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Blood Biomarkers of Aging and Multimorbidity Prognosis in Older Adults: Preliminary Results from the BIO-SIGN Project

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INTRODUCTION

Increased life expectancy is associated with the presence of multiple chronic diseases (i.e., multimorbidity), affecting health trajectories and care demands of older adults. The identification of a pool of accessible biomarkers that reflects specific endophenotypes of physiological dysregulation, may facilitate prognostication in older adults living with multimorbidity, offering a valuable tool for clinical decision-making and personalized interventions [1-3].The BIO-SIGN project aims to assess how a rich set of novel biomarkers, along with clinical, environmental and behavioral factors, interact in the definition of specific multimorbidity patterns and their association with negative outcomes, specifically all-cause mortality.

OBJECTIVES

First year of the project focused on two different objectives. First objective was the selection of a set of accessible and reliable biomarkers of multimorbidity, through extensive bibliographic research. Second objective was to identify homogeneous groups of multimorbid individuals (≥ 2 diseases), who share similar underlying disease patterns, using two Italian cohorts of randomly selected resident adult individuals.

METHODS

OBJECTIVE 1. A systematic review was conducted on PubMed and Web of Science to identify peer-reviewed studies assessing the association between individual biomarkers in human fluid samples and multimorbidity. Based on this review, a panel of significant blood biomarkers associated with multimorbidity was selected for further investigation in this study.

OBJECTIVE 2. The identification of multimorbidity patterns involved the two Italian cohorts of CUORE project [4] and Moli-sani project [5] (baselines 2008-2012 and 2005-2010, respectively), which share similar data collection methods. We focused on older adults aged 60-79 years. To ensure consistency and minimize data heterogeneity, a rigorous process of harmonization was applied. Population clinical characteristics were studied and homogeneous groups of individuals sharing similar underlying disease patterns were identified using Latent Class Analysis (LCA) [6]. Cox regression models were used to assess the association between multimorbidity patterns and mortality over 14 years of follow-up, with results pooled in a random-effect meta-analysis.

RESULTS

OBJECTIVE 1. SYSTEMATIC REVIEW FOR BIOMARKERS IDENTIFICATION

The systematic review identified several inflammatory and metabolic biomarkers, such as IL-6, triglycerides, LDL choles-

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terol and kidney and liver markers such as CyC, Aspartate aminotransferase and Alanine aminotransferase as being directly associated with multimorbidity. Additionally, neurodegeneration related biomarkers, including NfL and p-Tau 217, showed similar associations. Plasmatic level of Aβ40/42 showed a significant direct association with multimorbidity in less robust studies, while vitamin D displayed an inverse association with multimorbidity in two studies. Findings for other biomarkers such as TNFα receptor II, total cholesterol, HDL cholesterol, CRP, and Insulin-like growth factors 1 were inconsistent across studies. On the basis of the literature review, a list of blood biomarkers was selected to be assessed in relation to the aims of the BIO-SIGN project (Table 1). Furthermore, based on the researcher's expertise, standard pancreatic (insuline, C-peptide), cardiovascular (NT-proBNP), metabolic (glycemia), hepatic and renal (creatinine, albumine) biomarkers were included to the list along with emerging candidates linked to inflammatory, vascular, and hormonal dysregulation (GDF-15, I-CAM-1, V-CAM-1, leptine, MIG, GFAP) to ensure comprehensive coverage of relevant biological pathways.

OBJECTIVE 2. MULTIMORBIDITY PATTERNS IDENTIFICATION

In relation to the cohort studies, total samples of 3,695 individuals in CUORE (48% male, mean age 68.8 years [SD 5.6]) and 7,801 in Moli-sani (51% male, mean age 68.2 years [SD 5.4]) were evaluated and a total of 33 chronic diseases were considered. In both cohorts, six multimorbidity patterns were identified: hypercholesterolemia; metabolic, depression and cancer; cardiometabolic and respiratory; gastrointestinal, genitourinary and depression; respiratory; unspecific (i.e., no diseases overexpressed). A seventh pattern of multimorbidity-free participants was identified. Incidence rates of mortality were 1.7 and 1.9 per 100 person/years for CUORE and Moli-sani, respectively. When compared to participants without multimorbidity, those displaying a cardiometabolic and respiratory pattern were associated with the highest mortality (pooled HR 2.62; 95% CI 2.15-3.10), followed by unspecific (pooled HR 1.45; 95% CI 1.21-1.68), respiratory (pooled HR 1.33; 95% CI 1.01-1.64), and gastrointestinal, genitourinary, and depression (pooled HR 1.33; 95% CI 1.06-1.60).

CONCLUSIONS

During the first year of activity of BIOSIGN, we selected a panel of 25 blood biomarkers -across diverse diseases domains, as possible factors potentially able to define different endophenotypes of multimorbidity. Additionally, 6 different multimorbidity patterns were identified in two Italian cohorts and were differentially associated with survival. Further steps in the project will be to evaluate how biomarkers assessment can predict disease progressions and outcomes across these patterns. The identification of biomarkers as measurable prognosis factors for different homogeneous multimorbidity patterns in older adults may improve risk stratification, and prevent or reduce adverse health outcomes, including mortality. Such insights could enable personalized interventions and care plans and ensure a better allocation of health resources.

Biomarker	Disease domain
Interleukin-6 (IL-6)	*Inflammatory*
Tumor necrosis factor-alpha receptor 2 (TNFα receptor II)	
C Reactive protein (CRP)	
Monokine induced by gamma interferon γ (MIG)	
Intercellular adhesion molecule 1 (I-CAM-1)	*Inflammatory/ vascular*
Vascular cell adhesion molecule 1 (V-CAM-1)	
Growth Differentiation Factor 15 (GDF-15)	*Cardiovascular*
Pro B-type natriuretic peptide (NT-proBNP)	
High-density lipoprotein (HDL) cholesterol	*Metabolic*
Low-Density Lipoprotein (LDL cholesterol	*Metabolic*
Total cholesterol	*Metabolic*
Triglycerides	*Metabolic*
Glycemia	*Metabolic*
Creatinine	*Metabolic (renal)*
Cystatin C (CyC)	
Albumine	*Metabolic (hepatic/ renal)*
Insuline	*Metabolic (pancreatic)*
C-Peptide	*Metabolic (pancreatic)*
Leptine	*Metabolic/ hormonal*
Vitamin D	*Hormonal*
Phosphorylated Tau 217 (p-Tau217)	*Neurological*
Neurofilament-light chain (NfL)	
Amyloid Beta aa1-40 (Aβ40)	
Amyloid Beta aa1-42 (Aβ42)	
Glial fibrillary acidic protein (GFAP)	

Table 1. Panel of selected putative blood biomarkers of multimorbidity across diverse pathophysiological domains.

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