach (**Figure 1**) rooted in co-occurrence patterns among diseases, focusing on modelling and dissecting the intricate interconnectedness among diseases to uncover biomarkers, therapeutic targets, and potential interventions(21,22). Conversely, the conceptualization of the diseasome has given rise to a profusion of studies that delve into the temporal patterns of disease coexistence, often termed disease trajectories(23–25). These endeavours yield a more profound comprehension of the time-dependent associations between diseases, thereby establishing a promising foundation for identifying causal relationships among diseases(23–25).

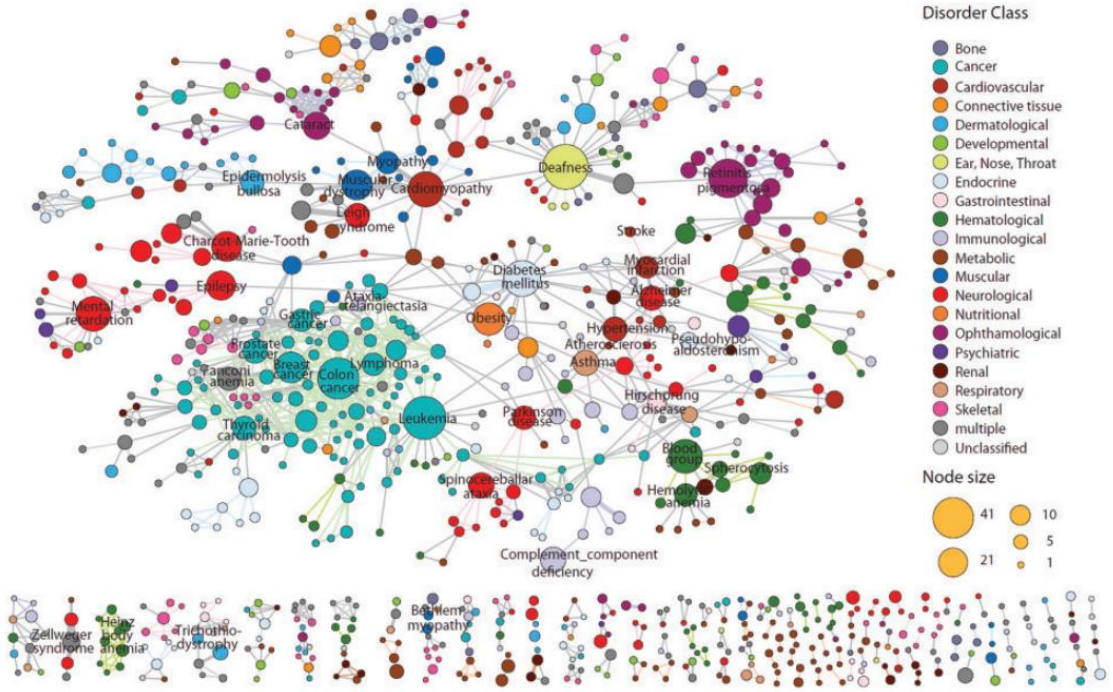


Figure 1: Network representation of the human diseasome. *Two disease nodes (represented as circles) are linked if they have overlapping genetic components based on disease-gene associations. The node size reflects the count of related disorders, while the colour differentiates disorders based on the affected organic system. Figure taken from* (21)*.*

In light of this, it is well-acknowledged that a disease-centred approach might lead to suboptimal treatment of patients with multiple, related and disabling chronic conditions, triggering the need to implement new practices to enhance the effectiveness of the health services(26). This understanding has prompted a re-evaluation of healthcare delivery, leading to the emergence of two interrelated and complementary avenues.

Firstly, there is a concurrent embrace of the principles of network medicine, coupled with a drive to comprehend the intricate interplays between diseases. This should be accompanied by developing personalised treatment strategies tailored for patients with multiple disease conditions(27–29). An essential aspect of this approach involves modifying treatment plans, with a keen focus on early detection and management of underlying risk factors aimed at averting the onset or progression of morbidity.

Secondly, the mainstream adoption of integrated care models and approaches that prioritise care coordination at distinct levels, such as primary care, specialised care,

and social care, to provide comprehensive and continuous care to patients with multimorbidity. This approach endeavours to enhance patient outcomes and diminish healthcare expenditures by mitigating the fragmentation of care and elevating care coordination.

The confluence of these dual dimensions is anticipated to pave the way for adopting a truly predictive, preventive, personalised, and participatory form of medicine referred to as P4 medicine(30), underpinned by a Systems Medicine approach(31). Systems medicine builds upon systems biology principles, using an interdisciplinary approach to integrate and analyse biological data across multiple scales to understand complex disease mechanisms and enhance personalized medical care (**Figure 2**).

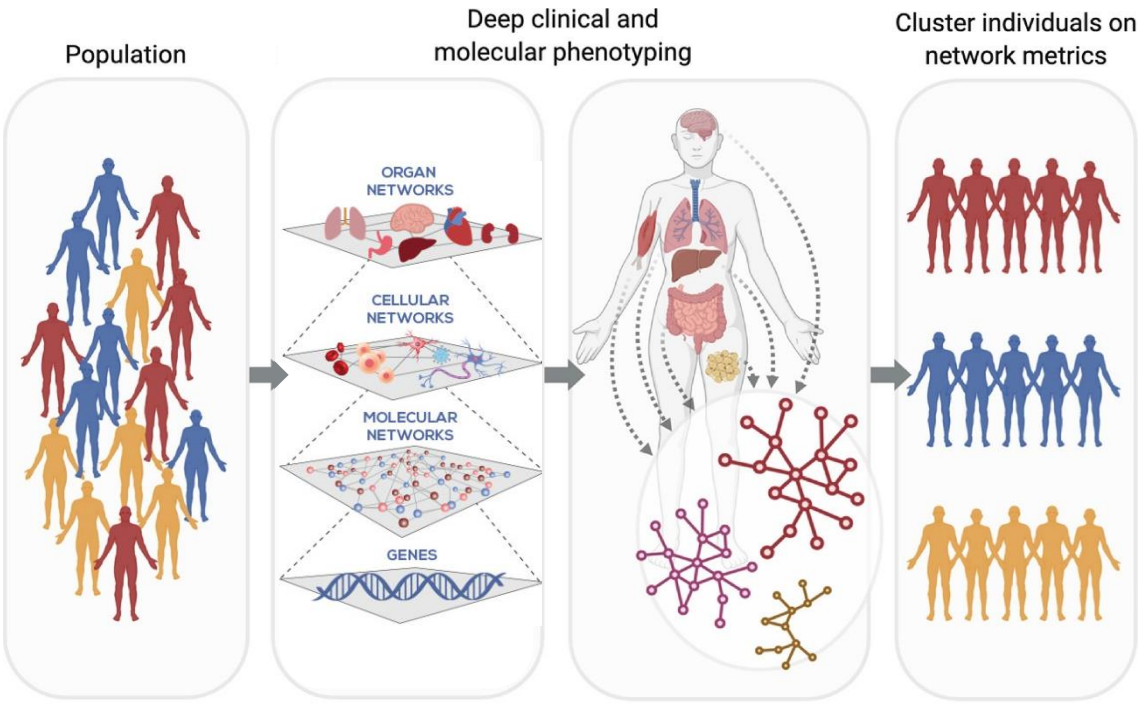


Figure 2: Systems medicine framework. *This representation elucidates the profound interplay of biological mechanisms at organic, cellular, molecular, and genetic levels, underlying health and disease states. By integrating molecular measurement techniques and a systems biology approach, systems medicine proposes a new medical paradigm geared towards individualized therapeutic interventions. Figure adapted from* (175).

1.1. Quantifying the Morbidity Burden: the need to risk-adjust for multimorbidity

The first attempts to assess the impact of multimorbidity started hand in hand with the digital transformation of the healthcare systems and creation of large administrative health databases, providing extensive population-based samples free from selection biases and facilitating long-term patient follow-up within real-life settings. The analysis of such databases revealed that the cumulative burden of the concurrent or pre-existing comorbidities, apart from the primary diagnosis, often influence clinical outcomes and raised the importance to adequately adjust for comorbidities(32).

This discovery led to the creation of the first standardized and objective comorbidity measures, or morbidity groupers, such as the Charlson Comorbidity Index (CCI)(33) and Elixhauser Index (EI)(34). Specifically, the CCI assigns weights to 19 selected medical conditions to predict 10-year mortality, while the EI considers 30 comorbidities to assess in-hospital mortality and length of stay; both are widely used in clinical settings to inform care decisions and predict patient outcomes. However, due to the limited exhaustiveness of their approach, more sophisticated tools have replaced them in daily clinical practice. In this matter, the Adjusted Clinical Groups (ACG)(35) developed by the Johns Hopkins University and its principal commercial competitor, the Clinical Risk Groups (CRG)(36) created by 3M™, are the most used methods to capture a patient's morbidity related health risks and stratify patients based on their health care requirements. Both systems are instrumental in promoting efficient and equitable healthcare resource distribution and envisioning patient health outcomes. Similarly, other solutions have been developed targeting specific populations such the All Patient Refined-Diagnosis Related Groups (APR-DRG)(37) system, that was conceived by 3M™ to assess hospital inpatients according to their reason for admission, severity of illness and risk of mortality. All these indicators have proven to be a dependable predictor of healthcare utilization and costs.

However, the alluded commercial tools, such as ACG, CRG and APR-DRG, have been found to be very costly and often difficult to adapt to different patient populations requiring expert knowledge, which opened the door to the provision of disruptive data-driven, more interpretable, and affordable alternatives that can outperform this dominant health risk assessment (HRA) solutions(38). A good example of such an

alternative open-source solutions are the Adjusted Morbidity Groups (AMG)(39,40) and the Queralt indices(41,42).

The Adjusted Morbidity Groups and the Queralt Indices

The AMG scoring was developed and implemented by the Spanish Health Ministry and the Catalan public health commissioner (CatSalut)(43). AMG is a morbidity grouper that reflects patients' disease burden in terms of the number and complexity of concomitant disorders. This is determined through a disease-specific weighting deduced from statistical analysis based on mortality and the utilisation of healthcare resources (**Figure 3**). Since its inception, the AMG has been instrumental in guiding health policy decision-making, benchmarking, and adjusting governance strategies. On the clinical arena, the AMG scoring of patients is displayed in primary care physicians' workstations and the shared clinical history(44) of Catalonia as a clinical decision support tool.

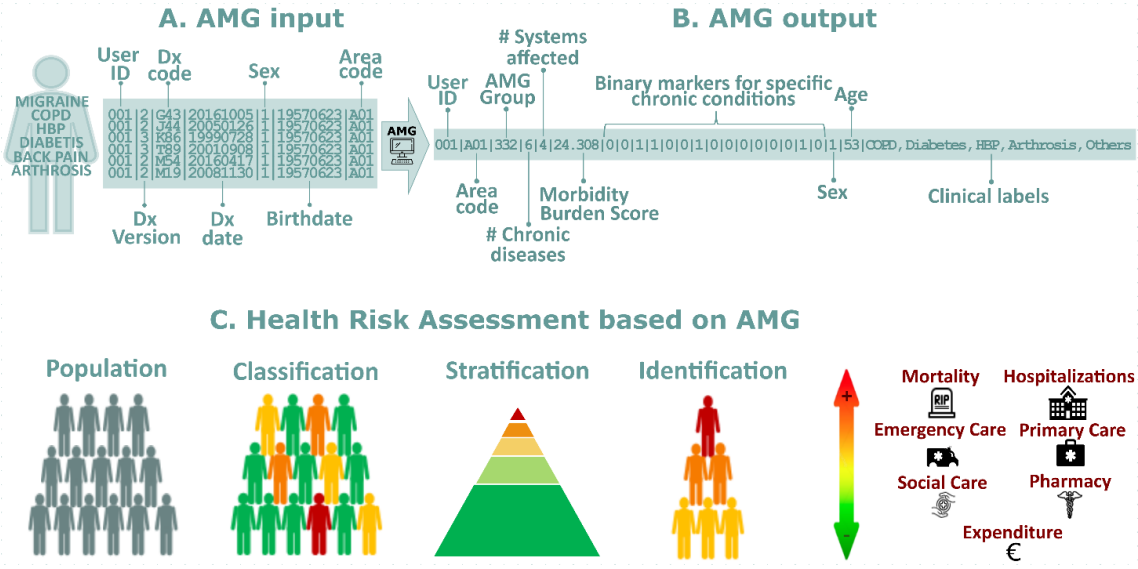


Figure 3: Panel A – AMG input: *Required input variables;* ***Panel B – AMG output:*** *Output variables. *Binary markers (presence/absence) of 15 chronic conditions (from left to right): diabetes mellitus, heart failure, chronic obstructive pulmonary disease, high blood pressure, depression, HIV/AIDS, chronic ischemic heart disease, stroke, chronic kidney disease, cirrhosis, osteoporosis, arthrosis, arthritis, dementia, chronic pain;* ***Panel C– Health Risk Assessment based on AMG:*** *The AMG scoring allows for three key actions:* ***Classification:*** *The population is categorised into specific groups based on their morbidity statuses, such as healthy, pregnancy and labour, acute disease, chronic disease in 1-4 systems, or active neoplasia, which are also*

divided into five degrees of severity. ***Stratification:*** *Individuals can be assigned a complexity score that reflects the care needs that people may have based on their health problems.* ***Identification:*** *Individuals with specific major chronic health problems can be identified, which helps track people with more complex care needs*

Novel research employing the AMG in several contexts has revealed promising prospects in identifying risk factors during the SARS-CoV-2 pandemic(45,46) and refining resource allocation tools(8,47,48). Also, an AMG-based analysis has shed light on the impact of multimorbidity burden in patients with specific chronic diseases, such Chronic Obstructive Pulmonary Disease (COPD)(49).

In pursuit of similar objectives, the Catalan Health system has recently spearheaded the development and internal validation of the Queralt indices to characterize the complexity of hospitalization episodes. These indices amalgamate information on pre-existing disease conditions before hospitalization, the severity of the primary cause of hospitalization, inpatient complications, and the complexity of care interventions (**Figure 4**).

The Queralt indices have demonstrated their reliability as a prognostic tool for prolonged hospital stays, intensive care requirements, and intrahospital mortality, the three primary clinical endpoints for which the tool has been primarily benchmarked(42). By utilizing Queralt indices, hospitals, healthcare professionals, payers, and regulators may acquire a more comprehensive understanding of the patients being treated, the associated costs, and, to a reasonable extent, the expected services and outcomes.

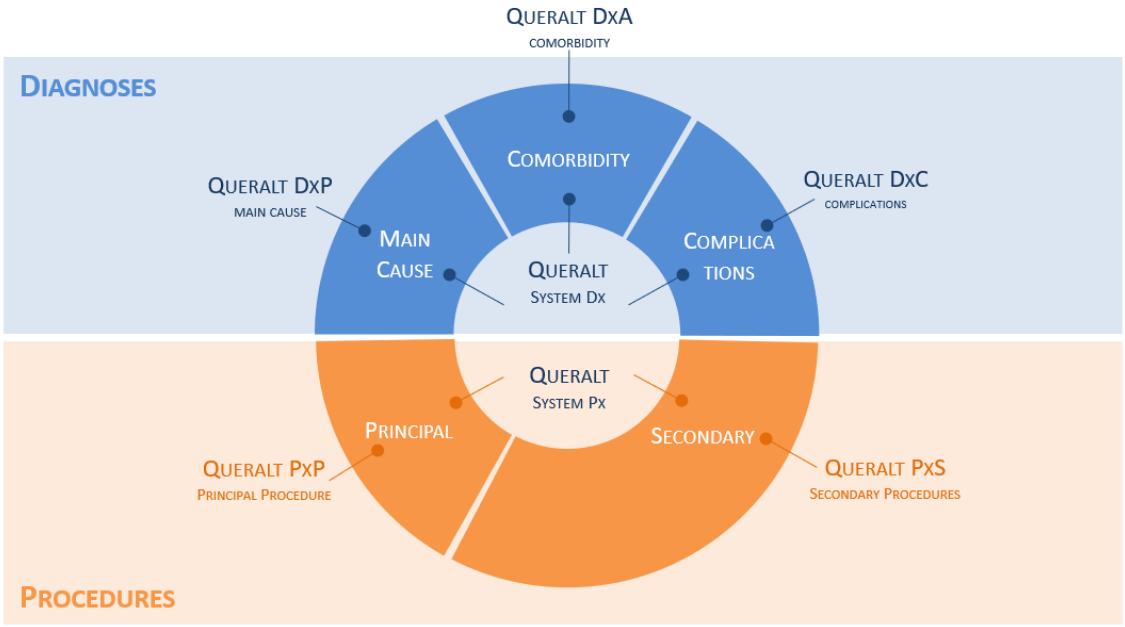


Figure 4: Diagram of the individual Queralt indices for disease diagnoses and clinical procedures. *The Queralt system summarise all the case-mix variables into a different numerical index, encompassing data on the main diagnosis for hospitalization and its comorbid conditions, as well as the complications during the stay. Conversely the Queralt system also considers the main and the secondary clinical procedures. The Queralt indices can aggregated in two domains: disease diagnoses (blue) and clinical procedures (orange). Figure designed by David Monterde (Catalan Health Institute – DS3).*

Overall, the morbidity groupers may help in identifying patients with multimorbidity and enhance the management of their care, but their utilization should not be undertaken in isolation. To be effective, morbidity groupers should form part of a broader health risk management strategy, either at population level or patient oriented, or combined.

2. HEALTH RISK ASSESSMENT FOR PATIENT-CENTRED CARE

HRA is any procedure devoted to characterizing, anticipating and mitigating morbidity-associated health risks and vulnerabilities for individuals and populations, and appears to be a crucial strategy to generate health value and achieve cost-containment. HRA is a valuable approach extensively applied in hospital settings, primary care, occupational health domains, and within health policymaking. HRA entails the identification of prospective health hazards and susceptibilities for both individuals and communities,

serving as a foundational basis for the formulation of targeted preventive and interventional strategies. The core objective of these strategies is to alleviate the burden imposed by disease. Illustrative instances of HRA utilization encompass identifying patients with an escalated risk of complications within hospital environments, pinpointing individuals and populations susceptible to developing chronic diseases in primary and community care and providing valuable insights to policymakers in crafting effective health programs and population-level initiatives.

At present, HRA is a crucial process in informing population health policy decisions, enhancing resource allocation, benchmarking and preventive strategy implementation (49–51). Whereas, within the clinical domain, HRA is focused on the construction computational predictive models to support clinical decision-making in a new medical paradigm(49–51). Integrating population-based and clinically oriented HRA approaches is vital, as they complement each other and play pivotal roles in adopting patient-centred care strategies.

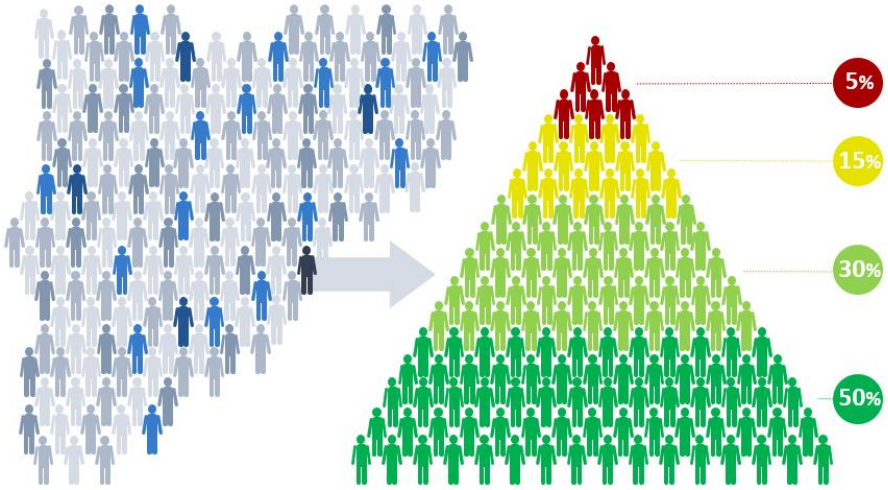
2.1. Population-based HRA

Population HRA entails adopting a holistic modelling strategy encompassing the entire population of a particular region, which results in the creation of stratification maps depicting the distribution of risk strata across the population, conforming a risk pyramid (**Figure 5**). This approach facilitates the identification of subsets of citizens with similar healthcare needs, allowing for effective case finding and screening(52).

Case finding focuses on the most vulnerable patients at the risk pyramid's apex, who are more likely to face significant disease decompensations leading to unexpected hospital admissions, functional deterioration, or death. This procedure is particularly useful in primary and specialized healthcare settings to identify and incorporate these individuals into regional programs designed for complex or advanced chronic patients.

In contrast, patient screening seeks to identify individuals in the mid to lower sections of the risk pyramid who might have latent or non-apparent illnesses. The aim is to facilitate early diagnosis and foster the application of cost-effective preventive

interventions to anticipate and modulate disease progression and prevent patients from escalating towards the tip of the pyramid.



	% Pop.	Mortality	Admissions	Expenditure	% Expend.
GMA-4	5	11,2	58,4	7.070	35,8
GMA-3	15	1,1	6,6	2.124	32,3
GMA-2	30	0,1	2,4	777	23,6
GMA-1	50	0,0	0,5	164	8,3
Catalonia	100	0,8	4,9	987	100,0

Figure 5: Example of the Catalan risk pyramid stratified using the AMG in 2014*. The table's third and fourth columns shows mortality rates and hospital admission rates (cases per 100 inhabitants). The fifth column presents the average annual cost per individual in €, while the final column displays the proportion of total healthcare spending by risk levels. Significantly, towards the tip of the risk pyramid (in red), there is an increase in mortality, likelihood of hospital admission, and healthcare costs, whereas the base of the pyramid (in green) indicates a healthy status. Figure adapted from* (50) *supplementary material.*

Health policies, benchmarking, resource allocation and multimorbidity adjusted reimbursement strategies

At organizational level, health risk stratification enables and informs the development of risk-adjusted health policies. Healthcare requirements are not uniformly spread across populations. In European countries, the top 5% of the population in terms of clinical complexity account for 50% of the total healthcare costs. To ensure the provision of top-tier healthcare, resource allocation should prioritize the population's needs rather than mere demand. In this context, risk-adjusted resource planning

policies based on the risk levels of specific populations lead to better financial management, enhanced preventive care implementation, and improved patient outcomes(53). Adopting this approach will lead to enhanced care quality and decreased expenses over time(54).

When oriented towards a population perspective, HRA tools and other registry covariates are instrumental in modelling health resource utilisation, aiming to optimise resource allocation in conjunction. As exemplified in **Figure 6**, when combined with sociodemographic attributes and historical data on patient interactions with the healthcare system, the AMG boosted the modelling of hospitalisation ratios for patients with COPD in Catalonia (ES) by utilising Generalized Linear Models. Notably, the analysis stressed that the risk strata drafted by the AMG emerged as the central predictive variable, outperforming factors such as age or visits within the emergency department.

Furthermore, HRA should facilitate benchmarking processes and assist healthcare providers and policymakers in evaluating the effectiveness of various interventions and comparing outcomes among diverse patient groups(55). This opens the door to value-based reimbursement strategies in healthcare that differ from traditional payment models as they prioritize the quality of care over the volume of services rendered(56,57). These models reward healthcare providers based on measurable outcomes, such as patient health improvements and cost reductions. Notable examples of value-based reimbursement strategies include accountable care organizations, bundled payments, and pay-for-performance models. These strategies incentivise healthcare providers to deliver high-quality care, leading to improved patient health, reduced healthcare expenses, and heightened patient satisfaction.

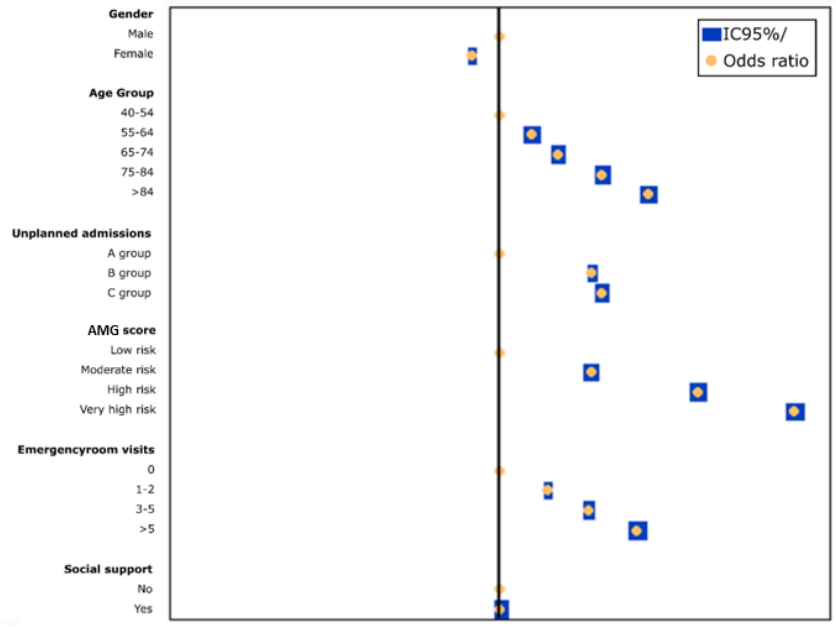


Figure 6: Predictive Model for All-Cause Hospitalization*. The visual display delineates the magnitude of the odds ratio for each model covariate, represented by yellow dots, accompanied by the respective 95% confidence intervals, depicted with blue rectangles. Figure taken from* (49) *supplementary material.*

Nevertheless, the efficacy of population based HRA interventions in efficiently managing overall population demand relies on identifying individuals most susceptible to adverse events and pinpointing those who are both at high risk and likely to respond positively to a specific intervention, essentially, those who can be impactable(58,59).

Impactability modelling(60) is a novel technique used in population health management to identify patients who are not only at risk of developing certain health conditions but also likely to benefit from certain interventions. It further sorts the sub-groups of at-risk patients, based on their probability of benefiting from various interventions or treatment plans. It is essential to recognise that while certain impactability modelling approaches can help diminish inequalities, others might exacerbate them. Therefore, conducting an equality impact assessment is crucial.

2.2. Clinically oriented HRA

In the clinical arena, HRA plays a significant role in informing and aiding clinical decision-making processes. Clinical decisions typically draw upon the health professional's knowledge, past experiences, and intuition. Rule-based decision-making grounded in solid medical evidence, often derived from randomized controlled trials (RCTs), plays a crucial role in enhancing the efficiency of the decision-making process(61). More recently, significant shifts in clinical research and practice have been catalysed by integrating systems biology methodologies and using information and communication technologies(30,62,63). These changes can potentially enhance clinical decision-making by incorporating holistic approaches, computational modelling, and predictive tools into clinical medicine(64,65).

These trends are prominently steering large-scale clinical applications toward the mainstream embrace of Clinical Decision Support Systems (CDSS) (**Figure 7**). CDSS, as defined, are computational models designed to aid directly in clinical decision making, in which characteristics of individual patients are used to generate patient-specific assessments or recommendations that are then presented to clinicians to support clinical decision making(66). It is important to note that this modelling approach must complement, rather than replace, clinical judgment, providing additional insights and guidance to healthcare professionals.

Integrating IT components into clinical decision-making began with translating expert knowledge—sourced either from hands-on clinical practice or medical literature—into rule-based 'if-then' formats (**Figure 7**). Over time, as the volume and complexity of patient-related data from diverse healthcare domains surged, a shift towards data-driven analysis methods arose. These methods promise to augment the capabilities of healthcare professionals, especially when it comes to making patient-centric decisions derived from the analysis of large databases. Within this framework, clinical decision-making encounters substantial challenges from integrating rapid progressions of computational sciences in digital medicine and artificial intelligence (AI) (**Figure 7**).

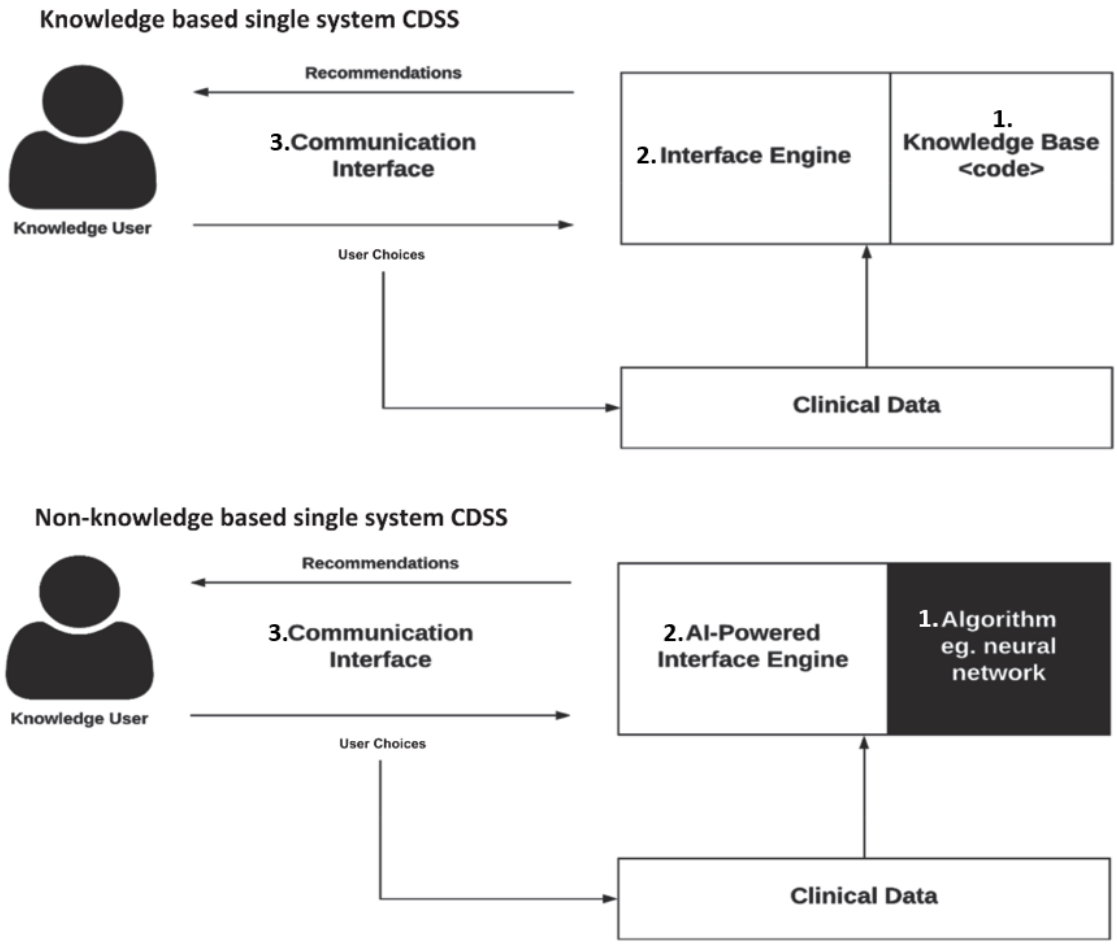


Figure 7: Diagram of key interactions in expert systems and data driven CDSS*. Three key elements are identified: 1)* ***The model*** *includes predefined rules for knowledge-based systems, decision-modelling algorithms for non-knowledge-based systems, and accessible data. 2)* ***The inference engine*** *processes either the programmed rules or those determined by AI, and combined with structured data, it analyses the patient's clinical information to produce an actionable result. 3)* ***The user interface*** *where the result is then displayed to the end-user, such as a physician, through a communication platform, which could be a website, application, or the frontend of an Electronic Health Record (EHR) system. The end-user interacts and engages with the system's recommendations in this interface. Figure taken from* (67)*.*

During the last decades CDSS have exhibited a profound maturation in specific contexts, extending their capabilities across a myriad of actionable clinical areas. One of the most solid advancements of CDSS is observed in terms of informing diagnostic procedures, concretely augmenting the extraction, visualization, and interpretation of medical images (e.g. tumour detection(68) or diabetic retinopathy diagnosis(69)) and analysis of laboratory test results (e.g. tumour grading(70) or automating blood cell counting(71)). Beyond their diagnostic prowess, CDSS have also demonstrated remarkable efficacy in automatizing administrative tasks, such as providing support for

clinical and diagnostic coding(72), ordering procedures and tests(73), sending immunization reminders(74), discharge planning (75) and patient triage(76). Through the automation of various processes, they facilitate a reduction in human-induced errors and enhance the overall efficiency of clinical operations. Such systematic automations further play a pivotal role in informed resource allocation and cost optimization(77).

However, CDSS respond to specific clinical queries, mainly designed for targeted populations. Moreover, their utilization in comprehensive clinical interventions is still limited. The statement is particularly true for managing complex chronic patients afflicted by a substantial multimorbidity burden. As described above, multimorbidity is a complex condition shaped by an intricate interplay of multiple health determinants, including medical history, nutrition, lifestyle behaviours, environmental exposures, genetic predispositions, employment, and other socio-economic risk factors(78).

In this context, implementing comprehensive methodologies for subject-specific risk prediction and stratification, encompassing a wide array of influencing covariates derived from multiple sources on patients' health and well-being, can heighten predictive precision and facilitate clinical decision-making grounded in robust estimations of individual prognosis.

The prospect of integrating these health determinants into holistic predictive models presents an exciting opportunity for CDSS(79–81), especially in the context of machine learning and predictive modelling. While traditional rule-based systems may face challenges assimilating these extensive datasets, AI-driven systems demonstrate a comparative advantage. However, this shift to complex models poses challenges. Key challenges include integrating data from diverse sources while safeguarding patient confidentiality, addressing inherent biases in AI models, and validating the precision of system recommendations. Additionally, the opacity of AI-driven decision-making processes, often termed “black boxes” adds complexity, that is, computational methods where the internal mechanisms and decision-making processes are not easily explainable(82). Despite these challenges, the potential benefits of a more integrated and multisource CDSS are pushing the evolution in this direction.

3. TOWARDS LEARNING HEALTHCARE SYSTEMS

Contemporary medical science is characterized by a dynamic flux of knowledge, with novel findings, methodologies, and new therapeutic opportunities emerging at an unprecedented pace. Therefore, continuously updating CDSS is essential to align with emergent medical data, knowledge, and practices. In this continuous adaptation process, two pivotal components have been identified to guarantee that practitioners consistently operate at the apex of evidence-based medical practice. Firstly, there is an imperative for the prompt validation and incorporation of research advancements into clinical practice in real work scenarios. Secondly, it is crucial to establish a feedback mechanism, enabling clinical learnings to reciprocally inform and refine research lines.

Addressing the abovementioned challenges inevitably narrows the gap between academia and clinical practice, opening a range of possibilities for cross-fertilization in both fields. This convergence triggers a virtuous cycle that ensures that clinical procedures are rooted in empirical evidence but also allows the nuances of practical patient care to inform and refine ongoing research. This ideal iterative model of knowledge exchange and application is known as the Learning Healthcare System (LHS)(83). While the concept is still nascent, projections suggest that this emerging paradigm will significantly influence health systems, steering the advanced stages of the shift towards a fully digital medical landscape. The benefits of the synergistic convergence between clinical practice and biomedical research inherent in the adoption of the LHS are elaborated comprehensively in **Appendix (Personalized Medicine meets Artificial Intelligence; Chapter 10: "Multilevel Modelling with AI: The Synergy-COPD Endeavour")**.

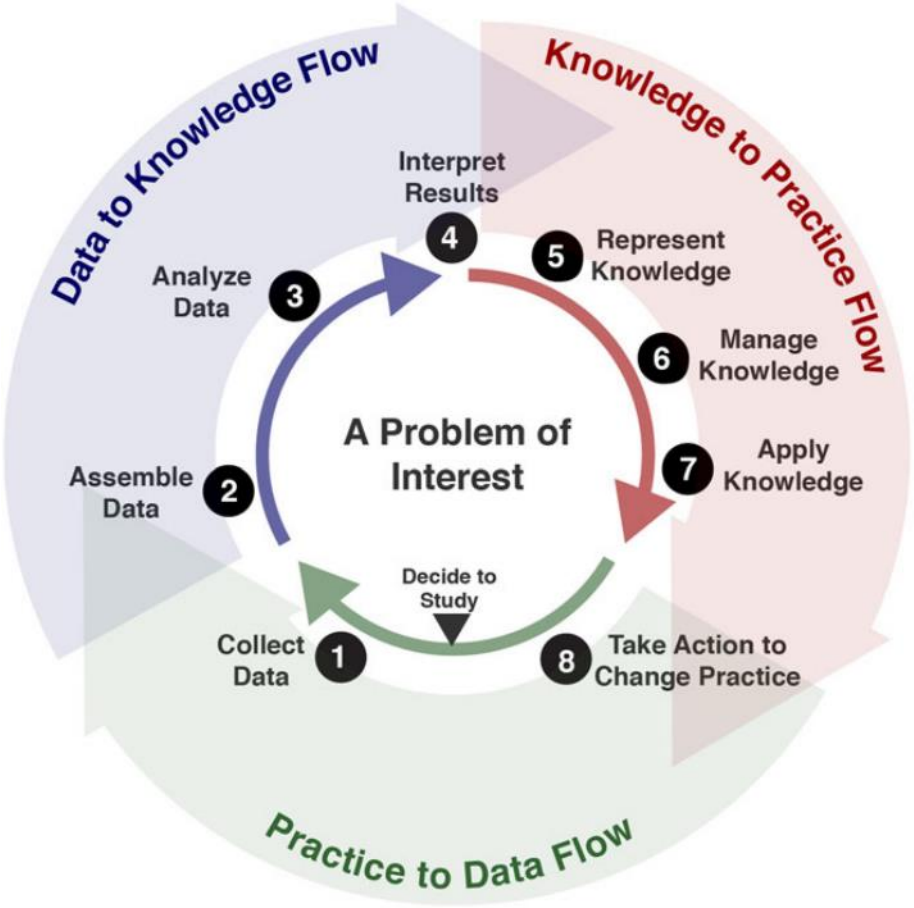


Figure 8: The iterative cycle of the learning health system *with 3 information flows and 8 steps. Figure taken from* (84).

The LHS, as depicted in **Figure 8**, serves as an illustrative example for a project aiming at learning how to enhance transitional care. The cycle begins with the collection of patients data (step 1), followed by its assembling (step 2) and subsequent analysis (step 3). From this analysis emerges a predictive model capable of estimating the risk of 30-day hospital readmission (step 4). This actionable model can be converted into a CDSS (step 5). Subsequently, this model can be operationalized to strengthen a predictive calculation service via its integration within an EHR or another health IT infrastructure (step 6). Now, it functions as applied knowledge (step 7). This integration facilitates the amalgamation of new information through the predictive model with individual-specific data, thus yielding the clinical problem under a new paradigm and offering potential clinical utility (step 8)."

A core element to support the above LHS strategy is the adoption of a Digital Health Framework (DHF)(85) at healthcare system level. The DHF includes elements such as data infrastructure, governance, stakeholder engagement, analytic capabilities, and a culture of continuous improvement. DHF shall ultimately contribute to enhance *in-silico* scientific analysis towards dynamic health risk assessment and patient stratification by means of holistic strategies for subject-specific predictive modelling(85,86). By leveraging DHF, LHS can efficiently capture and utilise health data to foster continuous learning, facilitate research, enable real-time monitoring, support personalised medicine, and drive evidence-based decision-making. The combination of LHS principles and a proper DHF infrastructure creates a synergistic approach to advancing healthcare quality, patient outcomes, and population health management.

3.1. Multisource Clinical Predictive Modelling

Adopting the LHS approach supported by a mature DHF would make it possible to face one of the great remaining challenges for the CDSS: integrating data from multiple determinants of health. This integration would enable the implementation of comprehensive methodologies for morbidity-adjusted subject-specific risk prediction and stratification and identify potential intervention targets to implement personalised, cost-efficient, patient-centred care plans. This approach know as Multisource Clinical Predictive Modelling (MCPM) (**Figure 9**), facilitates the integration of i) healthcare data form EHR, and health determinants from other domains including: ii) Population health registry data; iii) Informal care data including patients' self-tracking data, lifestyles, environmental, behavioural aspects, and sensors; and iv) Biomedical research omics data.

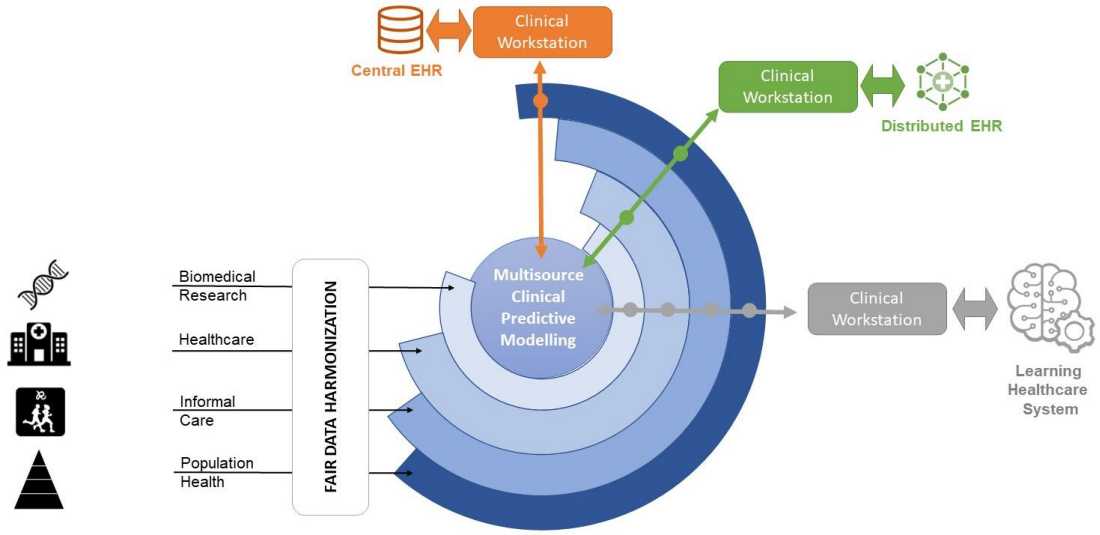


Figure 9: Dynamic enhancement of multisource clinical predictive modelling feeding clinical decision support systems (CDSS). *Development of enhanced clinical predictive modelling requires consideration, and eventual integration, of computational modelling of four different dimensions: (i) Underlying biological mechanisms (biomedical research); (ii) Current evidence-based clinical knowledge (healthcare); (iii) Patients' self-tracked data, including sensors, behavioural, environmental, and social information (informal care); and (iv) Population-based health risk assessment data (population health). Figure adapted from* (87)*. Additional information can be found in Annex 1 (Personalized Medicine meets Artificial Intelligence; Chapter 10: "Multilevel Modelling with AI: The Synergy-COPD Endeavour")*

Clinical information - Clinical data forms the foundational information about a patient's health and medical history, encompassing their diagnoses, treatment histories, immunization records, functional tests, and lab results. Currently, this data is systematically organized and stored within an EHR, which offers healthcare professionals a digital, comprehensive view of a patient's medical interactions and treatments. However, this information is not only restricted to health professionals. The personal health folders empower patients by allowing them to manage and compile their own health data fostering a proactive approach and enhancing patient involvement in their healthcare decision-making.

Population health - Increasing evidence indicates that the population-health risk predictive tools could enrich the spectrum of covariates considered in the patient-based HRA computational models(50). This approach fosters the integration of population-level risk assessment strategies and individual-level risk assessment geared towards supporting clinical decision-making. Recent research indicates that

incorporating population-based morbidity groupers, such ACG, CRG or AMG, in computational models, jointly with sociodemographic information, might aid in identifying early signs of unplanned hospital admissions, paving the way for programs aiming at preventing hospitalizations(88) and promote the application of cost-effective preventive interventions to anticipate and modulate disease progression.

Informal care - It's worth noting that incorporating informal health data into HRA not only introduces the potential for integrating health determinants outside the clinical scope but also facilitates enhanced patient monitoring beyond the confines of the healthcare facility. At this point, Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) assume significance, as they provide important feedback on a patient's health status and their experience of care(89,90). The ongoing debate surrounding the most appropriate methods for capturing these measures includes exploring standardized health questionnaires as well as emerging telemedicine and remote patient monitoring techniques(91,92), which often consider information collected from a wide spectrum of medical devices, ranging from wearable health trackers, such as heart rate monitors and step counters, to advanced diagnostic equipment, enabling accurate monitoring of vital signs, detecting abnormalities, and self-management of chronic conditions(91,92).

Biomedical research - Following a systems medicine approach, it is imperative to integrate omics-derived insights with clinical applications to augment our comprehension of disease mechanisms, prognostications, diagnostics, and therapeutic interventions. This necessitates a cyclical and bidirectional exchange between clinical explorations and the employment of computational, statistical, and multiscale mathematical analyses to delineate pathogenic mechanisms, disease trajectory, and therapeutic responses at a population and individual patient scale. Such models are instrumental in decoding complex biological data, elucidating the interrelations within a biological system that culminate in health or disease states, and thereby emerging as potent predictive tools for individualized health and disease trajectories(93,94).

Nonetheless, the integration of data encompassing the four domains mentioned above introduces a range of unresolved challenges. Avoiding for a moment the debate on the technological and architectural prerequisites imperative for integrating the alluded

data sources, the strategic implementation of the multisource approach confronts inherent constraints that hinder the realization of its full potential. These limitations arise due to the developmental immaturity inherent in specific domains of knowledge.

One of the main challenges is the collection of patients' PROMS and PREMS data in real-world settings, which remains unresolved. This limits the ability to gather comprehensive data on patient outcomes and experiences. Moreover, the lack of evidence-based protocols and integration into clinical workflows poses a challenge for the adoption of some approaches, resulting in diminished performance and efficacy gaps when are applied in real world settings(95,96). However, obstacles to implement PROM/PREM were apparently uniform across various patient groups and care environments. This indicates that strategies aimed at addressing contextual elements could significantly enhance the effectiveness of implementation(95).

Another distinctive challenge is the incorporation of omics data in MCPM targeting interventions in all-type multimorbid patients since most of the genetic biomarkers are narrowly related to specific groups of diseases or targeting precise metabolic pathways. Multimorbidity involves the interaction of several diseases and their underlying molecular mechanisms. Understanding the intricate interplay between various omics data points and their collective impact on health outcomes proposes a substantial biological challenge(97,98). In addition, developing comprehensive models that accurately capture the complex interactions between various omics layers and disease states requires the utilization of high-dimensional datasets. The analysis of such databases, can make traditional statistical methods less effective and require enormous computational resources to handle a large amount of information and provide complex results that are challenging to interpret and translate into actionable insights for clinicians and researchers(99).

4. FROM RESEARCH TO CLINICAL PRACTICE: PERSPECTIVES AND CHALLENGES

The cumulative evidence presented in the previous sections underlines the potential synergy between a systems medicine approach, integrated care, and computational medicine to enhance the management of multimorbid patients. However, despite strong evidence and worldwide efforts to promote the integrative confluence of these domains, still exists a substantial disparity between the growing proliferation of computational modelling studies in the academia and their adoption into clinical routines. Notable data evidence this gap; for instance, numerous CDSS have resulted in limited adoption or adverse effects on outcomes(100,101). Research indicates that as many as 95% of CDSS are dismissed(102). This is an alarming rate of non-adoption, suggesting that these tools' technical and academic aspects are robust but there are issues related to their practical application, user experience, or integration into clinical settings. Nevertheless, the landscape is not entirely pessimistic, approximately 52% to 66% of these tools contribute to enhancing process outcomes like appropriate drug selection, medical imaging interpretation or laboratory test analysis, whereas a 21% to 43% bring about improvements in clinical outcomes(102). This evidence highlights the potential efficacy of these systems, suggesting that, when appropriately employed, they can substantially refine clinical procedures, and thereby boosting patient care.

The factors contributing to the unsuccessful transition of the comprehensive MCPM approach from research environments to fully operational CDSS are multifaceted. These include suboptimal quality of clinical data, models with inadequate generalization or customization capabilities, challenges in integration with pre-existing systems and usability difficulties stemming from unintuitive interfaces for clinical practitioners(103,104). Moreover, additional barriers are present in the form of mistrust and cultural resistance within the clinical community, regulatory and legal issues, and financial constraints linked to the substantial costs associated with implementation(103,104).

These limitations highlight the need for targeted efforts to address knowledge gaps, secure adequate resources, develop effective deployment strategies, foster a culture of innovation and openness to change, and establish robust data privacy and security measures. By addressing these challenges, the implementation gap between

biomedical research and clinical practice should be minimised and the potential impact of CDSS will lead to improved healthcare decision-making and better patient outcomes.

All the determinants of non-adoption listed above are shown sequentially in the phases of model development and implementation depicted below (**Figure 10**).

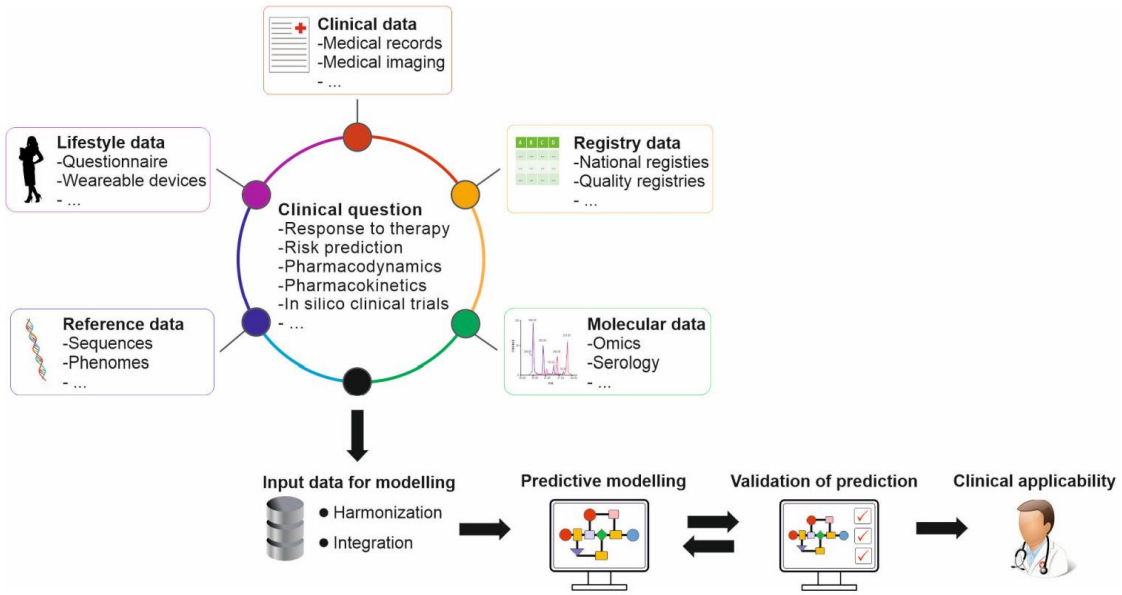


Figure 10: Diagram depicting the different phases of the development and implementation of a CDSS. *Creating a model commences with a clinical inquiry, succeeded by data collection. This data can be obtained through either a knowledge-driven method or a data-driven approach. To begin building the model, it is necessary to use consistent integration methods for the data being employed. Adhering to FAIR data principles and GDPR is essential for the model's development. Typically, the initial model undergoes multiple rounds of refinement and improvement to enhance its predictive capabilities. Accurate measurements and validation procedures are pivotal and should be transparent. Furthermore, ideally, the model's output and function should be interpretable and explainable. Figure taken from* (105)**.**

During this process, four well-defined bottlenecks have been identified:

1. **Model Development**: It is imperative to secure access to data from multiple sources, that is not only accurate but also allows interoperability. This multisource data aggregation is essential for constructing robust and comprehensive models. Even when data is accessible, its quality, diversity, and relevance can be a concern. Incomplete, outdated, or unrepresentative data can lead to models that are not robust or generalizable. Bias in the data, either

due to underrepresentation or skewed sampling, can propagate into the models, leading to unfair or inaccurate predictions.

2. **Model Validation**: Ensuring models' efficacy requires rigorous validation within real clinical environments. Such an evaluation aims to ascertain the models' applicability and effectiveness in clinical scenarios beyond controlled or simulated settings.
3. **Model Regulation**: In the contemporary data-driven era, it is crucial to ensure that these models adhere to established regulations such as the General Data Protection Regulation (GDPR) and other prevailing European legislative frameworks, such as the Medical Device Regulation (MDR). This ensures both ethical handlings of data and instils confidence in the potential users regarding the model's compliance with legal mandates.
4. **Model Adoption**: Eventual deployment and utilization in routine clinical practice requires overcoming inherent institutional and individual resistances to change. Additionally, barriers related to the acceptability and usability of new technological systems must be addressed to ensure smooth integration into existing workflows.

4.1. Model Development: Challenges and opportunities in data integration

Integrating data into CDSS presents an initial challenge, accessing and harmonising data from diverse sources. This crucial phase relies heavily on ensuring data is compliant with FAIR principles – ensuring it is findable, accessible, interoperable, and reusable. This is particularly important in multicentric data integration, wherein the information is often fragmented in different silos. This diversity of input data originating from different sources significantly impedes subsequent analyses and comparability of the results. Addressing this challenge necessitates two fundamental shifts at the organisational level. Starting with ensuring data interoperability, followed by equipping the system with the requisite architecture to facilitate collaborative workflows across distinct organisations.

Standardising health data: the rise, relevance, and role of healthcare data standards.

Achieving this data harmonization requires the utilization of suitable data standards. Data standards encompass specifications and directives that delineate a universal vocabulary and framework for capturing, storing, and exchanging healthcare-related information. Through this process, the standards play a pivotal role in ensuring data and metadata interoperability, elevating data quality, and serving as fundamental catalysts for result reproducibility(106). Several advancements in this area have led to the emergence of various health data standards, encompassing both commercial and community-driven efforts. These standards have been introduced to promote interoperability across diverse environments, fostering efficient exchange of electronic health information and enabling systematic analysis. Noteworthy examples include Health Level Seven International (HL7)(107), a set of standards for exchanging electronic health information between different systems and organizations, among them is highly relevant the HL7 Fast Healthcare Interoperability Resources (FHIR)(108), the latest standard from the HL7 organization, aiming to simplify the integration and exchange of health information. The Clinical Data Interchange Standards Consortium (CDISC)(109), that develops global standards for clinical research data and metadata. The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)(110), a standard for transforming data contained in observational databases into a common format, allowing for systematic analysis. And the OpenEHR(111), an open standard specification for semantic interoperability of health information systems, that describes the management and storage, retrieval, and exchange of health data in EHRs focused on enhancing data persistence. Also, ISO-13606(112) establishes a framework for EHR interoperability.

European initiatives for primary and secondary uses of health data: The European Health Data Space and EU-STANDS4PM

Currently, this concern is tackled by two pivotal projects at European level, following parallel and complementary approaches. On the one hand, the European Health Data Space (EHDS)(113) addresses the utilisation of health data for primary and secondary purposes, encompassing routinely collected healthcare data. The EHDS initiative aims

to establish a shared data environment for health-related information across Europe. The primary mission of EHDS centres on addressing specific challenges related to accessing and sharing electronic health data, striving to create a unified realm where individuals have control over their health data while enabling trusted and secure use by researchers, innovators, and policymakers, all while safeguarding privacy. Built on robust foundations of data privacy, interoperability, and security, including cybersecurity measures, EHDS is pivotal for citizen trust and project resilience and facilitating cooperation and information exchange among Member States.

Conversely, the effective repurposing of health data for computational modelling under personalized medicine research umbrella, is addressed by the EU-STANDS4PM(114) consortium, which has been working diligently to establish formal standards for precision medicine, and emit specific requirements and recommendations for the design, development and establishment of computational models for research purposes. EU-STANDS4PM is a Coordinating and Support Action funded under the European Commission's Horizon2020 framework program, carries a core objective of creating a pan-European expert platform. This platform seeks to evaluate existing standards and devise novel ones for data integration and sharing in the domain of computational modelling for personalised medicine. The project's scope encompasses evaluating national strategies for interoperable health data integration and creating a European framework for big data in personalised medicine. A recent outcome of this endeavour is the ISO/TS 9491-1:2023 "Biotechnology — Recommendations and requirements for predictive computational models in personalized medicine research — Part 1: Guidelines for constructing, verifying and validating models"(115). This framework will underpin the development of fresh in silico models with applications spanning drug discovery, clinical trial design, and other aspects of personalised medicine support.

Transitioning from Centralized to Decentralized Data Models

Additionally, incorporating multisource health data in a CDSS is inherent in the evolution from centralized to decentralized data models. In the former, data resides in a singular location and is accessed via a single interface. Conversely, the shift to a

decentralized model involves data being dispersed across various locations and accessed through a distributed system. A notable illustration is the federated data model, a technology that virtually amalgamates data from diverse sources, rendering it accessible within a standardized data framework. In federated data models, underlying data repositories continue to function autonomously, while data consumers can execute federated queries as if the data were consolidated. This holds particular appeal for organizations housing disparate database types, eliminating the need for users to be proficient in each database's query language. Another instance is the peer-to-peer data model, wherein data resides across multiple nodes within a network, allowing users direct access to the data from these nodes.

Moreover, as both clinical and biomedical datasets continue to grow in both quantity and size, an increasing number of participants in clinical studies are required to discern meaningful signals, potentially confounded by an array of biological, experimental, and environmental factors. Similarly, the computational demands necessary for the processing and analysis of these burgeoning data volumes, which are expanding on a daily basis, surpass the computational capabilities of research institutions. However, the biomedical research landscape and healthcare services, in a broader sense, have not yet fully embraced Big Data and cloud computing. Consequently, the task of generating new datasets by amalgamating clinical information and scientific knowledge remains a formidable challenge.

European Health Research and Innovation Cloud: paving the way for a cloud-based European healthcare infrastructure

In response to this challenge, the EU Digital Transformation of Healthcare Initiative (DIGICARE) aims to establish the essential groundwork for constructing a secure, adaptable, and decentralized digital healthcare infrastructure through the development of the "European Health Research and Innovation Cloud" (HRIC)(116). This initiative aspires to streamline data exchange and analysis for healthcare research across the EU while adhering to data protection regulations. HRIC will be constructed upon existing data infrastructures, integrating clinical best practices, and concentrating

on the specific community needs concerning technology, governance, management, regulation, and ethical prerequisites.

Cloud technologies allow data access and processing, provided that the cloud servers are situated within European territory, comprehensive data protection and security measures are in place, and a valid data processing agreement is established. Leveraging decentralized data within the cloud facilitates real-time algorithm execution, facilitating both data utilization and shared processing without generating localized data copies, thus offering significant advantages in data protection regulation. Furthermore, the cloud enables high-performance computational analyses, a feature posing management complexities for institutions constrained by limited computational resources.

4.2. Model Validation: from model development to clinical application and continuous validation

Another well-identified bottleneck that hinders the implementation of CDSS in clinical practice is the rigorous evaluation and validation of machine learning models before their practical implementation in clinical settings, ensuring that models exhibit accuracy, reliability, and generalizability across varying patient populations and diverse contexts.

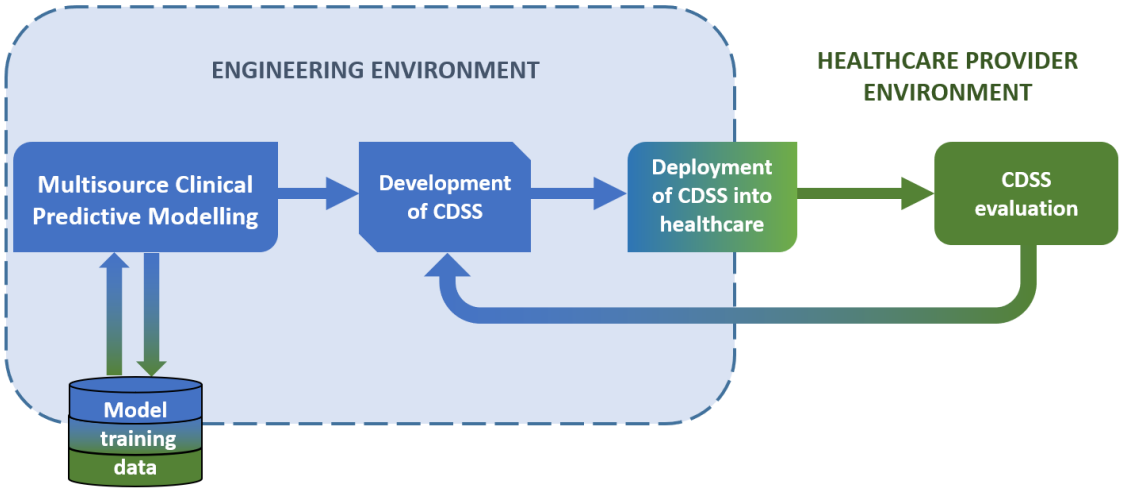


Figure 11: Diagram of the steps for the adoption of multisource clinical predictive models (MCPM), *including elaboration, training, evaluation and feeding clinical decision support systems (CDSS) to be applied in a real-world healthcare setting. Figure taken from (Annex 1 -*

(Personalized Medicine meets Artificial Intelligence; Chapter 10: "Multilevel Modelling with AI: The Synergy-COPD Endeavour").

Figure 11 illustrates the steps from model elaboration, model training, evaluation and feeding CDSS to be applied in a real-world healthcare setting. The personalized medicine approach to enhancing patient health typically begins by identifying the specific health aspect to be targeted and modelled, such as disease diagnosis, severity prognosis, or treatment response. Subsequently, the following step usually involves pinpointing pertinent data sources, encompassing various types and originating from clinical practice and research environments. Once this preliminary data preparation is accomplished, modelling is executed to foresee the clinically significant state. For effective clinical decision support, the resulting models must be integrated into workflows within the clinical setting. In general, models should undergo validation in an independent context beyond the engineering environment. Algorithms must demonstrate efficacy on new, previously unseen data from the same domain. Upon completion, these models can be applied in clinical settings to enhance patient health. However, it's imperative to ensure their sustained performance. CDSS might become outdated or less effective for certain patient groups, and their accuracy could diminish over time. Retraining CDSS may involve updating algorithms or data sources and adjusting decision-making rules. This proactive measure guarantees the continued precision and relevance of CDSS for the patient populations it serves.

Across this process, the context-specific nature of computational models is a recurring hurdle in both their development and validation. This means that the applicability of these models is limited to specific scenarios due to their restricted extrapolation capabilities. Furthermore, this contextual specificity makes it difficult to standardize, reuse, and report the results of these models. While there is consensus on the importance of validation and assessment, there are divergent opinions regarding the optimal validation methods. Some propose RCTs as the gold standard for validation, while others argue that local, autonomous validation studies may be more feasible and essential, particularly for algorithms with indirect patient care impacts(103). In light of this, it is important for researchers and practitioners to carefully consider the validation methods that are most appropriate for their specific context and goals. This

may involve a combination of approaches, including RCTs, simulation studies, and local validation studies.

It is also worth to mention that many software tools still lack provisions for open-access rights, sustained maintenance, version control, and standard software qualification. Paradoxically, despite their availability and endorsement by multiple tools, best practices are often not consistently applied(103).

4.3. Model Regulation: from data protection and ethics to AI regulations

The third challenge presents itself in two dimensions: first, it addresses the distribution and secondary utilization of health data among different organizations while ensuring full compliance with existing ethical legislation; second, it focuses on being compliant with prevailing regulations governing AI in healthcare.

The GDPR is a cornerstone in the regulatory landscape governing data privacy and protection. GDPR is especially relevant during the initial phases of model development due to its impact on data collection, usage, and overall project planning This regulatory frame establishes different directrices to be followed when delving into computational modelling, especially when using data-driven strategies.

Among these directrices is the principle of data minimization, especially pronounced within data-driven models where the relevance of the covariates may be ambiguous. This principle underscores the importance of ensuring organizations retain only the minimum necessary personal data. This measure mitigates risks associated with potential data breaches and upholds individuals' rights and privacy.

Moreover, the significance of data inclusivity cannot be understated, which entails capturing and reflecting a broad spectrum of demographic attributes, including diverse genders and ethnic backgrounds. Nevertheless, a nuanced ethical challenge arises when generating profound patient insights that transcend their immediate clinical needs, especially given the inherent moral principle of the "right not to know." It is also imperative to maintain a commitment to transparency by communicating the efficacy of these computational models when integrated into clinical practice, thereby equipping patients with a comprehensive understanding of the potential outcomes

and implications. Automated decision-making processes often exclude pivotal human intervention, posing concerns about preserving transparency rights. Apprehensions surrounding the interpretability and transparency of machine learning models pose considerable challenges, especially within healthcare settings where decisions wield substantial implications for patient well-being and safety.

In essence, computational models must undergo rigorous peer review and validation processes. To gain clinician adoption, they necessitate evaluation through research procedures such as RCTs and compliance with MDR, to bring CDSS to the Healthcare market as medical devices able to claim impact on healthcare outcomes. The European Commission is in the process of introducing a regulatory framework for AI, encompassing dedicated regulations for AI-powered medical devices. Supplementary guidelines(117) are accessible from both the European Commission and the Medical Device Coordination Group (MDCG), offering comprehensive insights into the classification and categorization of AI-incorporating medical devices. These documents outline the criteria for determining the risk level of a medical device and provide guidance on the conformity assessment procedures that must be followed.

4.4. Model Adoption: leveraging implementation science frameworks

The last hurdle to overcome is the resistance to change at the organizational and user level. In this regard, the lack of awareness or understanding of the benefits of CDSS and its potential impact on healthcare decision-making among healthcare providers, patients, and policymakers is hindering its widespread adoption and utilization(118). The healthcare industry, like any other sector, may face resistance to change or a reluctance to adopt new technologies or practices. Some healthcare providers, patients, and policymakers may be hesitant to embrace CDSS due to concerns about its integration into existing workflows, potential disruptions, or perceived complexities associated with adopting new technological solutions(119).

The exposed lack of explainability can make it difficult for clinicians to place their trust in and effectively employ these models in practical situations. It is well acknowledged that the opacity of black box algorithms may be more important for healthcare

professionals than simply knowing the accuracy of the predictions and can lead to poor acceptance of the solution. This nuance is especially pertinent in healthcare, where adopting AI-driven tools aims to augment clinical decisions and enhance patient care outcomes. Thus, the emphasis on explainable artificial intelligence (XAI) is gaining momentum within healthcare contexts, as it offers a lens into the AI decision-making process, ensuring that such decisions are transparent, accountable and trustworthy(119).

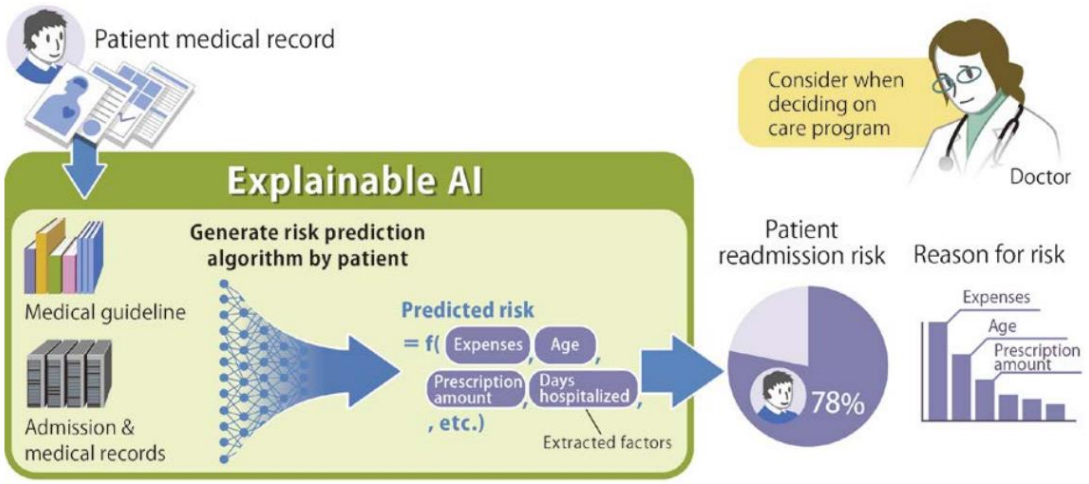


Figure 12: Predictive model for hospital readmissions embedded in an explainable Artificial Intelligence (XAI) interface*. The diagram illustrates a predictive model designed to anticipate hospital readmissions seamlessly incorporated within a XAI interface. The model's predictions are based on a holistic analysis of electronic health records (EHRs) and other relevant healthcare data. The AI interface offers transparency by elucidating the underlying factors contributing to the model's predictions. This facilitates a comprehensible and actionable understanding of the prediction process, ensuring its practical application within healthcare contexts. Figure taken from* (120)*.*

Also, implementing and maintaining HRA programs can require significant resources, including financial investments, infrastructure development, and staff training. Limited resources or funding can pose challenges in establishing effective HRA programs, and the lack of well-designed deployment strategies can further impede its successful implementation(103).

Implementing CDSS in real-world clinical workflows requires a comprehensive, evidence-based framework to guide the process. While implementation science (IS) frameworks exist specifically for health information technologies, current literature does not offer exhaustive guidelines covering all aspects of CDSS implementation.

There is a clear need for a robust IS framework that considers the unique challenges and contextual intricacies pivotal to the successful deployment of CDSS tools.

In light of this, the pragmatic application of IS frameworks, such as CFIR(121) or PRISM(122), can assist in several ways. Foremost among these is the provision of essential support structures necessary for the effective deployment of interventions, coupled with mechanisms to address and rectify unforeseen challenges swiftly. As part of this process, strategies must be developed to facilitate the smooth incorporation of the CDSS into routine clinical operations and effectively communicate these changes to end users. It's also imperative to reconvene with clinical leadership before deployment, particularly when the pre-implementation stage has been extensive or in scenarios where the health systems are undergoing significant transformations.

5. CHALLENGES ADDRESSED IN THE THESIS: THE THREE USE CASES

The thesis addressed multifaceted challenges within the HRA domain by employing a structured approach. These challenges are articulated and examined across three specific use cases.

Primarily, the PhD thesis investigates the influence of multimorbidity on complex HRA predictive models (**Use Case 1**). This comprehensive research pursues to formulate feasible, applicable and pragmatic predictive models that account for multimorbidity but also consider other determinants of health. This analysis would enable to effectively evaluate the health risks associated with hospitalization cases to improve service selection at admission and promote transitional care at discharge. This inquiry is grounded in realism, accounting for factors that may influence the adoption, paying specific attention to the systematic design and evaluation of models. Ans, aligned with Catalonia's digital transformation objectives, this use case is ultimately geared towards offering guidance on CDSS adoption strategies.

Additionally, the thesis also analyses the driving forces within the European healthcare landscape to transfer and adopt mature HRA strategies among regions, with particular emphasis on the use of morbidity groupers (**Use Case 2**). This was empirically tested under the umbrella of the transference of the AMG algorithm, allowing to evaluate

both enablers and barriers employing robust evaluative approaches grounded in well-established implementation frameworks for the transference and adoption of such tools in clinical and public health contexts. Also, this evaluation would allow to measure the algorithm's adaptability and effectiveness in different contexts.

Furthermore, the research delves into innovative strategies sought at integrating insights derived from disease trajectory studies into state-of-the-art HRA tools, such as the AMG algorithm (**Use Case 3**). This strategic integration seeks to strengthen the algorithm's capacity to predict the progression of multimorbidity and the emergence of new comorbid conditions with heightened accuracy. The exploration of these novel approaches holds the potential to significantly enhance the predictive capabilities of existing HRA methodologies, such as the AMG.

The work on this thesis has been carried out under the auspices of two concurrent European projects during 2020-2023.

Use Cases 1 and 2:

- The Joint Action on implementation of digitally enabled integrated person-centred care (JADECARE)(123), launched to confront the challenges of health transformation within the European Union. JADECARE's primary objectives encompass enhancing the capacity of health authorities to effectively address the multifaceted dimensions of health system transformation, with a particular emphasis on the shift towards digitally enabled, integrated, and person-centred care. In this context, HRA has been incorporated as a strategic component to facilitate the transition from the initial set of four original Good Practices (oGPs) to an extended network of twenty-one European regions participating as Next Adopters (NAs). Additionally, under the auspices of JADECARE, a collaborative endeavour was established with the OECD to undertake an evaluation of integrated care services within Catalonia. The focal point of this collaboration was the analysis of the heterogeneities and cost efficacy of the multiple Hospital at Home (HaH) programs deployed in Catalonia.

Use Case 3:

- The ERAPerMed project “Temporal disease map-based stratification of depression-related multimorbidities: towards quantitative investigations of patient trajectories and predictions of multi-target drug candidates” TRAJECTOME(124). TRAJECTOME sought to employ advanced machine learning techniques on publicly available health and biobank datasets to categorize depression-related multimorbidity by analysing comprehensive clinical patient pathways, medication records, and genome-wide polymorphism data.

5.1. Use Case 1: design, evaluation, and integration of computational predictive models for enhanced management of multimorbid patients

Rationale: Effectively managing complex multimorbid patients presents a substantial clinical hurdle, attributed to the well-documented correlation between the quantity and complexity of morbid conditions and elevated mortality rates, alongside the intensive consumption of healthcare resources(3). In this context, unplanned hospital admissions are an avoidable significant contributor to the burden of healthcare systems worldwide(2,125). Evidence-based integrated care interventions and comprehensive post-hospital discharge programs have demonstrated efficacy in mitigating hospitalizations among high-risk individuals(28,29). However, challenges such as the disparity between efficacy and real-world effectiveness, deficient patient risk stratification, and inadequately prepared healthcare personnel impede optimal clinical implementation(126). Thus, leveraging predictive modelling strategies emerges as a potentially potent approach for individualized risk assessment, serving as a preventive measure against morbidity-related adverse incidents that culminate in hospital readmissions.

Setting: HaH programs offer an ideal operational framework for testing an intervention infused with such attributes. In first place, HaH programs are widely accepted interventions for the effective management of patients afflicted by multimorbidity, particularly older adults with multiple chronic conditions. Secondly, HaH programs are declared a pertinent catalyst for fostering vertical integration between hospital care and community-based health and social services, enhancing the care continuum in an integrated care scenario. Despite the models' origination and validation within the

confines of Hospital Clínic de Barcelona (HCB), this use case explores the feasibility of extending the same methodology to the regional level. This involves the formulation of a comprehensive study protocol encompassing a database of over 200,000 discharges.

Expected impact: It is expected that this type of modelling can improve care-flows in hospital environments and improve personalized care based on clinical decision support in two areas. Firstly, during hospital admission, facilitating the assessment of intra-hospital risks and refining service selection. Service selection holds great importance in personalization and can potentially enhance health outcomes. Furthermore, this process encompasses the identification and mitigation of distinct determinants of health, thereby augmenting the effectiveness of interventions and minimizing potential risks. Secondly, during the discharge process, enabling the identification of potential risks during periods of heightened vulnerability such as the transition from hospital to the community. As well as, enabling the characterization of the patients' risk profiles, this approach would ultimately enable the provision of personalized care tailored to individual needs.

5.2. Use Case 2: exploring morbidity grouper adoption dynamics at the European level

Rationale: Several determinants impact the successful transference and adoption of population-based health risk assessment strategies. These determinants encompass accurate deployment planning, collaborative endeavours, and a holistic understanding of the unique challenges and requisites of different populations and contextual settings. Addressing the existing gap in information on building up an HRA strategy at the regional/country level and its potential for transferability and adaptability to other sites is still an unmet need.

Setting: Concretely, the thesis evaluates the transferability of the AMG tool from Catalonia (ES) to the regions of Marche (IT) and Viljandi hospital (EE) in the context of the project JADECARE. Importantly, it should be acknowledged that both the implementation contexts and the underlying applications of the tool in these regions diverge, aligning respectively with population health and population medicine

paradigms(127). Particularly, in the Marche region, a population health approach is employed to inform health policies, facilitate benchmarking, and support decision-making processes. Conversely, the endeavours undertaken in Viljandi hospital adhere to a population medicine approach. This approach involves the assembly of patient registries to screen potential candidates for a clinical program aiming at preventing hospitalizations for elderly patients with concomitant chronic conditions.

Expected impact: This dual approach should facilitate the identification of pivotal barriers and enablers for the effective adoption of population-based HRA on a European scale. Moreover, it facilitates the formulation of strategic propositions to harmonize population-oriented and clinically-driven HRA methodologies.

5.3. *Use Case 3:* leveraging morbidity metrics and disease trajectories

Rationale: This study is focused on major depressive disorder (MDD), due to its particular significance since it is frequently presented together with other mental health conditions, including anxiety disorders, histrionic personality disorder, and somatic symptom disorder(120). Furthermore, compelling evidence suggests that depression is intricately linked to an escalated risk of developing additional medical conditions, such as cardiovascular disease and diabetes(120). Grasping the clinical significance of depression and its intricate interplay with other conditions assumes paramount importance in ensuring accurate diagnosis, effective treatment, and enhanced patient outcomes. Furthermore, the proficient management of depression, along with its associated somatic and mental health manifestations, necessitates an all-encompassing approach that addresses the disorder's physiological and psychological dimensions(6,7). Developing a comprehensive risk score that leverage morbidity metrics of MDD and its comorbid conditions and disease network insights would contribute to allow identifying patients with different profiles of risk. As well as, paving the way to personalized interventions through the estimating the current morbidity burden and the risk of morbidity progression.

Setting: The innovation of the approach proposed is rooted in its utilization of a pioneering methodology to address a key constraint within the analysis of the

diseasome and disease trajectories. This limitation involves the emergence of spurious correlations between diseases due to indirect patterns of concurrence lacking causal connections. The number of falsely correlated diseases is susceptible to increase exponentially according to the number of diseases explored. To tackle this challenge, the project TRAJECTOME proposed the use of Sparse Bayesian Direct Multimorbidity Maps (BDMM)(128,129) methodology by effectively filtering out disease-mediated indirect relationships.

The main product of TRAJECTOME was generating a temporal disease map using BDMM to identify clusters of disease trajectories. This propitiated the ideal scenario to propel ancillary studies to establish the genetic, metabolic, and environmental risk profiles associated with these trajectories, accounting for factors such as sex and social disparities. As well as to explore innovative ways to assess the disease burden on individuals and health systems, considering the information on disease-disease concurrence patterns, and thus offering the tools the ability to adjust the impact of morbidity by disease clusters and increase its predictive power to anticipate multimorbidity's progression.

Expected impact: Utilizing this methodology offers a holistic and intricate perspective on the multifaceted nature of depression-related multimorbidity. It acknowledges that individuals with depression frequently encounter a spectrum of coexisting conditions, each exhibiting and progressing uniquely. This understanding transcends a bare enumeration of individual disorders, presenting a multifaceted evaluation that mirrors the patient's health. Such a comprehensive perspective fosters an interdisciplinary approach integrating psychiatric and somatic medicine. By initiating collaborative prevention strategies across specialties, healthcare practitioners can deliver a more integrative and efficacious care regime for patients with intricate health requirements. Moreover, effective stratification of depression-related multimorbidity can enhance precision medicine, particularly for patients in the early phases of MDD manifestation. Incorporating data-driven categorization into clinical routines can streamline patient screenings and referrals, making the process both efficient and economically viable.

APPENDIX

Rubèn González-Colom, Isaac Cano, Jordi Piera-Jiménez, Josep Roca. 2023. *Personalized Medicine meets Artificial Intelligence; Chapter 10: Multilevel Modelling with AI: The Synergy-COPD Endeavour*. Springer books. (Published)

Multilevel Modelling with AI: The Synergy-COPD Endeavour

10

Rubèn González-Colom, Isaac Cano, Jordi Piera-Jiménez, and Josep Roca

Abstract

Key lessons learnt in the Synergy-COPD project, that aimed at a systems medicine approach to patients with chronic obstructive pulmonary disease (COPD), contributed to formulate the concept of multisource predictive modelling for enhanced clinical risk assessment described in the chapter. Further research and innovation developments in the field, as well as practicalities learnt during the process of digitalization of the regional health system in Catalonia have been main sources for the current report that aims to provide a summary description of the steps needed for implementation and adoption of a Learning Healthcare System.

Keywords

Digitalization · Healthcare · Health sciences · Predictive modelling · Preventive medicine · Systems medicine

R. González-Colom · I. Cano · J. Roca (✉)
Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain
e-mail: jroca@clinic.cat

J. Piera-Jiménez
Catalan Health Service, Barcelona, Spain

Digitalization for the Sustainability of the Healthcare (DS3) - IDIBELL, Barcelona, Spain

Faculty of Informatics, Telecommunications and Multimedia, Universitat Oberta de Catalunya, Barcelona, Spain

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10.1 Multisource Predictive Modelling for Enhanced Clinical Risk Assessment

Physician's best judgement, combined with rules-based management, are the two components of conventional clinical decision-making across all healthcare tiers. While health professionals' judgement relies on knowledge, training, and experience; rules-based management consists of thresholds of target variables articulating evidence-based decision criteria, often emerging from randomized controlled trials (RCTs).

Current clinical practice is facing major challenges due to the enormous evolution of computational sciences, as well as quick progress of digital medicine towards large-scale clinical application. Computational modelling is already a powerful tool extensively used for highly standardized medical procedures, like analysis of imaging techniques. However, it is expected that multilevel predictive modelling will offer valuable support to enhance clinical decision-making, complementing but not substituting clinical judgement (Rajpurkar et al. 2022).

The use of dynamic multisource predictive modelling approaches for clinical decision support that establishes relationships between multilevel and multiscale sets of predictors, targeting specific health outcomes by the use of statistical techniques and/or Artificial Intelligence/Machine Learning (AI/ML), is still in its infancy (Doos et al. 2016). However, it is a natural step towards customization of care to individual patient's needs.

Several interconnected factors, such as: current changes in healthcare paradigm, well-identified complexities in the healthcare scenario, as well as complexities of multilevel data integration and data security and privacy, explain the barriers encountered to define, deploy, and adopt operational strategies to facilitate preventive, value-based (Porter 2008) healthcare for acute and chronic patients using computational modelling in real-world clinical settings, with a twofold aim: (i) to slow-down chronic patients' progression towards the tip of the population-based risk stratification pyramid through cost-effective preventive strategies; and (ii) to enhance reliable decision-making.

It has become widely accepted that health risk assessment for patient stratification is a relevant component in the strategies for regional adoption of integrated care because of its contribution in the design of healthcare policies and services using a population-based approach, as well as for enhanced clinical management for individual patients.

The foundations of health risk assessment proposed in the chapter rely on two concepts generated within the Synergy-COPD project (Synergy-COPD Consortium 2010). Briefly, Cano et al. (2014a) reported on the concept and operational aspects of a Digital Health Framework (DHF), defined as the articulation of open and modular digital components supporting the interplay among four types of data sources: (i) patients' self-tracking data including lifestyles, environmental, behavioural aspects, and sensors; (ii) healthcare data from electronic health records (HER); (iii) biomedical research data; and (iv) population-based registry data. The basic idea is that an operational DHF could overcome current health-related silos of information,

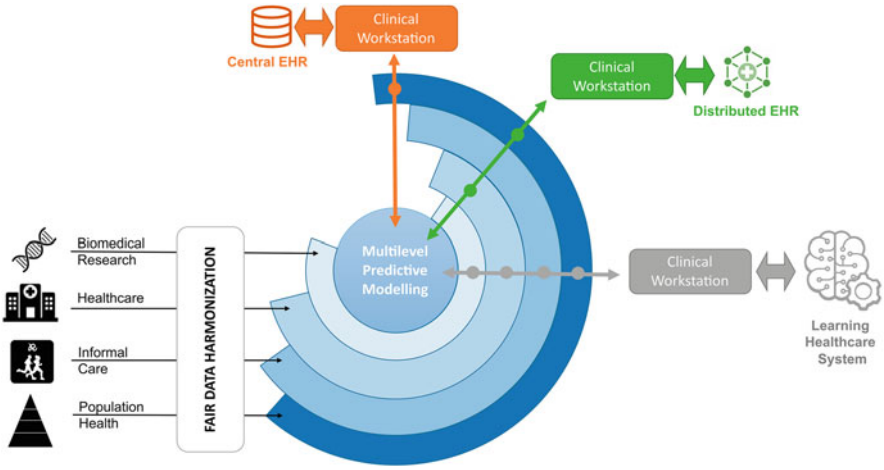

Fig. 10.1 Dynamic enhancement of multilevel clinical predictive modelling feeding clinical decision support systems (CDSS). Development of enhanced clinical predictive modelling requires consideration, and eventual integration, of computational modelling of four different dimensions: (i) Underlying biological mechanisms (biomedical research); (ii) Current evidence-based clinical knowledge (healthcare); (iii) Patients' self-tracked data, including sensors, behavioural, environmental, and social information (informal care); and (iv) Population-based health risk assessment data (population health). Figure taken from Roca et al. (2020)

being the core component of a Learning Healthcare System (LHS). The concept of LHS was first formulated in 2012 by the Institute of Medicine as a strategy to improve the quality and efficiency of healthcare (Ferguson 2012). Thereafter, the American Heart Association (AHA) (Maddox et al. 2017) further developed the practicalities of the LHS concept and proposed specific steps to make it operational and evaluate its implementation.

The second major pillar (Dueñas-Espín et al. 2016) refers to the huge potential for enhancing clinical risk predictive modelling by incorporating the four categories of variables alluded to above as covariates using a multilevel approach, as described in Fig. 10.1.

The analyses of facilitators and barriers expected in the deployment of multilevel clinical predictive modelling within a DHF clearly indicate that achievement of personalized management of patients into real-world scenarios will be a stepwise, medium-term, process requiring proper adoption strategies that must necessarily consider the different dimensions described in (Dueñas-Espín et al. 2016).

10.2 Computational Modelling for Enhanced Understanding and Management of COPD and Its Co-morbidities: The Synergy-COPD Project

Chronic Obstructive Pulmonary Disease (COPD) is a disorder that generates a high burden on healthcare systems worldwide (Murray and Lopez 2013; Blumenthal et al. 2016) being the third cause of mortality among chronic conditions, causing 3.23 million deaths in 2019 (Mathers et al. 2019), with a prevalence of 9–10% in adult population.

COPD generates an increasingly high healthcare impact mostly due to hospitalizations, partly avoidable with adequate patient stratification strategies leading to better selection of integrated care services. Despite highly relevant contributions of international recommendations for COPD management, mostly pulmonary-oriented, during the last twenty years (Halpin et al. 2021), it is nowadays widely accepted that optimal care of patients with COPD requires a systems medicine approach (as proposed in Roca et al. 2020; Roca et al. 2014). This is due to a combination of factors, such as important heterogeneities of patients' phenotypes, high rate of co-morbidities, and overlapping of diagnosis with other obstructive pulmonary diseases, with under- and overdiagnosis of the disorder (Diab et al. 2018).

The EU project Synergy-COPD (Synergy-COPD Consortium 2010), running from 2011 to 2014 (FP7-ICT-270086), was a systems research programme on multimorbidity taking COPD as a use case. The project focused on non-pulmonary phenomena often seen in patients with COPD addressing unknown aspects of skeletal muscle dysfunction/wasting (Maltais et al. 2014) and the phenomenon of co-morbidity clustering (Barnes 2015). The research was designed as an iterative process wherein data from several sources, encompassing animal experimentation (Davidsen et al. 2014), human studies (Rodríguez et al. 2011, 2012), epidemiological research and registry information (Vela et al. 2018; Gomez-Cabrero et al. 2016), were articulated and analysed using different, and in some cases complementary, computational modelling techniques. The details of the research design and methodological issues were reported in a dedicated monograph (Gomez-Cabrero et al. 2014) and the project outcomes addressing three biomedical areas: (i) Skeletal muscle dysfunction; (ii) COPD co-morbidities; and (iii) Proposals for enhanced transfer of knowledge into clinical practice, have been described in different scientific publications (Marín De Mas et al. 2017; Tényi et al. 2018a, b; Cano et al., 2014b).

Briefly, the project findings contributed to better understand the interplay of factors modulating non-pulmonary manifestations in patients with COPD. Abnormalities in co-regulation of core biological pathways (i.e. bioenergetics, inflammation, and tissue remodelling) at systemic level seem to play a central role on both skeletal muscle dysfunction and co-morbidity clustering (Fig. 10.2), with evidence of the relevant role of oxidative stress as a characteristic mechanism in these patients (Barnes 2015).

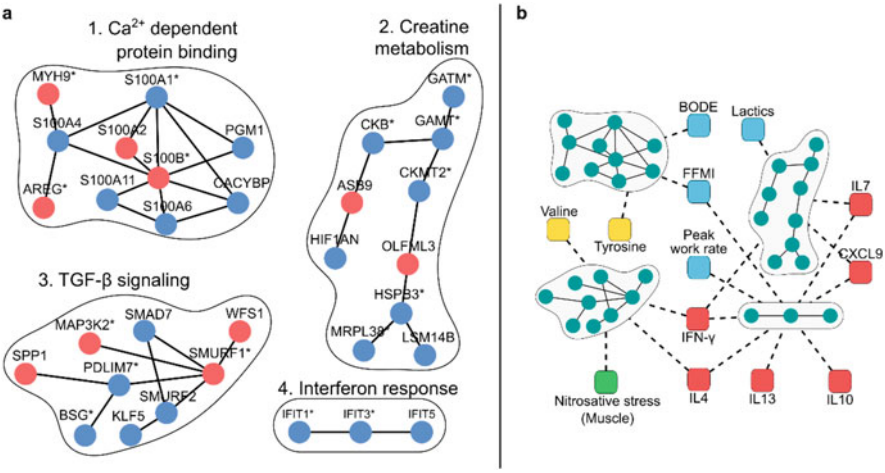

Fig. 10.2 Disease effects network modules. Panel (**a**) depicts the four network modules associated to COPD disease effects on skeletal muscle and their composing genes. Genes are coloured according to their differential regulation, namely: up regulation—red nodes; and down regulation—blue nodes. Significantly, differentially expressed genes are indicated by * (FDR ≤ 0.05). Panel (**b**) shows the significant correlations of independent measurements with any of the network modules' first three principal components. Blue squares depict exercise related independent variables; red squares show blood cytokines levels; yellow squares correspond to serum amino acids levels; and green squares represents redox biomarkers. It is noted that abnormal skeletal muscle findings, associated to poor patients' prognosis, showed significant correlations with aerobic capacity, but not with lung function measurements at rest (Tényi et al. 2018a). Figure taken from Roca et al. (2020)

Synergy-COPD generated experience on integration of records from approximately 13 million patients from the Medicare database with disease-gene maps that were derived from several resources including a semantic-derived knowledgebase (Gomez-Cabrero et al. 2016). The results demonstrated higher prevalence of most of the diseases, as comorbid conditions, seen in elderly patients with COPD compared with non-COPD subjects, an effect confirmed latter (Tényi et al. 2018b) in a regional EU dataset (1.4 million patients). Moreover, the analysis of temporal order of disease diagnosis showed that comorbid conditions in elderly patients with COPD tend to appear after the diagnosis of the obstructive disease, rather than before it. Overall, the results (Vela et al. 2018) demonstrated high impact of COPD co-morbidities on health risk stratification with major negative impact on mortality, hospitalizations, and use of healthcare resources (Fig. 10.3) and highly encourage developments of AI/ML tools using health registries and data from EHR to build robust health risk stratification strategies.

Figure 10.4 displays the distribution of individual costs per year in patients with COPD based on their multimorbidity level: from low (left column) to very high risk associated to co-morbidities (right column), indicating huge heterogeneities among patients' healthcare expenditure per year, explained by multimorbidity. The analysis of distribution of costs clearly indicates the high impact of hospitalizations and

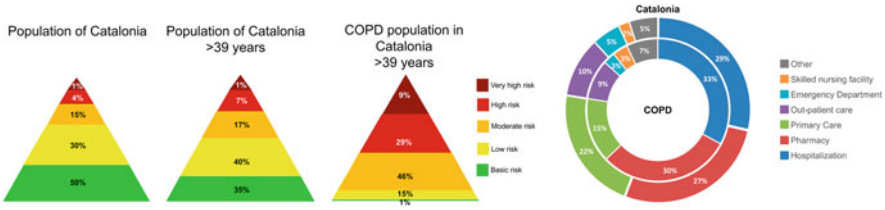

Fig. 10.3 Regional population-based study of patients with COPD. Left panel depicts three population-based risk stratification pyramids build using AMG as multimorbidity index: (i) Left, the entire regional population (7,7 M); (ii) Centre, citizens above 39 years; and, (iii) Right, display the distribution of the 264 k patients with COPD in the region across AMG risk grades: baseline (1%), low (15%), moderate (46%), high (29%), and very high risk (9%). Right panel depicts the distribution of individual costs per year comparing overall cost for the regional Health System expressed as percentages (outer circle) and the relative costs ascribed to patients with COPD (inner circle) in the left-hand side figure indicates that Hospitalization costs (€ 2291.8 M, 29%, and € 356.6 M, 33%, respectively) and, Pharmacy costs (€ 2193.4 M, 27%, and € 325.8 M, 33%) are relatively higher in COPD patients than in the overall health system; whereas, Primary Care costs (€ 1745.0 M, 22%, and € 158.9 M, 15%) are relatively lower in COPD than in the overall health system. The item: Others, includes home-based respiratory therapies, dialysis, outpatient rehabilitation, and non-urgent healthcare transportation (Vela et al. 2018)

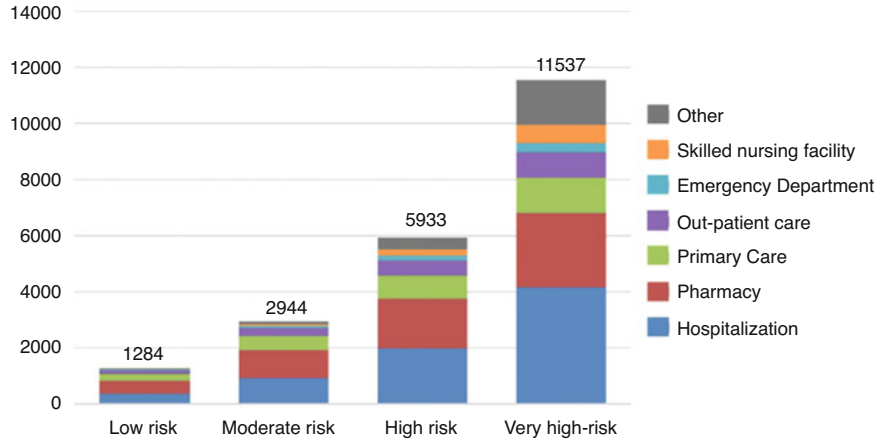

Fig. 10.4 Global yearly expenditure, expressed in €, of COPD patients by morbidity scoring at regional level (Vela et al. 2018) (264 k patients with COPD)

pharmacy on overall costs, as well as the relatively reduced impact of primary care on overall patients' cost.

All in all, the research strongly pointed out the need for a broader vision in the care and management of COPD by adopting a patient-oriented approach that addresses much more than just the pulmonary manifestations of the disease.

One of the major strengths of the Synergy-COPD project was the combination of well-defined biomedical goals with parallel technological developments beyond the

state of the art in terms of novel modelling approaches, knowledge generation tools, and digital technologies supporting care coordination.

10.3 Multilevel Data Integration and Advanced AI/ML: Beyond Synergy-COPD

Beyond the project lifespan, developments on multilevel data integration and advanced AI/ML are allowing to further explore factors modulating multimorbidity aiming at transferring novel knowledge into the clinical arena. Two specific areas raising high expectations are:

The use of sparse Bayesian Direct Morbidity Maps (BDMM) to improve construction of comorbidity patterns (Marx et al. 2017). The method shows clear advantages compared to conventional hypothesis-free exploration of comorbid conditions using pairwise methods often leading to confounders due to large number of pairwise associations arising indirectly through other comorbidity associations (Fig. 10.5).

Recent studies are benefiting from the experience of using BDMM for the analysis of multilevel datasets (Trajectome 2020). Consolidated achievements in the analysis of temporal disease map-based stratification of depression-related multimorbidity can be transferred to other chronic conditions, such as COPD to enhance our understanding of the use case, but also to improve management of co-morbidities in general.

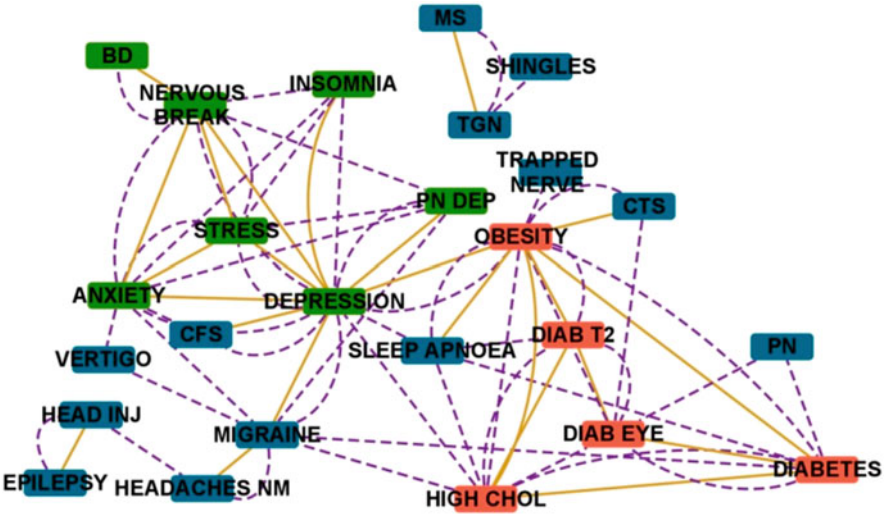

Fig. 10.5 Network representation of disease-disease comorbid relations assessed with pairwise χ^2 statistical associations (purple) and Bayesian Direct Multimorbidity Maps (BDMM – gold) in the UK Biobank dataset (Marx et al. 2017). In red metabolic syndromes, in blue diseases of the nervous system, and in green mental and behavioural disorders

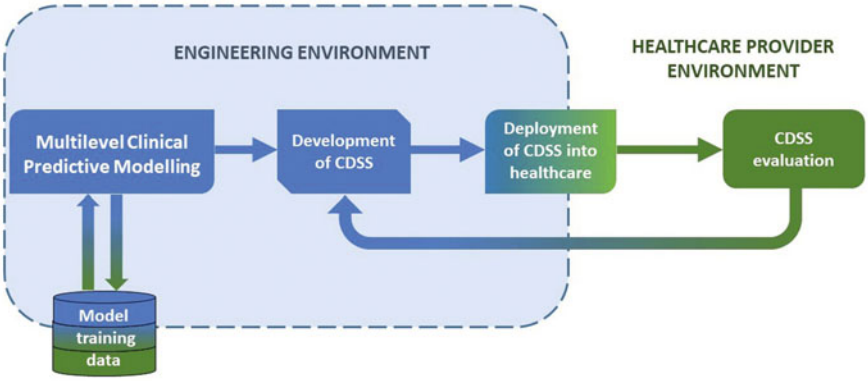

Fig. 10.6 Federated Learning approach for Multilevel data integration and advanced AI/ML. Development of enhanced dynamic clinical predictive modelling will require consideration, and eventual integration, of computational modelling of different dimensions, as described in Fig. 10.1. The current figure illustrates the steps from model elaboration, model training, evaluation and feeding clinical decision support systems (CDSS) to be applied in a real-world healthcare setting

A second area of interest is the use of the Adjusted Morbidity Groups (AMG) morbidity index (Monterde et al. 2016, 2018, 2020; Vela et al. 2021) as covariate in multilevel computational modelling (Calvo et al. 2020). It is of note that AMG is an open, publicly owned algorithm, weighted by the real impact of morbidities in each healthcare system. AMG offers clear advantages against all other morbidity indices. The algorithm is already extensively used for both policy makers and clinicians. Its site transferability has been proven and is currently being successfully tested at EU level within the ongoing Joint Action on implementation of digitally enabled integrated person-centred care (JADECARE 2020). Moreover, knowledge generated from BDMM, and disease trajectories could be used to enrich the current AMG tool to improve management of multimorbidity in general, beyond COPD.

Progress in this field needs to take advantage of Federated Learning (FL) (Rajpurkar et al. 2022) to decentralize AI/ML across data controllers to collaboratively learn a shared prediction model that ultimately could feed a clinical decision support system (CDSS) (Fig. 10.6). To this end, Bayesian multilevel systems-based analysis from consolidated methodological developments (Marx et al. 2017; Trajectome 2020) can be used to address fusion of heterogeneous information sources (registry data, clinical information, genetic information, and other biological markers) and outcomes from data owners.

However, further biomedical research is still needed to identify causal factors of co-morbidities clustering in COPD and to gain insight on the heterogeneities seen in these patients. Specific examples of target aspects requiring research are: (i) in-born genetic susceptibility; (ii) epigenetic changes associated with unhealthy lifestyles; and (iii) unknown interactions with gut microbiome, among others. Likewise, identification of plasma metabolomics patterns facilitating early identification of

subsets of patients with COPD that are candidates for secondary prevention of co-morbidities would also be a major achievement to significantly reduce the burden of multimorbidity.

With the perspective of some years after completion of the Synergy-COPD project, we can conclude that targeting COPD as a use case and adopting a systems approach to address the analysis of non-pulmonary phenomena in these patients was a right choice because it facilitated to the researchers involved to think "outside of the box". On the other hand, the concurrence of three intertwined phenomena: (i) relatively poor knowledge of underlying mechanisms; (ii) marked heterogeneities of these patients; and (iii) taxonomy problems (Celli and Augustì 2018) perfectly justified the choice for a systems approach.

Moreover, the analysis of co-morbidities in these patients has provided relevant new knowledge on multimorbidity in general, with high positive impact on management strategies for chronic patients aiming at effectively reduce the burden of non-communicable conditions on health systems. A major lesson learnt was the huge potential of multilevel integrative analyses of registry data, biomedical research information, EHR and patients' self-tracking data for enhanced clinical decision support, as displayed in Fig. 10.1. It clearly constitutes a high priority to pave the way towards enhanced clinical management and personalized medicine for patients with chronic disorders (Dueñas-Espín et al. 2016).

10.4 From Systems Medicine to Integrated Care

All the above results indicate that convergence between a systems medicine approach to chronic disorders and care coordination, integrated care (JADECARE 2020), may conform an optimal scenario to foster cross-fertilization between biomedical research and clinical practice (Ferguson 2012; Maddox et al. 2017). The two approaches have several common aspects: (i) holistic and multidisciplinary approach; (ii) use of computational modelling; and (iii) digitalization as enabler. It is clear, however, that optimal efficiencies can only be obtained by incorporating a new healthcare setting represented by LHS, as alluded to above.

In a LHS, digitalization of healthcare is a fundament pillar to foster quick transfer and application of scientific knowledge into the clinical scenario. It simultaneously facilitates data collection and gain novel insights from real-world settings towards academia promoting both healthcare discovery and scientific innovation. Such that a LHS generates a virtuous cycle stimulating value-based healthcare as well as scientific excellence in an iterative manner. It is of note that the model, LHS, implies strong complementarities, and synergies, between classical study designs to generate evidence on efficacy, such as randomized clinical trials, and novel methodological approaches targeting generation of evidence in real-life scenarios. The process ultimately results in a necessary reduction of the efficacy-effectiveness gap seen in clinical interventions, which is often limiting healthcare value generation.

The LHS relies on the existence of an operational DHF including two main components. One of them is accessibility of interoperable health-related data

covering different domains: (i) clinical data across healthcare layers, (ii) population-health registries; (iii) patient's self-tracking data encompassing citizens reported outcomes and experience of care, sensor monitoring and environmental information; and (iv) biological research data relevant for clinical purposes. The second key component of the DHF are tools that process data, such as predictive modelling, defined care paths and clinical decision support embedded into care paths. Such tools should contribute to gain on accessibility, personalization, as well as predictive and preventive approach to value-based healthcare. A building blocks strategy for implementation and sustainable adoption of such a system is needed to ensure interoperability of reliable data, technological maturity, compliance with the regulatory frame and a prepared workforce ensuring professionals engagement and active participation of citizens. Computed patient risk then can be used to stratify patients to intervention groups that help in the optimal service selection for the patient with a preventive approach. The real challenge is to define and implement appropriate strategies fostering evolution towards the new health scenario.

10.5 Deployment and Adoption Strategies

While the conceptual frame of multilevel clinical predictive modelling, as well as the final desirable healthcare scenario, is well-defined; deployment and adoption of the novel approach are exceedingly challenging with similar barriers and facilitators already mentioned for deployment of LHS. However, there are specific steps for any given computational modelling that should be considered for a successful deployment and adoption of enhanced multilevel clinical risk assessment, as briefly described below:

1. *Digitalization and standardization to a common data model.* There is a need for resolving how enhanced risk prediction can be implemented within country and organizational boundaries in a manner that supports federated AI/ML learning and that has a standard base, international user-base, and data volume content base large enough to warrant investment. A choice is to build on existing standards promoted by the European Health Data & Evidence Network (EHDEN) for data harmonization to a common data model that can scale.
2. *Data acquisition using federated learning.* Healthcare organizations should adopt a new framework to facilitate a shift from a "break-fix" to a "predict-prevent" model of healthcare to deliver better patient outcomes, while preserving data security and privacy to ensure citizen's trust. It should be achieved providing healthcare organizations a decentralized federated learning model, as the underlying GDPR-compliant framework for harmonizing existing and newly acquired datasets. Such a federated learning model allows the creation of a suite of tools and the testing of data AI/ML readiness by supplying existing risk prediction and patient stratification algorithms to local teams without exchanging the data itself.
3. *Co-design and development of a collaborative learning framework for accelerating the use of multilevel assessment in clinical care.* Use of currently

available tools from the Observational Health Data Sciences and Informatics (OHDSI) multi-stakeholder, interdisciplinary and collaborative programme to drive implementation of multilevel predictive models. By achieving this specific objective, clinicians and medical professionals will be involved throughout an AI/ML development process that will conclude with validated tools for health risk assessment and patient stratification.

4. *To drive inclusive and equitable utilization of data and risk prediction models.* The development of Best Practices to act as beacons of excellence internationally to ensure risk prediction models can be relied upon for fair outputs that aid decision-making and translate to daily life in support of clinical care. To this end, it will foster a transparent data and AI/ML eco-system that can be open to ethical and technical challenge to build trust and utilization. Health care professionals should be able to utilize robust, trustworthy, and privacy-preserving computational modelling that provide quantitative indicators valuable to identify and prioritize individuals with higher risk.
5. *To perform proof of concept, as well as clinical validation, studies in real-world settings.* There is a need for organizing evaluation studies in real-world settings to in silico assess the technical robustness of the developed AI/ML tools for risk assessment. Based on the evaluation studies, specific personalized preventive interventions should be piloted to assess healthcare value generation in comparison to the standard-of-care. Maturity of AI/ML tools in terms of Technology Readiness Level (TRL = 9) and health value generation will ultimately determine adoption provided that regulatory acceptability prior to deployment is demonstrated. Case-related reimbursement models to incentivize adoption could be envisaged.

10.6 Conclusions

Current evidence fosters multilevel integrative analyses including registry data, biomedical research information, EHR and patients' self-tracking data to elaborate, assess, and deploy predictive modelling, using AI/ML tools, for patients' stratification to properly pave the way towards enhanced clinical management and truly predictive, preventive, personalized, and participatory medicine, or "P4 medicine" (Auffray et al. 2010).

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HYPOTHESIS

This PhD thesis postulates that multimorbidity is one of the principal factors driving adverse health events, such as emergency room visits, hospitalizations, and mortality.

The thesis contends that the integration of holistic strategies for subject-specific risk prediction and stratification, which account for multimorbidity and consider multiple determinants influencing patients' health, can significantly improve predictive accuracy and aid clinical decision-making by providing reliable estimates of individual prognosis.

OBJECTIVES

Objective 1: ***To develop predictive models considering multimorbidity burden and other health determinants to facilitate enhanced service selection during hospital admission and offer guidance for effective transitional care.*** i) Develop predictive models in a Hospital at Home setting to evaluate the risk of mortality and in-hospital readmission, both during the home hospitalization episode and within 30 days after discharge (**Article 1**). ii) Assess the predictive model's ability to generalize to conventional hospitalizations and predict the risk of mortality and readmission within 90 days after discharge (**Article 2**). iii) Evaluate the overall readiness of Hospital at Home at a population-wide level (**Article 3**) and establish protocols for the scalation and adoption of the predictive models at the regional level.

Article 1: Mireia Calvo, **Rubèn González-Colom**, Núria Seijas, Emili Vela, Carme Hernández, Guillem Batiste, Felip Miralles, Josep Roca, Isaac Cano, Raimon Jané. 2020. *Health Outcomes from Home Hospitalization: Multisource Predictive Modelling*. Journal of Medical Internet Research (JMIR). (Accepted, IF: 7.4, Q1, Health Informatics)

Article 2: Rubèn González-Colom, Carmen Herranz, Emili Vela, David Monterde, Joan Carles Contel, Antoni Sisó-Almirall, Jordi Piera-Jiménez, Josep Roca, Isaac Cano. 2023. *Prevention of Unplanned Hospital Admissions in Multimorbid Patients Using Computational Modelling: Observational Retrospective Cohort Study*. Journal of Medical Internet Research (JMIR). (Accepted, IF: 7.4, Q1, Health Informatics)

Article 3: Rubèn González-Colom, Gerard Carot-Sans, Emili Vela, Mireia Espallargues, Carme Hernández, Francesc Xavier Jiménez, David Nicolás, Montserrat Suárez, Elvira Torné, Eulalia Villegas-Bruguera, Fernando Ozores, Isaac Cano, Jordi Piera-Jiménez, Josep Roca. 2023. *Five years of Hospital at Home adoption in Catalonia: impact and challenges*. BMC Health Services Research. (In review, IF: 2.8, Q1, Health policy)

Objective 2: ***To assess the transferability and adoption of the Adjusted Morbidity Groups in the European framework and identify key barriers and facilitators its effective adoption at national/regional level.*** *i)* To assess the transference and implementation of the Adjusted Morbidity Groups algorithm in Marche (IT) region and Viljandi Hospital (EE), and issue tailored recommendations for the adoption of population-based health risk assessment tools facilitating the articulation between population-based and clinical-oriented HRA (**Article 4**).

Article 4: Rubèn González-Colom, David Monterde, Roberta Papa, Mart Kull, Andres Anier, Francesco Balducci, Isaac Cano, Marc Coca, Marco De Marco, Giulia Franceschini, Saima Hinno, Marco Pompili, Emili Vela, Jordi Piera-Jiménez, Pol Pérez, Josep Roca. 2023. *Toward adoption of health risk assessment in population-based and clinical scenarios*. International Journal of Integrated Care (IJIC). (In review, IF: 2.4, Q2, Health policy)

Objective 3: ***To explore novel morbidity-adjusted risk indicators that integrate information derived from disease trajectory studies enhancing their predictive capabilities at envisaging disease progression.*** *i)* To develop an assess an advanced disease stratification methodology using temporal patient profiles, tailored to depression and its comorbidities, to evaluate the burden of depression on individuals and healthcare systems and anticipate the risk of disease progression (**Article 5**).

Article 5: Rubèn González-Colom, Kangkana Mitra, Emili Vela, Andras Gezsi, Teemu Paajanen, Zsofia Gal, Gabor Hullam, Hannu Mäkinen, Tamas Nagy, Mikko Kuokkanen, Jordi Piera-Jiménez, Josep Roca, Peter Antal, Gabriella Juhasz, Isaac Cano. 2023. *Multicentric validation of a Multimorbidity Adjusted Disability Score to stratify depression-related risks using temporal disease maps*. Journal of Medical Internet Research (JMIR). (In review, IF: 7.4, Q1, Health Informatics)

MATERIALS, METHODS AND RESULTS

ARTICLE 1

Mireia Calvo, **Rubèn González-Colom**, Núria Seijas, Emili Vela, Carme Hernández, Guillem Batiste, Felip Miralles, Josep Roca, Isaac Cano, Raimon Jané. 2020. *Health Outcomes from Home Hospitalization: Multisource Predictive Modelling*. Journal of Medical Internet Research (JMIR).

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Health Outcomes from Home Hospitalization: Multisource Predictive Modeling

Mireia Calvo[1], PhD; Rubèn González[2], MSc; Núria Seijas[2], MSc, RN; Emili Vela[3], MSc; Carme Hernández[2], PhD; Guillem Batiste[2], MD; Felip Miralles[4], PhD; Josep Roca[2], MD, PhD; Isaac Cano[2*], PhD; Raimon Jané[1*], PhD

[1]Institute for Bioengineering of Catalonia (IBEC), Barcelona Institute of Science and Technology (BIST), Universitat Politècnica de Catalunya (UPC), CIBER-BBN, Barcelona, Spain

[2]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona (UB), Barcelona, Spain

[3]Àrea de sistemes d'informació, Servei Català de la Salut, Barcelona, Spain

[4]Eurecat, Technology Center of Catalonia, Barcelona, Spain

[*]these authors contributed equally

Corresponding Author:
Isaac Cano, PhD
Hospital Clínic de Barcelona
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Universitat de Barcelona (UB)
Villarroel 170
Barcelona, 08036
Spain
Phone: 34 932275540
Email: ISCANO@clinic.cat

Abstract

Background: Home hospitalization is widely accepted as a cost-effective alternative to conventional hospitalization for selected patients. A recent analysis of the home hospitalization and early discharge (HH/ED) program at Hospital Clínic de Barcelona over a 10-year period demonstrated high levels of acceptance by patients and professionals, as well as health value-based generation at the provider and health-system levels. However, health risk assessment was identified as an unmet need with the potential to enhance clinical decision making.

Objective: The objective of this study is to generate and assess predictive models of mortality and in-hospital admission at entry and at HH/ED discharge.

Methods: Predictive modeling of mortality and in-hospital admission was done in 2 different scenarios: at entry into the HH/ED program and at discharge, from January 2009 to December 2015. Multisource predictive variables, including standard clinical data, patients' functional features, and population health risk assessment, were considered.

Results: We studied 1925 HH/ED patients by applying a random forest classifier, as it showed the best performance. Average results of the area under the receiver operating characteristic curve (AUROC; sensitivity/specificity) for the prediction of mortality were 0.88 (0.81/0.76) and 0.89 (0.81/0.81) at entry and at home hospitalization discharge, respectively; the AUROC (sensitivity/specificity) values for in-hospital admission were 0.71 (0.67/0.64) and 0.70 (0.71/0.61) at entry and at home hospitalization discharge, respectively.

Conclusions: The results showed potential for feeding clinical decision support systems aimed at supporting health professionals for inclusion of candidates into the HH/ED program, and have the capacity to guide transitions toward community-based care at HH discharge.

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KEYWORDS

home hospitalization; health risk assessment; predictive modeling; chronic care; integrated care; modeling; hospitalization; health risk; prediction; mortality; clinical decision support

Introduction

Home Hospitalization and Early Discharge at the Hospital Clinic of Barcelona

Home hospitalization (HH)/early discharge (ED) programs [1-6] show substantial site heterogeneities in terms of service workflows and organizational aspects. However, overall, they have demonstrated maturity and health care value generation [7] such that it is well accepted that HH/ED constitutes an effective alternative to inpatient care for a select group of patients requiring hospital admission.

The characteristics of the deployment and adoption of the HH/ED program at Hospital Clinic of Barcelona (HCB) were recently described in a report [8]. In this report, HH/ED is defined as a service providing acute, home-based, short-term, complex interventions aimed at substituting conventional hospitalization fully with HH [7,9] or partially with ED [10]. The service at HCB is delivered by trained hospital personnel, and it is provided for a period of time that is not longer than the expected length of hospital stay for the patients' diagnostic related groups involved [11]. The Hospital retains the entire clinical, fiscal, and legal responsibilities. Virtual beds are used to support the required administrative and clinical processes. The report concluded that HH/ED for acute medical and surgical patients in a real-world setting was safe, generated healthcare efficiencies, and was well accepted by 98% of patients and professionals [8]. Moreover, the study stressed the potential of HH/ED to strengthen care coordination between highly specialized hospital-based care and home-based services involving different levels of complexity [8].

Currently, the HH/ED program at HCB is a mainstream, mature service that is offered 24 hours a day, 7 days a week, all year round, with 48 virtual beds available per day. It is the first choice for eligible patients requiring hospital admission when attended in the Emergency Department, and it serves the entire Health district of Barcelona Eixample-Esquerra, which has 540,000 inhabitants.

It is well accepted that the key health outcomes that define the success of hospitalization at home [8] are mortality and unplanned emergency room consultations that lead to in-hospital admissions, either during the home hospitalization episode or during the 30-day period after discharge. This study relies on the assumption that multisource predictive modeling facilitating clinical decision support at 2 key time points—(1) at entry, and (2) at HH/ED discharge—could be useful to enhance service outcomes. Risk assessment at entry may contribute to reducing undesirable events during the episode of HH/ED, whereas the assessment of unexpected events after discharge will likely contribute to improving transitional care [12,13] and better definition of personalized care pathways within a care continuum scenario [14].

The Use of Multisource Predictive Modeling for Enhanced Risk Assessment

This study was designed to elaborate and assess the potential of a machine learning approach to the prediction of mortality and hospital admission at entry and at discharge from HH/ED. A key specificity of the study is the use of various data sources to estimate the 2 outcomes, mortality and hospital re-admission, as conventional inpatient care. In addition to classical clinical and biological information obtained from electronic medical records (EMR), we have also considered the inclusion of Catalan population–health risk assessment scoring, known as Adjusted Morbidity Groups (GMA) [15,16], and purposely collected data on patients' performance and frailty.

The GMA is an open, publicly owned algorithm that does not rely on expert-based fixed coefficients. Such characteristics provide a high degree of flexibility for multisource predictive modeling and good potential for transferability to other sites, as demonstrated through its validation and current use in 13 of the 17 health regions in Spain, encompassing approximately 38,000,000 citizens [15]. It is fully operational since 2015 for health policy purposes and for clinicians in primary care workstations, providing yearly updated risk stratification with a population health orientation. It takes into account multimorbidity and complexity, that is, impact on health care, using data across health care tiers stored in the Catalan Health Surveillance System.

The approach adopted in this study was based on the hypothesis that the application of holistic strategies for subject-specific risk prediction and stratification, which consider multisource covariates influencing patient health, could increase predictive accuracy and facilitate clinical decision-making based on sound estimates of individual prognosis [17]. Developed predictive models were evaluated on a real-world database, which included all cases admitted to HH/ED at HCB from January 2009 to December 2015.

Methods

Dataset

Retrospective data from 1936 patients admitted to the HH/ED program at HCB from January 2009 to December 2015 (Table 1S in Multimedia Appendix 1) were considered in the analyses carried out to elaborate the predictive modeling of mortality and hospital re-admission at 2 time points: (1) at entry into HH/ED, and (2) at discharge from the HH/ED program. HH/ED at HCB is run as a transversal program, under the responsibility of the medical and nurse directors of the Hospital, serving the different clinical specialties. Patients included in the HH/ED show a broad spectrum of primary diagnoses, as displayed in Table 1S in Multimedia Appendix 1.

The potential covariates considered for predictive modeling purposes (Table 2S in Multimedia Appendix 1) encompassed 3 dimensions: (1) standard clinical and biological information obtained from EMRs; (2) patients' functional performance and frailty data, specifically collected to characterize these patients; and (3) GMA scoring indicating multimorbidity, complexity, and patients' allocation into the population–health risk stratification pyramid.

Ethical Approval

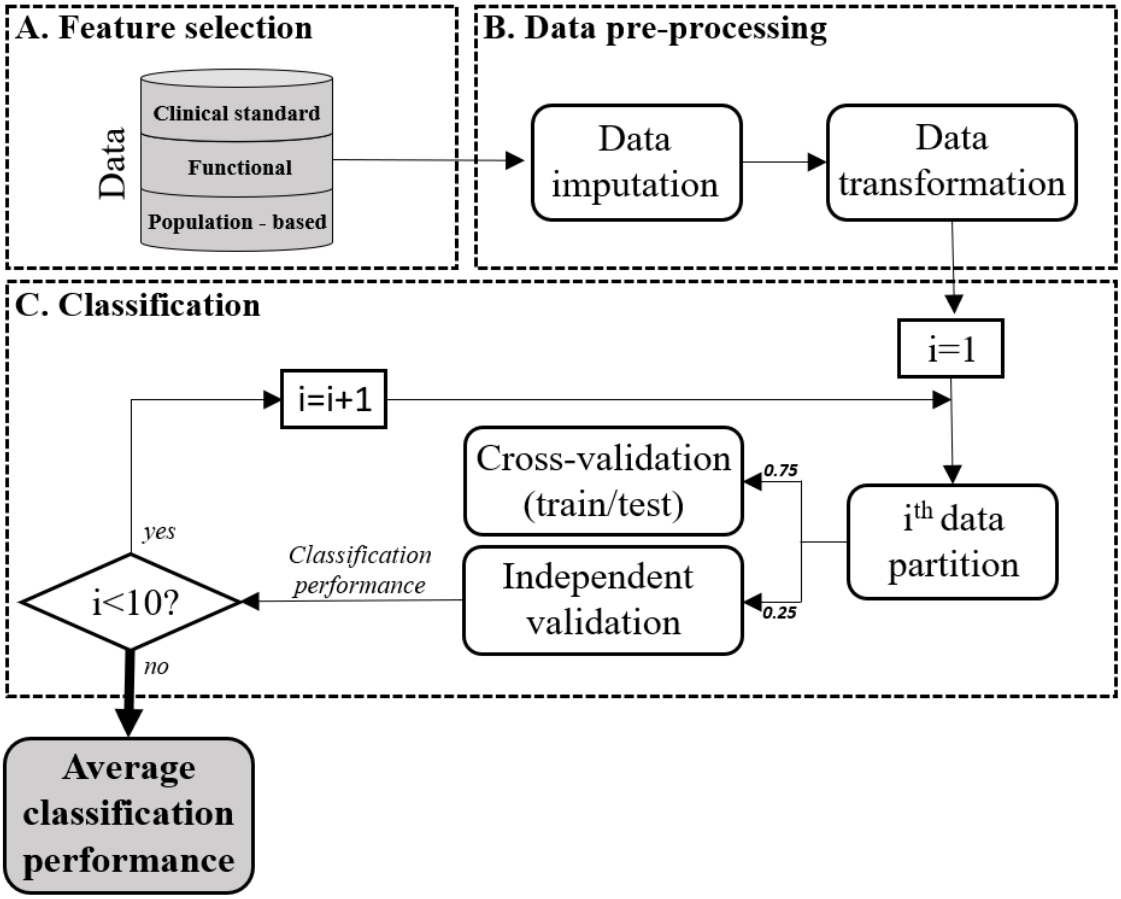
The Ethical Committee for Human Research at HCB approved the study, and all participants signed an informed consent prior

to any procedure. The program was registered at ClinicalTrials.gov: NCT03130283.

Predictive Analytics Workflow

Figure 1 illustrates the global methodology proposed to identify patients at risk of re-admission or death after HH discharge; the elaboration of predictive modeling followed 3 successive steps: (1) feature selection, (2) data preprocessing, and (3) classification.

Figure 1. Predictive analytics workflow, composed of 3 main steps: (A) feature selection, (B) data preprocessing, and (C) classification.



Feature Selection

Feature selection refers to different processes involving data cleaning, selection of variables to be considered for predictive modelling, as well as selection of the final set of patients included in the analyses.

Data Preprocessing

In order to handle the impact of missing values, a robust method was designed for mixed-type data imputation. To this end, the missForest algorithm was applied to the whole dataset [18]. Moreover, we applied a rediscretization of some categorical variables to avoid under-represented categories.

Classification

Different strategies were considered for the elaboration of predictive models in this study. Specifically, 3 of them were explored in detail (Multimedia Appendix 1); that is, logistic regression and 2 machine learning approaches: a decision tree and random forest classifiers.

For model training, the dataset was 10-times divided in (1) a training subset, taking 75% of randomly selected cases, and (2) a validation subset with the remaining 25% of cases. For each data partition, the model was trained using 4-fold cross-validation on the training subset. As successful cases (ie, survivors not requiring hospital admission) were far superior in number, the effect of class imbalance was reduced by applying a random stratified-sampling strategy [19].

Model performance was assessed by computing the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, and score metrics in the validation subset. Score is a measure of prediction accuracy and is defined as the weighted harmonic mean of the sensitivity and specificity of the model. The final performance of the models was assessed as the average performance of all independent validations.

As indicated above, the methodology was applied to predict 2 types of events: (1) mortality, and (2) in-hospital admission until 30-days after HH/ED discharge. Risk assessment was conducted in 2 different scenarios: (1) at entry into the HH/ED program, and (2) at discharge. Accordingly, the analyses led to 4 different risk models (RM): (1) RM1 accounts for predicting the need for conventional hospitalization at entry into the HH/ED program; (2) RM2 predicts mortality during the study period assessed at entry; (3) RM3 refers to predictive modeling of conventional hospital admissions assessed at HH/ED

discharge; and (4) RM4 predicts mortality during the study period assessed at HH/ED discharge. The risk of mortality and re-admission during HH at entry was not assessed due to the scarcity of unsuccessful cases during HH/ED.

Results

Study Population

All 1936 patients admitted to the HH/ED program at HCB during the study period were included in the research. However, the analyses conducted in the study were based on 1925 cases; 4 cases were discarded for having unrecoverable wrong data and 7 for having missing mandatory data. The mean age of the study group was 70.85 (SD 14.88) years; 1201 (62.4%) were men and 724 (37.6%) were women. The list of main diagnoses is depicted in Table 1S in Multimedia Appendix 1. Up to 64 variables, grouped into the 3 categories indicated above, were considered in the analyses (Table 2S in Multimedia Appendix 1).

To characterize different subpopulations of risk, patients were classified as undergoing successful and unsuccessful home hospitalization stays based on their re-admission and mortality during the study period and 30 days after hospital discharge (Tables 1-2). Of the 1925 patients admitted to the HH/ED program, 3 (0.2%) patients died and 96 (5.0%) cases were eventually readmitted to the hospital due to complications of heterogeneous origin during HH/ED. Of the remaining 1922 patients, within 30 days after HH/ED discharge, 37 (1.9%) patients died and 210 (10.9%) cases were identified as falling into the unsuccessful groups when analyzing re-admission risk. Tables 1 and 2 summarize the baseline characteristics of both study groups, according to mortality and re-admission, respectively.

Mortality was higher in elderly (P<.001) and comorbid patients, GMA (P=.02), and the Charlson Comorbidity Index (P=.001), especially in those with cardiovascular (P<.001) and oncologic disorders (P=.019). Mortality was lower in postoperative patients (P<.001) and in those with respiratory diseases (P=.005). Interestingly, in-hospital re-admission was only slightly associated with higher age (P=.003) and a major complexity of comorbid conditions, GMA (P<.001), and the Charlson Comorbidity Index (P<.001), without well-defined associations with the characteristics of the main diagnosis.

Table 1. Clinical characteristics of successful and unsuccessful home hospitalization (HH) cases (n=1925) based on mortality.

Patient characteristics	Successful cases (n=1885)	Unsuccessful cases during HH (n=3)	Unsuccessful cases 30 days after HH discharge (n=37)	*P* value[a]
Age, mean (SD)	70.7 (14.9)	89.3 (15.1)	77.9 (10.6)	<.001
Sex, n (%)				
Male	1181 (62.7)	1 (33.3)	19 (51.3)	.145
Female	704 (37.3)	2 (66.6)	18 (48.7)	.145
GMA, mean (SD)	21.3 (13.5)	21.4 (3.1)	27.0 (14.2)	.020
Charlson Comorbidity Index, mean (SD)	4.3 (2.8)	5.7 (4.9)	5.8 (2.7)	.001
Diagnostic group, n (%)				
Cardiology	202 (10.7)	1 (33.3)	16 (43.2)	<.001
Respiratory	583 (30.9)	0 (0.0)	5 (13.6)	.005
Oncology	145 (7.7)	0 (0.0)	8 (21.6)	.019
Surgery	375 (19.9)	0 (0.0)	0 (0.0)	<.001
Other medical acute conditions	580 (30.8)	2 (66.7)	8 (21.6)	.440

[a]*P* values were calculated comparing successful and unsuccessful groups during the full period.

Table 2. Clinical characteristics of successful and unsuccessful home hospitalization (HH) cases (n=1925) based on re-admission.

Patient characteristics	Successful cases (n=1638)	Unsuccessful cases during HH (n=96)	Unsuccessful cases 30 days after HH discharge (n=210)	*P* value[a]
Age, mean (SD)	70.5 (15.2)	72.9 (14.8)	73.2 (11.9)	.003
Sex, n (%)				
Male	1007 (61.6)	63 (65.6)	142 (67.6)	.056
Female	631 (38.4)	33 (34.4)	68 (32.4)	.056
GMA, mean (SD)	20.3 (13.1)	26.8 (15.0)	28.7 (14.7)	<.001
Charlson Comorbidity Index, mean (SD)	4.1 (2.8)	5.3 (2.6)	5.6 (2.6)	<.001
Diagnostic group, n (%)				
Cardiology	162 (9.9)	24 (25.0)	38 (18.1)	.068
Respiratory	507 (30.9)	24 (25.0)	62 (29.5)	.722
Oncology	113 (6.9)	8 (8.3)	32 (15.2)	.123
Surgery	340 (20.8)	14 (14.6)	23 (11.0)	.136
Other medical acute conditions	516 (31.5)	26 (27.1)	55 (26.2)	.450

[a]*P* values were calculated comparing successful and unsuccessful groups during the full period.

Predictive Modeling

Different modeling approaches were considered for this purpose, including logistic regression, decision trees, and random forests. The averaged AUROC of each modeling approach that was considered is presented in Table 3.

Among the different modeling strategies developed, random forest classifier (Figure 2) showed the best performance averaged over the 4 risk scenarios.

Table 4 summarizes the performance of the 4 predictive models proposed in the study for in-hospital admission (RM1 and RM3) and for mortality (RM2 and RM4); Multimedia Appendix 2 depicts the relative weight, expressed as the mean decrease in accuracy (MDA) [20], of the 10 most relevant variables for each of the 4 predictive models.

Table 3. Area under the receiver operating characteristic curve (AUROC; sensitivity/specificity) performance of the modeling strategies explored.

Model	Mean AUROC (sensitivity/ specificity)	RM1 AUROC (sensitivity/ specificity)	RM2 AUROC (sensitivity/ specificity)	RM3 AUROC (sensitivity/ specificity)	RM4 AUROC (sensitivity/ specificity)
Logistic regression	0.58 (0.54/0.57)	0.65 (0.68/0.58)	0.54 (0.50/0.59)	0.59 (0.61/0.52)	0.54 (0.38/0.58)
Decision tree	0.59 (0.81/0.47)	0.62 (0.82/0.43)	0.64 (0.88/0.51)	0.57 (0.64/0.42)	0.64 (0.88/0.52)
Random forest	0.80 (0.75/0.71)	0.71 (0.67/0.64)	0.88 (0.81/0.76)	0.70 (0.71/0.61)	0.89 (0.81/0.81)

Figure 2. Overview of the predictive modeling strategy taking, as an example, prediction of re-admission at home hospitalization discharge. Upper-left table: metrics used for model performance assessment; AUC: area under the receiver operating characteristic curve. Center figure: representation of 1 decision tree using a random subset of features; on the nodes, threshold values for each variable determine the path from the root to the leaves (0.5 for Boolean variables), moving toward the left when the decision rule is meet; on a random forest model, final predictions are averaged over multiple decision trees. Upper-right table: 3 categories of data that are included in the models. *GMA category 404; 40: patient with active neoplasms; 4: high complexity conditions (percentile between 0.85 and 0.95).

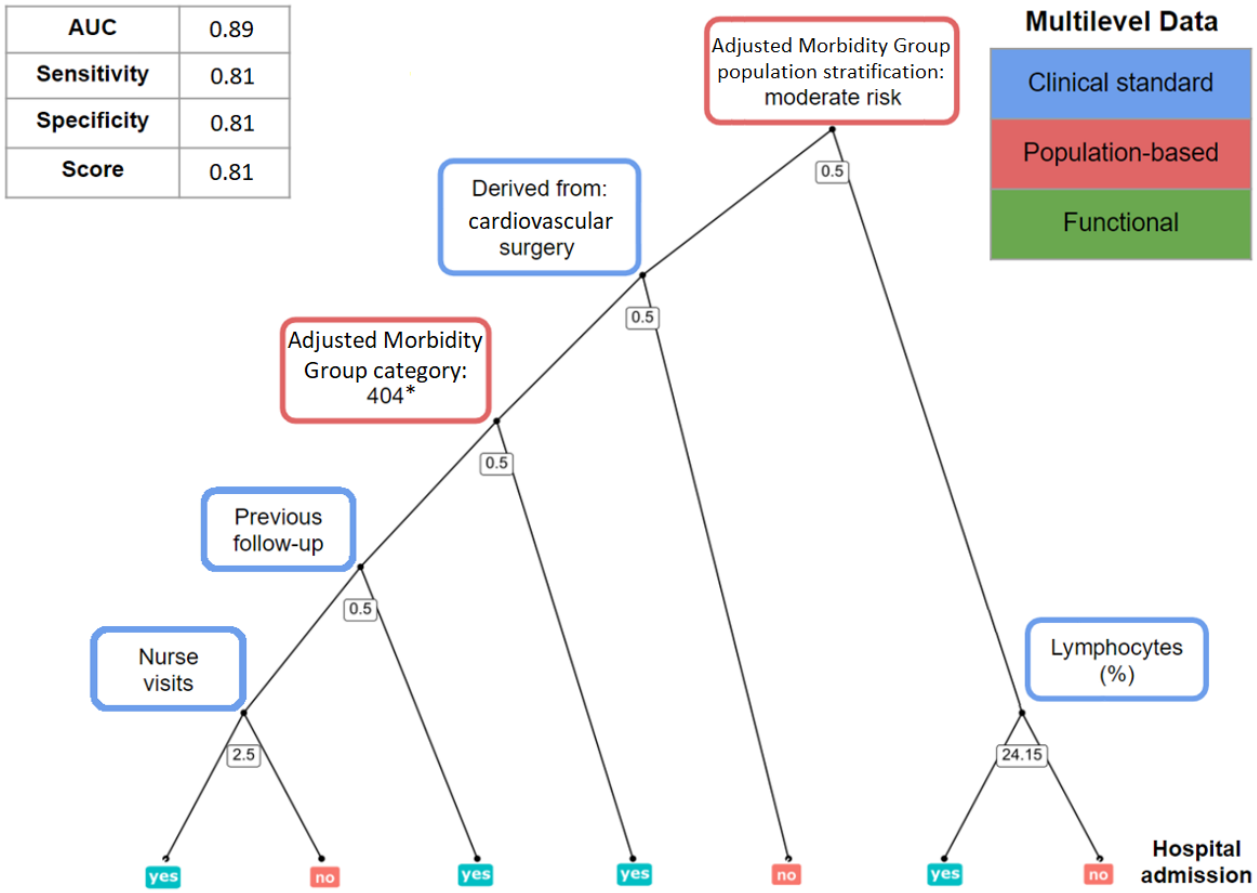


Table 4. Average results of the performance of the 4 home-hospitalization/early discharge (HH/ED) predictive risk models (RM).

Model	AUROC[a], mean (SD)	Sensitivity, mean (SD)	Specificity, mean (SD)	Score, mean (SD)
Readmission risk at HH/ED admission (RM1)	0.71 (0.03)	0.67 (0.06)	0.64 (0.05)	0.66 (0.03)
Readmission risk at HH/ED discharge (RM3)	0.70 (0.02)	0.71 (0.06)	0.61 (0.05)	0.66 (0.03)
Mortality risk at HH/ED admission (RM2)	0.88 (0.04)	0.81 (0.09)	0.76 (0.04)	0.78 (0.06)
Mortality risk at HH/ED discharge (RM4)	0.89 (0.04)	0.81 (0.12)	0.81 (0.05)	0.81 (0.06)

[a]AUROC: area under the receiver operating characteristic curve.

For risk of in-hospital admissions (Multimedia Appendix 2, panels A and C), multimorbidity (expressed as GMA scoring) showed the highest predictive impact, followed by red cell distribution width (RDW). Other top predictors were polypharmacy, body mass index (BMI), a few biological variables (blood cells characteristics and glucose), and physical and mental status.

For risk of mortality (Multimedia Appendix 2, panels B and D), RDW and physical status at entry (assessed using the SF-36 questionnaire [21]) showed the highest impact in the models.

Notably, enriching the model with information acquired during HH/ED (Multimedia Appendix 2, panels C and D), several variables gained importance, such as hospital admissions during HH/ED, length of current hospitalization period, and nursing home visits.

Discussion

Principal Findings

The current research has developed and internally validated 4 machine learning algorithms predicting the risk of in-hospital admission and mortality for patients undergoing home-based

hospitalization until 30-days after discharge from the service at HCB, from 2009 to 2015. Predictions of the 2 undesirable events were performed at 2 specific time points: at entry and at discharge from home-based hospitalization.

The study design was formulated and adopted under the hypothesis that robust predictions could be useful for clinical decision making: (1) to decide patients' admission into the HH/ED service (RM1 and RM2); and (2) to personalize care paths for transitional care, as well as for enhanced vertical integration between specialized care and community-based services, both at patients' discharge from HH.

A unique aspect of this research is that predictors considered in the analyses encompass 3 different categories of variables (Table 2S in Multimedia Appendix 1): (1) clinical data and biological information [22-24] extracted from patients' electronic medical records; (2) additional variables often not considered in the clinical records specifically collected in the research protocol to reflect patients' functional capacities and health care resources; and (3) information from GMA, the population-based, health-risk assessment tool developed and implemented in Catalonia (ES) [15,16,25].

We understand that the multisource approach adopted in this research was the most appropriate to elaborate predictive modeling in a highly heterogeneous group of patients undergoing HH/ED, in terms of clinical diagnosis and frailty status [8]. The results depicted in Table 4, in terms of AUROC and score values, indicate the reasonably good performance of the predictive models as compared to recent studies on similar scenarios [26], demonstrating the feasibility of the proposed approach and leveraging the advantages of applying machine learning in clinical risk prediction contexts in front of more traditional approaches based on standard multiple regression analyses [27]. Moreover, Multimedia Appendix 2 (panels A-D) shows a high relative contribution of variables usually not considered to be of clinical standard or relevant biological information recorded in the EMR. Overall, our results indicate that our multisource approach significantly contributes to enhanced health risk assessment with a potentially high impact on clinical decision support.

Limitations of the Study and Lessons Learned for Clinical Application

We have not been able to identify literature on predictive modeling specifically addressing HH/ED. It may partly be due to the heterogeneity of orientations and characteristics of the ongoing HH/ED programs among sites. This fact constitutes a limitation regarding the potential for generalization of the results of this research to other sites. However, we understand that the multisource approach undertaken in this study shows enormous potential for risk assessment regarding mortality and early re-admissions of hospitalizations in general, and may show high applicability beyond the field of HH/ED. The predictive modeling undertaken in the study should be useful for defining the characteristics of personalized care paths of transitional care after hospital discharge. As indicated above, the results can have a high impact on shaping the interactions between specialized and community-based care in patients with high risk for hospital re-admissions.

A major general limitation of machine learning approaches such as the one proposed here is the fact that they can be considered "black-box" solutions, difficult to interpret by clinicians. Our work, however, is based on random forest models that provide interpretable information regarding variable importance (Multimedia Appendix 2, panels A-D) and even model visualization, thus facilitating the understanding of their predictions. We believe that the clinical interpretation of the predictors may require different approaches; for example, variables like age and diagnosis should be individually assessed for clinical judgment, while others, like the different GMA parametrization (including the Charlson Index), should be assessed by taking the category as a whole (and likewise, abnormalities in some blood test variables). On the other hand, this study indicates that the impact of patients' functional status on outcomes is high. However, some of the measurements included in this category are not scalable in the clinical scenario (ie, SF36). Therefore, our results clearly indicate that surrogates with higher applicability [28,29] should likely be considered for inclusion in real-life clinical settings. This could be achieved through patients' self-tracking equipment (ie, apps) that provides information on different dimensions characterizing the functional performance of the patient, namely physical and psychological status, wellbeing, activation, etc.

It is acknowledged that the generalization of the use of new clinical scores generated from predictive modeling needs external validation on other patient cohorts or in different timeframes, and even on the development of impact studies in real-world settings [30]. Apart from being costly, such a validation process can show limitations partly due to rapidly evolving clinical environments, as is the case for HH/ED at HCB, expanded to the entire health district of Eixample-Esquerra during 2018. The new scenario implies great changes in the clinical environment, patients' characteristics, and data sources prompting the need for designing dynamic models in the context of learning health systems (LHS) [31,32]. It is of note that within a mature digital health scenario, the multisource predictive modeling approach could be enriched with other sources of data, such as patient self-reported data and data from social care. The lack of digital maturity of the current ecosystems constitutes a limiting factor for now, but in the near future, risk assessment tools are expected to improve in terms of robustness, potential for generalization of the results, and incorporation of a dynamic predictive approach.

Steps Toward Dynamic Learning Health Systems

There is little doubt about the high potential shown by the digital transformation of health as part of a large-scale adoption of integrated care. It is acknowledged, however, that practical applications of this vision face major limitations when it comes to accessing and mining health data stored in distributed silos of information. However, it seems clear that integrating and analyzing highly complex data would open new avenues for digital health in the clinical arena.

The integration of biomedical research information systems with in-place electronic health records in hospitals and in primary care centers having interoperability with patients' self-tracking information would enable the development of

innovative, dynamic predictive modeling approaches, opening up entirely new and fascinating scenarios for an interplay between clinical practice and biomedical research [33,34]. We have identified 4 main interrelated enablers of this scenario [15,17,35]: (1) cloud-based tools and services allowing secure analysis of patient-centric distributed and multi-disciplinary health-related information; (2) systems medicine approaches to generate clinical predictive modeling to feed clinical decision support systems and patient decision support systems; (3) implementation and evaluation strategies for real-world implementation and assessment of cloud-based services, and (4) governance, regulatory aspects, and service adoption throughout the health care systems; these are all key to harnessing the strengths and opportunities of LHS.

Combined actions involving organizational changes with the engagement of all stakeholders, selective adoption of novel biomedical and digital tools, and the achievement of financial sustainability through enhanced accountability and entrepreneurial actions should pave the way toward the transition to LHS.

Conclusions

This study proves the potential of the proposed multisource machine-learning models for the prediction of risk of re-admissions and deaths in patients undergoing home-based hospitalization in a real-world setting. Further steps beyond this study include the development of dynamic clinical decision support systems allowing progression towards sustainable patient-centered health care services.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

On-line supplementary material: Multisource Predictive Modelling of Health Outcomes from Home Hospitalization.
[DOCX File , 333 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Relative importance measures based on the mean decrease in accuracy (MDA) of the 10 most relevant variables for each model. GMA: morbidity adjusted group; BMI: body mass index; RDW: red cell distribution width; HH: home hospitalization.
[DOCX File , 17 KB-Multimedia Appendix 2]

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Abbreviations

AUROC: area under the receiver operating characteristic curve
ED: early discharge
EMR: electronic medical records
GMA: Adjusted Morbidity Groups
HCB: Hospital Clínic de Barcelona
HH: Home Hospitalization
LHS: Learning Health Systems
MDA: mean decrease in accuracy
RDW: red cell distribution width
RM: risk model

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Prevention of Unplanned Hospital Admissions in Multimorbid Patients Using Computational Modeling: Observational Retrospective Cohort Study

Rubèn González-Colom[1], MSc; Carmen Herranz[2], MSc, RNC; Emili Vela[3,4], MSc; David Monterde[4,5], MSc; Joan Carles Contel[6], MSc; Antoni Sisó-Almirall[2], MD, PhD; Jordi Piera-Jiménez[3,4,7], MSc; Josep Roca[1], MD, PhD; Isaac Cano[1], PhD

[1]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

[2]Consorci d'Atenció Primària de Salut Barcelona Esquerra (CAPSBE), Primary Healthcare Transversal Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[3]Catalan Health Service, Barcelona, Spain

[4]Digitalization for the Sustainability of the Healthcare System DS3-IDIBELL, L'Hospitalet de Llobregat, Spain

[5]Catalan Institute of Health, Barcelona, Spain

[6]Health Department Generalitat de Catalunya, Barcelona, Spain

[7]Faculty of Informatics, Multimedia and Telecommunications, Universitat Oberta de Catalunya, Barcelona, Spain

Corresponding Author:
Rubèn González-Colom, MSc
Hospital Clínic de Barcelona
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
Universitat de Barcelona
Villarroel 170
Barcelona, 08036
Spain
Phone: 34 686626947
Email: rgonzalezc@recerca.clinic.cat

Abstract

Background: Enhanced management of multimorbidity constitutes a major clinical challenge. Multimorbidity shows well-established causal relationships with the high use of health care resources and, specifically, with unplanned hospital admissions. Enhanced patient stratification is vital for achieving effectiveness through personalized postdischarge service selection.

Objective: The study has a 2-fold aim: (1) generation and assessment of predictive models of mortality and readmission at 90 days after discharge; and (2) characterization of patients' profiles for personalized service selection purposes.

Methods: Gradient boosting techniques were used to generate predictive models based on multisource data (registries, clinical/functional and social support) from 761 nonsurgical patients admitted in a tertiary hospital over 12 months (October 2017 to November 2018). K-means clustering was used to characterize patient profiles.

Results: Performance (area under the receiver operating characteristic curve, sensitivity, and specificity) of the predictive models was 0.82, 0.78, and 0.70 and 0.72, 0.70, and 0.63 for mortality and readmissions, respectively. A total of 4 patients' profiles were identified. In brief, the reference patients (cluster 1; 281/761, 36.9%), 53.7% (151/281) men and mean age of 71 (SD 16) years, showed 3.6% (10/281) mortality and 15.7% (44/281) readmissions at 90 days following discharge. The unhealthy lifestyle habit profile (cluster 2; 179/761, 23.5%) predominantly comprised males (137/179, 76.5%) with similar age, mean 70 (SD 13) years, but showed slightly higher mortality (10/179, 5.6%) and markedly higher readmission rate (49/179, 27.4%). Patients in the frailty profile (cluster 3; 152/761, 19.9%) were older (mean 81 years, SD 13 years) and predominantly female (63/152, 41.4%, males). They showed medical complexity with a high level of social vulnerability and the highest mortality rate (23/152, 15.1%), but with a similar hospitalization rate (39/152, 25.7%) compared with cluster 2. Finally, the medical complexity profile (cluster 4; 149/761, 19.6%), mean age 83 (SD 9) years, 55.7% (83/149) males, showed the highest clinical complexity resulting in 12.8% (19/149) mortality and the highest readmission rate (56/149, 37.6%).

Conclusions: The results indicated the potential to predict mortality and morbidity-related adverse events leading to unplanned hospital readmissions. The resulting patient profiles fostered recommendations for personalized service selection with the capacity for value generation.

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KEYWORDS

health risk assessment; health risk profiles; transitional care; hospital readmissions; mortality

Introduction

Enhanced management of multimorbidity constitutes a major clinical challenge because the number and complexity of morbid conditions show well-established causal relationships with mortality and high use of health care resources [1], with unplanned hospital admissions being a key determinant of the multimorbidity-induced high burden on health care systems worldwide [2,3].

Evidence-based efficacy of integrated care interventions to prevent hospitalizations in high-risk patients has been demonstrated [4,5]. Likewise, comprehensive programs to enhance care during transitions after hospital discharge can reduce all-cause early hospital readmissions in chronically ill patients, which is particularly effective in mid/long-term evaluations [6,7]. However, the scalability and adoption of such preventive interventions in real-life scenarios are often limited by an efficacy-effectiveness gap. Poor patient risk stratification and insufficient workforce preparation for the care continuum have been identified as critical limiting factors for effective clinical practice [8].

In this regard, multisource clinical predictive modeling approaches, considering various determinants of health (eg, clinical, social, populational, lifestyle), have become an effective strategy for subject-specific risk assessment to prevent morbidity-related adverse events leading to hospital readmissions [9-13].

This research work aimed to enhance chronic patients' stratification at hospital discharge, characterize patients' risk profiles for generating recommendations on postdischarge care transitions [14,15], and improve personalized preventive care pathways within a care continuum scenario [16]. To this end, multiple data sources (ie, primary care, social care, hospital-based data, and registry information) from distinct domains (ie, medical complexity, disability scoring, unhealthy lifestyle factors, and social frailty) have been considered.

Methods

Study Design, Population, Potential Predictors, and Data Sources

This is an observational retrospective cohort study of patients discharged from the Hospital Clínic of Barcelona (HCB) from October 2017 to November 2018. The study population included nonsurgical patients admitted to the hospital avoidance program (n=441) and the corresponding controls undergoing conventional hospitalization (n=441), as reported in detail in Herranz et al [17].

Key determinants of health from the clinical and social domains were considered (Table 1): (1) sociodemographic information; (2) population-based registry indicators on morbidity and complexity; (3) patients' functional characteristics; (4) frailty and social risk indicators; (5) unhealthy lifestyle habits; (6) utilization of health care resources; (7) clinical and biological data collected during the acute episode; and (8) immunization records. It is of note that multimorbidity and complexity were characterized by the Catalan population–based health risk assessment scoring, known as Adjusted Morbidity Groups (AMG) [18-21], an aggregative index that indicates the burden of an individual's morbid conditions through a disease-specific weighting deduced from statistical analysis based on mortality and the utilization of health services; by contrast, the acute episode complexity was characterized by the Queralt Indices [22,23] that combine information on (1) preexisting comorbidities; (2) in-hospital complications; (3) principal discharge diagnoses; (4) main procedure; and (5) secondary procedures performed during hospitalization. For predictive modeling purposes, the different Queralt Indices have been aggregated into a single score, referred to as the composite Queralt Index.

Table 1. List of variables considered for predictive modeling and clustering analysis.[a]

Variables	Description
Sociodemographic data	
1: Age (100%)	Patient's age (numerical)
1: Gender (100%)	Patient's sex (binary, male/female)
1: HBA (100%)	Health Basic Area (categorical, 105 levels)
Medical complexity	
3: AMG score [18-21] (100%)	Adjusted Morbidity Groups score (numerical)
2: SIIP Plan [24] (90.45%)	Shared Individual Intervention Plan (binary, yes/no)
2: CCP [24] (90.45%)	Complex chronic patient (binary, yes/no)
2: ACP [24] (90.45%)	Advanced chronic patient (binary, yes/no)
Patient's functional capacity	
2: Barthel [25] (90.45%)	Barthel Index (numerical, 0-100)
2: Lawton Brody [26] (82.97%)	Lawton Brody Index (numerical, 0-8)
2: Pfeiffer [27] (90.58%)	Pfeiffer Index (numerical, 0-10)
2: Braden [28] (78.71%)	Braden Index (numerical, 0-23)
2: Geriatric syndrome [29] (100%)	Geriatric syndrome label (binary, yes/no)
Social frailty indicators	
2: MNA [30] (71.87%)	Mini Nutritional Assessment Index (numerical, 0-30)
2: TSRI [31] (100%)	Table of Social Risk Indicators (numerical, 0-6)
2: Barber [32] (81.9%)	Barber Index (numerical, 0-9)
2: Dependence (100%)	Dependence label (binary, yes/no)
Unhealthy lifestyle habits	
2: BMI (74.19%)	BMI (numerical)
2: Physical activity (75.61%)	Patient's physical activity (categorical, 3 levels)
2: Alcohol intake (73.94%)	Patient's alcohol intake (categorical, 3 levels)
2: Smoking (73.03%)	Patient's smoking habits (categorical, 3 levels)
Use of health care resources	
3: Hospital admissions (100%)	Number of admissions during the previous 12 months (numerical)
3: Emergency room visits (100%)	Number of emergency room visits during the previous 12 months (numerical)
3: Primary care encounters (100%)	Number of encounters with primary care professionals during the previous 12 months (numerical)
3: Outpatient visits (100%)	Number of specialized care outpatient visits during the previous 12 months (numerical)
3: Medication (100%)	Number of drugs prescribed during the previous 12 months (numerical)
3: Health care expenditure (100%)	Total health care expenses of the previous 12 months in euros (numerical)
Acute episode complexity	
1: Composite Queralt Index [22,23] (100%)	Composite Queralt Index (numerical)
1: Type of hospitalization (100%)	Type of hospitalization (binary, hospital avoidance/usual care)
1: Length of stay (100%)	Total hospitalization days (numerical)
1: Number of active diagnoses (100%)	Number of active diagnoses at admission (numerical)
1: Leukocyte[a] (87.33%)	Leukocyte count (numerical)
1: Lymphocytes[a] (87.33%)	Percentage of lymphocytes (numerical)
1: Hemoglobin[a] (87.33%)	Hemoglobin concentration (numerical)
1: RDW[a] (87.33%)	Red blood cell distribution width (numerical)

Variables	Description
1: Glucose[a] (87.33%)	Glucose concentration (numerical)
1: Creatinine[a] (87.33%)	Creatinine concentration (numerical)
1: Sodium[a] (87.33%)	Sodium concentration (numerical)
1: Potassium[a] (87.33%)	Potassium concentration (numerical)
Immunization records	
2: Vaccination, flu[a] (100%)	Flu vaccine administration (binary, yes/no)
2: Vaccination, pneumococcal 13[a] (100%)	Pneumococcal 13 vaccine administration (binary, yes/no)
2: Vaccination, pneumococcal 23[a] (100%)	Pneumococcal 23 vaccine administration (binary, yes/no)

[a]Variables used only for predictive modeling purposes. The number before the variable's name indicates the database from which the information was retrieved: (1) HCB's electronic medical records; (2) primary care's electronic medical records; and (3) the Catalan Health Surveillance System. The percentages of data availability are displayed after variable's name.

Potential predictors (Table 1) were retrieved from 3 different data sources: (1) HCB's electronic medical records (EMRs); (2) primary care's EMR; and (3) the Catalan Health Surveillance System (CHSS) [33]. The latter contains information on clinical diagnoses, medication, and resource utilization from the hospital and primary care. The CHSS is regularly fed from EMR data of all public health care providers in Catalonia paid by CatSalut, the single public payer in Catalonia (ES), which uses it for billing purposes, population-health risk assessment, and allocation of resources. Databases are linked through a unique identification number used for public assurance purposes.

Ethical Approval

The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethical Committee for Human Research at the Hospital Clínic of Barcelona (26/04/2017, 2017-0451 and 2017-0452). All data were handled according to the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union and the local regulatory framework regarding data protection. Study investigators only had access to a fully anonymized database. Data from other health administrative databases were linked and deidentified by a team not involved in the study analysis.

Outcomes

The predictive modeling for enhanced patient stratification assessed 2 primary outcomes occurring up to 90 days after discharge: mortality and all-cause hospital readmissions. The clustering analysis allowed the identification and characterization of patients with different risk profiles for personalized service selection purposes. Moreover, the 90-day postdischarge service-utilization trajectories of the identified patients' risk profiles were analyzed.

Data Analytics Workflow

From the initial set of 882 patients, 107 were eliminated due to the absence of unrecoverable indispensable data. An additional 14 patients were rejected for subsequent analyses because they died during the hospitalization, resulting in a cohort of 761 patients.

It is to be noted that we observed elevated patterns of missingness in most of the variables recorded in the primary care databases. This was due, in part, to the fact that a vast majority of questionnaires used to assess patient functional characteristics, frailty, and social risks are systematically administered only in elders or patients with explicit evidence of vulnerability or functional decline. Therefore, we imputed baseline levels for Barthel [25], Lawton-Brody [26], Pfeiffer [27], Braden [28], Mini Nutritional Assessment [30], Table of Social Risk Indicators [31], Barber [32] questionnaires in all patients younger than 70 years with no formal diagnosis involving significant levels of dependence, vulnerability, or functional decline. Appendix S1 in Multimedia Appendix 1 presents the diagnostic codes considered for imputation in this initial round (see also [25-32,34]). After that, all variables with percentages of missingness higher than 30% were excluded from the study database. The remaining incomplete registers were imputed using the MissForest [35] algorithm, a robust method for mixed-type data imputation. Furthermore, the categorical features used to encode smoking and alcohol abuse habits were rediscretized to avoid underrepresented categories.

To avoid overfitting, we removed from the study data set all highly correlated features using a Pearson coefficient of 0.75 as a threshold value. In addition, we applied a low variance filtering to remove the features with very few unique values. For this issue, we set the threshold for the ratio between the frequency of the most common value and the frequency of the second most common value to 95:5. The final set of predictors is displayed in Table 1.

According to the results of previous predictive modeling experiences in similar settings, reported in Calvo et al [11], we used gradient boosting machines [36] to forecast 2 binary deleterious events occurring up to 90 days after hospital discharge: (1) mortality and (2) all-cause hospital readmissions. We used a grid search to fine-tune the gradient boosting machine parameters (number of trees=1500, maximum number of nodes per tree=5, shrinkage=0.01, and minimum number of observations in terminal nodes=7). The models were trained and tested using a Monte Carlo cross-validation approach with 10 replicates, using 75% of the data for training and the

remaining 25% for testing. In addition, every training data partition was 4-fold cross-validated to determine the training and validation splits, accounting for 75% and 25% of the training data partition, respectively. To minimize the effect of class imbalance on the target outcomes caused by the scarcity of unsuccessful cases, we used a random stratified sampling technique [37] to generate the train/test data splits. In addition, to estimate the relative importance of the variables within the predictive models, we performed a mean decrease in accuracy (MDA) analysis. Finally, both predictive models were evaluated, according to the average results of all the independent validations, using the following metrics: area under the receiver operating characteristic curve (AUROC), sensitivity (SE), and specificity (SP). We also calculated the 95% CI for the AUROC using 2000 bootstrapped stratified replicates.

For personalized service selection purposes, we used the K-means clustering algorithm [38,39] to generate groups of patients with similar clinical and social risk profiles. We used the average silhouette method [40] to determine the optimal number of clusters. Finally, the baseline characteristics and patient service utilization trajectories up to 90 days after hospital discharge for all risk profiles identified in this process were assessed.

Categorical variables were summarized as absolute values and frequencies, whereas continuous variables were represented by the mean and the SD or the median and interquartile range. ANOVA, together with post hoc pairwise *t* test (unpaired, 2-tailed), and Kruskal-Wallis, together with post hoc pairwise Wilcoxon tests, were used to assess changes in numeric outcomes, as needed. The Fisher exact test was used to assess changes in categorical variables. Bonferroni adjustments were used in multiple pairwise comparisons. The threshold for statistical significance was set at .05. In addition, to enable multidimensional data combination and to enhance risk profiles (ie, clusters) comparison and visualization, all features were rescaled into a 0-1 range using a minimum-maximum normalization approach. Afterward, all features were aggregated, averaged, and displayed in radar plots in 7 categories that mimic the groups of aforesaid variables, specifically (1) age, (2) medical complexity, (3) functional capacity, (4) social frailty, (5) unhealthy lifestyle habits, (6) use of health care resources, and (7) acute episode complexity.

All the statistical analyses were conducted using R version 4.1.1 [41] (The R Foundation)

Results

Characteristics of the Study Population

The average age of the study population was 75.9 (SD 14.51) years. Of the 761 patients overall, 434 (57%) were men and the remaining (n=327, 42.9%) were women. Besides, 63/761 (8.3%) patients died during the following 90 days after hospital discharge, 188/761 (24.7%) had to be readmitted within the study period, and 308/761 (40.5%) had unplanned emergency room (ER) visits. Table 2 presents selected characteristics of the study population, as well as pairwise comparisons between successful and unsuccessful groups: (1) survivors and deceased patients; and (2) patients not requiring hospital readmission and readmitted patients.

In brief, mortality and hospital readmission rates were higher in elders (age: $P<.001$), in highly comorbid and complex patients (AMG: $P<.001$), and in individuals with higher composite Queralt Index ($P<.001$) when combining the severity of the acute episode with the preexisting comorbidity burden. In the entire study group, 77.4% (589/761) of the patients were allocated above the P_{95} of the AMG scoring distribution in Catalonia, the tip of the population-based risk stratification pyramid. The survivors presented a similar distribution (533/698, 76.4%, $\geq P_{95}$), but patients that died after discharge showed a significantly higher ($P<.001$) AMG scoring (56/63, 88.9%, $\geq P_{95}$). Likewise, AMG scoring was markedly lower ($P<.001$) in patients not requiring readmissions (424/573, 74.0%, $\geq P_{95}$) than in those rehospitalized within the 90-day study period (165/188, 87.8%, $\geq P_{95}$). A similar pattern was seen in the composite Queralt Index, reflecting both patient's complexity and severity of the acute episode ($P<.001$). As expected, total health expenditure at the health system level during the 12 months before the acute episode was also significantly higher in the unsuccessful subgroups than in the entire study group or the successful subsets of patients.

Functional capacity loss (Barthel: $P<.001$) and social frailty and dependence (Barber: $P<.001$; Table S1 in Multimedia Appendix 1) were also identified as potential risk factors for both mortality and hospital readmission. A gender bias was observed in readmitted patients, with men showing a higher hospitalization rate ($P=.02$). A detailed description of all variables included in the analyses is depicted in Table S1 in Multimedia Appendix 1, wherein characteristics of those patients requiring unplanned ER visits during the study period are also displayed.

Table 2. Selected traits of the study group depending on mortality and all-cause hospital readmissions.

Variables	All patients (n=761)	Mortality			Readmission		
		Successful (n=698)	Unsuccessful (n=63)	*P* value[a]	Successful (n=573)	Unsuccessful (n=188)	*P* value[a]
Demographics							
Male, n (%)	434 (57.03)	404 (57.88)	30 (47.62)	—	313 (54.62)	121 (64.36)	.02
Female, n (%)	327 (42.97)	294 (42.12)	33 (52.38)	—	260 (45.38)	67 (35.64)	.02
Age, mean (SD)	75.06 (14.51)	74.27 (14.53)	83.87 (10.92)	<.001	74.18 (14.87)	77.77 (13.14)	.001
Medical complexity							
AMG[b] score, mean (SD)	26.35 (14.39)	25.64 (13.97)	34.27 (16.53)	<.001	24.21 (12.95)	32.89 (16.47)	<.001
AMG category, n (%)				<.001			<.001
Very low risk <P_{50}	2 (0.26)	2 (0.29)	0 (0)	—	2 (0.35)	0 (0)	—
Low risk [P_{50}-P_{80})	30 (3.94)	30 (4.3)	0 (0)	—	28 (4.89)	2 (1.06)	.003
Moderate risk [P_{80}-P_{95})	140 (18.4)	133 (19.05)	7 (11.11)	—	119 (20.77)	21 (11.17)	.005
High risk [P_{95}-P_{99})	182 (23.92)	172 (24.64)	10 (15.87)	—	147 (25.65)	35 (18.62)	—
Very high risk ≥P_{99}	407 (53.48)	361 (51.72)	46 (73.02)	<.001	277 (48.34)	130 (69.15)	<.001
Use of health care resources; 12 months before admission							
Health care expenditure in euros[c], median (IQR)	4164 (2466-7198)	4033 (2418-6930)	5979 (2930-11,072)	<.001	3772 (2260-6343)	5495 (3448-11,235)	<.001
Acute episode complexity							
Length of stay; mean (SD)	7.67 (5.20)	7.42 (4.72)	10.46 (8.49)	.006	7.51 (4.84)	8.11 (6.16)	—
Composite Queralt Index, mean (SD)	72.73 (30.41)	70.69 (30.02)	95.31 (25.27)	<.001	68.92 (29.75)	84.33 (29.52)	<.001

[a]Only *P* values ≤.05 have been presented.

[b]AMG: Adjusted Morbidity Group.

[c]€1=US $1.08.

Predictive Modeling

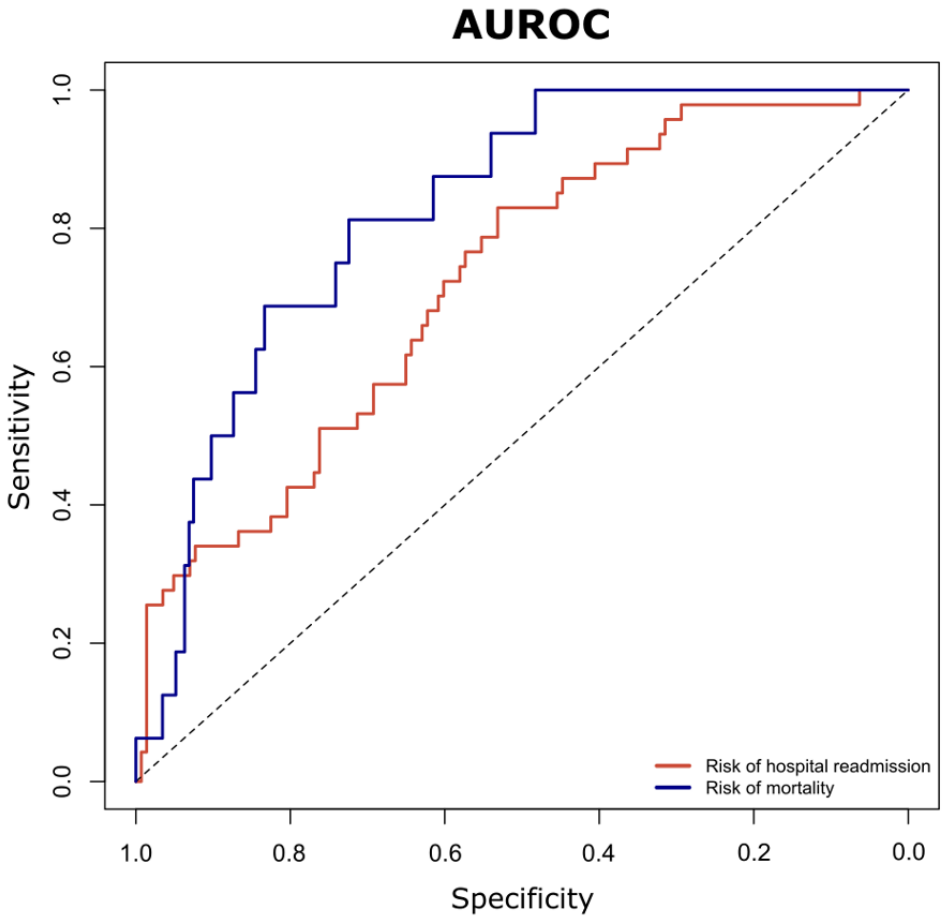
Figure 1 depicts the average performance of the predictive models over the cross-validation process. The mean performance of the models expressed as AUROC (CI; SE/SP) was 0.82 (0.74-0.90; 0.78/0.70) and 0.72 (0.64-0.80; 0.70/0.63) for mortality and all-cause hospital readmission risk, respectively.

Table 3 displays the variable importance weights, according to the MDA analysis, of the 15 most meaningful predictors for both predictive models developed within this study. It is of note that the top 5 predictors for mortality, responsible for 49% accuracy prediction in the MDA analysis, were age (16.7%), composite Queralt Index (12.3%), length of stay (7.7%), Pressure Sore Risk assessed by the Braden scale (6.4%), and heterogeneity of red cell volume/size (6.1%). Overall, variables expressing (1) aging, (2) severity of the acute episode (composite Queralt Index, length of stay, and biological blood markers measured during admission); (3) multimorbidity (number of prescriptions, AMG score, BMI); and (4) frailty (Pfeiffer index) were at the top of the list of the most influential traits modulating mortality after discharge.

Likewise, the top 5 predictors for readmissions during the 90 days after discharge explained 48% accuracy prediction in the MDA analysis. These were the composite Queralt Index (14.8%), blood lymphocytes cell count (10.8%), total health expenditure in the previous year (9.0%), age (8.4%), and AMG score (5.4%). Again, variables associated with the severity of the acute episode (composite Queralt index, peripheral blood biological markers, length of stay), age, multimorbidity (AMG score, health expenditure before the acute episode, BMI, number of specialist outpatient visits), and social frailty (Barber Index) were the main determinants of risk of readmission during the study period.

It should be noted that the predictive role of each of the individual components of the Queralt Index were assessed separately; however, the optimal models' performance was achieved using Queralt as a composite index.

Figure 1. Pooled average receiver operating characteristic curves for both predictive models: risk of mortality is indicated in blue, whereas risk of hospital readmission is indicated in red. The performance of the models is expressed according to the average area under the receiver operating characteristic curves (AUROC), sensitivity, and specificity.



Model	*AUROC, mean (SD)*	*Sensitivity, mean (SD)*	*Specificity, mean (SD)*
Risk of mortality up to 90 days after discharge	0.82 (0.03)	0.78 (0.08)	0.70 (0.04)
Risk of hospital readmission up to 90 days after discharge	0.72 (0.02)	0.70 (0.05)	0.63 (0.05)

Table 3. The 15 most meaningful predictors for mortality and readmission.

Variable	Variable importance, %
Predictors for mortality	
Age	16.67
Composite Queralt Index	12.31
Length of stay	7.68
Braden Index	6.43
Red cell distribution width	6.08
Hemoglobin concentration	4.13
Number of prescriptions	3.42
Lymphocytes count	3.31
Sodium concentration	3.29
Adjusted Morbidity Group score	3.06
BMI	2.97
Potassium concentration	2.95
Total health care expenditure	2.75
Glucose concentration	2.40
Pfeiffer Index	2.25
Predictors for readmission	
Composite Queralt Index	14.77
Lymphocytes count	10.81
Total health care expenditure	8.96
Age	8.42
Adjusted Morbidity Group score	5.35
Creatinine concentration	5.33
BMI	4.30
Number of primary care visits	4.05
Hemoglobin concentration	3.92
Glucose concentration	3.50
Leukocyte count	3.24
Number of specialized care visits	3.04
Red cell distribution width	2.70
Length of stay	2.53
Barber Index	2.11

Patient's Clustering and Postdischarge Trajectories

We identified 4 relevant clusters of patients whose hallmark characteristics are depicted in Figure 2. The information displayed in the clustering infographics (Figure 2) was normalized and aggregated into scores of 0 to 1 for each of the 7 main dimensions considered in the clustering analysis. The figure also displays mortality rates, hospital admissions, and unplanned ER visits for each cluster during the study period. Each cluster was named according to the most relevant characteristic of the subset of patients: cluster 1 (reference), cluster 2 (unhealthy lifestyle habits), cluster 3 (social frailty), and cluster 4 (medical complexity). An extensive comparison among the 4 clinical groups is displayed in Table S2 in Multimedia Appendix 1.

Figure 2. Radar plots of the main characteristics of the 4 clusters. All the features are normalized and grouped into 7 categories: (1) age; (2) medical complexity; (3) functional capacity; (4) social frailty; (5) unhealthy lifestyle habits; (6) use of health care resources; and (7) acute episode complexity. The mortality rates, hospital admissions, and unplanned emergency room visits are displayed in red. ER: emergency room.

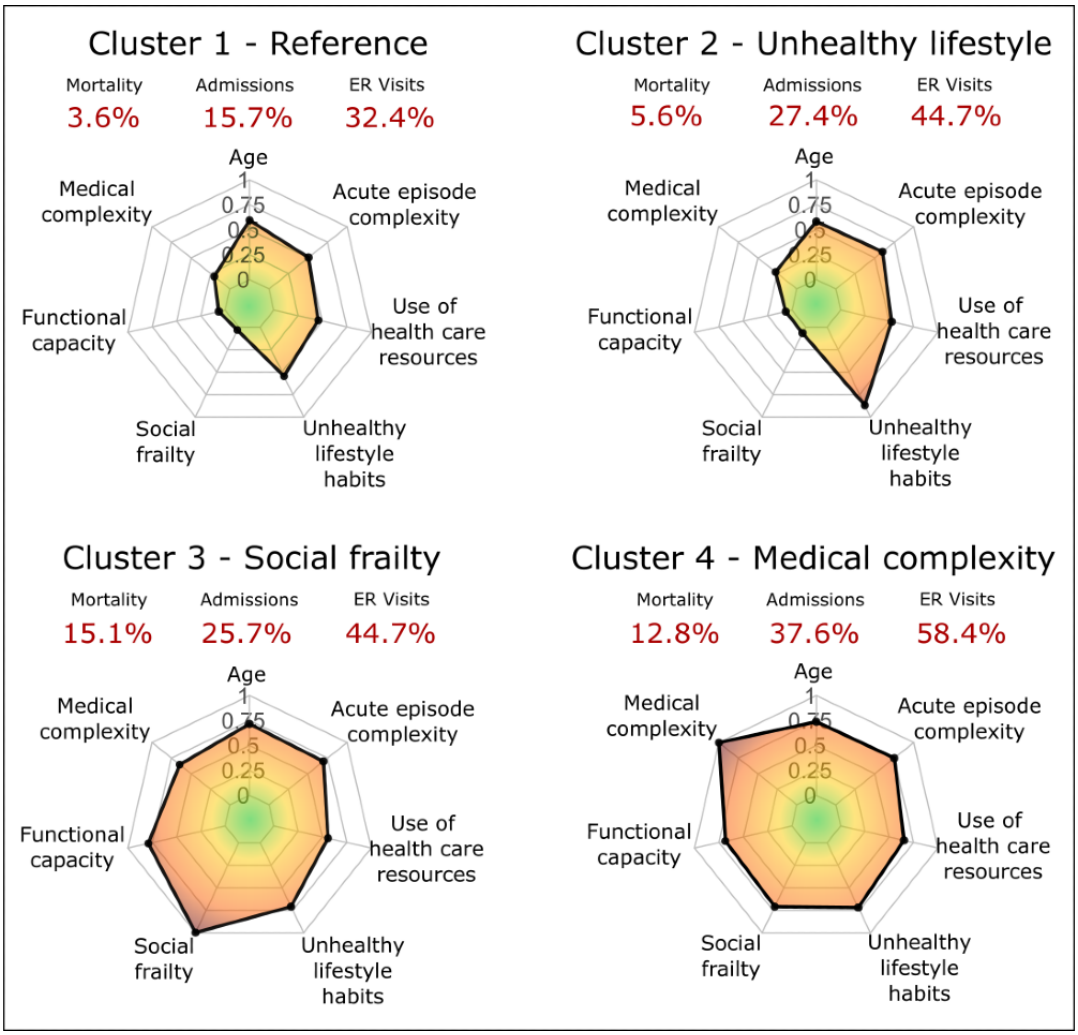
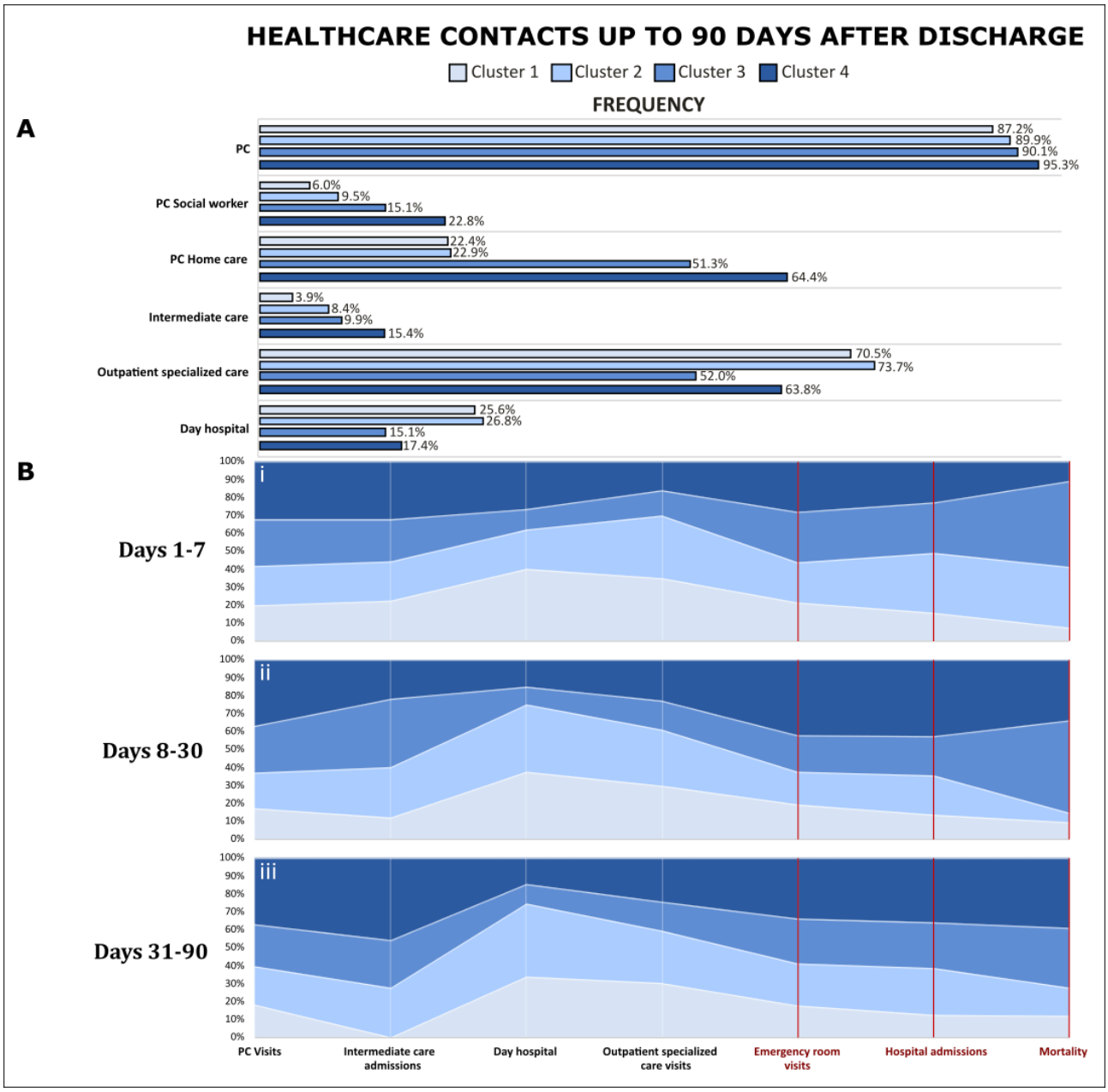


Figure 3 displays the postdischarge trajectories of patients up to 90 days. Figure 3A depicts rates of patient encounters with health care professionals in each cluster at different levels, namely: (1) primary care (physicians/nurses visits, home-based programs, and social workers visits); (2) intermediate care centers; and (3) specialized care (outpatient clinics and day hospitals visits). Figure 3B displays the postdischarge trajectories for each cluster of patients considering 3 consecutive phases: (1) the first week after discharge (panel i); (2) the 3 subsequent weeks (panel ii); and (3) the last 2 months of the study period (panel iii). For each panel, the ordinate (y-axis) indicates the relative frequencies of each cluster for the variables shown in the abscissa (x-axis), namely: (1) use of health care resources (primary care visits, intermediate care admissions, and specialized care visits), and (2) main outcomes (ER visits, postdischarge hospitalizations, and mortality). Patients' characteristics of each cluster and the associated postdischarge trajectories are briefly described below. A vast assessment of the health care resources used by the 4 clinical groups up to 90 days after hospital discharge is displayed as follows: (1) rates of patient encounters with health care professionals by cluster (Table S3 in Multimedia Appendix 1); and (2) the total number of contacts with health care professionals by cluster (Table S4 in Multimedia Appendix 1).

The so-called reference patients (cluster 1; 281/761, 36.9%) showed a mean age of 71.0 (SD 15.6) years, with 151/281 (53.7%) being male. The mean AMG scoring was 19.4 (SD 11.0), which corresponds to an elevated morbidity burden, close to the P_{95} of the population-based risk stratification pyramid. Of these, 63/281 (22.4%) patients were included in home care programs targeting complex chronic patients. The average health care expenditure during the previous 12 months of the acute episode was €5491 (US $5952).

Cluster 1 showed the lowest rates of mortality (10/281, 3.6%), readmissions (44/281, 15.7%), and ER visits (91/281, 32.4%) during the 90 days after discharge with no substantial differences among the 3 periods depicted in Figure 3B: (1) the first week, (2) the subsequent 3 weeks, and (3) the last 2 months.

Figure 3. Patients' trajectories by cluster during the 90-day postdischarge follow-up. (A) Itemized health care contact rates in each cluster. (B) Itemized relative frequencies of the total health care contacts (white) and health outcomes (red) in each cluster assessed in 3 time intervals: (i) days 1-7; (ii) days 8-30; and (iii) days 31-90. PC: primary care.



Patients with an unhealthy lifestyle habit profile (cluster 2; 179/179, 23.5%) had a similar age to cluster 1, with a mean of 69.9 (SD 13.4) years; interestingly, 137/179 (76.5%) patients in this cluster were male. The most relevant features in terms of lifestyle were sedentarism, tobacco smoking, and alcohol abuse (Table S2 in Multimedia Appendix 1). The mean AMG scoring was 23.7 (SD 11.7), close to P_{97} of the risk stratification pyramid. The number of patients included in home-based care programs due to complex chronic conditions was 41/179 (22.9%), a figure close to that seen in cluster 1. The average baseline health care expenditure was €6037 (US $6544).

Patients in cluster 2 patients presented a slightly higher mortality rate (10/179, 5.6%), but remarkably higher rates of readmissions (49/179, 27.4%) and ER consultations (80/179, 44.7%) than the reference subset. It is of note, however, that their age, level of functional and social frailty, as well as medical complexity did not show differences with cluster 1. Most importantly, this subset of patients showed a high rate of early mortality during the first week (Figure 3B), corresponding to the 4/10 (40%) deceased patients in this cluster (Table S3 in Multimedia Appendix 1). In addition, the rate of readmissions during the follow-up period was slightly higher than that observed in cluster 3 (39/152, 25.7%).

Patients in the social frailty profile (cluster 3; 152/761, 20%) were older than those in the previous clusters, mean age 81.10 (SD 12.67) years, and only 63/152 (41.4%) were male. Their mean AMG score was high, 30.0 (SD 12.7), corresponding to P_{98}. A high percentage of the group (78/152, 51.3%) was included in home-based care programs, and their average baseline health care expenditure was €6232 (US $6755). They presented high levels of medical complexity and functional frailty, but the most characteristic feature was the presence of

social frailty. Predominant traits of the group were elderly females with medical complexity and high social vulnerability.

The social frailty group showed the highest rate of mortality (23/152, 15.1%), but similar rates of readmissions (39/152, 25.7%) and ER consultations (68/152, 44.7%) than cluster 2. As displayed in Figure 3B, the mortality rate in the group was higher during the first month after discharge as compared with the last 2-month study period.

Finally, the medical complexity profile (cluster 4; 149/761, 19.6%) integrates a higher proportion of elderly patients, mean age of 82.8 (SD 8.7) years, like in cluster 3, but the patients were predominantly male, 83/149 (55.7%). Their mean AMG was higher than that in the other clusters, mean 39.0 (SD 15.6). This group showed the highest percentage of patients undergoing home-based care programs, 96/149 (64.4%). These patients presented marked functional impairment, as well as medical complexity, with poor outcomes in terms of mortality (19/149, 12.8%), readmissions (56/149, 37.6%), and unplanned ER visits (87/149, 58.4%). Both mortality and readmission rates increased after the first week (Figure 3B) and remained constant throughout the study. The group showed the highest health care expenditure during the previous year: €8510 (US $9224).

As depicted in Figure 3A, the 4 clusters presented high rates of primary care visits with minor differences among them. Clusters 3 and 4 clearly showed the highest use of community-based resources (ie, home-based care programs and visits to social workers and intermediate care), whereas clusters 1 and 2 presented a higher use of specialized care resources, outpatient visits, and day hospital visits than the two other clusters.

Discussion

Principal Findings

This study had a 2-fold aim: (1) to assess the risk of mortality and readmission during 90 days after discharge from a tertiary hospital, and (2) to characterize patients' profiles and their postdischarge trajectories during the study period. The primary purpose of the research was to enhance transitional care after discharge, considering both patients' risk level and the specificities of their profiles by assessing different dimensions. A careful analysis discarded any impact on the study results associated with patients' entry point, hospital avoidance program, or conventional hospitalization [17]. Notably, 77.4% (589/761) of the overall study group fell into the top 5% of the regional population-based risk stratification pyramid built-up using the AMG scoring distribution.

Predictive Modeling

According to the state-of-the-art results [9-12], the proposed machine learning strategy used for computational modeling was adequate to achieve acceptable performance of the predictive models assessing mortality and readmission risks during the study period. The study offers a promising scenario for the future use of computational modeling to feed clinical decision support systems. In addition, the results of this research may guide health professionals in refining personalized transitional care strategies with an integrated care approach, fostering vertical integration between specialized and community-based care, and health and social care.

The results indicate that the most relevant predictors fell into the following 5 categories: (1) age, (2) severity of the acute episode, (3) multimorbidity and complexity, (4) functional, and (5) social frailty. Such a pattern of predictors is fully aligned with a previous report [11] on the predictive modeling of patients undergoing the Hospital at Home (HaH) program at HCB between 2011 and 2015. The statistical analysis in this study suggested synergies between the complexity of the baseline patient's condition (ie, AMG score) and the severity of the acute episode (ie, composite Queralt Index) leading to increased risk of postdischarge deleterious events. Accordingly, the 2 indices, AMG and Queralt Index, should be included as covariates in the predictions. Moreover, the MDA analysis of the predictive models indicated that different individual variables might play a significant predictive role in the modeling despite having possible weak collinearities.

Cluster Analysis

The purpose of the cluster analysis was to contribute to defining transitional care pathways fitting the requirements of the identified subsets of patients. In this regard, it seems reasonable to assume that cluster 1, the reference profile, includes candidates for standard patient-centered transitional care. Moreover, this study allowed identifying 2 different care scenarios that are described below.

Patients included in cluster 2, unhealthy lifestyle habits, appear as candidates for preventive strategies that promote healthy lifestyles, including target-oriented cognitive behavioral therapies. Such interventions should be initiated or intensified during the acute episode and continued at the community level with an appropriate follow-up. It is of note that patients within this cluster were predominantly men, with no significant differences in terms of age and medical/social baseline conditions, or severity of the acute episode, as compared with the reference profile. The major distinctive traits were actionable factors, predominantly tobacco smoking and sedentarism but sometimes also alcohol addiction. It should be highlighted that these patients show potentially avoidable high mortality rates during the first week after discharge and potentially avoidable high rates of ER consultations and readmissions across the entire study period.

Clusters 3 (social frailty) and 4 (medical complexity) define a different scenario with common requirements and cluster-specific needs. The 2 subsets include elderly patients, on average 11 years older than clusters 1 and 2, with higher AMG scoring ($\geq P_{98}$). Typical recommendations for these 2 clusters are to focus on care-oriented interventions rather than cure and optimizing home-based services to prevent unplanned ER visits and readmissions. To our understanding, clusters 3 and 4 define an ideal scenario for productive interactions among HaH resources, intermediate care, home-based primary care programs, and social support resources. While patients in cluster 3 deserve specific actions to solve social requirements, interventions in cluster 4 should combine addressing complex medical needs, attention to the social context, and providing care based on people's multidimensional needs.

Strengths and Limitations

This study shows strengths that provide some uniqueness to the analysis. The articulation of the different data sets described in the "Methods" section represented a significant logistic effort to generate multilevel predictive modeling encompassing different key dimensions that ensured a comprehensive patient characterization. Moreover, the study design used all patients' information across the health system during 3 successive periods, namely, (1) the entire year before the admission; (2) the acute episode triggering hospitalization; and (3) the 90 days after discharge, which provided the basis for the 2-step protocol using robust statistical tools that were used in this study. Overall, the predictive modeling approach adopted in this study has an exploratory nature while reinforcing conclusions regarding the main determinants of patient outcomes after hospitalization from our prior studies [11].

However, we also acknowledge 2 main study limitations. First, by design, the research was performed on a relatively narrow segment of patients close to the tip of the population-based risk stratification pyramid. Second, the size of the entire study group and the 4 clusters contained a limited number of patients, which may weaken some of the conclusions.

While accepting that the research represents a valuable contribution toward risk stratification of transitional care, we acknowledge that additional studies will be needed to validate the predictive modeling in larger independent populations. Future implementation research should be planned to transform computational modeling into decision support tools to be sustainably adopted, and dynamically updated, into clinical workstations for routine use across health care tiers.

Value-Generating Strategies for the Management of Multimorbidity

Overview

Despite the aforementioned limitations, our report provides highly valuable information and messages that support well-defined strategies leading to enhanced management of multimorbidity in an integrated care scenario showing a clear potential for value generation. We have identified, however, some challenges, at least at 3 different layers.

Enhanced Transitional Care After Hospital Discharge

As mentioned earlier, this study has an exploratory nature. The results obtained should require further testing and validation using a large independent study group. Such a study is currently ongoing using a large data set from Catalonia (ES) that includes more than 100,000 patients discharged from different providers following a similar study design. The primary aim of the initiative [42] is to assess the impact and site transferability of HaH. Still, it will also allow validation of the lessons learnt in this study, and it should be the basis for future initiatives that aim to test the recommendations for the different clusters of patients identified in this report.

Generating Decision Support Tools for Clinicians

This study aimed to generate decision support tools for clinicians that foster vertical and horizontal integration with a collaborative adaptive case management approach [43]. However, the transfer of the potential of predictive computational modeling approaches, such as the one reported in this research, into decision support tools integrated into clinicians' workstations constitutes a major challenge involving several levels of complexity, namely, (1) use of appropriate predictors ensuring their availability; (2) testing and continuously assessing clinical decision support systems; and (3) design of user-friendly and properly profiled user interfaces. However, we note that recent digitalization initiatives suited for integrated care scenarios [44] may provide relevant novel contributions to the field.

The Generalization of the Approach to Other Use Cases

The current strategy for enhanced transitional care after discharge can be reasonably transferred to the prevention of acute episodes of exacerbation leading to unplanned hospitalizations in high-risk chronic patients. Previous reports have shown the efficacy of preventive interventions [45], as well as proven the need for proper stratification and workforce preparation to generate effectiveness in real-life settings [8]. Our results clearly cover some of the identified needs. However, the most promising scenario is the use of multilevel computational modeling [11,18] for early prediction of target clusters of comorbid conditions (ie, cardiovascular, chronic obstructive pulmonary disease, type 2 diabetes) in susceptible patients. This approach should contribute to the deployment and sustainable adoption of preventive strategies for the management of chronic patients aiming at delaying, or even stopping, their progress toward the tip of the risk stratification pyramid [46,47].

Conclusions

This study combines multilevel predictive modeling and cluster analysis in a population of comprehensively characterized complex chronic patients discharged from a university hospital. The results indicated the potential to predict mortality and morbidity-related adverse events leading to unplanned hospital readmissions. The resulting patient profiles fostered recommendations for personalized service selection with the capacity for value generation. The lessons learnt show a promising scenario for generating clinical decision support tools for clinicians, enabling value generation within an integrated care scenario involving vertical and horizontal integration.

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Data Availability

Data for this study are not publicly available due to patient privacy concerns. The scripts used in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the writing of this paper and approved the final draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Diagnostic codes, baseline characteristics of the clinical groups, and rates of patient encounter with health care professionals. [DOCX File , 65 KB-Multimedia Appendix 1]

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Abbreviations

AMG: Adjusted Morbidity Groups
AUROC: area under the receiver operating characteristic curve
CHSS: Catalan Health Surveillance System
EMR: electronic medical record
ER: emergency room
HaH: Hospital at Home
HCB: Hospital Clínic of Barcelona
MDA: mean decrease in accuracy
MNA: Mini Nutritional Assessment
SE: sensitivity
SP: specificity
TSRI: Table of Social Risk Indicators

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Five years of Hospital at Home adoption in Catalonia: impact and challenges

Rubèn González-Colom, MSc [1], Gerard Carot-Sans, PhD [2,3], Emili Vela, MSc [2,3], Mireia Espallargues, MD, PhD [4], Carme Hernández, RN, PhD [1], Francesc Xavier Jiménez, MD, PhD [5], David Nicolás, MD, PhD [1], Montserrat Suárez, MSc [2], Elvira Torné, MD, PhD [2], Eulalia Villegas-Bruguera, MD, PhD [6], Fernando Ozores, MSc [1], Isaac Cano, PhD [1], Jordi Piera-Jiménez, PhD [2,3,7] and Josep Roca, MD, PhD [1] on behalf of the JADECARE consortium

[1] Hospital Clínic de Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Universitat de Barcelona. Barcelona, Spain

[2] Catalan Health Service. Barcelona, Spain

[3] Digitalization for the Sustainability of the Healthcare (DS3) - IDIBELL. Barcelona, Spain

[4] Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS). Barcelona, Spain

[5] Hospital Vall d'Hebron. Barcelona, Spain

[6] Hospital Dos de Maig. Consorci Sanitari Integral. Barcelona, Spain

[7] Faculty of Informatics, Telecommunications and Multimedia, Universitat Oberta de Catalunya. Barcelona, Spain

Corresponding Author: Rubèn González-Colom
C/ Villarroel, 170, 08036, Barcelona, Spain
+34 686626947
rgonzalezc@recerca.clinic.cat

ABSTRACT

Background: Hospital at home (HaH) was increasingly implemented in Catalonia (7.7 M citizens, Spain) achieving regional adoption within the 2011-2015 Health Plan. This study aimed to assess population-wide HaH outcomes over five years (2015-2019) in a consolidated regional program and provide context-independent recommendations for continuous quality improvement of the service.

Methods: A mixed-methods approach was adopted, combining population-based retrospective analyses of registry information with qualitative research. HaH (admission avoidance modality) was compared with a conventional hospitalization group using propensity score matching techniques. We evaluated the 12-month period before the admission, the hospitalization, and use of healthcare resources at 30 days after discharge. A panel of experts discussed the results and provided recommendations for monitoring HaH services.

Results: The adoption of HaH steadily increased from 5,185 to 8,086 episodes/year (total episodes 31,901; mean age 73 (SD 17) years; 79% high-risk patients. Mortality rates were similar between HaH and conventional hospitalization within the episode [76 (0.31%) vs. 112 (0.45%)] and at 30-days after discharge [973(3.94%) vs. 1112(3.24%)]. Likewise, the rates of hospital re-admissions at 30 days after discharge were also similar between groups: 2,00 (8.08%) vs. 1,63 (6.58%)] or ER visits [4,11 (16.62%) vs. 3,97 (16.03%). The 27 hospitals assessed showed high variability in patients' age, multimorbidity, severity of episodes, recurrences, and length of stay of HaH episodes. Recommendations aiming at enhancing service delivery were produced.

Conclusions: Besides confirming safety and value generation of HaH for selected patients, we found that this service is delivered in a case-mix of different scenarios, encouraging hospital-profiled monitoring of the service.

Keywords*:* Hospital at Home; Implementation Science; Integrated Care; Key Performance Indicators; Multimorbidity.

BACKGROUND

Two decades after the first report assessing hospital at home (HaH) services,[1] this type of care has raised increasing interest as an alternative to inpatient care for selected groups.[2–4] HaH, delivered to entirely substituting the conventional hospitalization, has been associated with several advantages, including patient safety, reduction of nosocomial complications, similar or even better health outcomes compared to conventional hospitalization, high satisfaction levels from both patients and caregivers, and cost savings. In addition, by releasing physical beds, HaH contributes to building capacity for highly specialized care inpatient hospitalization. Moreover, in an integrated care scenario, HaH may become a relevant driver of vertical integration between hospital care and community-based health and social services by enhancing the care continuum.

However, heterogeneities of HaH service profiles are acknowledged, explaining poor comparability among reported experiences.[5] The findings in the literature raise several controversies in different areas, comprising the results of HaH in specific patient groups, modalities of HaH (e.g., admission avoidance or early supported discharge), the most appropriate implementation strategies for HaH services, and the quality-of-care delivery after service adoption.[4] These controversies, and subsequent lack of consensus preclude standardization and continuous quality improvement (CQI) of the service in real-world settings.[4] Therefore, understanding the heterogeneities behind the HaH has become crucial to define service-specific key performance indicators (KPIs) that can be used to ensure quality and sustainability over time and adjust the country-specific regulations of the service.

In Catalonia, a 7.7 million citizens region in North-East Spain with a single public payer (Catalan Health Service),[6,7] HaH was successfully deployed during the 2011-2015 regional Health Plan.[6,8–10] The HaH outcomes from that period were used to establish a specific reimbursement scheme based on all patient-refined diagnosis-related groups (APR-DRG)[11,12] and aimed at consolidating large-scale

adoption of HaH services by hospitals across the region.[13] Based on this early experience of HaH implementation at the healthcare system level, Catalonia was selected as Best Practices site for the service in the "Joint Action on implementation of digitally enabled integrated person-centered care" (JADECARE),[14] a program conducted by the European Union, in collaboration with the OECD to promote the assessment and transferability of innovative services with a care continuum approach.[15]

With the aim to provide an accurate perspective of the impact of this service and aid future implementers in identifying general, context-independent performance indicators to monitor HaH services, we conducted a mixed-methods study that includes a quantitative retrospective assessment of HaH patients' characteristics and outcomes, and a co-creation process with a group of experts in HaH.

METHODS

Overview of study design

The current study combined quantitative and qualitative research methodologies. The quantitative study was a retrospective observational analysis of the characteristics of HaH recipients and health results of hospitalizations occurred between January 1, 2015, and December 31, 2019. To select HaH episodes in the admission avoidance modality, we selected patients with unplanned hospitalizations and less than 24 hours between hospital entry and HaH registration. For the qualitative assessment, we conducted focus groups and surveys[16] with a panel of experts in HaH to interpret the results of the quantitative analysis and generate recommendations for CQI.

The quantitative study was reported according to the STROBE[17] guidelines for observational studies, and the qualitative analysis was reported according to the SRQR[18] guidelines.

Population and data sources

All data used in the quantitative analysis were retrieved from the Catalan Health Surveillance System (CHSS).[19] Since 2011, the CHSS has collected detailed information on the utilization of healthcare resources by the entire population of Catalonia. The CHSS assembles information on the use of healthcare resources across healthcare tiers, drugs, and other billable healthcare costs, such as non-urgent medical transportation, outpatient rehabilitation, respiratory therapies, and dialysis. We screened the CHSS for all episodes of HaH reported in Catalonia during the study period.

The same database was used to create a retrospectively-matched control group of contemporary conventional hospitalizations. The control group was created using a 1-to-1 propensity score matching (PSM)[20,21] and Genetic Matching[22] technique based on GENetic Optimization Using Derivatives (GENOUD)[23] algorithm to check and improve covariate balance iteratively. To ensure the comparability of the matched episodes, we screened contemporary admissions within the same hospital with identical Medicare Diagnosis Related Group[12] category. In addition, the patient's baseline characteristics were characterized and matched using data on demographics (i.e., age and gender), utilization of healthcare resources during the previous year (i.e., hospital admissions, emergency room visits, number of pharmacological prescriptions and the total healthcare expenditure), clinical and social risk factors (i.e., the morbidity burden, using the Adjusted Morbidity Groups[24,25] (AMG) score, and the presence of active diagnoses related with health-related social needs[26]).

The overall comparability of the matched group was assessed using the Mahalanobis distance,[27] and Rubin's B and Rubin's R metrics. Comparability after PSM was considered acceptable if Rubin's B was less than 0.25 and Rubin's R was between 0.5 and 2.[28]

Variables and Outcomes

The baseline characteristics of study patients (i.e., before admission) included age, sex, morbidity burden measured using the AMG score, hospitalizations, emergency room admissions, and expenditure within the past year. Information regarding the HaH episode included the length of stay (LoS) and the complexity of hospitalization, measured using two case-mix tools: the Case Mix Index-APR-DRG v35 (CMI),[29] broadly used for payment purposes, and the Queralt index,[30,31] recently developed by the Catalan Institute of Health and showing higher performance for predicting general hospitalization endpoints. Readmissions in in-hospital settings and visits to the emergency room without the need to discontinue HaH were also considered clinical outcomes of the HaH episode.

Besides the baseline and episode characteristics, we gathered information regarding healthcare expenditure, hospitalizations, and visits to the emergency room within the 30-days after discharge. Expenditure information was obtained from reimbursements by the Catalan Health Service,[32] since no operational costs[33,34] were available for the entire study group. HaH delivery is reimbursed as a specific healthcare service, with case costs estimated based on the APR-DRG categories of the main diagnostic. Other relevant outcomes included mortality, during the hospitalization and 30 days after discharge.

Statistical analysis

Before the analysis, we removed from the databases all the incomplete records, duplicate entries, and outliers with unrepresentative baseline characteristics or anomalous LoS with a Z-value greater than $|3|$.

Since *p-values* tend to drop in large population-based samples, yielding significant differences in most comparisons,[35] we used effect size measures to compare the baseline characteristics of the matched

HaH individuals with their respective controls to establish the impact of the intervention. Cohen's D test was used to determine the effect size in numerical variables; the magnitude of the difference was assessed according to the following ranges: weak (< 0.20), small (0.2 – 0.5), moderate (0.5 – 0.8), large (0.8 -1.3), and very large (>1.3). Cohen's W test was used for categorical variables, with the following ranges used to assess the magnitude of difference: weak (< 0.10), small (0.1 – 0.3), moderate (0.3 – 0.5), and large (>50). We computed 1,000 bootstrap replicates in both scenarios to generate the 95% CI.

Categorical variables were summarized as absolute values and percentages, whereas continuous variables were described by the mean and the standard deviation or the median and the interquartile range as appropriate.

To analyze heterogeneity among hospitals regarding the patient profile, we described the age and the morbidity burden (measured using the AMG index) of HaH patients in each center. We also assessed the inclusion bias of each center by measuring the difference in mean age and AMG index between HaH and conventional hospitalizations admitted for the exact cause within the same hospital. Heterogeneity was also assessed regarding the LoS, the complexity of the episode and the repetition rate among HaH patients. In addition to the descriptive analysis, we addressed heterogeneity by conducting an ancillary cluster analysis using the K-means[36] algorithm, incorporating information on the category of the hospital based on the number of hospital beds and their role in their corresponding health district. The average silhouette[37] method was used to determine the optimal number of clusters.

All the data analyses were performed using R,[38] version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Qualitative assessment

The qualitative study, which followed a grounded theory approach, included two focus group sessions with HaH experts. The first session aimed at interpreting the results obtained in the quantitative analysis described above, whereas the second session sought to discuss the efficiency and value generation of HaH (considering the heterogeneities and challenges of the service) and providing recommendations of core KPIs for CQI of HaH delivery after service adoption. The second session was preceded by the administration of a questionnaire (Supplementary material S1) for assessing the consensus strength. Experts were also provided with the 2020 consensus document aiming at regional standardization of HaH.[13]

The panel of 7 experts included 1-to-2 representatives of the most relevant organizations in implementing or assessing HaH services in Catalonia: two members from the Catalan-Balearic Society of Hospital at Home,[39] two staff members from the Catalan Health Service,[40] one staff member from the Health Quality and Assessment Agency of Catalonia (AQuAS),[41] and two HaH experts from the local JADECARE team. Four out of the seven experts were clinical leaders of different HaH programs. A qualitative research and service design specialist was recruited as a facilitator for planning and leading the expert panel discussions. An extended description of the methodological details is provided in the online Supplementary material S1.

RESULTS

Adoption and characteristics of hospital at home

The CHSS registry recorded 31,901 episodes of HaH among the 27 hospitals offering this service to their catchment populations (**Figure 1**). Overall, the activity of HaH steadily increased during the study

period from 5,185 to 8,086 episodes per year. **Supplemental Material - Table 1S** depicts yearly HaH activity for each individual hospital.

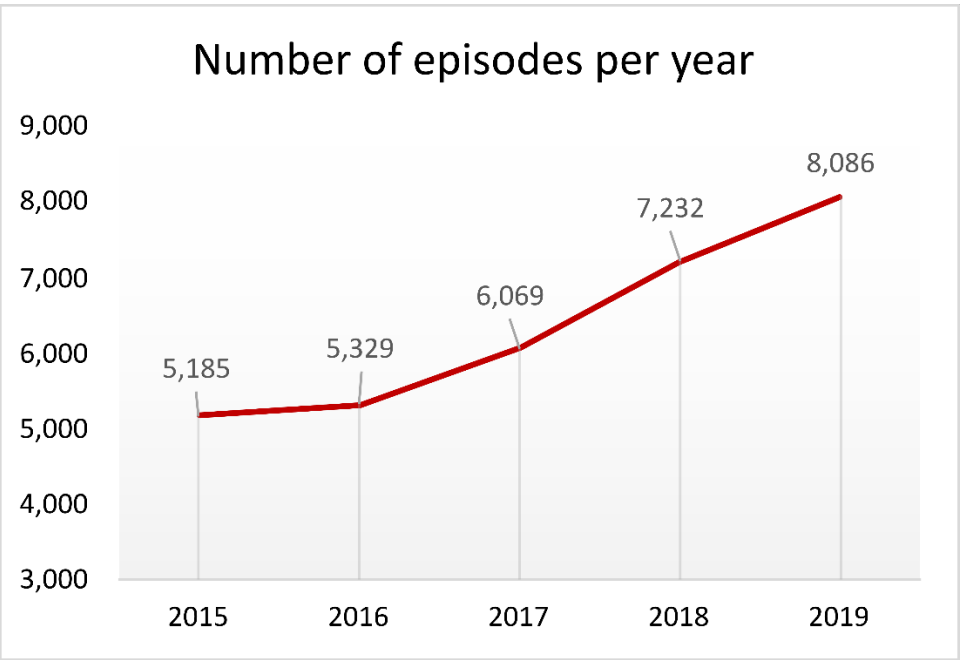

FIGURE 1 – Number of admissions in HaH programs registered in 27 hospitals from Catalonia between 2015-2019.

Table 1 summarizes the main characteristics of the patients included in HaH, distinguishing among three relevant timeframes, covering the patient's baseline characteristics before the admission, the hospitalization episode, and the health outcomes assessed at 30-days post-discharge. On average, HaH patients were older, with a slightly higher prevalence of women. A substantial proportion of HaH episodes corresponded to high-risk patients (i.e., with AMG score above the 95th percentile of the AMG distribution for the entire population of Catalonia). The study group showed a substantial prevalence of health-related social needs associated with housing and economic conditions. Overall, HaH had high use of healthcare resources during the year before the acute episode.

The acute episode showed low mortality rates in HaH and moderate levels of complexity, measured using the Queralt index and CMI. HaH was interrupted in 1,706 (5.35%) cases, with patients requiring re-admission to in-hospital settings. Moreover, 1,339 (4.20%) patients visited the emergency room without the need to discontinue the HaH. The ten leading main diagnoses at discharge in HaH are depicted in **Figure 2**.

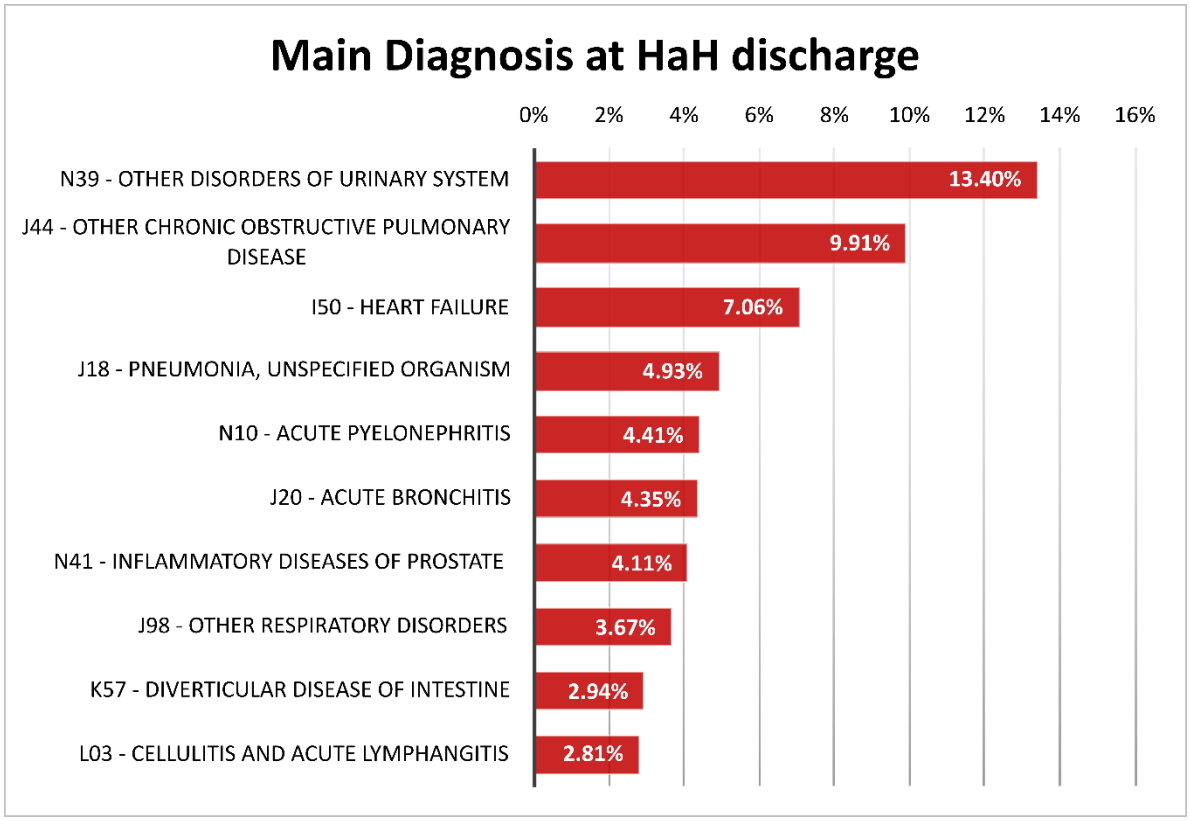

FIGURE 2 – Top 10 of most prevalent main diagnosis at discharge in patients admitted in HaH.

TABLE 1 – Patient's clinical characteristics and outcomes of the intervention of all patients admitted in HaH.

	HaH= 31,901
DEMOGRAPHICS & MORBIDITY-COMPLEXITY	
***Age, mean (sd)**	73.11 (16.73)
***Gender; n (%)**	
Male	15,214 (47.69)
Female	16,687 (52.31)
***AMG, mean (sd)**	29.51 (16.48)
AMG category, n (%)	
Very low risk < P_{50}	266 (0.83)
Low risk [P_{50} - P_{80})	1,769 (5.55)
Moderate risk [P_{80}-P_{95})	4,723 (14.81)
High risk [P_{95}-P_{99})	5,476 (17.17)
Very high risk ≥ P_{99}	19,667 (61.64)
***Patients with HRSN associated to housing and economic conditions, n (%)**	5,063 (15.86)
***Patients with HRSN associated to family and social environment, n (%)**	9,903 (31.03)
Patients receiving palliative care, n (%)	1,437 (4.5)
USE OF RESOURCES 12 MONTHS BEFORE ADMISSION	
***Patients requiring hospital admissions, n (%)**	15,957 (50.16)
***Patients requiring emergency room visits, n (%)**	25,812 (81.14)
***Total Expenditure in €, median (P_{25}-P_{75})**	4,153.4 (1,695.8 - 8424.6)
HOME HOSPITALIZATION EPISODE	
LoS, mean (sd)	8.47 (6.34)
Patients requiring in-hospital all-cause readmissions, n (%)	1,706 (5.35)
Patients requiring emergency room visits without in-hospital readmission, n (%)	1,339 (4.20)
Mortality, n (%)	103 (0.32)
Queralt Index, mean (sd)	28.34 (16.24)
Case Mix Index	0.66
USE OF RESOURCES 30 DAYS AFTER DISCHARGE	
Mortality, n (%)	1,383 (4.35)
Patients requiring hospital admissions, n (%)	3,327 (10.42)
Patients requiring emergency room visits, n (%)	6,136 (19.29)
Total Expenditure in €, median (P_{25}-P_{75})	279.1 (119.3 - 758.7)

*AMG stands for Adjusted Morbidity Groups, HRSN for health-related social needs and LoS for length of stay. * Matching variables.*

Comparisons between hospital at home and conventional hospitalizations

Table 2 compares the characteristics of HaH with its matched control group of patients under conventional hospitalization. Mortality during the acute episode was low and similar between

intervention and controls. The effect size analyses indicated that the severity of the acute episodes, measured using the Queralt index and the CMI, was significantly higher in conventional hospitalizations than in HaH. Also, the LoS was significantly longer in HaH than in conventional hospitalizations. Despite the statistical significance, the differences observed in all endpoints between HaH and conventional hospitalization were associated with a small effect size (i.e., the differences between groups were 0.2 to 0.5 times the SD).

During the 30 days after discharge, mortality rates were low, with no differences between the intervention and the control group. Likewise, re-admissions, visits to the emergency room, and healthcare expenditure were also similar between HaH and controls.

TABLE 2 – Comparison of patients' clinical characteristics and the outcomes of the intervention between HaH and controls.

	Matched HaH n= 24,802	Matched control n= 24,802	Effect size (CI)
DEMOGRAPHICS & MORBIDITY-COMPLEXITY			
Age, mean (sd)	73.15 (16.31)	72.73 (16.29)	-0.03 [-0.04, -0.01]
Gender; n (%)			
Male	11,644 (46.95)	11,984 (48.32)	0.01 [0.01, 0.02]
Female	13,158 (53.05)	12,818 (51.68)	
AMG, mean (sd)	28.36 (15.81)	27.87 (15.82)	-0.03 [-0.05, -0.01]
Patients with HRSN associated to housing and economic conditions, n (%)	2,986 (12.04)	2,935 (11.83)	-0.01 [-0.01, 0.02]
Patients with HRSN associated to family and social environment, n (%)	7,229 (29.15)	7,072 (28.51)	-0.01 [-0.01, -0.03]
Patients receiving palliative care, n (%)	937 (3.78)	621 (2.5)	-0.71 [-0.06, -0.09]
USE OF RESOURCES 12 MONTHS BEFORE ADMISSION			
Patients requiring hospital admissions, n (%)	11,580 (46.83)	11,050 (44.75)	-0.01 [-0.01, 0.03]
Patients requiring emergency room visits, n (%)	19,611 (79.31)	18,427 (74.63)	-0.02 [-0.04, 0.00]
Total Expenditure in €, median (P_{25}-P_{75})	3,697.46 (1,522.40 – 7422.74)	3,399.38 (1380.34 – 7163.79)	-0.01 [-0.01, -0.03]
HOSPITALIZATION EPISODE			

LoS, mean (sd)	8.46 (6.05)	7.09 (5.83)	-0.23 [-0.25, -0.21]
Patients requiring in-hospital all-cause re-admissions, n (%)	1,204 (4.85)	N.A.	N.A.
Patients requiring emergency room visits without in-hospital readmission, n (%)	923 (3.72)	N.A.	N.A.
Mortality, n (%)	76 (0.31)	112 (0.45)	0.01 [0.01, 0.02]
Queralt Index, mean (sd)	28.04 (15.55)	36.69 (21.96)	0.45 [0.40, 0.53]
Case Mix Index	0.65	0.74	0.32 [0.31, 0.34]
USE OF RESOURCES 30 DAYS AFTER DISCHARGE			
Mortality, n (%)	973 (3.94)	1112 (4.5)	0.01 [0.01, 0.02]
Patients requiring hospital admissions, n (%)	2,003 (8.08)	1,625 (6.58)	-0.07 [-0.09, -0.06]
Patients requiring emergency room visits, n (%)	4,109 (16.62)	3,968 (16.07)	-0.01 [-0.03, 0.01]
Total Expenditure in €, median (P_{25}-P_{75})	809.92 (344.65 – 2,276.98)	681.11 (285.89 – 1,786.66)	-0.03 [-0.05, -0.02]
Rubin's B	0.003		
Rubin's R	1.001		

AMG stands for Adjusted Morbidity Groups, HRSN for health-related social needs and LoS for length of stay. The comparability of the matched groups is assessed by Rubin's B and Rubin's R, considered acceptable if Rubin's B is less than 0.25 and Rubin's R is between 0.5 and 2.

Heterogeneities among hospitals

Comparisons among the 27 hospitals showed huge heterogeneities in HaH, in several dimensions, including age at admission (hospital mean values ranging from 62.16 to 83.39 years), multimorbidity-complexity within the 12-month period before admission expressed by AMG scoring (from 19.47 to 38.79), and severity of the acute episode assessed either using the APR-DRG (from 0.54 to 0.87) or the Queralt index (from 13.34 to 42.31). Likewise, similar inter-hospital variability was also observed in all other two variables analyzed: LoS (from 4.8 to 14.7 days) and percent of repeaters, indicating patients with more than one HaH episode during the study period (from 8.8% to 33.6%).

Qualitative assessments and expert recommendations

The full set of results of the quantitative analyses (**Supplemental Material - Figures 1S-8S** and **Tables 2S-4S**) were presented to the panel of experts for discussion and interpretation. A detailed list of highlights from the two qualitative sessions is provided in the Supplementary Material.

Overall, the experts agreed that HaH is safe and provides value to the healthcare system, with similar health outcomes than conventional hospitalization, and positive impacts on patients' and professionals' experience. HaH may also result in savings associated with fewer personnel and structure requirements.[4,42] Nevertheless, there was consensus regarding the limitations of case-mix tools currently used (e.g., APR-DRG) to fully reflect the care needs (and, therefore, actual costs) of HaH patients. The experts agreed that new and more accurate case-mix tools should be developed, and studies based on analytical accounting should be conducted to appropriately quantify economic impact of HaH.

The experts agreed that heterogeneity in patient profile and outcomes was expected and identified three important sources of this heterogeneity: i) maturity of HaH teams (i.e., mature teams tend to admit older and more complex patients), ii) hospital strategies to use HaH in a sub-set of patients with specific diagnoses, and iii) local ecosystem (e.g., lack or availability of certain integrated care services in the area).

Considering the exhaustive list of KPIs provided in the local 2020 recommendation document and the potential heterogeneities and challenges of this service identified in the current study, the group of experts created and selected a set of 16 KPIs that are generalizable to other healthcare system environments for continuous monitoring of HaH quality (**Figure 3**).

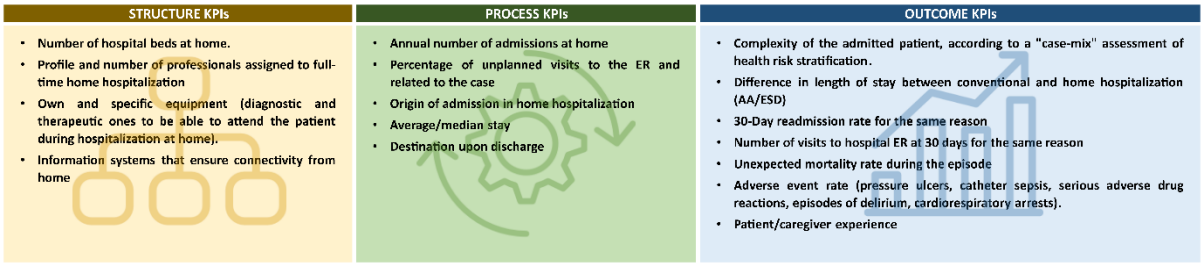

FIGURE 3 – List of proposed KPIs selected from the 2020 document on regional HaH standardization[13].

DISCUSSION

The mixed-methods approach adopted in the current research contributed to enriching the interpretation, and enhancing the potential for generalization of the results, of the retrospective quantitative assessment of consolidated HaH delivery in 27 different hospitals of the same healthcare system. The outcomes observed in HaH were aligned with relevant reports[1–4,43–47] fully supporting the healthcare value generation of HaH, as well as its potential for capacity building of hospital beds and contributions to the care continuum. Overall, the study outcomes encourage further expansion of the regional adoption of HaH, following the recommendations generated by the group of experts.

The panel of experts fully agreed with the need for continuous long-term monitoring of CQI after successfully adopting the service. In Catalonia, a consensus document for monitoring HaH services identified a comprehensive list of resources needed for adequate HaH service delivery and nearly 70 KPIs suited to the local characteristics and the type of data collected by the information systems of the Catalan Health Service.[13] In the current work, the experts identified a list of 16 essential KPIs to be considered for monitoring HaH services regardless of the characteristics of the healthcare system.

One of the intriguing features of HaH is the capacity of this service to save costs. Thus, although most studies appear to support the idea that HaH saves hospitalization costs, reviews addressing this issue

have warned about the low quality and potential biases associated with the assessment of this outcome.[48,49] The experts participating in qualitative sessions reached two important conclusions in this regard. First, this question cannot be fully answered without analytic accounting approaches. Owing to the relative lack of maturity and high heterogeneity of HaH services, the reimbursement approach to cost assessment does not appropriately reflect the actual resource use. In our environment, some hospitals have adopted analytical cost assessments that allow an accurate assessment of costs.[33,34] However, the cost assessment in most of them had to be approached from a reimbursement perspective, limiting the strength of conclusions in this regard. Second, the experts agreed that case-mix tools typically used (and generally accepted) for reimbursement purposes (e.g., DRG) are relatively well suited to reflect the care needs of individuals admitted to conventional hospitalization but fail to do so in HaH. The expert group agreed that the implementation of analytical accounting should be extended to all hospitals to build up adequate reimbursement strategies. This approach would contribute to enhancing investments in healthcare innovation that, in turn, generate efficiencies both at hospital and health system levels. Analytical accounting would also provide a rationale for specific reimbursement plans favoring hospital-profiled service delivery. Alternatively, more accurate risk stratification models recently developed[30] should be explored as tools for a complexity-driven approach to reimbursement of HaH services.

The observed heterogeneities are consistent with disparities found in the literature.[2–4] However, the assessment of multiple hospitals within the same healthcare system allowed us to investigate these differences regardless of the healthcare structure, payment model, cultural constraints and/or type of professionals involved that may vary between countries and systems. Aside from the type of hospital, the experts identified other sources of heterogeneity that may arise when deploying HaH at the healthcare system level. These sources of heterogeneity include strategic decisions at the hospital

level (e.g., use HaH to boost a particular type of service without compromising the number of beds) or contextual service availability (e.g., use HaH to counteract the lack of intermediated care services in a given area). Countries willing to deploy HaH across the healthcare system should be aware of these potential heterogeneities when planning assessment and payment models.

Study limitations

We acknowledge some intrinsic limitations of the current study, mostly related to the use of registry data without information on details of both complexities and clinical incidences during HaH episodes. Despite the application of an accurate matching strategy between intervention and control groups, such as the clinical decision triggering patient admission to HaH instead of conventional hospitalization, which was poorly registered in the records. Moreover, the lack of analytical costs was also an important constraint assessment of the potential of value generation of HaH, as well as to explore the impact of reimbursement policies on hospitals' heterogeneities. As described above, all economic calculations in the current study were based on expenditure data.[32] However, we believe that the characteristics of the study design and the availability of clinical and analytical data from the area[33,34] positively influenced the analyses carried out in the current research and facilitated recommendations for enhancing the quality of service delivery that can be generalized to other integrated care services.

CONCLUSIONS

The current study confirms safety and value generation of HaH. The service efficiently reduced hospital occupation and showed high potential to foster continuity of care, which encourages further expansion of the program at regional level.

We found that HaH is delivered in a heterogeneous case-mix of healthcare scenarios that may also result in heterogeneous outcomes. Therefore, aside from general key performance indicators, hospital-profiled indicators should be established to monitor for CQI of the service after adoption.

Our analysis and highlights of the panel of experts may help policymakers to anticipate features of this service in the advent of a system-wide implementation of HaH. Likewise, the recommendations from a panel of experts provided in this study can be used as basis for planning HaH monitoring in other countries.

LIST OF ABBREVIATIONS

AMG – Adjusted Morbidity Groups.

APR -DRG – All-Patient Refined Diagnosis Related Groups.

CHSS – Catalan Health Surveillance System.

CMI – Case Mix Index.

CQI - Continuous Quality Improvement

LoS – Length of Stay.

HaH – Hospital at Home.

KPI – Key Performance Indicator.

PSM – Propensity Score Matching.

DECLARATIONS

Ethics approval and consent to participate

The Ethical Committee for Human Research at Hospital Clinic de Barcelona approved the study on September 8, 2021 (HCB/2021/0768) in the context of the EU project "Joint Action on implementation of digitally enabled integrated person-centered care" (JADECARE). All the data were handled in compliance with the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union. Although no interventions out of routine care were applied, the study was conducted according to relevant legal requirements (Biomedical Research Act 14/2007 of July 3).

The Ethical Committee for Human Research at Hospital Clinic de Barcelona waived the need to obtain informed consent for the collection, analysis and publication of the retrospectively obtained and fully anonymized data for this non-interventional study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

JR, IC, and JPJ designed the study and directed the project. RGC led the execution of the quantitative analysis, processed the experimental data, performed the statistical analysis and created the figures. EV generated the study database and provided statistical support. GCS led the execution of the qualitative research, developed the study surveys, and summarized the conclusions of the focus groups. FO designed and moderated the focus groups. ME, CH, FXJ, DN, MS, ET, EVB provided data and insightful information to the study. The manuscript was first drafted by RGC, JR, and GCS and thoroughly revised by EV, ME, CH, FXJ, DN, MS, ET, EVB, FO, IC, and JPJ. All authors approved the final version of the manuscript and are accountable for all aspects of the work in ensuring its accuracy and integrity.

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ARTICLE 4

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Toward adoption of health risk assessment in population-based and clinical scenarios

Ruben Gonzalez-Colom[1], David Monterde[2,3], Roberta Papa[4], Mart Kull[5], Andres Anier[5], Francesco Balducci[4], Isaac Cano[1], Marc Coca[3,6], Marco De Marco[4], Giulia Franceschini[4], Saima Hinno[5], Marco Pompili[4], Emili Vela[3,6], Jordi Piera-Jiménez[3,6,7], Pol Pérez[6] and Josep Roca[1] on behalf of the JADECARE consortium

[1] Hospital Clínic de Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Universitat de Barcelona. Barcelona, Spain

[2] Catalan Institute of Health. Barcelona, Spain

[3] Digitalization for the Sustainability of the Healthcare (DS3) - IDIBELL. Barcelona, Spain

[4] Regional Health Agency, Marche Region. Ancona, Italy

[5] Viljandi Hospital. Viljandi, Estonia

[6] Catalan Health Service, CatSalut. Barcelona, Spain

[7] Faculty of Informatics, Telecommunications and Multimedia, Universitat Oberta de Catalunya. Barcelona, Spain

Corresponding Author: Rubèn González-Colom
C/ Villarroel, 170, 08036, Barcelona, Spain
+34 686626947
rgonzalezc@recerca.clinic.cat

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ABSTRACT

Introduction: Health risk assessment (HRA) strategies are cornerstone for health systems transformation toward value-based patient-centred care. However, steps for HRA adoption are undefined. This report analyses the process of transference of the Adjusted Morbidity Groups (AMG) algorithm from the Catalan Good Practice to the Marche region (IT) and to Viljandi Hospital (EE), within the JADECARE initiative (2020-2023).

Description: The implementation research approach involved a twelve-month pre-implementation period to assess feasibility and define the local action plans, followed by a sixteen-month implementation phase. During the two periods, a well-defined combination of experience-based co-design and quality improvement methodologies were applied.

Discussion: The evolution of the Catalan HRA strategy (2010-2023) illustrates its potential for health systems transformation, as well as its transferability. The main barriers and facilitators for HRA adoption were identified. The report proposes a set of key steps to facilitate site customized deployment of HRA contributing to define a roadmap to foster large-scale adoption across Europe.

Conclusions: Successful adoption of the AMG algorithm was achieved in the two sites confirming transferability. Marche identified the key requirements for a population-based HRA strategy, whereas Viljandi Hospital proved its potential for clinical use paving the way toward value-based healthcare strategies.

Key words: Health Risk Assessment, Adjusted Morbidity Groups, Integrated Care, Predictive modelling.

BACKGROUND & OBJECTIVES

Health risk assessment (HRA) is a comprehensive approach that entails identifying, evaluating, and prioritising potential health risks and vulnerabilities for individuals and populations and identifying possible measures to reduce or mitigate their effects.

Deploying appropriate HRA strategies is a cornerstone for population risk stratification and constructing the corresponding population risk pyramid. It has become essential for informing health policy decisions, allocating resources, benchmarking, implementing preventive strategies and selecting appropriate healthcare services(1–3). Likewise, in the clinical arena, HRA is a building block for generating predictive models to support clinical decision-making(4,5). Indeed, population-based, and clinically-oriented HRA approaches are complementary elements needed to efficiently adopt integrated patient-centred care strategies. Deploying and adopting well-planned HRA strategies constitute an obligatory step toward the maturity of precision medicine(6).

Moreover, the momentum propitiated by the continuous progress in digital technologies for data capture and management, artificial intelligence and the advances in medical sciences are shaping novel and stimulating scenarios for health promotion and care and positioning predictive medicine at the forefront(7–9). Despite the promising potential of HRA, there is a noticeable gap between its benefits and its current application, attributed to several limitations, including the utilisation of suboptimal risk assessment tools, the insufficient engagement of health professionals, the application of ineffective or inexistent deployment strategies, and unresolved ethical and regulatory issues(10,11).

The Joint Action on implementation of digitally enabled integrated person-centred care (JADECARE)(12), an ongoing initiative launched to face the challenges of the transformation of health in the European Union, has included HRA as a strategic block to transfer from four original Good Practices (oGPs) to other twenty-one European regions participating as Next Adopters (NAs).

The central aims of JADECARE are to reinforce the capacity of health authorities for successfully addressing all the crucial aspects of health system transformation, in particular, the transition to digitally enabled, integrated, person-centred care, and to support the best practice transfer from the oGPs to the corresponding NAs. The current integrated case reports:

1) The evolution of the HRA strategy in one of the JADECARE oGPs (i.e., Catalonia, ES) from 2011-2020.
2) The description of the implementation process followed to transfer a population-based risk assessment tool from Catalonia to two NAs: Marche region (IT) and Estonia (EE).
3) The lessons learnt in the form of recommendations to foster the adoption of enhanced health risk assessment across the EU.

The report aims to identify key barriers and facilitators for effective adoption across Europe of population-based health risk assessment at the regional/country levels and formulate proposals facilitating the articulation between population-based and clinically-oriented HRA.

DESCRIPTION OF THE CARE PRACTICE

HRA IN CATALONIA: 2011-2020

The 2011-2015 Catalan Health Plan(13) fostered key achievements in digital health transformation, the progressive implementation of person-centred integrated care services and the adoption of an initial population-based HRA strategy. This transitory HRA strategy was based on the commercial solution "Clinical Risk Groups" (CRG)(14) from vendor 3M™ and oriented toward modelling healthcare costs for resource allocation and benchmarking.

This initial HRA strategy laid the groundwork for a population-based risk stratification program with a case-finding approach focused on preventing adverse health events, managing high-risk chronic patients, and early detecting end-of-life patients(15,16). This HRA approach acknowledged the close relationship between frailty and multimorbidity while recognizing their distinct nature as independent risk factors. Additionally, it introduced specific scales for the evaluation of each factor individually. The clinical complexity level was assigned based on multimorbidity scoring, transitively using CRGs, and the clinical judgment of primary care physicians. Complex patients were classified into two groups: complex chronic patients (CCP), approximately 4% of the population, and advanced chronic patients (ACP), representing approximately 1% of the population with limited life expectancy. Specific community-based management plans, aiming at integrating health and social care, were defined for these two categories of patients(15). An overall description of the care model for people with frailty and multimorbidity in Catalonia, tested during the 2011-2015 Health Plan, has been recently reported in (17).

The need for refining the assessment of the multimorbidity burden triggered the creation of the Adjusted Morbidity Groups (AMG)(18,19), a new morbidity grouper that reflects patients' disease burden in terms of the number and complexity of concomitant disorders through a disease-specific weighting deduced from statistical analysis based on mortality and the utilisation of healthcare resources. The AMG tool was jointly launched in 2015 by the Spanish Health Ministry and the Catalan public health commissioner (CatSalut). A significant achievement was the development of a dashboard to monitor the population's multimorbidity burden and the use of healthcare known as Modules for Monitoring Quality Indicators ("Moduls pel Seguiment d'Indicadors de Qualitat", MSIQ)(20), which generates and displays customised key performance indicators (KPIs) with aggregated data to inform health policy decisions, benchmarking, and governance.

On the clinical side, the AMG scoring of the patient is currently displayed in the workstation of the primary care physicians and the shared clinical history(21) as a support tool in the clinical setting.

During the 2016-2020 Catalan Health Plan(22), the utilisation of AMG for HRA purposes was validated in different regions of Spain, covering a population of approximately 38 million citizens and showing good transferability in all cases(23). This period witnessed three significant advancements in Catalonia's HRA strategy:

1) The execution of several studies testing the contribution of the AMG in different HRA settings, such as the identified risk factors during the SARS-CoV-2 pandemic(24,25), the refinement of tools for resources allocation(26–29), the analysis of the effect of the multimorbidity burden in patients with chronic obstructive pulmonary disease (COPD)(30), and assessing the use of AMG in complex clinical predictive models for short-term clinical outcomes predictions after hospital discharge(4,5).

2) The creation of the Catalan Health Information System Master Plan published in 2019(31) established the basis for the transformation to a new digital-health paradigm based on a knowledge-driven platform and adopting the Open-EHR standard as a reference.

3) The development and internal validation of the Queralt indices(32,33) to characterise the complexity of hospitalisation episodes, combining information on the principal discharge diagnosis, pre-existing comorbidities, in-hospital complications and all the procedures performed during hospitalisation.

Figure 1 depicts the information required from NAs to use the AMG, the outputs obtained, and the key uses of AMG.

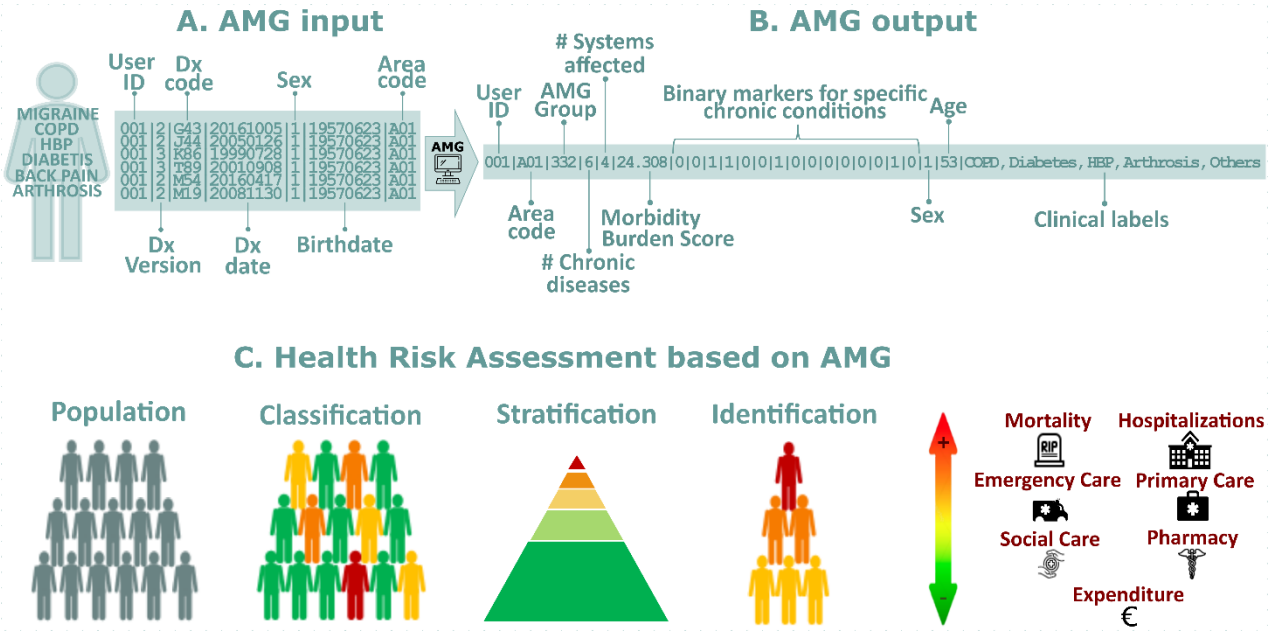

Figure 1- Panel A - AMG input: *Required input variables to compute AMG****; Panel B – AMG output:*** *Output variables of the AMG algorithm. *Binary markers (presence/absence) of 15 chronic conditions (from left to right): diabetes mellitus, heart failure, chronic obstructive pulmonary disease, high blood pressure, depression, HIV/AIDS, chronic ischemic heart disease, stroke, chronic kidney disease, cirrhosis, osteoporosis, arthrosis, arthritis, dementia, chronic pain;* ***Panel C– Health Risk Assessment based on AMG:*** *The AMG scoring allows for three key actions:* ***Classification:*** *The population is categorised into specific groups based on their morbidity statuses, such as healthy, pregnancy and labour, acute disease, chronic disease in 1-4 systems, or active neoplasia, which are also divided into five degrees of severity.* ***Stratification:*** *Each individual can be assigned a complexity score that reflects the care needs that people may have based on their health problems.* ***Identification:*** *Individuals with specific major chronic health problems can be identified, which helps track people with more complex care needs.*

PRE-IMPLEMENTATION (October 2020 – September 2021)

Within JADECARE, the AMG was transferred to the Marche region and Estonia. The Marche region has a regionally based healthcare system, providing universal coverage to 1,480,839 citizens of which 25.4% are 65 years and older. Life expectancy is of 81 years for men and 85.2 for women. In comparison, Estonia has compulsory solidarity-based health insurance, financed by the health insurance budget through the Estonian Health Insurance Fund, covering 1,322,765 citizens, 29.0% aged 65 years and older. Life expectancy at birth is 72.8 years for men and 81.4 for women.

In Estonia, the initial implementation site for the AMG transfer was chosen was Viljandi County with approximately 30 general practitioners and one general hospital providing specialist care for around 50,000 inhabitants.

Table 1 describes the context and the trigger that motivated the adoption of the AMG in the Marche region and Estonia, alongside the local aims of each NA and the main challenges identified by the oGP leaders. Specific Local Action Plans were designed to fulfil the needs of each NA, as reported in detail in the **Supplementary Material**. The pre-implementation phase concluded once the implementation feasibility study was successful in each site.

Table 1 - Summary of the pre-implementation process, including the context and trigger, the aims, the baseline situation, and the challenges faced in the Marche region and Estonia.

	Marche region	Estonia
Context and trigger	1) The high burden of non-communicable diseases (NCDs) and the need for more efficient management of affected patients. 2) The need for support decision-making in healthcare services and policies and analyse the utilisation of healthcare resources in alignment with national regulations defining population stratification as a prerequisite for healthcare planning (e.g. National Plan for Chronicity, 2016; National Decree on standards and organisation of community services, 2022).	1) Digital infrastructure to support integrated care was piloted in Estonia with minimal impact and long-term traction, and there was not yet region-wide coverage. Likewise, social and healthcare service coordination is in an early phase. 2) The different and non-aligned payment schemes for hospital and ambulatory care impact incentivising the transformation from case-based care to a population health-oriented care model with social services integration to care. 3) Risk stratification and case-finding tools were needed to facilitate high-risk patient identification for regional care-management and service integration.
Aims	1) To test and adopt the AMG population stratification algorithm, suitably adapted to the regional context and the available health data. 2) To display a regional dashboard for health policy purposes, benchmarking, and decision-making processes.	1) To develop an integrated clinical program to prevent hospitalisations and target elders with concomitant chronic diseases and social health determinants. 2) To adopt the AMG for service selection. 3) To leverage the acquired expertise and progress towards innovative value-based reimbursement models, aiming to establish Viljandi Hospital as an accountable care organization. 4) To escalate the adoption of AMG for population stratification at country-level.
Baseline situation	The Regional Healthcare Administrative Databases (HADs), used at regional and national levels to monitor healthcare system expenditures and performance, gather information on healthcare services provided to citizens (e.g., hospitalisations, emergency-urgency, homecare, exemption codes, etc.). Common standard models and coding systems, such as DRGs(34) and ICD-9-CM(35), are used across all regions. However, each HAD has its unique structure, unit level, content, and rules for data input. Data linkage across HADs is facilitated using a unique anonymised patient ID code.	The Estonian Health Insurance Fund claims database was used for model data input. In Estonian universal healthcare and single payer model this database entails almost all medical care claims in the country. The database follows a single standard with ICD-10-CM(36) coding, DRGs. Data linkage and access was granted though ethics committee approval and is not easily available as standard. Data was analysed in anonymised format using unique patient ID codes. All AMG analyses were performed by the regional medical authorities under the ethics committee approved application with support from the oGP.
Challenges	1) To fulfil the initial feasibility test. 2) To overcome potential technical problems in dynamically assembling the dataset required to feed the AMG algorithm using heterogeneous data sources. 3) The site showed an explicit limitation in the use of HRA tools due to the GDPR-related legislation at the Italian level regarding the secondary use of health data.	1) To fulfil the feasibility test. 2) To ensure firm commitments of the Estonian government (Ministry of Social Affairs), as well as getting traction and commitment by the Estonian Health Insurance Fund to the project. 3) To overcome potential technical problems in dynamically assembling the dataset required to feed computational modelling for health risk stratification.

Results of the feasibility analysis

To assess the transferability of the AMG tool, independent feasibility tests were conducted in each of the adopting regions. To perform the AMG feasibility analysis in the Marche region, fully anonymized information on disease diagnostics from 2015 to 2019 was extracted from three independent databases: the hospital admissions, the emergency department, and the exemption codes for chronic and rare diseases databases. Integrating all the medical information resulted in 5,939,199 diagnostic codes associated with 1,367,181 citizens. In Estonia, the AMG feasibility study was conducted with 25,930 diagnostic codes related to 4,765 citizens treated in Viljandi Hospital in 2018.

The feasibility analysis evaluated the comprehensiveness of the clinical information accessed and the discrimination capacity of the AMG algorithm to identify high-risk individuals allocated in seven morbidity groups: healthy, pregnancy, acute disease, 1 or 2-3 or ≥ 4 chronic diseases, and active neoplasia.

When evaluating the feasibility study, it is imperative to consider the databases' dual approach and purpose. The Marche database is a population health database(37), built for informing health policies, benchmarking, and supporting decision-making processes. On the other hand, the Viljandi database follows a population medicine approach(37), assembling patient registries to screen candidates for a clinical program geared towards preventing hospitalisations for elderly patients with concomitant chronic conditions.

The feasibility tests were deemed successful if the following conditions were met:

1)The algorithm effectively discriminated the patients with different risk profiles within specific age and gender groups, especially in older individuals more susceptible to multimorbidity.

2)The algorithm distinguished between the seven AMG disease groups. It's worth noting that the relative frequencies of these groups may differ depending on the database's nature.

3)The results showed a positive correlation between the clinical complexity of the AMG disease groups and the disease burden evaluated using the AMG Morbidity Burden Index.

The feasibility analysis results are shown in **Figure 2**. In **Panel A**, the distribution of the five subgroups of complexity is depicted according to age and gender. As expected, the demographic characteristics of the population treated in Viljandi utilised in this feasibility study differ from the Viljandi county's population. Overall, the AMG algorithm proficiently distinguished patients with varying risk profiles in specific age and gender categories. **Panel B** shows the distribution of the seven AMG morbidity groups' complexity level, represented by the average Morbidity Burden Score. In the Marche region and Estonia, roughly 50% of the population suffers at least one chronic disease and 20% developed multimorbidity, while 5% has an active neoplasm. Notably, the analysis of the population treated in Viljandi Hospital revealed a higher fraction of

citizens with acute morbid conditions due to the hospital nature of the database. When comparing the relative distribution of AMG disease groups between the adopting regions and Catalonia, notable disparities emerge in terms of the prevalence of patients with multimorbidity. These variations can be attributed to the availability of primary care registries, which is a condition exclusively fulfilled in the Catalan context. This underscores the critical importance of integrating health data from diverse levels. The complexity of the disease groups and the AMG Morbidity Burden Score showed a strong positive correlation, being slightly higher in the Marche region due to the exhaustivity of the diagnostic records at different healthcare levels and the increased length of the study period.

Based on the assessment made by the oGP specialists and the findings presented, it was determined that the databases generated by both adopters, the Marche region and Estonia, were mature and ready to expedite the implementation of the AMG.

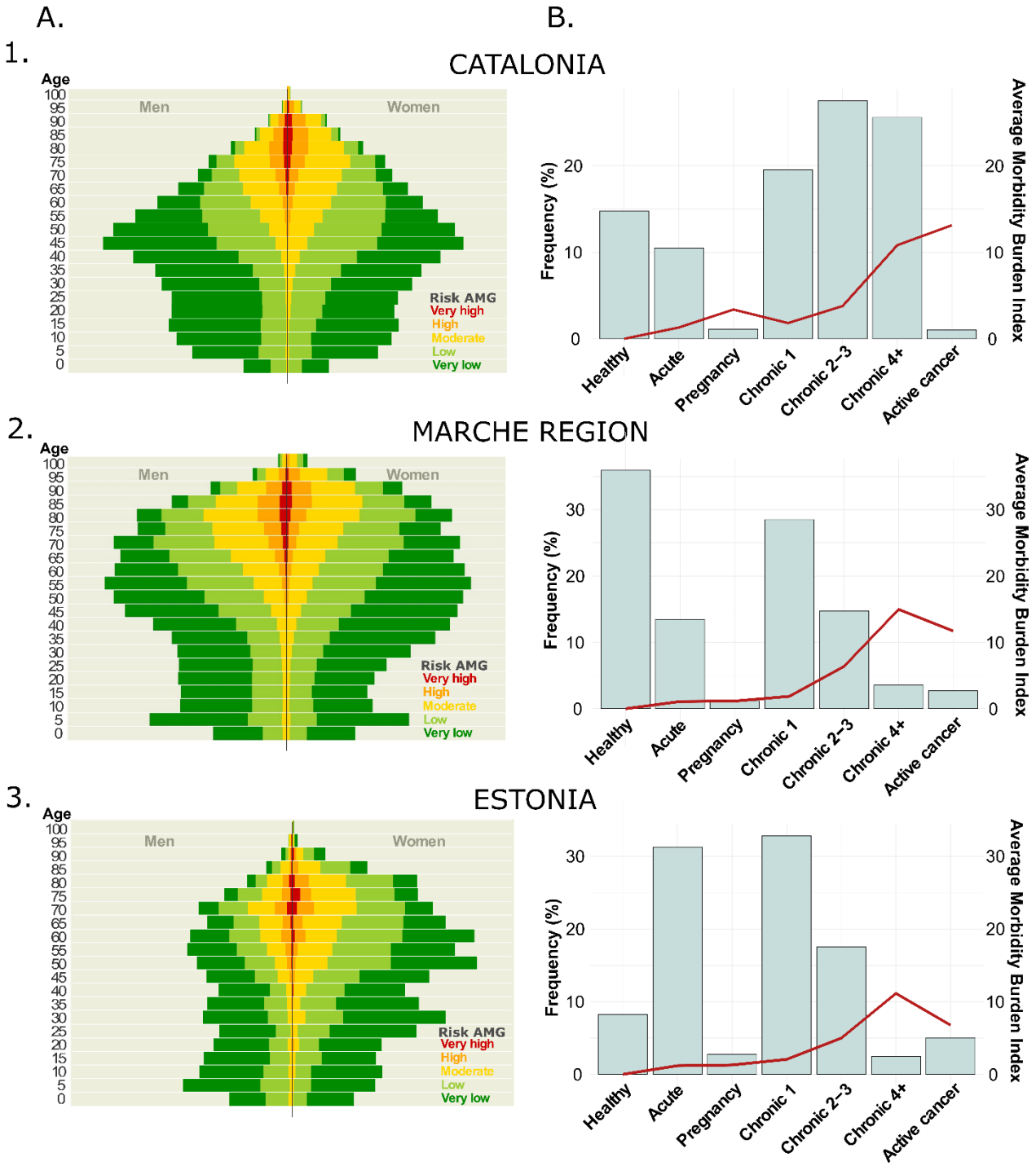

Figure 2- Results of the feasibility analysis: *in Catalonia (1) and the adoption regions, Marche Region (2) and Estonia (3).* ***Panel A - AMG risk distribution:*** *itemised by age and gender;* ***Panel B – AMG disease groups:*** *distribution of the seven AMG morbidity groups (bars): healthy, pregnancy, acute disease, 1 or 2-3 or≥ 4 chronic diseases, and active neoplasia, and their average Morbidity Burden Score (line).*

IMPLEMENTATION (October 2021-January 2023)

On October 2021, the Local Action Plans (LAPs) in Marche and Estonia were already available, and the corresponding NA Working Groups were prepared to undertake two Plan-Do-Study-Act (PDSA) cycles(38).

The details of the PDSA cycles are reported in the **Supplementary Material**. A major midterm milestone of the implementation phase was the HRA Thematic Workshop, held in Viljandi Hospital on 14-15 June 2022. The workshop delimitated the bases for deploying population-based HRA strategies focused on AMG and the Queralt indices. A recording of the session can be found in the **Supplementary Material**.

Marche

Implementation achievements - 1) dynamic regional dataset preparation merging information from different existing data sources, 2) data cleaning and automatization of the generation of the regional dataset, 3) elaboration and analysis of the risk assessment pyramid at regional level demonstrating association between GMA scoring and local use of resources, 4) preparation of the logistics for local sustainability of the setting; and 5) design of the regional dashboard to facilitate regional health governance. The technicalities of the implementation and the assessment of the implementation process will be reported in a forthcoming paper.

Sustainability Action Plan - 1) to complete the integration of the tool into the regional IT infrastructure, adding further healthcare databases and defining supportive actions to improve the quality and completeness of healthcare data. 2) to implement the dashboard in computational, technical, and graphical terms, adding maps aimed to visualize healthcare services adjusted to social-health care planning regulations and integrating it in the regional IT infrastructure. 3) to promote the use of the HRA tools by regional and clinical managers and share our experience for the discussions on the secondary use of health data.

Estonia

Implementation achievements – 1) Generating a protocol, already approved by the local Ethics committee for a pragmatic randomized control trial (n= 1000), to test effectiveness and value generation of an integrated care intervention to prevent hospitalizations targeting community-based patients with high-risk of admissions and enhancing transitional care post-discharge to reduce early readmissions (PAIK 2022-2025). 2) AMG will be used as inclusion criteria and to modulate the characteristics of the intervention and the Queralt indices will be employed to characterize hospitalization episodes contributing to personalize transitional care after discharge.

Sustainability Action Plan - 1) to successfully execute the PAIK 2022-2025 project using AMG and Queralt indices as risk assessment tools.2) to generate sound proposals for innovative reimbursement modalities.3) to achieve country-wide scalability of risk prediction approaches based on AMG and Queralt.4) to initiate a debate on the scalability of integrated care services involving innovative reimbursement modalities in Estonia.

PERSPECTIVES BEYOND IMPLEMENTATION

The section describes the status of the HRA in Catalonia and briefly reports the overarching analysis of the process of transference to the two NAs, leading to recommendations for the generalisation of the case practice at the European level.

Evolution of the Catalan oGP during JADECARE

The 2020 Catalan Health Information System Master Plan has sparked ongoing technological innovations that offer significant opportunities in predictive modelling aiming at supporting clinical decision-making for healthcare professionals and provide patients with decision support tools to empower self-management(39–41) . Also, specific initiatives have been launched to enhance transitional care and reduce early readmissions after hospital discharge(4,5). Moreover, efforts are devoted to the practicalities of adoption of such predictive modelling tools in real-world settings, involving: 1) training and continuous evaluation of clinical decision support systems embedded into integrated care services, 2) pragmatic use of implementation science tools to foster engagement of health professionals, and 3) ethical and regulatory aspects including refinement of the regional PADRIS program(42) for secondary use of health data.

In Catalonia, research, and innovation in HRA are currently focused on two target areas. Firstly, to address unmet needs associated with enhanced predictive modelling considering four potential sources of variables: 1) clinical information, 2) registry data with a population health approach, 3) patients' self-reported information (PROMs and PREMs) and self-monitoring data, and 4) biomedical research data, as defined in (1). A key learning from the different studies done using the AMG algorithm since 2015 is that multimorbidity has a central explanatory role in health risk assessment, more than classical variables like age, which prompts the inclusion of the AMG scoring as a fix covariate in multisource predictive modelling.

A second field of research interest is the potential evolutions of AMG incorporating information on patients' disease trajectories(43,44). Although these novel computational developments are still far from being applicable in clinical settings, they present exciting prospects or precision medicine in patients with NCDs.

Overarching analysis

The case practice identifies the process of transference and adoption of the AMG algorithm and a site-tailored dashboard using aggregated data as the two key components necessary for establishing fundamental HRA functionalities.

While Marche adopted a population-health approach considering the use of healthcare resources from the entire geographical area, Viljandi Hospital in Estonia implemented a more limited regional population-medicine orientation with a single hospital as a local integrator and lead in a regional health improvement

initiative. As depicted in **Figure 2**, the differences in terms of sources and composition of input data had significant impacts on the distribution of AMG scoring among Catalonia (**Figure 2** - **Panel 1**, population-health data from all healthcare tiers), Marche (**Figure 2** - **Panel 2**, population-health data with poor representation of primary care) and Viljandi Hospital (**Figure 2** - **Panel 3**, population-medicine approach based on hospital information). Accordingly, population-health databases, as those used in Marche region, must comprise information on disease diagnostics from all individuals within the region, gathered from various tiers of the healthcare system (e.g. primary care, community, hospital, etc.). It is expected to find a significant fraction of the healthy population and cases with transitory health problems, both concentrated in the youngest fraction of the population. The remaining population is expected to suffer at least chronicity and many of them to develop multimorbidity; among them is expected to find a small fraction of complex chronic patients.

On the other hand, if the analysis is conducted following a population medicine approach, as done in Viljandi, the sample should be representative of the population treated at the hospital during the period assessed, both in terms of demographic parameters and the clinical profiles of the patients. In light of this, a highly biased population is expected to be older than the hospital's catching area average. Also, a substantial increase in the frequency of patients experiencing mainly acute and chronic conditions is anticipated.

Consequently, the composition of the input datasets plays a crucial role in modulating both purposes and suitability of adopting HRA strategies. In the current case practice, Marche's approach was adequate to cover health policy aspects, resources allocation, benchmarking, and governance at the regional level, even though limitations due to GDPR constraints at the Italian level should be acknowledged. In contrast, the HRA orientation adopted by Viljandi Hospital was beneficial in the design process of the PAIK2 protocol (2023-2025), aiming at generating evidence of the effectiveness of an integrated care intervention to prevent hospitalisations in high-risk patients and transitional care. It is of note that the process of developing the case practice in the two sites has generated knowledge and skills that will be needed to elaborate future site-customised comprehensive HRA strategies, as described in the case of Catalonia.

In summary, the essential maturity requirements for sustainable HRA strategies are: 1) to achieve solid political commitment at the regional/country level fostering necessary interactions, top-down and bottom-up, among key stakeholders; 2) to have an essential digital maturity at the site level to satisfactorily pass the feasibility analysis; 3) to overcome potential limitations due to local application of GDPR; 4) to use highly applicable implementation science tools fostering engagement of all stakeholders, health policy managers and health professionals, during the process elaboration and deployment of the local HRA strategy; and 5) to develop/adopt a regulatory framework for secondary use of health data, needed for business intelligence

and the elaboration of computational modelling for clinical applications. **Table 2** depicts the steps identified during the transference process to define a roadmap for adopting site-customised HRA strategies.

Moreover, using the HRA tools described in the case practice as open-source software and articulating public-private collaborations supporting productive interactions and networking among sites are essential to speed up transferability and large-scale adoption of HRA strategies at the European level.

Table 2 – Checklist of key steps for site adoption of Health Risk Assessment (HRA)

Key steps	Description
1.Scope definition	Identify the purpose, focus/use and ambition of the HRA initiative
2.Source population	Population-health or Population-medicine. For each option, identify specificities of the source population
3.Planned updates	Periodicity of source data update (i.e. yearly basis)
4.Model (Morbidity grouper)	Morbidity grouper selected: AMG, CRG, ACG, others
5.Input variables (Fig. 1)	Minimum variables of the morbidity grouper plus additional variables selected for inclusion in the HRA modelling.
6.Data source(s) *(data sources and ownership have technical/managerial implications)*	1. Input data are extracted from one owned data source 2. Input data are extracted from different owned data sources 3. Input data are extracted from one data set source not owned 4. Input data are extracted from several data sets not owned
7. Predictive modelling	Identify statistical methods, Machine Learning, Deep Learning, etc…
8. Output variables (Fig 1)	Variables generated by the predictive modelling approach
9. Feasibility assessment	Includes characterization of site maturity and preliminary testing of the HRA tools to ensure minimum quality before implementation
10. Technological logistics	The complexity of the digital setting is closely related to the characteristics of the data sources and ambition of the HRA strategy. It requires assessment of sustainability over time in terms of technological and human resources.
11. Initial assessment of the core predictive modelling	Quality assessment to be carried out immediately after deployment to define further steps leading to a sustainable HRA program
12. Quality assurance program	Continuous quality assurance checking of the HRA program after sustainable adoption
13.Dashboard preparation	Initial identification of key performance indicators (KPIs) to be monitored after adoption, as well as subsequent enrichment of the dashboard with novel KPIs as required.
14. Stakeholders' engagement	Highly applicable implementation research tools in place to foster engagement of users. The professional profiles will depend on the focus of HRA: policy makers, managers, clinical professionals, etc…
15. Additional functionalities & Roadmap for further developments	Successful HRA adoption leads to initiatives to expand use and ambition requiring development of additional functionalities (predictive modelling) and definition of a roadmap for further developments either in the health policy area, management, clinical applications and/or research-innovation.

DISCUSSION

The current report is filling an existing gap in information on building up an HRA strategy at the regional/country level, as described for Catalonia, and its potential for transferability to other sites. Moreover, the Marche and Viljandi Hospital process generated a helpful checklist for generalising such transference to other sites across Europe.

The case practice has also recognised the convenience of further collaboration among regions beyond JADECARE to keep progressing toward mature HRA strategies contributing to paving the way for precision medicine. Moreover, the use of the current and future available algorithms (i.e. AMG, Queralt, etc..), and dashboards, as open-source software, as well as the provision of consultancy services supporting future next adopters, were identified as core elements to foster the adoption of efficient HRA strategies across Europe. To this end, the elaboration of a survey to be administered to all JADECARE's sites is strongly encouraged. The main aim is characterising the status and needs of all NAs regarding HRA. The information from the survey gathered before the project end can contribute to refining a large-scale implementation protocol to be customised at the site level beyond the project lifetime.

LESSONS LEARNED

The analysis of the HRA strategies in Catalonia (2010-2023), as well as the process of transference and adoption of the AMG in Marche (IT) and Viljandi Hospital (EE) within JADECARE, 2020-2023, generated the following key learnings aiming at fostering large-scale adoption of HRA across Europe:

1. Adopting comprehensive HRA strategies, including multimorbidity weight (AMG scoring) as a central component, constitutes a key element fostering health systems transformation toward value-based healthcare with a patient-centred approach.

2. Population-based and clinically-oriented HRA must be considered complementary and highly synergistic. However, ethical and regulatory aspects for secondary use of health data must be appropriately assessed and locally implemented.

3. Transferability of AMG across sites with diverse source data models is feasible, provided that the key input variables are available, the source population is well-characterized, and adequate data management with quality assurance over time is in place.

4. The current analysis identified the relevant steps to be considered for a generic protocol aiming at the implementation of HRA at a regional level.

5. Short-term elaboration of a map describing both maturity levels and needs for HRA adoption in the twenty-one JADECARE sites could provide the necessary information to define a roadmap leading to large-scale implementation of HRA across Europe.

CONCLUSIONS

The current study describes the evolution and the potential of the HRA strategy adopted in Catalonia since 2010. It also illustrates the transferability of the AMG algorithm in two different scenarios. Moreover, the case practice identified relevant barriers/facilitators modulating the adoption of HRA at regional level and elaborated a set of key steps to be considered for site deployment of HRA. Last, but not least, the report proposes initial steps to define a roadmap aiming at fostering large-scale implementation of HRA across Europe.

ETHICAL APPROVAL

This research exclusively employed fully anonymized retrospective health records sourced from administrative databases. Consequently, in compliance with prevailing legislation in the regions where the analyses were conducted, neither informed consent nor ethical committee approval was required. All the analytical procedures were undertaken under the auspices of the JADECARE project.

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ACRONYMS

ACP: Advanced Chronic Patients

AMG: Adjusted Morbidity Groups

CCP: Complex Chronic Patients

COPD: Chronic Obstructive Pulmonary Disease

CRG: Clinical Risk Groups

GDPR: General Data Protection Regulation

HAD: Healthcare Administrative Database

HRA: Health Risk Assessment

KPI: Key Performance Indicator

LAP: Local Action Plan

MSIQ: Modules for Monitoring Quality Indicators ("Moduls pel Seguiment d'Indicadors de Qualitat")

NA: Next Adopter

NCD: Non-Communicable Disease

oGP: Original Good Practice

PDSA: Plan-Do-Study-Act

PREM: Patient Reported Experience Measure

PROM: Patient Reported Outcome Measure

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ARTICLE 5

Rubèn González-Colom, Kangkana Mitra, Emili Vela, Andras Gezsi, Teemu Paajanen, Zsofia Gal, Gabor Hullam, Hannu Mäkinen, Tamas Nagy, Mikko Kuokkanen, Jordi Piera-Jiménez, Josep Roca, Peter Antal, Gabriella Juhasz, Isaac Cano. 2023. *Multicentric validation of a Multimorbidity Adjusted Disability Score to stratify depression-related risks using temporal disease maps*. Journal of Medical Internet Research (JMIR).

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Multicentric validation of a Multimorbidity Adjusted Disability Score to stratify depression-related risks using temporal disease maps.

Rubèn González-Colom[1], Kangkana Mitra[1], Emili Vela[2,3], Andras Gezsi[4], Teemu Paajanen[5], Zsofia Gal[6,7], Gabor Hullam[4,7], *Hannu Mäkinen[5],* Tamas Nagy[4,6,7], *Mikko Kuokkanen[5,8,9], Jordi Piera-Jiménez[2,3,10], Josep Roca[1,12,13], Peter Antal[4,#], Gabriella Juhasz[6,7,#] and Isaac Cano[1,13,#]*

1) Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS). Barcelona, Spain.
2) Catalan Health Service. Barcelona, Spain
3) Digitalization for the Sustainability of the Healthcare (DS3) - IDIBELL. Barcelona, Spain
4) Department of Measurement and Information Systems, Budapest University of Technology and Economics. Budapest, Hungary
5) Department of Public Health and Welfare, Finnish Health and Welfare Institute. Helsinki, Finland.
6) Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University. Budapest, Hungary.
7) NAP3.0-SE, Neuropsychopharmacology Research Group, Hungarian Brain Research Program, Semmelweis University. Budapest, Hungary
8) Department of Human Genetics and South Texas Diabetes and Obesity Institute, School of Medicine at University of Texas Rio Grande Valley, Brownsville, United States.
9) Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki. Helsinki, Finland.
10) Faculty of Informatics, Telecommunications and Multimedia, Universitat Oberta de Catalunya. Barcelona, Spain.
11) Hospital Clínic de Barcelona. Barcelona, Spain.
12) Universitat de Barcelona. Barcelona, Spain.

# - The authors contributed equally.

Corresponding Author: Isaac Cano

C/Rosselló 149-153, 08036, Barcelona

+34 932275707

iscano@recerca.clinic.cat

ABSTRACT

In the EU project TRAJECTOME, we used a novel methodology to identify temporal disease maps of depression and highly prevalent co-occurring disease conditions. This information was combined with disability weights established by the Global Burden of Disease Study 2019 to create a depression-related health risk assessment tool, the Multimorbidity Adjusted Disability Score (MADS). MADS was used to stratify over one million cases from three different cohorts and evaluate the impact on utilisation of healthcare resources, mortality, pharmacological burden, healthcare expenditure and multimorbidity progression. Results indicate statistically significant associations between MADS and increased mortality rate (P <.001), heightened healthcare utilization (i.e. emergency room visits P <.001; hospitalizations P <.001; pharmaceutical prescriptions P <.001; total healthcare expenditure P <.001), and a higher risk of disease progression and incidence of new depression-related comorbidities. MADS seems to be a promising approach to predict depression-related health risk and depression's impact on individuals and healthcare systems, which can be tested in other diseases; nevertheless, clinical validation is still necessary.

Keywords*:* Health Risk Assessment, Multimorbidity, Disease Trajectories, Major Depressive Disorder.

INTRODUCTION

The continuously increasing prevalence of multimorbidity is a pressing concern tied to complex clinical situations that can markedly impair patients' quality of life and result in escalated healthcare costs[1,2]. It is widely accepted that diseases can frequently co-occur in specific patterns forming clusters. Particularly noteworthy is the cluster of Major Depressive Disorder (MDD) [F32 and F33 ICD-10-CM[3]] and other mental and somatic illnesses. Furthermore, it is recognised that individuals afflicted with MDD may encounter additional obstacles in effectively managing their overall health[4,5], a feature that heightens the possibility that a disease-centred approach might lead to suboptimal management of patients with multiple, related and disabling chronic conditions[6].

To evaluate patients' clinical complexity and managing the impact of multimorbidity on individuals and healthcare systems[7], multimorbidity-adjusted health risk assessment (HRA) tools[8–12] have become fundamental instruments. Nevertheless, while the current approaches for HRA can certainly capture the burden of disease on individuals, they often fall short in envisaging disease progression and anticipating the onset of new comorbid conditions[13]. In contrast, the conceptualization of the diseasome[14] sparked the appearance of a plethora of studies investigating the temporal patterns of disease concurrence, or disease trajectories[15,16], yielding a better understanding of the time-dependent relationships among diseases and establishing a promising landscape to identify disease-disease causal relationships. Notably, these relationships are not arbitrary and frequently align with shared risk factors and/or underlying pathophysiological mechanisms[17–19]. Nevertheless, the traditional method of detecting disease co-occurrence has been deemed flawed as it may inadvertently generate false correlations between diseases, arising indirectly through multiple pairwise comparisons, exponentially increasing as the number of diseases examined escalates[20]. In this regard, sparse Bayesian Direct Multimorbidity Maps (BDMMs)[20,21] showed to be a promising solution by filtering indirect disease associations.

The current observational retrospective multicentric cohort study employed BDMMs to investigate temporal disease maps among MDD and highly prevalent disease conditions[22] in the context of the ERAPERMED EU project TRAJECTOME[23]. The study combined the results of the temporal disease maps identified in TRAJECTOME and the disability weights (DW)[24] documented in the 2019 revision of the Global Burden of Diseases study (GBD), to develop and validate a Multimorbidity Adjusted Disability Score (MADS). The DW represents the degree of health loss caused by a specific disease. Our objective was twofold: 1) Identifying patients with different profiles of risk and assessing the disease burden of MDD and its comorbidities on individuals and health systems; and 2) Estimating the risk of morbidity progression and the onset of MDD comorbid conditions.

The development and evaluation of MADS involved the following steps:

Step 1 - Computing age-dependent disease-disease probabilities of relevance (PR) using the BDMM method in four age intervals (0-20, 0-40, 0-60, and 0-70 years). This analysis resulted in an inhomogeneous dynamic Bayesian network that determined the PR for MDD against the most prevalent co-occurring diseases in the three European cohorts considered in TRAJECTOME, namely: The Catalan Health Surveillance System (CHSS)[25], the UK Biobank (UKB)[26], and The Finnish National Institute for Health and Welfare cohort (THL)[27]. THL cohort amalgamates information from Finrisk[28] 1992, 1997, 2002, 2007, 2012, Finhealth[29] 2017 and Health[30] 2000/2011 studies.

Step 2 – Combining the PR of every disease condition assessed in the study with their correspondent DW, extracted from the GBD 2019 study, we estimated the morbidity burden caused by MDD and its comorbid conditions. MADS was computed following a multiplicative combination of PR and DW of all the disease conditions present in an individual.

Step 3 - Using MADS to stratify patients into different risk levels corresponding to different percentiles of the population-based risk pyramid of each patient cohort.

Step 4 - Finally, the correspondence between the MADS risk strata and health outcomes were analysed through a cross-sectional analysis of utilisation of healthcare resources, mortality, pharmacological burden, and healthcare expenditure, and a longitudinal analysis of disease prevalence and incidence of new disease onsets. The results were validated through a multicentric replication of the findings in the three study cohorts, including 1,041,014 individuals.

RESULTS

Sociodemographic characteristics of the study cohorts

One of the first results is the characterisation of the three study cohorts and compared the sociodemographic attributes of their MADS risk groups (**Table 1**). All the individuals were classified into distinct risk strata based on quantiles of MADS distribution within the source population, resulting in the formation of the subsequent risk pyramid: Very low risk tier ($\leq P_{50}$); Low risk tier (P_{50}-P_{80}]; Moderate risk tier (P_{80}-P_{90}]; High risk tier (P_{90}-P_{95}]; Very high risk tier ($> P_{99}$).

To comprehend the inherent sociodemographic disparities across the cohorts under study, it is imperative to underscore the fundamental distinctions in their composition. Specifically, the THL and UKB cohorts predominantly consist of data derived from biobanks with a specific focus on the middle-aged and elderly population. In contrast, the CHSS cohort represents a population-based sample that encompasses all the population spectrum.

It is worth noting that a common pattern is observed among all the cohorts in the age distribution of the citizens at-risk. Although MADS is an additive morbidity grouper, it is not monotonically increasing with age. Remarkably, a notable proportion of high-risk cases were observed within the age range of 40 to 60 years, when depression typically manifests for the first time on average.

A divergence in the sex distribution across the risk strata is observable and especially noticeable in CHSS and UKB cohorts where the morbidity burden associated with depression and its related diseases is amplified women (P<.001). Likewise, the disability caused by depression and its comorbidities is larger in families with fewer economic resources (P<.001). Overall, the prevalence of MDD is greater in UKB than in the other cohorts. However, upon analysing the allocation of the population afflicted with depression in the risk pyramid, a total of 22,238 individuals (57.79% of those diagnosed with MDD) are categorized in the "high" and "very high" risk tiers in the CHSS cohort, whereas the number of individuals diagnosed with MDD that are allocated at the tip of the risk pyramid is 920 (40.22%) in THL and 23,409 (43.78%) in UKB.

Table 1 *– Demographic characteristics of each stratum of the MADS risk pyramid in the three study cohorts: CHSS[25], UKB[26] and THL[27].*

Risk Pyramid Tiers	**N**			**Age, mean (SD)**			**Sex, n (%)** **M = Male** **F = Female**			**Household Income, n (%)** **L = Low (< 18k €)** **M = Medium (18-100k €)** **H = High (> 100k €)**			**Major Depressive Disorder Prevalence, n (%)**		
	CHSS	**THL**	**UKB**	**CHSS**	**THL**	**UKB**	**CHSS**	**THL**	**UKB**	**CHSS**	**THL**	**UKB**	**CHSS**	**THL**	**UKB**
All cases	507,549	30,961	502,504	45.36 (23.07)	64.27 (14.28)	61.48 (9.31)	M: 237,598 (46.81) F: 269,951 (53.19)	M: 14,435 (46.62) F: 16,526 (53.38)	M: 229,122 (45.60) F: 273,382 (54.40)	L: 262,753 (51.77) M: 223,369 (44.01) H: 21,427 (4.22)	L: 11,489 (37.11) M: 10,025 (32.38) H: 9,447 (30.51)	L: 117,737 (23.43) M: 358,492 (71.34) H: 26,275 (5.23)	38,479 (7.58)	2,287 (7.39)	53,466 (10.64)
P value	N.A.	N.A.	N.A.	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Very high risk $> P_{99}$	5,651	310	5,026	55.74 (18.83)	68.83 (14.86)	61.7 (8.75)	M: 2,322 (41.09) F: 3,329 (58.91)	M: 129 (41.61) F: 181 (58.39)	M: 2,207 (43.91) F: 2,819 (56.09)	L: 4,343 (76.85) M: 1,251 (22.14) H:	L: 191 (61.61) M: 77 (24.84) H:	L: 2,285 (45.46) M: 2,620 (52.13) H:	3,870 (68.48)	186 (60.00)	4,370 (86.95)

										57 (1.01)	42 (13.55)	121 (2.41)			
High risk ($P_{95} – P_{99}$]	22,894	1,238	20,084	60.08 (20)	65.12 (15.10)	63.2 (8.74)	M: 7,170 (31.32) F: 15,724 (68.68)	M: 559 (45.15) F: 679 (54.85)	M: 7,545 (37.57) F: 12,539 (62.43)	L: 14,568 (63.63) M: 7,946 (34.71) H: 380 (1.66)	L: 690 (55.74) M: 327 (26.42) H: 221 (17.85)	L: 7,626 (37.97) M: 12,003 (59.76) H: 455 (2.27)	18,368 (80.23)	734 (59.29)	19,039 (94.8)
Moderate risk ($P_{80} – P_{95}$]	84,371	4,644	75,378	54.56 (21.87)	68.86 (14.77)	63.6 (9.02)	M: 34,462 (40.85) F: 49,909 (59.15)	M: 2,201 (47.41) F: 2,441 (52.59)	M: 34,282 (45.48) F: 41,096 (54.52)	L: 49,818 (59.05) M: 32,822 (38.9) H: 1,731 (2.05)	L: 2,285 (49.22) M: 1,437 (30.96) H: 920 (19.82)	L: 23,208 (30.79) M: 49,684 (65.91) H: 2,486 (3.3)	16,241 (19.25)	1,367 (29.45)	25,776 (34.2)
Low risk ($P_{50} – P_{80}$]	162,170	9,266	150,759	47.66 (24.2)	66.16 (14.15)	62.2 (9.39)	M: 77,082 (47.53) F: 85,088 (52.47)	M: 4,132 (44.58) F: 5,137 (55.42)	M: 70,550 (46.80) F: 80,209 (53.20)	L: 85,936 (52.99) M: 71,429 (44.05) H: 4,805 (2.96)	L: 3,623 (39.09) M: 3,081 (33.24) H: 2,565 (27.67)	L: 36,773 (24.39) M: 106,441 (70.6) H: 7,545 (5)	0 (0)	0 (0.00)	2,002 (1.33)
Very low risk ≤ P_{50}	232,463	15,503	251,257	38.72 (20.72)	61.62 (13.55)	60.3 (9.22)	M: 116,562 (50.14) F: 115,901 (49.86)	M: 7,414 (47.83) F: 8,088 (52.17)	M: 114,538 (45.59) F: 136,719 (54.41)	L: 108,088 (46.5) M: 109,921 (47.29) H: 14,454 (6.22)	L: 4,700 (30.32) M: 5,103 (32.92) H: 5,699 (36.76)	L: 47,845 (19.04) M: 187,744 (74.72) H: 15,668 (6.24)	0 (0)	0 (0.00)	2,279 (0.91)

The prevalence of depression was calculated considering both F32 and F33 ICD-10-CM diagnostic codes. Kruskal-Wallis tests were used to assess changes in the target outcomes according to the risk pyramid tiers. Abbreviations: CHSS: Catalan Health Surveillance System cohort; THL: The Finnish National Institute for Health and Welfare biobank cohort; UKB: UK biobank cohort.

Assessment of the MADS risk groups

Assessment of the PRs

Analysing the relationship between MDD and the morbidities assessed in the study is essential to interpret the MADS risk strata. This analysis revealed various relevant connections between MDD and the diseases investigated, encompassing both acute and chronic conditions, with the latter being particularly noteworthy due to their non-transient nature. Notably, the cluster of mental and behavioural disorders showed the highest average PRs in depression, but relevant associations also emerge among MDD and specific chronic somatic diseases affecting multiple organic systems (**Figure 1**).

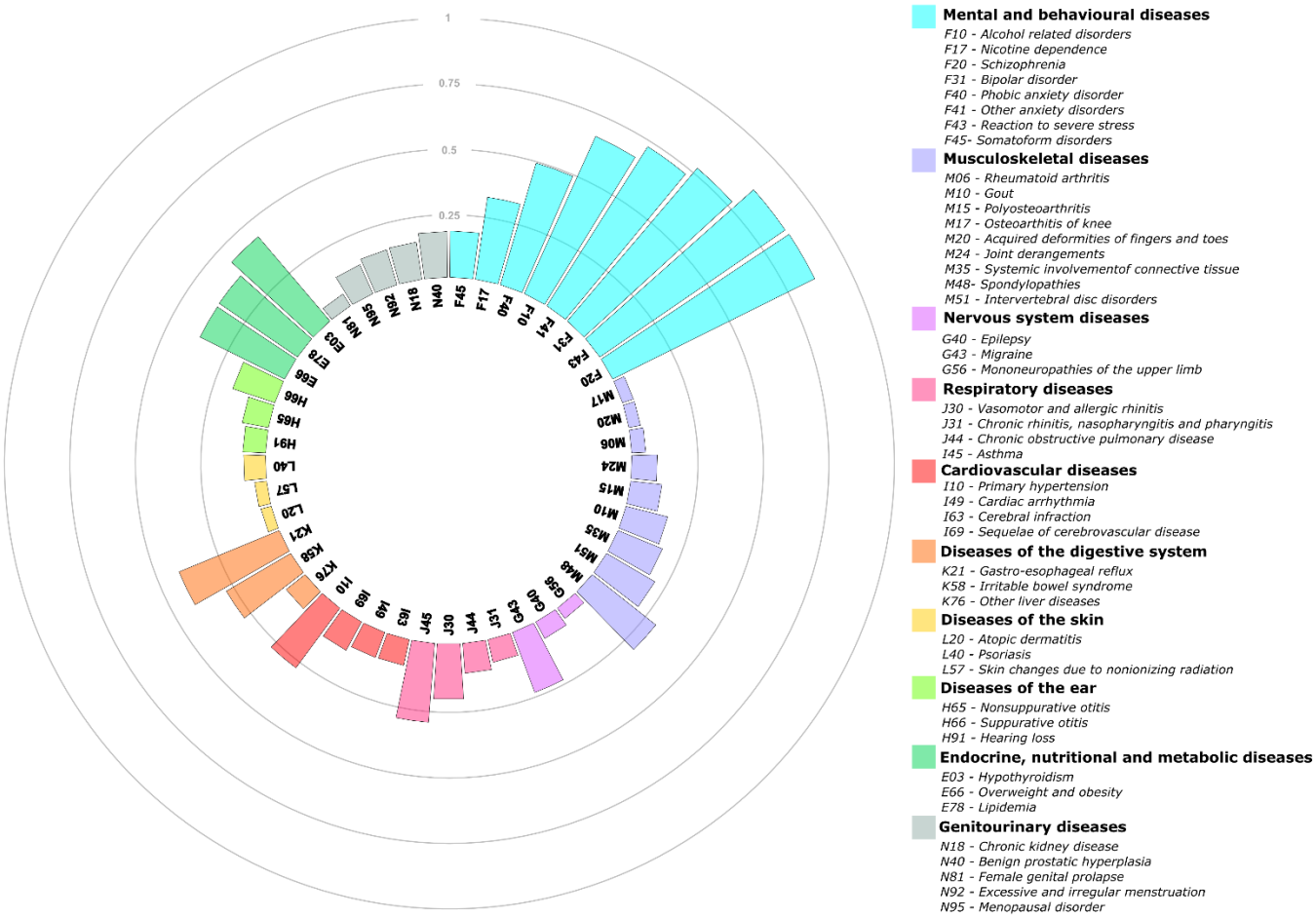

Figure 1 – Average probabilities of relevance between Major Depressive Disorder and 45 chronic conditions utilized to compute MADS.

Utilisation of healthcare resources

The evaluation of the impact of MADS risk groups on healthcare systems was conducted by investigating the correlation between the MADS risk categories and the utilization of health resources over the 12-month period following the MADS assessment within the CHSS cohort (**Table 2**). The results illustrate a significant and gradual pattern of increased healthcare utilization as individuals progress from lower MADS risk tiers to higher risk tiers, reflecting an escalation in healthcare needs and requirements. Overall, patients with higher MADS scores exhibit a greater likelihood of experiencing morbidity-related adverse events, which subsequently leads to recurrent interactions with healthcare systems across multiple levels. These interactions include higher frequencies of primary care visits (P<.001), specialized outpatient visits (P<.001), emergency room visits (P<.001), hospital admissions (P<.001) and ambulatory visits in mental health centres (P<.001) as well as an increased pharmacological burden (P<.001).

Table 2 *–Utilization of healthcare resources over 12 months in each stratum of the MADS risk pyramid for the CHSS cohort.*

Risk Pyramid Tiers	**Primary Care visits** (per person)	**Specialized Outpatient visits** (per person)	**Emergency Room visits** (visits/100 inhabitants)	**Hospital admissions** (admissions/100 inhabitants)	**Mental Health visits** (visits/100 inhabitants)	**Number of prescriptions** (per person)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Very high risk $> P_{99}$	12.50	3.07	135.00	28.50	554.00	8.02
High risk $(P_{95} – P_{99}]$	11.90	2.56	87.20	20.60	136.00	7.48
Moderate risk $(P_{80} – P_{95}]$	9.03	1.82	61.90	14.50	44.20	5.11
Low risk $(P_{50} – P_{80}]$	6.21	1.21	42.40	8.87	15.10	3.20
Very low risk $\leq P_{50}$	2.96	0.50	23.40	3.25	5.96	1.07

Kruskal-Wallis tests were used to assess changes in the target outcomes according to the risk pyramid tiers.

Mortality and healthcare expenditure

Moreover, we performed a cross-sectional analysis investigating mortality rates and the healthcare expenditure within the 12 months following the MADS assessment, expressed as the average healthcare expenditure per capita and differentiating among pharmaceutical and non-pharmaceutical costs, within the CHSS and THL cohorts (**Table 3**). The reported mortality rates (P<.001) were 5 to 20 times higher in the high-risk strata than in low-risk individuals.

Likewise, the average healthcare expenditure per person, comprising both pharmacological (P<.001) and non-pharmacological spending (P<.001), was significantly higher for the individuals allocated at the tip of the risk pyramid than for those allocated at the bottom of the pyramid.

Table 3: *Mortality rates and pharmacological and non-pharmacological healthcare expenditure in €, over 12 months, in each stratum of the MADS risk pyramid in CHSS[25] and THL[27].*

Risk Pyramid Tiers	**Mortality** (cases/1k inhabitants)		**Pharmacological expenditure in €** (per person)		**Hospitalization expenditure in €** (per person)		**Total expenditure in €** (per person)
	CHSS	**THL**	**CHSS**	**THL**	**CHSS**	**THL**	**CHSS**
P value	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Very high risk $> P_{99}$	46.2	36.0	1,214	966	539	270	12,517
High risk $(P_{95} – P_{99}]$	41.5	33.7	772	1,131	383	340	8,404
Moderate risk $(P_{80} – P_{95}]$	25.5	32.2	485	1,077	270	254	5,209
Low risk $(P_{50} – P_{80}]$	11.5	14.8	292	810	165	185	3,075
Very low risk $\leq P_{50}$	2.57	7.3	99	363	60	123	1,192

Kruskal-Wallis tests and Fisher exact tests were used to assess changes in the target outcomes according to the risk pyramid tiers. Abbreviations: CHSS: Catalan Health Surveillance System cohort; THL: The Finnish National Institute for Health and Welfare biobank cohort.

Pharmacological burden

The study also examined the pharmacological burden on individuals after a 12-month period following the MADS assessment (**Table 4**). The findings indicate a significant positive association between the various risk strata and heightened pharmaceutical utilization, which is consistently observed across all cohorts. Specifically, individuals allocated at the top of the risk pyramid demonstrate significantly higher utilization of antidepressants (P<.001), antipsychotics (P<.001), anxiolytics (P<.001), and sedatives (P<.001) compared to those in lower risk categories, leading to a surge in the cost of medication.

Table 4: *Prescription of depression related pharmacological treatments over 12 months in each stratum of the MADS risk pyramid in CHSS[25], UKB[26] and THL[27].*

Risk Pyramid Tiers	Antipsychotic (N05A) (per person)			Anxiolytic (N05B) (per person)			Hypnotics and sedatives (N05C) (per person)			Antidepressant (N06A) (per person)		
	CHSS	**THL**	**UKB**	**CHSS**	**THL**	**UKB**	**CHSS**	**THL**	**UKB**	**CHSS**	**THL**	**UKB**
P value	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Very high risk $> P_{99}$	0.75	0.60	0.33	0.47	0.21	0.27	0.15	0.14	0.24	0.79	0.43	0.80
High risk $(P_{95} – P_{99}]$	0.20	0.27	0.18	0.46	0.19	0.20	0.10	0.12	0.19	0.66	0.41	0.71
Moderate risk $(P_{80} – P_{95}]$	0.07	0.08	0.15	0.28	0.08	0.16	0.05	0.10	0.18	0.27	0.27	0.54
Low risk $(P_{50} – P_{80}]$	0.03	0.03	0.13	0.14	0.04	0.12	0.02	0.07	0.13	0.08	0.11	0.36
Very low risk $\leq P_{50}$	0.01	0.01	0.11	0.04	0.02	0.09	0.01	0.04	0.10	0.02	0.06	0.26

For recurrently dispensed medication only the first prescription was considered in the analysis. Kruskal-Wallis tests were used to assess changes in the target outcomes according to the risk pyramid tiers. Abbreviations: CHSS: Catalan Health Surveillance System cohort; THL: The Finnish National Institute for Health and Welfare biobank cohort; UKB: UK biobank cohort.

To evaluate the influence of age and sex on the outcomes examined in this section, we replicated all the previously presented results, categorizing the outcomes by sex and age and reported them in the **Supplementary material – Appendix 1**. The results suggest that the morbidity burden in individuals might be a primary driver influencing the occurrence of adverse health events and the heightened utilization of healthcare resources.

Multimorbidity progression

We performed a longitudinal analysis in the CHSS cohort for investigating the prevalence and incidence of new MDD-associated diagnoses and its highly relevant comorbid conditions in 5-year intervals after MADS assessment for depression throughout the patients' lifespan (**Figure 2**), allowing for a comprehensive examination of disease patterns over time. **Figure 2** only displays a representative selection of the results, the plots for all the disease conditions analysed in this study, as well as the results found in THL and UKB cohorts, are reported in the **Supplementary material – Appendix 2**.

In general, both MDD (**Figure 2 – Panel A**), and the comorbid conditions investigated in this study exhibit a positive correlation between the MADS risk tiers and the current prevalence and incidence of new disease onsets within a subsequent 5-year interval. Notably the prevalence of the studied diseases is significantly higher than the population average in the high-risk groups. Distinct patterns are discernible for certain disorders. For instance,

conditions characterized by minimal disability, such as, gastro-oesophageal reflux (**Figure 2 – Panel D**), insomnia, back pain, and overweight, exhibit consistent upward trends, with both incidence and prevalence steadily increasing throughout the lifespan. In contrast, more disabling diseases like schizophrenia (**Figure 2 – Panel B**), bipolar disorder, and alcohol abuse (**Figure 2 – Panel C**), which precipitate rapid health deterioration and reduce life expectancy, attain peak prevalence and incidence levels during middle-aged adulthood, followed by a decline in later stages of life. These findings suggest a premature mortality among individuals afflicted by such conditions.

It is worth noting that in certain age intervals, the incidence of new MDD-related disease onsets is higher in the high-risk group compared to the very high-risk group. This phenomenon is explained due to the method employed to calculate the MADS, as the high-risk group primarily comprises individuals with highly disabling diseases (high DW) that are closely associated with depression (high PR), such as schizophrenia or bipolar disorder. It is also noteworthy that the 5-years incidence of certain disorders is very low. Considering that the high-risk and very high-risk groups represent only 4% and 1% of the sample size respectively, the effects of the variance are especially noticeable, leading to the observable pronounced sawtooth patterns on the chart.

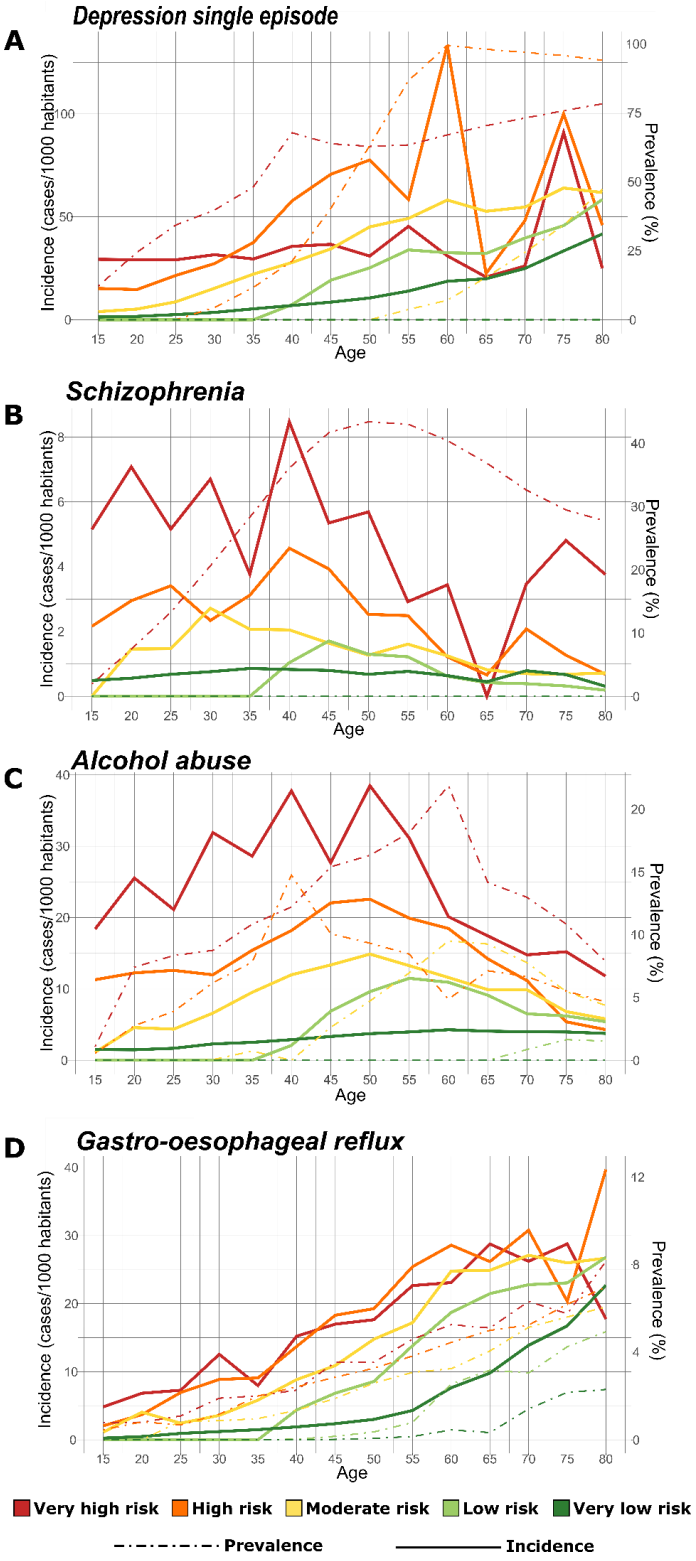

Figure 2 *-* ***Longitudinal analysis of disease prevalence and incidence of new disease onsets*** *in CHSS cohort in four target disease conditions: Panel A) MDD single episode (ICD-10-CM: F32); Panel B) schizophrenia (ICD-10-CM: F20); Panel C) mental disorders related to alcohol abuse (ICD-10-CM: F10); Panel D) gastro-oesophageal reflux (ICD-10-CM: K21). Disease incidence is assessed in a 5-years interval, plotted in the left y-axis and represented with solid lines. Disease prevalence is plotted in the right y-axis and represented with dashed lines. The line colours correspond to the MADS risk pyramid tiers: red: very high-risk group; orange: high-risk group; yellow: medium-risk group; light green: low-risk group; green: very low-risk group.*

DISCUSSION

Main findings

MADS seems to provide a unique and more comprehensive understanding of the complex nature of depression-related multimorbidity. This approach recognizes that individuals with depression often experience a range of comorbid conditions that may manifest and evolve differently over time. By capturing this dynamic aspect, MADS offers a nuanced assessment that goes beyond a mere checklist of discrete disorders. The novelty of the MADS approach lies in its capability to serve as the first morbidity grouper that incorporates information pertaining to disease trajectories, while improving the filtering of indirect disease associations using BDMMs.

In the current investigation, we have unearthed robust correlations between the MADS risk strata and the extent of deleterious impact caused by MDD and its comorbid conditions. Such associations indicate the presence of specific health risks and an escalated utilization of healthcare resources. Furthermore, a positive association has emerged between the levels of pharmacological and non-pharmacological healthcare expenditures and the different tiers of MADS risk. Also, the analysis has revealed an augmented risk of disease progression within the high-risk groups (high and very high-risk), as indicated by a heightened incidence of new-onset depression-related illnesses within a 12-month period after MADS assessment. Similarly, mortality rates have exhibited elevated values in these high-risk groups.

The findings presented in this study are underpinned by the complementary studies conducted within the TRAJECTOME project[22] that have established a better understanding of the complex multimorbidity landscape associated with MDD across an individual's lifespan, encompassing both modifiable and genetic risk factors.

Potential impact in personalized medicine

By assessing whether MADS is appropriate for stratification of depression-related multimorbidity, we attempted to confirm its potential for contributing to precision medicine of patients with MDD who are in their early stages of MDD development[31]. Despite all advances toward adopting a personalised approach in mental health services, and more specifically in the treatment of depressive disorders, several challenges still limit its clinical utility[32]. The data-driven categorization of MADS in clinical practice may help facilitate further screenings and referrals of patients in a cost-effective manner.

The results reported in this study not only reaffirm the well-established link between multimorbidity and adverse outcomes such as a decline in functional status, compromised quality of life, and increased mortality rates[33] but also shed light on the significant burden imposed on individuals and healthcare systems. The strain on resource

allocation and overall healthcare spending is a pressing concern that necessitates effective strategies for addressing and managing multimorbidity[34].

In this context, the assessment of individual health risks and patient stratification emerges as crucial approaches that enable the implementation of predictive and preventive measures in healthcare. By identifying individuals at higher risk and tailoring interventions accordingly, healthcare providers can proactively intervene, potentially averting or mitigating the progression of diseases and optimizing patient outcomes. These strategies not only yield immediate value in terms of improved patient care but also lay the foundation for the broader adoption of integrated care and precision medicine, particularly in the management of chronic conditions[35].

Moreover, the findings of this study highlight the potential of preventive strategies targeted at mental disorders, including substance abuse disorders, depressive disorders, and schizophrenia, to reduce the incidence of negative clinical outcomes in somatic health conditions. These important implications for clinical practice call for a comprehensive and interdisciplinary approach that bridges the gap between psychiatric and somatic medicine. By developing cross-specialty preventive strategies, healthcare professionals can provide more holistic and effective care for individuals with complex health needs, ensuring that both their mental and physical health are adequately addressed[4].

Further developments

The methodological approach used to develop MADS has proven to be effective in measuring the impact of an index disease and its principal comorbidities both in individuals and healthcare systems.

Furthermore, it is expected that MADS approach might be used in other well-established clusters of non-communicable diseases. By leveraging this targeted approach, MADS can be adapted to other disease clusters with shared characteristics, enabling a more precise assessment of disease burden and comorbidity patterns. Since MADS was constructed using only the calculations derived from the BDMM analysis of 86 disease conditions previously screened from a large set of disease conditions, MADS focuses only on the health problems directly related to the index disease (i.e., MDD) and ignores the surrounding effects of the uncorrelated comorbid conditions.

Finally, MADS, or derived scores, can be integrated as part of holistic strategies for subject-specific risk assessment that combines information on various patient's determinants of health, also known as Multisource Clinical Predictive Modelling (MCPM). The integration of MADS with other pertinent risk factors and clinical information within MCPM approaches offers a comprehensive framework for conducting risk assessments and implementing personalized interventions in the clinical arena[36,37]. This statement was grounded on the hypothesis that the

implementation of comprehensive strategies for subject-specific risk prediction and stratification, incorporating multiple sources of covariates influencing patients' health, could enhance the accuracy of predictions and facilitate informed clinical decision-making by providing reliable estimates of individual prognosis[38]. This strategy is expected to support the implementation and long-term use of preventive measures for managing chronic patients, with the goal of delaying or preventing their progression to the highest risk level on the stratification pyramid[39].

The current study also provided good prospects for utilization of the disease trajectories to enhance the performance of existing state-of-the-art morbidity groupers, such as the Adjusted Morbidity Groups (AMG)[2,12]. AMG system is currently used in Catalonia (ES; 7M inhabitants), both for health policy and clinical purposes, and promoted for its transferability to other EU regions by the EU joint Action on implementation of digitally enabled integrated person-centred care (JADECARE)[40]. Unlike the current approach based on DW, the AMG score employs a disease-specific weighting derived from statistical analysis incorporating mortality and healthcare service utilization data. This approach would allow the creation of tools adjustable to the characteristics of each healthcare system, adapting to the impact of a particular disease condition into a specific region and improving the generalisation capacity of the tool.

Limitations of the current approach

Despite meeting expectations and validating the hypothesis by which the study was conceived, the authors acknowledge a series of limitations leading to suboptimal results and limited potential for adaptation and generalization that should be undertaken to bring MADS, or an indicator derived from it to real world implementation.

In the current research, the use of estimations of mean DW[41] to assess the burden of disease conditions has achieved desirable results, and is conceptually justified, but undoubtedly exhibits major limitations. In an ideal clinical scenario, each disease diagnosis indicated in the patient's electronic medical record should be accompanied by the characterization of three key dimensions: i) severity of the diagnosis, ii) rate of disease progression, and iii) impact on disability. However, the degree of maturity for the characterization of the last two dimensions, disease progression and disability, is rather poor because of the complexities involved in their assessment. In other words, the authors are acknowledging the weakness associated with the current use of DW, but they are stressing the importance of incorporating such dimension, directly assessed on individual basis, in future evolutions of MADS.

A noteworthy aspect that should be acknowledged is that factors such as the advancement of diagnostic techniques, the digitization of medical records, and the modifications in disease taxonomy and classification over

time, have contributed to a more exhaustive documentation of the disease states in the most recent health records. Consequently, this fact could lead to imprecisions estimating the disease onset ages in the older individuals.

CONCLUSIONS

MADS showed to be a promising approach to estimate multimorbidity-adjusted risk of disease progression and measure MDD's impact on individuals and healthcare systems, which could be tested in other diseases. The novelty of the MADS approach lies in its unique capability to incorporate disease trajectories, providing a comprehensive understanding of depression-related morbidity burden. In this regard, the BDMM method played a crucial role in isolating and identifying true direct disease associations. Nevertheless, clinical validation is imperative before considering the widespread adoption of MADS in routine clinical practice.

METHODS

Data sources

The study was conducted utilizing data from three public health cohorts, namely:

1) **The Catalan Health Surveillance System (CHSS)** - The main cohort used in MADS development was extracted from the CHSS. Operated by a single-public payer (CatSalut)[42] since 2011, the CHSS gathers information across healthcare tiers on the utilization of public healthcare resources, pharmacological prescriptions, and patients' basic demographic data, including registries of 7.5 million citizens from the entire region of Catalonia (ES). Nevertheless, for MADS development purposes we considered only registry data from the citizens resident in the entire Health District of Barcelona-Esquerra (AISBE) between 1st of January of 2011 and 31st of December of 2019 (n=654,913). To validate the results of MADS, we retrieved additional information from CHSS corresponding to the 12 months posterior to MADS assessment, from 1st of January of 2020 to 31st of December of 2020. It is to note that, all the deceased patients in addition to those who moved their residence outside of AISBE district between 2011 and 2019 were discarded from the validation analysis, the remaining subset of patients comprises 508,990 individuals.

2) **The United Kingdom Biobank (UKB)** – The UKB data considered in this study contained medical and phenotypic data from participants aged between 37-93 years. Recruitment was based on NHS patient registers and initial assessment visits were carried out between 3rd of March of 2006 and 1st of October of

2010 (n = 502,504). Analysed data included disease diagnosis and onset time, medication prescriptions, and socio-economic descriptors.

3) **The Finnish National Institute for Health and Welfare biobank (THL)** - THL cohort integrates information from Finrisk[28] 1992, 1997, 2002, 2007, 2012, Finhealth[29] 2017 and Health[30] 2000/2011 studies. For the consensual clustering 41,092 participants were used from Finnish population surveys. After data cleaning, 30,961 participants remained from Finnish population surveys. These participants of age 20-100 were chosen at random from the Finnish population and represented different parts of Finland.

Ethical approval

As a multicentric study, TRAJECTOME accessed multiple cohorts' data, all subject to the legal regulations of their respective regions of origin and obtained the necessary approvals from the corresponding ethics committees.

For CHSS cohort, the Ethical Committee for Human Research at Hospital Clinic de Barcelona approved the core study of TRAJECTOME on the 24th of March of 2021 (HCB/2020/1051) and subsequently approved the analysis for the generation and validation of MADS on the 25th of July of 2022 (HCB/2022/0720).

UK Biobank received ethical approval from the National Research Ethics Service Committee Northwest–Haydock (ref. 11/NW/0382).

The THL cohort integrates information from the Finrisk databases: 1997 (Ethical committee of National Public Health Institute. Statement 38/96. 30.10.1996), 2002 (Helsinki University Hospital, Ethical committee of epidemiology and public health, Statement 87/2001. Reference 558/E3/2001. 19.12.2001), 2007 (Helsinki University Hospital, Coordinating ethics committee, Dnro HUS 229/EO/2006, 20.6.2006) and 2012 (Helsinki University Hospital, Coordinating ethics committee, Dnro HUS 162/13/03/11, 1.12.2011); the FinHealth 2017 (Helsinki University Hospital, Coordinating ethics committee, 37/13/03/00/2016 22.3.2016) and the Health 2000-2011 databases (Ethical committee of National Public Health Institute, 8/99/12. Helsinki University Hospital, Ethical committee of epidemiology and public health, 407/E3/2000. 31.05.2000 and 17.06.2011).

The ethics committees exempted the requirement to obtain informed consent for the analysis, and publication of retrospectively acquired and fully anonymized data in the context of this non-interventional study.

All the data was handled in compliance with the General Data Protection Regulation 2016/679, which safeguards data protection and privacy for all individuals in the European Union. The study was conducted in conformity with the Helsinki Declaration (Stronghold Version, Brazil, October 2013) and in accordance with the protocol and the relevant legal requirements (Biomedical Research Act 14/2007 of 3 July).

Building the Multimorbidity Adjusted Disability Score

The development of MADS intertwined four development and evaluation steps (**Figure 3**): Step 1) Computing age-dependent disease-disease probabilities of relevance; Step 2) Extracting and aggregating the DW; Step 3) Generating the MADS risk pyramid; and Step 4). Evaluation of MADS risk strata.

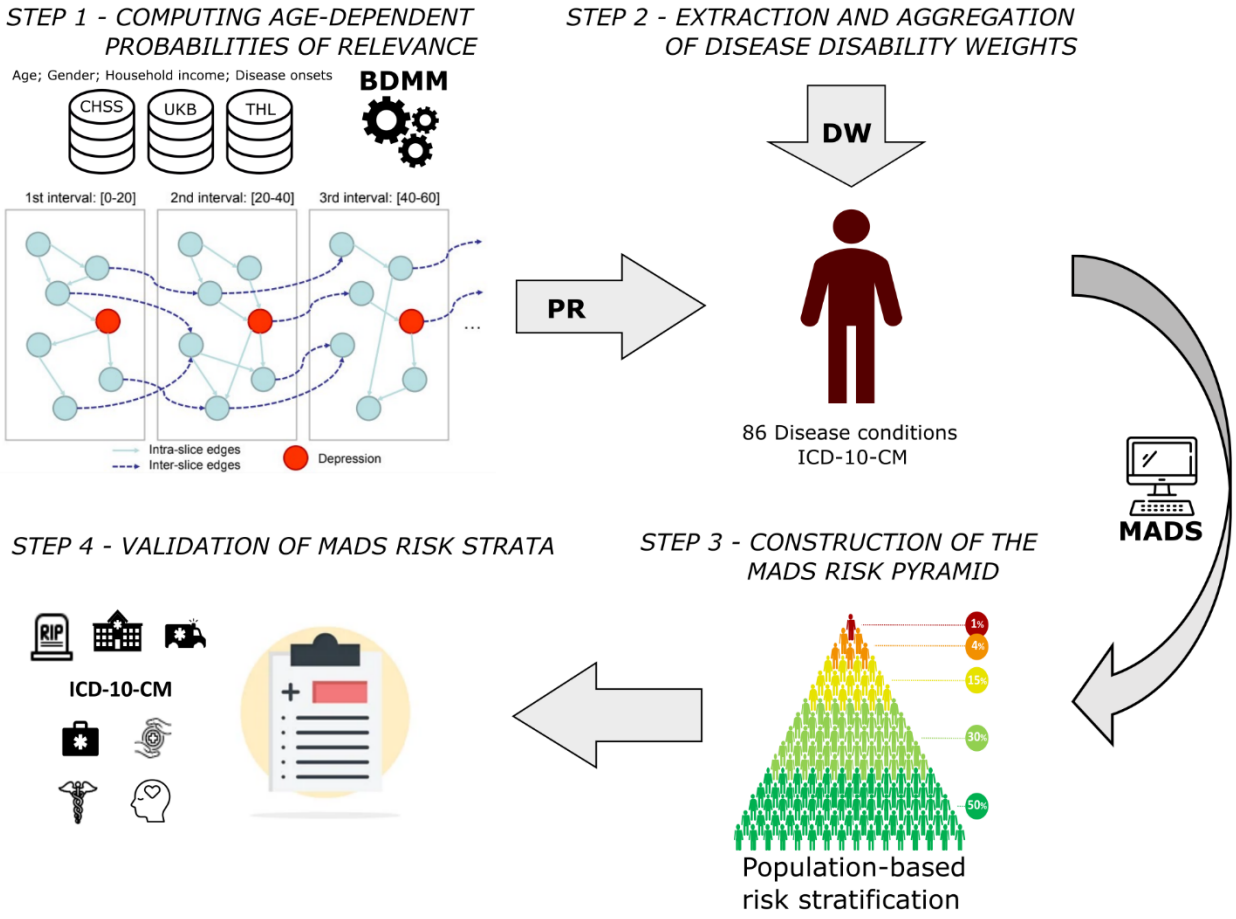

Figure 3 - Workflow for building and validation of the MADS. *BDMM stands for Bayesian Direct Multimorbidity Maps, PR for Probabilities of Relevance, and DW for Disability Weights.*

STEP 1- COMPUTING AGE-DEPENDENT PROBABILITIES OF RELEVANCE

BDMMs were used to assess direct and indirect associations between MDD and a set of 86 potential comorbid conditions. The set of 86 disease conditions considered in the study had a prevalence greater than 1% in all the study cohorts. The list of diseases and their associated ICD-10-CM[3] codes are displayed in the **Supplementary material – Appendix 3**.

This step considered information on: 1) **Disease diagnosis**: Disease conditions were catalogued using the first three characters of ICD-10-CM codes; 2) **Age at disease onset time**: The age at disease onset corresponds to the first diagnosis in a lifetime for each ICD-10-CM code; 3) **Sex**; and, 4) **Socio-economic status**: annual average total household income (before tax with co-payment exemption) as a categorical variable with 3 categories: a) Less than 18,000; b) 18,000 to 100,000; c) Greater than 100,000. Thresholds are given in EUR.

BDMM analysis resulted in an inhomogeneous dynamic Bayesian network, which was utilised to compute temporal PR, ranging from 0 (no association) to 1 (strong association), for MDD in conjunction with sex, socio-economic status, and the set of 86 predetermined consensual diseases[22]. To construct the trajectories, the PR was calculated in four different age ranges: 0-20, 0-40, 0-60, and 0-70 years of age. The PR calculated and utilized for MADS computation are reported in the **Supplementary material – Appendix 4**. Further details regarding the core analysis conducted in TRAJECTOME can be found in [22].

STEP 2 - EXTRACTION AND AGGREGATION OF DISEASE DISABILITY WEIGHTS (DW)

MADS was developed by weighting the DWs of single diseases according to their estimated PR against MDD. DWs indicate the degree of health loss, based on several health outcomes, and are used as indicators of the total of disability caused by a certain health condition or disease. Often, the DWs present specific disability scores tailored to the severity of the disease. The disease categories, their severity distribution and their associated DWs utilised in this study were extracted from the GBD studies of 2019 and reported in the **Supplementary material – Appendix 3**.

DWs were extracted and aggregated as follows: 1) We considered only the DW of MDD and the set of 86 disease codes; 2) We considered the DW of all the chronic conditions diagnosed in patients' lifetime, whereas, since the disability caused by acute illnesses is transitory, the DWs for the acute diseases diagnosed more than 12 months before the MADS assessment were arbitrary set to 0 (no disability); 3) Due to the unavailability of information on the severity of diagnoses, we determined the DWs of each disease condition by calculating the weighted mean of the DWs associated to the disease severity categories and their prevalence. In instances where the severity distribution was not available, we computed the arithmetic mean of the DWs of each severity category; 4) We

finally weighted the DWs according to the PR of each disease condition with respect to MDD, the PR were adjusted according to age of disease onset, discretized in the following intervals 0-20, 20-40, 40-60, >60 years old.

Since the DWs do not account for multimorbidity in their estimates, the utilization of DW independently can cause inaccuracies in burden of disease estimations, particularly in ageing populations that include large proportions of persons with two or more disabling disease conditions[43]. Consequently, we combined the DW and the PR for all the disease conditions present in one individual following a multiplicative approach (**Eq. 1**)[44], aggregating several DW in a single score that accounts for the overall disability caused by numerous concurrent chronic conditions, in which every comorbid disease increases the utility loss of a patient, though it is less than the sum of the utility loss of both diseases independently.

(Eq. 1)

$$\mathrm{MADS} = 1 - \prod_{k=i}^{n}(1 - PR_i * DW_i)$$

"DW" stands for Disability Weight, "PR" Probability of Relevance and "n" is the number of diseases present in one individual.

STEP 3 - CONSTRUCTION OF THE MADS RISK PYRAMID

Once calculated, MADS was utilised to stratify patients in different levels of risk according to the quantiles of its distribution in the source population, producing the following risk pyramid: 1) Very low risk (≤ P_{50}); 2) Low risk (P_{50}-P_{80}]; 3) Moderate risk (P_{80}-P_{90}]; 4) High risk (P_{90}-P_{95}]; 5) Very high risk (> P_{99}).

STEP 4 - EVALUATION OF MADS RISK STRATA

The validation of the results encompassed two interconnected analyses: 1) A cross-sectional validation of health outcomes; and 2) a longitudinal analysis of disease prevalence and incidence of new onsets.

CROSS-SECTIONAL VALIDATION OF HEALTH OUTCOMES AND USE OF HEALTHCARE RESOURCES

To validate the results of MADS, we conducted a cross-sectional analysis of clinical outcomes within the 12 months following the MADS assessment. The burden of MDD and its comorbidities on patients and healthcare providers, corresponding to each risk group of the MADS risk pyramid, was assessed using the following features (the parameters evaluated in each cohort may vary depending on the availability of the requested information in the source databases):

1) **Prescriptions of psycholeptic and psychoanaleptic drugs** (Information available in all the databases) The prescribed medication was catalogued using the first 4 characters from ATC[45] codes, resulting in the following categories: *Antipsychotics (N05A), Anxiolytics (N05B), Hypnotics and sedatives (N05C) and Antidepressants (N06A).*
2) **Cost of the pharmacological prescriptions in €** *(*Information available only in *CHSS and THL).*
3) **Mortality rates** *(*Information available only in *CHSS and THL).*
4) **Contacts and encounters with healthcare professionals** *(*Information available only in *CHSS)* Encompassing: i) primary care visits; ii) specialised care outpatient visits; iii) ambulatory visits in mental health centres; iv) emergency room visits; v) planned and unplanned hospital admissions; and vi) admissions in mental health centres.
5) ***Total healthcare expenditure*** *(*Information available only in *CHSS)* Including: i) direct healthcare delivery costs; ii) pharmacological costs; and iii) other billable healthcare costs, such as non-urgent medical transportation, ambulatory rehabilitation, domiciliary oxygen therapy, and dialysis.

We assessed the effect of sex and age replicating the analyses disaggregated by sex and age. The age ranges were discretized in the following categories: 0-20, 20-40, 40-60, >60 years.

LONGITUDINAL ANALYSIS OF DISEASE PREVALENCE AND INCIDENCE OF NEW ONSETS

To address the age-dependency of disease onsets we performed a longitudinal analysis of the prevalence of a target disease and the incidence of new diagnostics within the 5 years following the MADS assessment.

We iteratively computed MADS in five-year intervals throughout the patients' life. Within each interval, the population was stratified based on the MADS distribution. Subsequently, within each risk tier, the prevalence of the target disease and the incidence of new disease onset over the subsequent five years were calculated. Only individuals with complete information for the next interval at each timepoint of the analysis were included.

In the analysis we considered only the disease conditions with a PR against MDD ≥ 0.80 in at least one of the four age intervals assessed, namely: 0-20, 0-40, 0-60 and 0-70**.** Resulting in the following set of mental diseases: *MDD (F32-F33), schizophrenia (F20), bipolar disorder (F31), anxiety related disorders (F40-F41), stress related disorders (F43), mental disorders related to alcohol abuse (F10), insomnia (G47).* And the following somatic diseases: *dorsalgia (M54), soft tissue disorders not classified elsewhere (M79), irritable bowel syndrome (K58), overweight and obesity (E66) and gastro-oesophageal reflux (K21).*

Statistical analysis

Mortality rates were summarised as cases per 1,000 inhabitants, whereas numeric health outcomes variables were described by the average number of cases per person, per 100 inhabitants or per 1,000 inhabitants according to their prevalence. Average healthcare expenditures are reported in € per person. To evaluate changes in the target outcomes across the risk pyramid tiers, Kruskal-Wallis tests and Fisher exact tests were employed accordingly. Statistical significance was determined by considering a P-value less than .05 in all analyses.

All the data analyses were performed using R[46], version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). The MADS algorithm was fully developed and tested in the CHSS database and transferred to the other sites through an R programming executable script.

The study is reported according to the STROBE[23] guidelines for observational studies.

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Data Availability

Data for this study are not publicly available due to patient privacy concerns. The scripts used to compute MADS are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the writing of this paper and approved the final draft.

Conflicts of Interest

None declared.

ACRONYMS

AISBE- Health District of Barcelona-Esquerra

AMG – Adjusted Morbidity Groups

BDMM – Bayesian Direct Morbidity Maps

CHSS – Catalan Health Surveillance System

DW – Disability Weights

GBD - Global Burden of Disease

MADS – Multimorbidity Adjusted Disability Score

MCPM – Multisource Clinical Predictive Modelling

MDD – Major Depressive Disorder

PR – Probability of Relevance

THL - Finnish National Institute for Health and Welfare Biobank

UKB – United Kingdom Biobank

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DISCUSSION

The thesis discussion follows a structured approach, starting with a brief summary of the main insights. Then, each use case is discussed in detail, covering its main findings, limitations, the remaining challenges to achieve applicability in real-world scenarios, and potential future research areas.

6. INSIGHTS FROM THE THREE USE USES

The first use case addressed the design and implementation of predictive modelling that combines multimorbidity indices (e.g., AMG and Queralt) with other health determinants for patient risk stratification at hospital entry and at discharge. The choice of these time points was deliberate, aligning with the imperative to refine service selection upon admission (conventional in-hospital admission vs HaH) and enhance transitional care upon discharge, respectively.

The former is essential in optimizing therapeutic pathways, enhancing care efficacy, and ensuring patient safety(130,131). This aspect was rigorously appraised within the HaH program at HCB (**Article 1**), where home-based fatality and intervention failures resulting in in-hospital readmission were modelled.

Conversely, the latter, centred on transitional care, evaluated the mortality risk and short-term readmission post-hospitalization, spanning 30 to 90 days. This evaluation aimed to strengthen the discharge process safety, customize it to individual patient needs, and foster vertical and horizontal integration within the healthcare continuum, ensuring that patients are handled over effectively to the next phase of their care journey(132,133).

The assessment of the predictive models for the prevention of readmissions and mortality for the improvement of hospital-community transitions has had a central role in the thesis, conducted in a tri-phasic evaluation, commencing with a service-specific model (i.e., HaH) (**Article 1**), transitioning to a generalizable model suitable for

all-type hospitalizations (**Article 2**), and finalizing in an assessment of the broader Catalan healthcare context (**Article 3**) to extrapolate this approach systemically.

In all contexts, the predictive ability of the models produced commendable results, outperforming other methods documented in existing literature and demonstrating genuine potential to provide clinical decision support(134–136). This use case tackled a few pressing challenges in the field, addressing issues such as feature selection, data accessibility, model design and evaluation, explainability of the predictions, as well as challenges associated with model's generalisation and adaptability across different scenarios. However, specific areas remain for exploration and debate. These include the steps needed for model's implementation as CDSS in real-world settings, the subsequent clinical validation, and the continuous assessment and maintenance of the models.

The second use case delved into the practicalities of transferring and adopting a mature HRA strategy, developed in the Catalan oGP over the last decade, across diverse European regions. In this regard, **Article 4** examined the determinants behind adopting and deploying the AMG, an open-source, population-based, predictive tool. The study assessed the guided transference of the AMG to two European regions: Marche region (IT) and Viljandi county (EE).

These two settings, Marche and Viljandi, partially represent the organizational diversity of European healthcare services. Furthermore, they convey two different approaches: population health and population medicine(127), respectively. This bifocal approach has facilitated the generation of tailored recommendations for AMG adoption across diverse EU sites, addressing key issues like minimum data set access, GDPR interpretation, and data exploitation through dashboards and KPIs.

Despite the recommendations issued are valid and generalizable, it is acknowledged that for drawing a unified set of implementation guidelines that considers the diversity of the entire European healthcare landscape, additional research is needed to understand the current situation of each member state. Otherwise, adopting HRA tools can lead to inefficiencies, wasted resources, and even potential harms.

Finally, **Article 5** sought to explore the feasibility of incorporating procedures relevant to the study of disease trajectories and novel techniques for analysing dependency relationships between concomitant diseases to generate the next generation of morbidity groupers. This aims to better adjust the estimations of the burden of morbidity to clusters of diseases and improve the ability to anticipate the progression of multimorbidity.

The findings, focused on MDD, revealed a link between identified risk tiers and adverse health outcomes, including increased healthcare resource use and mortality rates. After an initial validation using data from Spain(137), the UK(138), and Finland(139–141), the method shows potential to enhance the integration of psychiatric and somatic medicine, potentially improving the prevention and treatment of depression-related multimorbidities.

Despite **Article 5** achieved positive results and met the defined objectives, certain aspects remain under discussion. Key debate topics include refining the initial approach for enhanced scalability and generalizability and further explore whether such novel methods to explore the diseasome, as well as the role of disease trajectories, can enhance existing open-source tools' efficiency, such as the AMG system.

The three use cases addressed in the thesis, while distinct, form a cohesive, and novel, analytical approach to different facets of multimorbidity. Moreover, the research outcomes show the high potential of articulating population-based and clinically oriented HRA. The following section analyses, for each use case, main findings, study limitations, as well as the challenges and opportunities for future work.

7. Evaluation and integration of predictive modelling for enhanced management of multimorbid patients (Use Case 1)

Multimorbidity's central influence in risk evaluation – The predictive models reported in **Articles 1** and **2** stand out for their capacity to describe the logic behind the predictions, achieved through the Mean Decrease in Accuracy (MDA) analysis. This was an essential element for the assessment of the two predictive modelling

examples(142). Not only does this ensure transparency, but it also allows for a systematic ranking of variables, highlighting their relative importance within the models: (1) service selection at HaH admission; and (2) transitional care after discharge.

In the two scenarios, both aiming at informing service selection or personalisation of transitional care, the results indicated that the most relevant analysed predictors available at hospital admission fell into the following six categories: (1) age, (2) multimorbidity and complexity (e.g. AMG score), (3) functional capacity (e.g. SF36(143) survey, Barthel(144) and Braden(145) indices), (4) social frailty (e.g. MNA(146) and Barber(147) indices), (5) lab test results (e.g. complete blood counts), and (6) history of utilisation of healthcare resources (e.g. number of medical prescriptions, healthcare expenditure of the previous 12 months, number of hospitalisations of the previous 12 months). Notably, for transitional care modelling, vital information acquired during hospitalization, such as (7) the severity of the acute episode and treatment details (e.g., Queralt indices), was also integrated. Among them, the clinical complexity associated with multimorbidity was identified as the leading risk factor in the individual prognosis of adverse health events.

It is crucial to acknowledge the pivotal role that multimorbidity groupers play in capturing the clinical complexity of individuals, especially the baseline burden of morbidity (i.e., AMG score) and the severity of the acute episode (i.e., Queralt indices). Moreover, the statistical analysis conducted in these studies suggested synergies between integrating measures of the complexity of the baseline patient's condition and the severity of the acute episode, leading to an increased risk of post-discharge deleterious events. In addition, factors such as biological data or laboratory tests (e.g., blood counts), social risk indicators, and functional capacity impairment metrics have significantly contributed to enhancing the models' predictive accuracy.

Selecting the covariates for each predictive model is essential to ensure the models' optimal performance, as well as to enhance their generalization capacity. Additionally, feature selection must aim to guarantee compatibility with the system's data repositories, further ensuring interoperability. Accordingly, there was a deliberate transition from manually gathering data in research contexts to harnessing integrated

data from primary care (i.e., eCAP), electronic hospital records (i.e., SAP), and health registries (i.e., Catalan Health Surveillance System(137); CHSS). This strategic shift significantly reinforced the model's generalization, as illustrated in the methodological progression from **Article 1** to **Article 2**.

Towards patient-centred transitional care **-** The clustering analysis performed in **Article 2** aimed to complement the risk analysis delineating transitional care pathways tailored to distinct patient groups, allowing both identifying patients at risk and propose personalised post discharge health pathways. Four clusters were identified: Cluster 1 represents standard patient-centred transitional care. Patients in cluster 2, were primarily men with unhealthy habits like smoking and sedentarism. These patients could benefit from preventive strategies and cognitive behavioural therapies initiated during acute episodes and extended into community settings. These patients exhibited high post-discharge mortality rates and frequent ER visits. Clusters 3 and 4, which comprise older patients with high social and medical complexity, respectively, have the highest mortality index and rates of visits to emergency rooms and hospitalization.

Patients allocated on clusters 3 and 4 necessitate care-focused interventions and optimised home-based services. Collaborative efforts between HaH resources, intermediate care, and primary care programs are vital for assisting patients in these clusters, with cluster 3 requiring social support and cluster 4 needing attention to complex medical and multidimensional needs. In this context, three cardinal interventions emerge: (1) therapeutic interventions, (2) supportive care, and (3) end-of-life measures. Therapeutic interventions, typically executed within specialized medical environments, are geared towards the precise diagnosis, treatment, and mitigation of pathological conditions. Supportive care facilitates the transition of patients from acute medical settings to domiciliary or community-centric care, highlighting the significance of patient empowerment, therapeutic adherence, and post-discharge surveillance. On the other hand, end-of-life care measures transition from aggressive therapeutics to a concentration on palliation, ensuring patient comfort and upholding their dignity while concurrently aligning medical undertakings with the patient's predetermined preferences. Cumulatively, these interventions offer an

intricate blueprint for transitional care, holistically addressing patients' medical and comprehensive necessities throughout their healthcare continuum.

Overall, incorporating complex computational risk models, that consider both risk stratification and profiling, into clinical routines can streamline patient screenings and referrals, making the process both efficient, economically viable and with high levels of acceptance by patients/relatives, as well as by health professionals. Moreover, such approach postulates to be one of the principal catalysts to bridge the effectiveness gap between RCT's and real-world interventions(148,149), as well as promoting the integration of the system(150–152), vertically, between primary and specialized care, as well as horizontally, between the clinic and socio-health care.

7.1. Main limitations

Overall, this research highlights the potential of computational models for service improvement. The next steps involve real-world validation and converting these models into actionable clinical support tools. While the implementation challenges extend beyond the scope of this thesis, two critical hurdles for real-world application have been identified: 1) the need for validation and continuous assessment of the models in real-world scenarios, and 2) the factors limiting their clinical interpretability, usability, and adoption.

The ongoing evaluation and validation of the integrated clinical decision support mechanisms - Continuous evaluation of the models is essential to: 1) Uphold their predictive accuracy and reliability; 2) Adapt to evolving diagnostic techniques and therapeutic interventions; 3) Respond to shifts in population demographics; and 4) Guarantee patient safety. Solutions encompass automated feedback loops for real-time user insights, regular model calibrations, and external unbiased assessments. Incorporating adaptive learning allows for model updates with new data, while demographic sensitivity testing maintains accuracy across diverse patient groups. Monitoring systems ensure patient safety, and stakeholder feedback, performance dashboards, and periodic reviews keep the model’s integrity and efficacy in check.

The crafting of intuitive, user-centric interfaces tailored to specific user profiles **-** In this PhD thesis, a central emphasis was on developing AI models with a strong focus on explaining the logic of the predictions. This was achieved using algorithms based on decision trees and enhanced by additional analytical methods, such as the MDA analysis, to boost prediction clarity and transparency. However, some challenges remained out of the scope of the thesis such the integration of the models into real world healthcare processes. In this regard, some elements to consider are: 1) Deploying of integration channels, such as Application Programming Interfaces (APIs) or middleware, for effective data communication with existing infrastructure. 2) Employing techniques like Local Interpretable Model-agnostic Explanations (LIME)(153), Shapley Additive Explanations (SHAP)(154) or Anchor(155) methods to enhance understanding and transparency in AI predictions. 3) Integrating with advanced Business Intelligence platforms is indispensable for tracking model performance and outcomes, enabling clear, real-time visual insights via tailored dashboards. 4) Equipping systems with alert functions and continuous feedback loops may help to maintain model precision and promptly address any discrepancies or changes in prediction trend.

7.2. Challenges and Opportunities

While our findings elucidate the potential of the computational models to improve service selection and personalized transitional care paths after hospitalization aiming at providing guided transitions from hospital setting to the community. The immediate future pushes deeper into validating the models, especially in larger cohorts and in real life-clinical settings. There is an impending necessity to translate the empirical strengths of our computational models into tangible clinician tools, bridging the gap between advanced analytics and bedside clinical decisions.

This process inevitably necessitates the evaluation of two facets: (1) Determining if the observed results are specific to HCB or if they can be generalisable to other centres. (2) Clinically validate the models and establish the basis for integrating the models into existing workflows.

The outcome of the first assessment should indicate whether the issue can be tackled at a territorial level, promoting the implementation of predictive and management tools at the Catalan level. This external validation allows exploring whether the developed modelling strategy can be applied at the health system level and potentially incorporated into Catalonia's new shared clinical history.

In this regard, the insights generated from the study of almost 100,000 hospitalisation episodes (**Article 3**), both from home and conventional hospitalisation regimes, play a crucial role. The regional assessment of HaH in 27 hospitals across Catalonia revealed the heterogeneity in the profiles of the treated population. The study observed variations that align with existing literature(156–158). The research identified differences across multiple parameters, including age upon admission, multimorbidity-complexity as measured by the AMG score within the 12 months preceding admission, and the acuteness of the episode as assessed by both the APR-DRG and Queralt index metrics. Analogous discrepancies were evident in other assessed metrics, such as the duration of hospital stay. These heterogeneities were influenced by strategic decisions at the hospital level, partly conditioned by the hospital's geographical location, its territorial role, number of beds, and the facility's specialisation and technological advancement. The noticeable heterogeneities observed across the 27 health centres challenge the feasibility of the multicentric approach, suggesting potential generalisation issues and the importance of tailoring HRA strategies to each healthcare provider. To address this specific issue, customisation of the data models due to adjustments in the available covariates and in-house specific training of the models is highly recommended.

Moreover, another constraining factor arises in the accessibility of clinical data belonging to the healthcare providers and the approach's viability when relying exclusively on registry data. This evolution might result in the omission of specific hospital data, necessitating a re-evaluation of model performance and the identification of alternative indicators for certain variables potentially derived from registry data. Nevertheless, accessing hospital data sources is also essential for utilising metrics like the Queralt indices and combining this information with the clinical data

on the EHR and diagnostic tests. Therefore, parallel actions are recommended in two distinct areas: the healthcare system and the clinical level.

To assess the viability of the approach under consideration, the foundation for a study protocol has been proposed (**Table 1**). The study would involve the reanalysis of over 200,000 hospital episodes in Catalonia (**Article 3**), followed by a focused sub-study at the HCB.

The analysis adopts a macro-level perspective. Here, the focus is not merely on reanalysis but on a more intricate reengineering of the models stemming from insights from the vast dataset of over 200,000 hospital episodes in Catalonia, as described in **Article 3**. The reengineering effort would entail the strategic incorporation of system covariates. The fundamental objective behind this is to rigorously test the generalizability of the approach across diverse healthcare settings in Catalonia. Given the previously recognised disparities and heterogeneities, this modelling seeks to ascertain if the approach can be standardised, benefiting a broad spectrum of healthcare institutions regardless of their strategic decisions, geographical positioning, or technological infrastructure.

Transitioning from the expansive view of the regional approach, the second analysis narrows its scope to the HCB. This focused sub-study on a smaller, more specific subset of data seeks to accomplish two critical objectives. First, it aims to validate the preliminary findings (**Article 2**) by testing the models against an independent population, ensuring that the insights are not merely coincidental or skewed by the earlier dataset. This validation aims to reaffirm the credibility, accuracy, and potential applicability of the models. Second, and equally vital, is the objective to chart a roadmap for the real-world implementation and testing of the proposed solution. Such a strategy must encompass the nuances of integrating the computational models into the HCB's existing workflows, laying the foundation for practical applicability, and measuring real-time efficacy for the continuous evaluation and retraining of the models.

Table 1: Overview of the proposed study protocol on predictive modelling for guiding post-hospital discharge transitions. *This table offers a detailed summary of the study aiming to predict re-admissions and support post-hospital discharge transitions.*

Prediction of re-admissions and support in post-hospital discharge transitions	
Study cohort	207,152 hospitalization episodes in the region of Catalonia (27 healthcare providers), from the 1st of January 2015 to the 31st of December 2019. Among them, 175,238 episodes were conventional hospitalizations and the remaining 31,914 were HaH discharges. The corresponding numbers for HCB were 13,542 divided in 10,740 and 2,802 discharges for conventional and HaH hospitalisations, respectively.
Databases	1. Registry data extracted entirely from CHSS database. 2. Clinical data from HCB EHRs.
Variables	Reported in **Articles 2 and 3**
Predictive modelling generation and assessment of CDSS	
Objectives	**O1.** Elaborate predictive modelling of the risk of mortality and post-discharge readmissions, applicable in the clinical scenario, using: i) the entire dataset, ii) by healthcare provider, and iii) clusters of providers identified in **Article 3**. **O2.** Elaborate specific modelling for HCB, enriched with clinical information. Retrospective evaluation of the modelling using HCB discharge data from 2022. **O3.** Design and testing of a CDSS fed by predictive modelling developed with HCB data (O2). **O4.** Test the implementation process, with IS tools, in a real world setting at HCB. **O5.** Design and testing of a CDSS fed by predictive modelling (O1) for potential integration and use in the future Catalan clinical record.
Expected outcomes	**EO1.** Generation of predictive modelling for risk assessment of adverse events within 30 days of hospital discharge, such as mortality and unplanned hospital readmissions; with the aim of optimizing transitional care strategies and the prevention of income from the community in high-risk patients. **EO2.** Design and assess the process of implementation, adoption, and continuous evaluation of the resulting CDSS at HCB (O2-O4). **EO3**. Define a roadmap for regional implementation and assessment of the CDSS generated in O1 and O5.

8. EXPLORING MORBIDITY GROUPER ADOPTION DYNAMICS IN EUROPE (USE CASE 2)

Population-health and population-medicine approaches - The second use case reviewed the transference and adoption of the AMG algorithm and a customised dashboard using aggregated data, a pivotal element for informing and monitoring primary HRA interventions. Marche applied a broad population-health perspective, utilizing resources across the region, encompassing multi-tiered healthcare system data, including hospital data and chronic care registries. In contrast, Viljandi hospital in Estonia employed a narrower, regional population-medicine approach focused on data representative of hospital-treated individuals, leading to an older and more acute or chronically ill patient sample. Data sources and composition differences significantly influenced AMG scoring distributions among Catalonia, Marche, and Viljandi. The input data type profoundly affected the goals and appropriateness of HRA strategies. While Marche's approach suited regional health policy and governance, Viljandi's approach informed the PAIK2(159) protocol design addressing prevention of unplanned hospitalizations.

The Marche region's approach effectively achieved the integration of the AMG algorithm and a customized dashboard for the regional exploitation of data to inform health policy, resource allocation, benchmarking, and governance. In this regard, a pivotal achievement was to overcome potential technical problems in dynamically assembling the dataset required to feed the AMG algorithm using heterogeneous data sources. Moreover, the process of transfer, anticipated future challenges for consideration comprise overcoming the constraints in implementation of HRA tools, such as the AMG algorithm in clinical settings. This problem stems from the legislative nuances of the GDPR within the Italian jurisdiction, explicitly concerning the secondary utilization of health data. Nevertheless, this is not a uniqueness of the Italian legislation. While the GDPR binds all member states, individual countries frequently enact supplementary regulations to address specific concerns. For instance, Germany has implemented the BDSG, France operates under the Data Protection Act with CNIL oversight, and the Netherlands has adopted the UAVG. These legislations introduce

specific distinctions related to health data, often emphasizing the necessity for explicit consent and potentially complicating such data's secondary use.

On the other hand, in the context of the implementation of PAIK2 protocol in Viljandi hospital, the AMG algorithm assumed a pivotal role in screening patients for potential inclusion in a preventive intervention targeting to reduce unplanned re-hospitalization rates among high-risk chronic patients. This initiative is congruent with the local findings and assessments delineated in the first use case, targeting to enhance transitional care. In addition, the success of PAIK2 may hold key implications for healthcare governance and strategy in Estonia. Successful execution and outcome of this initiative would contribute to securing robust commitments from the Estonian government (i.e. Ministry of Social Affairs) and the Estonian Health Insurance Fund, promoting the escalation of this approach nationwide. The accumulated experience from Viljandi becomes particularly valuable in this context. With the expertise gathered from the Viljandi hospital initiatives, there is a strategic inclination towards pioneering value-based reimbursement models. With collaboration from Optimedis, this innovation aspires to position Viljandi Hospital at the forefront of healthcare transformation by establishing it as an accountable care organization.

Both operations have fostered the expertise required for future tailored HRA strategies. In this regard, the following key elements were identified as major requirements: 1) ensure political commitment, 2) have sufficient digital infrastructure, to ensure interoperability among needed datasets, as well as appropriate dynamic data management 3) overcome potential limitations due to GDPR compliance, 4) use IS tools to foster stakeholder engagement, and 5) develop or adopt a regulatory framework for secondary health data use.

8.1. Main limitations

The European healthcare mosaic: Insights from Marche & Viljandi in European healthcare - The European healthcare panorama, with its intricate interplay of diverse systems, that has adopted models ranging from the Bismarck and Beveridge systems to mixed models often seen in transitional countries of Eastern Europe(160,161) often

presents challenges that demand innovative and adaptable solutions. Within this complex mosaic, the achievements observed in the regions of Marche and Viljandi stand as examples to what can be accomplished with the proper combination of methodology, technology, and vision.

Within this diversity, the GDPR stands as a unifying force, setting stringent standards for patient data protection. However, it also presents challenges due to varying GDPR interpretations. For instance, in Marche, these interpretations restricted the utility of the AMG in guiding regional-level HRA using aggregate data, precluding the use of personal data, constraining a more granular, patient-level approach and thereby impeding the execution of personalised clinical interventions. These variances can affect how patient data is collected, processed, and used for HRA, as well as hinder cross-border health research.

Within European healthcare, there is an evident rise of private insurers coexisting with public systems, leading to a bifurcated healthcare paradigm, exemplified in Estonia (e.g., Viljandi). This dualistic healthcare ecosystem inadvertently leads to system fragmentation and generates information silos and conflicts over health data ownership. Consequently, this fractured landscape poses considerable challenges to the efficient design and deployment of comprehensive HRA interventions, potentially undermining optimal patient care outcomes. Underpinning these systems are varied reimbursement models. From traditional fee-for-service structures and capitation methods to the more contemporary value-based reimbursements and salary-based models. In this regard, HRA may lay the groundwork for value-based care by aligning reimbursements with patient outcomes, not just services rendered. This would incentivise providers to prioritise high-quality, patient-focused care, fostering a more sustainable and efficient healthcare system.

The complexities listed above, illustrated in **Article 4** by regions like Marche and Viljandi, presented intricate challenges, especially with GDPR interpretations, balancing public and private healthcare, and adopting new reimbursement models. While the role of HRA and methodologies like AMG is emphasised, these insights are preliminary. Further research is essential to validate these observations, considering a

variety of morbidity groupers beyond AMG, and to craft tailored strategies for adoption and mainstream utilisation in each European region.

8.2. Challenges and Opportunities

As discussed in the limitations alluded to above, the European healthcare landscape is a complex mixture of diverse systems, traditions, and innovations. This leads to the consideration of the immense potential inherent in flexible, adaptable, data-driven, and open-source HRA solutions such as the AMGs. Nevertheless, without a comprehensive understanding of the current state of each member state, the adoption of HRA tools may result in inefficiency, resource wastage, and potential risks.

In this regard, the JADECARE consortium brought together a diverse group of stakeholders from 21 European regions and healthcare organizations. Therefore, the project offers a good opportunity to conduct a systematic and comprehensive evaluation, of the readiness for mainstream adoption of HRA tools across Europe and elucidate challenges to overcome. By harnessing the collective expertise of its members, JADECARE is positioned to provide different perspectives, experiences, and insights.

For this purpose, it is highly recommended to devise a survey for all JADECARE locations, 4 original Good Practices (oGP) and 21 Next Adopters (NAs). **Table 2** offers a detailed conceptual framework for this survey, meticulously capturing each healthcare system's intricate details and distinct readiness levels. This initiative has been presented in the project's final conference (September 2023), and the execution is proposed for the following six months. As an integral component of the JADECARE framework, the collaboration of the four oGP is essential. The insights from this survey will lay the foundation for a unified HRA protocol that acknowledges the diversity of the European healthcare landscape, learns from its heterogeneity, and seeks to create a harmonised strategy for the future. This study would provide invaluable data for current stakeholders and pave the way for future collaborations, innovations, and strategies to optimize the implementation of HRA tools across Europe beyond JADECARE.

In addition to the challenges mentioned above, two critical facets merit attention. Primarily, an amplified imperative exists to bridge the interface between clinical and research data. Addressing this on an EU-wide scale is crucial for facilitating efficient cross-border collaboration. Noteworthy initiatives such as EHDS, ELIXIR, and STAND4PM have demonstrated advancements in this domain. Subsequently, the systematic integration in health data repositories of patient-centric data, specifically PROMs and PREMs, whether derived from biosensors or self-administered standardised health questionnaires, emerges as a fundamental requirement. It should be noted that while these domains were not the central examination of this thesis, their relevance is acknowledged in the concluding passages of the discussion.

***Table 2**: **Proposed scheme of the survey framework designed to assess JADECARE's healthcare systems' diversity and readiness in HRA tool implementation.** It covers topics from basic respondent information to intricate details on tool effectiveness, approach strategies, system maturity, reimbursement models, and future adoption strategies. A detailed format of the survey will be produced upon approval of the concept.*

JADECARE survey protocol: heterogeneities & maturity in HRA tools implementation	
Objective	Evaluate the diversity and readiness among JADECARE partners in implementing HRA tools.
Target respondents	Members from the 21 NAs and 4 oGPs representing different healthcare entities and fulfilling various roles.
Section 0: General information	
Name and country, entity, department, and respondent's role	
Section 1: Current HRA tools assessment	
Existing tools	List and briefly describe the HRA tools currently in use.
Effectiveness and gaps	Evaluate the effectiveness of current tools, identifying any gaps or flaws in their approach or application.
Section 2: Approach and strategy	
Source population focus	Determine whether the approach is population-health or population-medicine and elucidate their specificities.
Impact of data sources	Describe the composition of input data sources available.
Purpose & suitability	Detail purposes of the HRA and how the composition of input datasets may influence the suitability and objectives of HRA strategies.

Section 3: Maturity and implementation	
Political commitment	Describe the level of support and commitment from regional/country leadership.
Digital infrastructure	Assess the current digital maturity at the site and anticipated improvements.
GDPR Constraints	Expose the challenges associated with GDPR compliance
Secondary health data utilization	Describe the present framework, or plans, for using secondary health data, especially in business intelligence and computational modelling for clinical applications.
Implementation science tools	Enumerate and discuss the tools or strategies employed to encourage stakeholder engagement and streamline HRA adoption.
Section 4: Insights on reimbursement models	
Current model description	Detail the existing reimbursement model, emphasizing its main components and principles
Impact on HRA	Discuss how the current reimbursement model influences HRA strategies, practices, and outcomes
Alignment with patient outcomes	Evaluate if and how the reimbursement model aligns with and incentivizes improved patient outcomes.
Section 5: Strategies for wider adoption	
Open-source availability	Discuss the advantages, challenges, or concerns regarding the use of open-source software for HRA tools.
Collaboration strategies	Share experiences or plans on public-private collaborations that promote productive interactions and regional networking.

9. LEVERAGING MORBIDITY METRICS AND DISEASE TRAJECTORIES (USE CASE 3)

Integrating disease trajectories on morbidity groupers for risk stratification: a proof of concept **-** The final manuscript (**Article 5**) aimed to elucidate a proof of concept for formulating a novel morbidity grouper (i.e., the MADS). This new grouper seeks to optimize HRA tools in adjusting the assessment of the morbidity burden considering a principal disease and a cluster of its direct comorbid conditions throughout a sophisticated filtration of spurious disease associations achieved using BDMMs. Crucially, MADS offers an enhanced perspective on multimorbidity progression by

integrating data derived from temporal disease maps obtained from trajectory analyses. In this study, MDD served solely as an illustrative use case.

The research identified strong correlations between MADS risk levels and the adverse effects of MDD and related conditions, indicating higher health risks (higher MADS score) was associated with increased healthcare resource use. A statistically significant association resulted between MADS risk levels and both pharmacological and non-pharmacological healthcare expenditures. Also, high-risk groups showed a greater likelihood of disease progression and higher mortality rates within a year of MADS assessment. These findings reinforce the already described connection between multimorbidity (see "**Multimorbidity's central influence in risk evaluation"**) and adverse outcomes such as functional decline, reduced quality of life, and higher mortality rates but also underscore the immense burden borne by individuals and the healthcare system.

Furthermore, MADS provided a unique and more comprehensive understanding of the complex nature of depression-related multimorbidity. It acknowledged that individuals with depression frequently encounter a spectrum of coexisting conditions, each exhibiting and progressing uniquely. This understanding transcends a bare enumeration of individual disorders, presenting a multifaceted evaluation that mirrors the patient's health. Such a comprehensive perspective fosters an interdisciplinary approach integrating psychiatric and somatic medicine. By initiating collaborative prevention strategies across specialities, healthcare practitioners can deliver a more integrative and efficacious care regime for patients with intricate health requirements.

9.1. Main limitations

From theory to practice: The challenge of generalizing MADS approach - While **Article 5** predominantly achieves its objectives and supports its underpinning hypothesis, it is essential to recognize a significant limitation in the MADS methodology: the utilization of the Global Burden of Disease (GBD) 2019(162) Disability Weights (DW)(5,162,163) to approximate disease burden. Though this

methodology has provided satisfactory outcomes and maintains a theoretical foundation, it is not without its inherent challenges.

A significant challenge arises in estimating disease severity since this information is not present in the accessed health registries. Ideally, each EHR diagnosis should specify the severity, progression rate, and resulting disability of the disease. However, precisely determining disease progression and disability is complex, primarily due to the multifaceted nature of such assessments. Using average values and severity distributions can occasionally result in over or underestimating individual morbidity burdens.

Furthermore, even with regular weight updates, employing DW introduces a degree of rigidity, reducing adaptability of the solution to specific environments. The morbidity burden of diseases on individuals and health systems can differ across regions, contingent on the matureness of the local health programs. An automated weight adjustment model, grounded in the statistical analysis of regional health data, would be advantageous to address to such diverse realities. Such an approach could also capture the impacts of less prevalent diseases, which are not considered in the GBD studies.

9.2. Challenges and Opportunities

The successful evaluation of the initial proof of concept with MADS paves the way for new avenues of research. Beyond the clinical validation of MADS, which is a mandatory next step, there are two pivotal areas to address. First, as mentioned previously, the tool's flexibility concerning the weights used to measure morbidity burden is first. Second is the deeper exploration of the tool's potential beyond the depression use case, escalating the approach to assessing other Non-Communicable Diseases (NCDs), broadening its impact, and paving the way for a holistic understanding and enhanced management of multimorbidity.

This consideration naturally highlights potential cross-fertilisation opportunities between MADS and AMG. Since the inherent methodology of AMG relies on disease-specific weights derived from statistical analyses incorporating mortality and

healthcare service utilisation data, this would allow MADS to calibrate disease impact according to specific health systems and regions. Conversely, MADS could offer AMG the capability to tailor its approach to specific disease clusters, enhancing its predictive accuracy in forecasting the progression of multimorbidity.

Currently, the AMG system presents to the practitioners with up to 15 binary indicators signifying the current presence or absence of major prevalent chronic health problems, namely: diabetes mellitus, heart failure, chronic obstructive pulmonary disease, high blood pressure, depression, HIV/AIDS, chronic ischemic heart disease, stroke, chronic kidney disease, cirrhosis, osteoporosis, arthrosis, arthritis, dementia, chronic pain. In this context, MADS approach could enhance these markers' predictive quality, transforming them into specific probabilistic risk indicators correlated with NCD disease clusters. This enhancement would strengthen patient risk characterization, facilitate early identification of emerging conditions, and promote predictive medicine, bridging the gap between specialized and community care. It would empower healthcare practitioners to make informed decisions and provide personalized interventions and referrals that align with each patient's unique risks and needs. This integration can improve the coordination and continuity of care, ensuring that patients receive the appropriate support and interventions across different healthcare settings.

In summary, the proposed research aims to develop accessory functions for the AMG tool, enhancing its capacity to predict multimorbidity progression while allowing to tailor its disease burden analysis to specific NCDs and associated comorbidities. The key objectives of this initiative are:

1. Utilizing the interplay between MADS and AMG to adjust the morbidity burden analyses to distinct disease clusters.
2. Amplifying AMG's predictive prowess for multimorbidity progression through integrating age-dependent disease-disease association weights from trajectory analyses.
3. Enhancing flexibility and generalization by replacing the current DW with the AMG weighting system.

To achieve these aims, the MADS methodology should be integrated into the AMG framework, complementing its existing binary indicators for NCDs with more sophisticated probabilistic risk measures related to distinct NCD clusters.

This endeavour is expected to yield a comprehensive understanding of multimorbidity dynamics, refined weightings tailored to specific disease clusters, and evolved risk indicators that offer granular insights into potential disease pathways associated with specific NCD categories.

Finally, the three distinct use cases converge to form a comprehensive research roadmap that aligns with the Catalan HRA strategy, fully described in **Article 4**, and charts a plan for the EU-wide transferability of its mature facets. Collectively, these cases do not merely function as isolated analyses but coalesce to stress the thesis as a coherent, integrative exploration into advancing HRA methodologies. While the studies have illustrated a path forward, they have also sharply identified existing limitations, and there is a cognizant understanding of the need to evolve further and adapt to achieve the ideal environments for comprehensive HRA application.

10. BRIDGING TODAY AND TOMORROW: PREPARING FOR NEW FRONTIERS.

In the thesis introduction, the MCPM is portrayed as the ultimate goal for predictive modelling strategies. The essence of this approach has been distilled in the models developed in this thesis, emphasising the integration of various health determinants into a unique risk model. However, the realisation of a multilevel model that incorporates data from the four essential domains, namely: 1) clinical data, 2) population health, 3) informal care, and 4) biomedical research, remains as a utopia.

This can partly be attributed to the complexities of integrating omics data, encompassing genomics, transcriptomics, proteomics, and metabolomics, into holistic modelling strategies. Research has indicated that the disease-specific nature of omics biomarkers presents challenges for its universal application across a spectrum of disease conditions(164). Although the potential of omics research is vast it is still an emerging field, as highlighted in the findings reported by high-impact research projects such as the Human Genome Project(165) or the International Human Epigenome

Consortium(166). Continuous advancements are being made, but a comprehensive understanding of the interplay among the human genome, interactome and diseasome remains elusive(167–169). Another factoring that hinders the practical application of multiomics data in the proposed modelling strategies is the vastness of omics datasets. Their hyperdimensional nature needs advanced computational tools and deep expertise for practical analysis and application. It should also be mentioned that there is no standard model for the persistence of omics data, as is the case with clinical data, like with OpenEHR(170). Nevertheless, despite these challenges, the current modelling approach has demonstrated notable efficacy. Its accomplishments are evidence to its potential, even without completely embracing the MCPM model. With advancements in omics research and the refinement of our computational capabilities, the MCPM as it is conceptualized should soon become a reality.

In addition, the multisource data integration requires for deep interdisciplinary collaboration. However, the current healthcare processes, built on traditional workflows, are no longer sufficient to meet the multifaceted demands of today's challenges on collaborative healthcare. The emergence of Adaptive Case Management (ACM)(171,172) tools offers promising prospects in this scenario. ACM tools, designed with adaptability at their core, facilitate seamless communication among professionals and empower them to respond to individual patients' dynamic needs. By integrating these tools, healthcare systems can transition from rigid procedural routines to more fluid, responsive, and patient-centric models, ensuring that care is comprehensive and tailored to the unique requirements of each patient. Embedding AI risk assessment models within ACM is still an unmet need and would represent a significant advancement in pursuing safer, more effective, and highly personalized healthcare(172).

Other factors such as the absence of standard data models or the lack of the appropriate infrastructure have been also determinant to limit the adoption of the MCPM approach coupled within the LHS framework (**see Appendix: Personalized Medicine meets Artificial Intelligence; Chapter 10: "Multilevel Modelling with AI: The Synergy-COPD Endeavour" for more information**), which is still considered an idealised vision for the future of healthcare. However, this scenario is getting closer

every day. Locally, the Catalan health system recognises this momentum, fostering governmental initiatives such as the Catalan Information Systems Master Plan(173). This is not mere technological upgrades but strategic endeavours to reconfigure healthcare's foundation.

The Master plan's main aim is to generate a new clinical history based on OpenEHR, to generate a unique and common data model that all SISCAT(174) stakeholders will use to register, store, exchange, and process health-related information. In addition, the model also contemplates the generation of an analytical repository (**Figure 13**), boasting a range of analytical tools, varying in complexity, designed to perform multiple tasks.

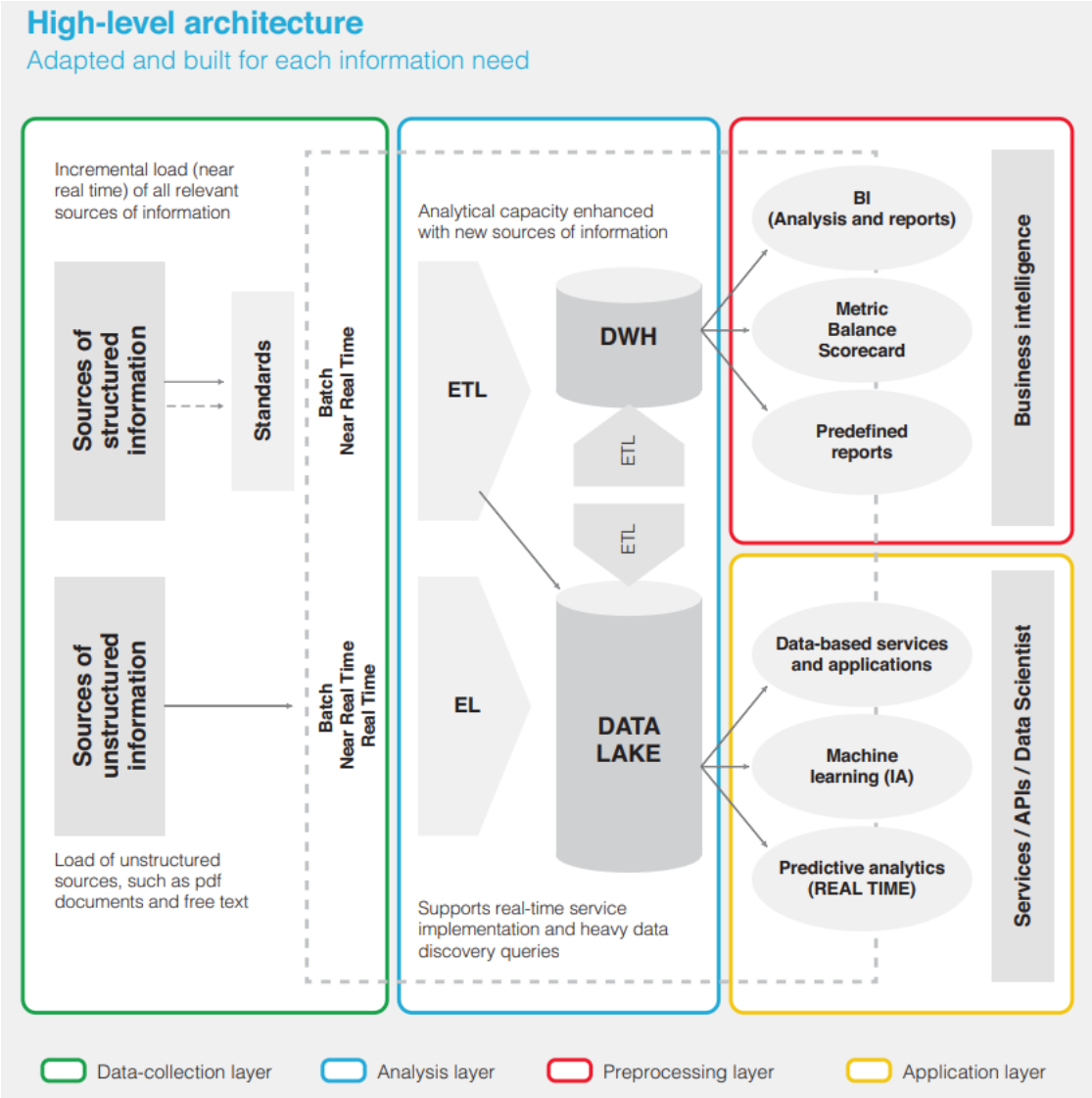

Figure 13: Diagram of the architecture of the analytical repository conceived in the Catalan Information Systems Master Plan. *The data collection layer integrates cloud services with*

necessary structured and unstructured on-site data sources. The analysis layer manages the extraction of data from varied sources, converting it to the appropriate format for storage and analysis in the target data lake or warehouse. The application layer offers a gateway to standard platform services for data analytics, while the preprocessing layer ensures the business intelligence applications integrate with specific clinical workstations and patient portals. Figure taken from (173).

These tools serve diverse purposes, from generating reports and dashboards, performing searches in indexed fields, undertaking multidimensional analyses, and devising AI-powered tools, recommendations, and clinical instruments. Over time, this repository is projected to incorporate various data types from public health, mental health, social care, and unstructured data sources, including textual content, imagery, and digital media platforms. Envisioning such comprehensive predictive models, as discussed in this PhD thesis, accentuates the significance of weaving together diverse datasets.

In this regard, transitioning from academical formulations such as this PhD thesis to tangible, real-world implementation marks a pivotal milestone for any healthcare advancement. In this regard, the Catalan health system, with its mature digital infrastructure, offers an unparalleled environment for such a transformation. Within this ecosystem, the models presented in this thesis would not be just assessed; also contextualized, enhanced, and optimized, benefiting from the system's comprehensive data resources, robust infrastructure, and analytical capabilities. This thesis could contribute in fostering innovations to undergo rigorous inspection, iterative refinement, and continuous evaluation, ensuring maximum utility for both patients and healthcare professionals aligning perfectly with the principles of a LHS.

CONCLUSIONS

1. Embracing holistic health risk assessment strategies that considers multimorbidity assessment and other health determinants is fundamental for steering health system transformations towards patient-focused, value-driven healthcare.

2. The assessment of the burden of multimorbidity is a core driver in risk evaluations of chronic care. The use of morbidity groupers becomes crucial in predictive modelling, offering advantages ranging from the characterisation of clinical complexity to the reduction of the analysis's dimensionality, favouring the models' explainability.

3. Population-based and clinically oriented health risk assessment are complementary and synergistic entities. Nevertheless, the ethical and regulatory dimensions of using health data for clinical forecasting must be thoroughly evaluated, and the interventions must be tailored to the local legislation.

4. The transference and adoption of mature health risk assessment strategies across different sites is achievable, if the following conditions are met:
    a. Strong political commitment.
    b. Appropriate digital infrastructure ensuring dynamic interoperability among needed datasets.
    c. Willingness to overcome potential limitations for secondary health data use, due to GDPR compliance.

5. Incorporating insights from disease trajectories analysis, in terms of temporal disease-disease association weights, while improving the filtering of indirect disease associations using Bayesian direct multimorbidity maps, reported promising prospects to adjust the morbidity burden assessment to an index

disease and its comorbid conditions and enhance the prediction of the progression of multimorbidity.

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