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Review article

Biomarkers of multimorbidity: A systematic review

Maria Beatrice Zazzara [a,b,*], Federico Triolo [c], Leonardo Biscetti [d], Ersilia Paparazzo [e], Marco Fiorillo [f], Davide Liborio Vetrano [c,g,1], Graziano Onder [a,b,1], on behalf of the BIO-SIGN Study Investigators

[a] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[b] Department of Aging, Orthopaedics and Rheumatological Sciences, Università Cattolica del Sacro Cuore, Rome, Italy
[c] Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet Stockholm University, Sweden
[d] Section of Neurology, Italian National Research Center on Aging (IRCCS INRCA), Ancona, Italy
[e] Laboratory of Pharmacoepidemiology and Biostatistics, Italian National Research Center on Aging (IRCCS INRCA), Cosenza, Italy
[f] Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, CS, Italy
[g] Stockholm Gerontology Research Center, Stockholm, Sweden

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ABSTRACT

The development of multiple chronic diseases in the same individual (i.e., multimorbidity) results from the loss of homeostasis across several biological systems. Identifying pathophysiological pathways common to multiple diseases, using accessible biomarkers, could increase our understanding of multimorbidity and improve its prognostication and management. We conducted a systematic review of peer-reviewed articles published till September 2024 that investigated biomarkers of multimorbidity. Due to study heterogeneity, a synthesis without meta-analysis was performed on 43 studies employing harvest plots based on direction of effect, sample size and study quality. Findings highlight how inflammatory and metabolic biomarkers, such as interleukin-6 (IL-6) and glycated haemoglobin (HbA1c) especially, but also triglycerides, low-density lipoprotein (LDL) cholesterol and kidney and liver markers, along with markers of neurodegeneration including Neurofilament Light Chain (NfL) and Phospho-Tau 217 (p-tau 217), were directly associated with multimorbidity. Nonetheless, evidence for hormonal and vascular activation markers, as well as more novel geroscience biomarkers, remains limited. These markers could have a key role in identifying individuals at high risk of developing or worsening multimorbidity. The review also highlights how methodological challenges, including heterogeneity in study design, populations, and multimorbidity definitions, impact on comparability and generalizability of findings. Addressing these gaps through standardized, longitudinal studies and multi-omics approaches is crucial to improve our understanding of the pathophysiological mechanisms of multimorbidity. In summary, this review outlines the independent association of diverse biomarkers with multimorbidity, opening to the possibility of identifying specific pathophysiological pathways for risk stratification and possible target of future personalized interventions.

Abbreviations: Aβ, Amyloid beta; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CSF, Cerebrospinal fluid; CXCL9, C-X-C motif ligand 9; DEHAS, Dehydroepiandrosterone sulfate; DMRs, Differentially Methylated Regions; EAA, Epigenetic age acceleration; EDA-FN, Extra domain A fibronectin; FN, Fibronectin; GFAP, Glial fibrillary acidic protein; HbA1c, glycated haemoglobin; HDL, High-density lipoprotein; IAGE, Inflammatory aging clock; IGF-1, Insulin-like growth factor 1; IL-1RA, Interleukin-1 receptor antagonist; IL-6, Interleukin-6; LDL, Low-density lipoprotein; MiR-181a, MicroRNA-181a; NfL, Neurofilament Light Chain; NLR, Neutrophil-to-lymphocyte ratio; PBMCs, Peripheral blood mononuclear cells; P-Tau, Phosphorylated Tau; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RDW, Red blood cell distribution width; SIRPB2, Signal regulatory protein beta-2; STNFAR1, Soluble Tumor Necrosis Factor Receptor 1; STNFAR2, Soluble Tumor Necrosis Factor Receptor 2; SOM, Self-Organizing Map; TNF-α, Tumor Necrosis Factor-alpha; TNFR1, Tumor Necrosis Factor Receptor 1; TNFR2, Tumor Necrosis Factor Receptor 2; T-tau, Total tau.

* Correspondence to: Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Francesco Vito 1, Rome 00168, Italy.
E-mail addresses: mariabeatricezazzara@policlinicogemelli.it, mariabeatrice.zazzara@unicatt.it (M.B. Zazzara).

[1] These authors contributed equally to the work and share last authorship.

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1. Introduction

Multimorbidity, the co-existence of multiple chronic diseases within an individual, is a common chronic condition encountered in old age, direct expression of aging itself and reflection of increased life expectancy. As advances in medical treatments have reduced the mortality rates of several diseases, such as cardiovascular diseases or malignancies, and transformed many of them into conditions with a chronic course and progression, prevalence of multimorbidity has increased sharply (Marengoni et al., 2011). Multimorbidity affects approximately 55–98 % of individuals aged 65 years and older, depending on the criteria used to define this condition and the sample assessed, and represents a significant public health challenge, complicating patients' management, heightening the risk of adverse outcomes, and increasing healthcare costs (Marengoni et al., 2011; Calderón-Larrañaga et al., 2017; Vetrano et al., 2019; Johnston et al., 2019). Consequently, multimorbidity is considered as a key barrier to achieving healthy aging.

The geroscience hypothesis suggests that aging itself might serve as the primary risk factor for the development of chronic diseases and multimorbidity. This hypothesis proposes that cumulative biological deficits, perturbations in the hallmarks of aging and the depletion of physiological resources associated with aging may represent the pathophysiological substrate of most of age-related conditions (López-Otín et al., 2013, 2023; Sierra et al., 2021; Sierra, 2016a, 2016b). By identifying and targeting the biological mechanisms of aging, it might be possible to delay or prevent the onset of multiple age-related conditions, thereby extending healthspan and reducing the overall burden of disease in the aging population (Longo et al., 2015). As a corollary to the geroscience hypothesis, the analysis of a single biomarker would probably be unsuccessful in capturing the intrinsic complexity of age-related conditions (Longo et al., 2015; Justice et al., 2018). Conversely, the assessment of multiple biomarkers would potentially be able to provide new insights into the dynamic and multifaceted nature of multimorbidity. Biomarkers of aging and multimorbidity should reflect the underlying biology of these phenomena, with changes in biomarker levels correlating to changes in disease susceptibility and functional decline (Justice et al., 2018). Consequently, in the framework of multimorbidity, biomarkers should represent endophenotypes for physiological dysregulation that may support early diagnosis, tracking of diseases progression, clinical decision-making and assessment of treatment response. From a research perspective, biomarkers can be simple and reliable tools for measuring and monitoring biological processes underlying multimorbidity and aging (Langenberg et al., 2023). Despite the increasing recognition of multimorbidity's significance, the current body of literature on this topic is sparse. A systematic review aimed at assessing physiological markers associated with multimorbidity, published in 2018, was limited in terms of number of relevant studied identified (a total of five) and did not specifically focus on the adult population (Ferreira et al., 2018). Together, the limitations of this latter review, along with the consistent expanding body of research in this area published in the last years, underscore a critical translational gap requiring an updated synthesis of the evidence that must be addressed to advance scientific understanding and improve clinical management in this field (Longo et al., 2015; Langenberg et al., 2023).

On this background, we performed a systematic review of the literature to provide a comprehensive and updated evaluation of fluid biomarkers associated with presence and development of multimorbidity. Based on the study results, we identified knowledge gaps and future perspectives in this field.

2. Methods

This is a systematic review encompassing published peer-reviewed studies assessing on the association between individual fluid biomarkers and multimorbidity. Scientific articles were reviewed regardless of study design, multimorbidity operationalization or type of fluid biomarkers. The protocol of the present study was registered a priori in the International prospective register of systematic reviews PROSPERO (registration number CRD42024616185) and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (checklist available as Supplementary Material). For the present study, no ethics committee approval was required.

2.1. Search strategy and studies sources

We conducted a systematic review of studies retrieved from PubMed and Web of Science. We restricted the search to studies published in the English language up to September 2024. To ensure an updated search, we performed a hand-search of the reference lists of the included articles to identify any additional relevant studies. Complete search strategies are available in Supplementary Materials.

2.2. Studies eligibility criteria, selection, and data extraction

Titles and abstracts of the studies were screened by four independent assessors (MBZ, LB, EP and MF). In cases where the relevance of a study could not be determined based on the title alone, the abstract was also reviewed to support the screening decision. The article selection process was conducted using Rayyan (Ouzzani et al., 2016).

Studies were selected if they focused on biomarkers assessed in human fluid samples in relation to prevalent (cross-sectional studies) or incident (longitudinal studies) multimorbidity or patterns/clusters of multimorbidity in adult populations (>=18 years). Multimorbidity was defined as the co-presence of two or more chronic diseases or in terms of number of diseases or accumulation of diseases over time. Any type of biomarker assessed in any biological fluid was considered (e.g., serum, plasma, blood, cerebrospinal fluid, saliva, urine, etc.); imaging biomarkers (i.e. radiological techniques) were not included. Studies were included, regardless of study design (i.e., cross-sectional and longitudinal analyses) or study settings (e.g., community-based, clinical samples). Studies were excluded if they focused on specific index diseases (e.g., diabetes with co-morbidities), were not published in peer-reviewed journals (i.e. conference proceedings, unpublished data), or did not present original research (e.g., case reports, reviews, commentaries).

The articles selected by at least two of the four independent assessors underwent full-text examination. Any disagreement regarding inclusion was resolved through consensus among the assessors and other co-authors (FT and DLV). Two assessors (MBZ and FT) independently extracted the following information from the included studies: study design, population study, number of participants included in the study, age and sex distribution of the study population, definition of multimorbidity and number of diseases evaluated to identify multimorbidity, type of biomarkers assessed, main results of the study selected in relation to the association biomarkers-multimorbidity.

2.3. Assessment of risk of bias

The quality of the included studies was evaluated independently by two assessors (LB and EP) using a modified version of Newcastle-Ottawa scale (NOS) for cohort and cross-sectional studies (Wells et al., 2012; Moskalewicz and Oremus, 2020). Details of the modifications made to the scale are provided in the supplementary material (Supplementary Text: "Quality Assessment"). For Cross-sectional studies, the final scoring was categorized as high (9–10 points), good (7–8 points), acceptable (4–6 points), low (<4 points). Cohort studies were classified as high (10–11 points), good (7–9 points), acceptable (4–6 points), low (<4 points).

2.4. Data synthesis

A narrative synthesis of the review findings was performed, with

summary data from each included study presented in tables. Due to the heterogeneity of the retrieved studies in terms of study designs, populations, multimorbidity definitions, biomarker types, and analytical approaches, a synthesis without meta-analysis (Campbell et al., 2020) was conducted using harvest plots to visually summarize the main findings. Harvest plots provide a standardized visual overview of the distribution and direction of the association between multimorbidity and various biomarkers, while also appraising critical factors such as sample size and study quality. Specifically, the harvest plots included 5 panels, each representing a different biomarker domain: inflammatory, metabolic, neurodegenerative, hormonal and vascular biomarkers. This classification was carried out by consensus incorporating the authors' multidisciplinary expertise and background geroscience. The five panels were further split in three segments to classify studies reporting an inverse, null or direct association, respectively. Direct associations were defined when increasing values of the biomarkers were significantly linked to increased risk (or similar measures) of multimorbidity. Null associations were defined as the lack of a statistically significant correlation between the biomarker and multimorbidity. Finally, an inverse association identified significant correlation between increased values of a biomarker and decreased risk of multimorbidity. Each bar depicted within the plot represents an association between multimorbidity and the biomarker, with the bar height indicating either the sample size or the quality score of the study. The quality of the study was also categorized into high, good, acceptable and low. Bars were further color-coded according to the design of the study (i.e., cross-sectional or cohort studies). If the same study presented two different types of analysis (i.e. cross-sectional and longitudinal associations), each association was represented by a differ bar in the harvest plot. Results from studies that encompassed a broad panel of biomarkers (e.g., -omics data, biological clocks) were narratively summarized in accordance with the main biomarker domain.

3. Results

The flowchart detailing the screening process of the articles is presented in Fig. 1. Overall, 43 observational studies out of the 4676 articles retrieved were identified as relevant for this work. The main characteristics and findings of selected studies are summarized in Supplementary Table S1. Studied differed in terms of study designs, populations, multimorbidity definitions, biomarker types, and analytical approaches. Briefly, sample size of the studies ranged from 23 to 700,000 participants, with a mean/median age varying from 38 to 89 years old. Among the studies, 16 had a longitudinal design, 19 a cross-sectional one while 4 studies presented both longitudinal and cross-sectional analysis. Most of the studies were carried out in the United

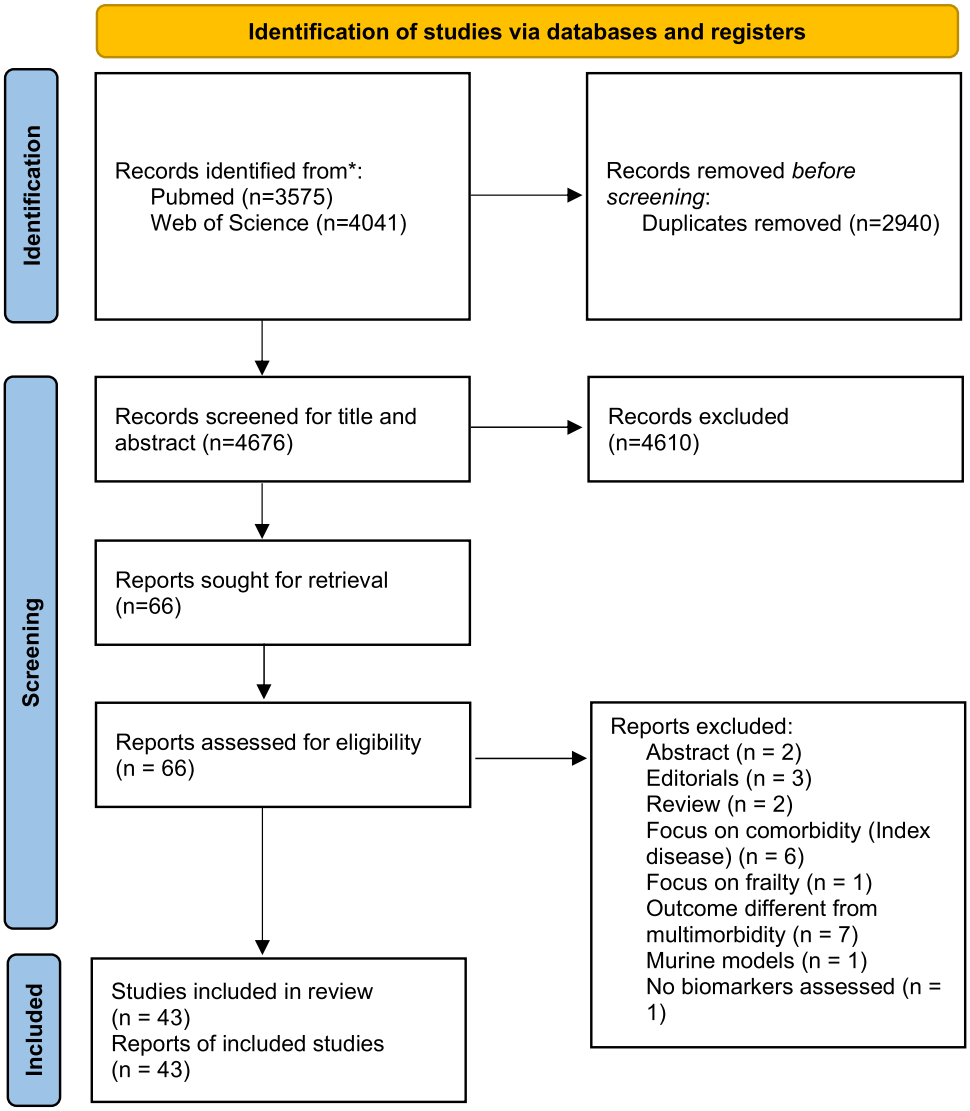

Fig. 1. PRISMA 2020 flow diagram.

States of America (n = 9) and China (n = 8). Across European countries, most studies were conducted in Spain (n = 6) and Italy (n = 5).

In terms of study quality, most of the longitudinal studies were evaluated of high (n = 10) or good (n = 8) quality. In contrast, eleven cross-sectional studies were rated as good quality while the rest of them were deemed of acceptable quality (n = 13) (Supplementary Fig. S1).

The definition of multimorbidity was heterogeneous across studies. In most studies multimorbidity was defined as the co-occurrence of two or more diseases, while in some studies multimorbidity was operationalized as the overall count of diseases. Moreover, 16 studies measured multimorbidity through different weighted score or scales such as the Charlson Comorbidity Index (CCI) (Charlson et al., 1987) or the Cumulative Illness Rating Scale (Conwell et al., 1993). Three studies operationalized multimorbidity both in terms of count of diseases or co-occurrence or/and patterns of multimorbidity (Aerqin et al., 2024; Ren et al., 2024; Villén et al., 2020). The total number of chronic conditions evaluated significantly differed across studies, ranging from a minimum number of three conditions assessed to a total number of 60. The main chronic conditions included in the assessment for multimorbidity were diabetes (in more than >90 % of the studies) and cerebrovascular disease in about 82 % of the studies, while the least represented were mainly related to psychiatric conditions, rarer neurological conditions or chromosomal abnormalities (9 %) (Supplementary eTable S2, Supplementary Table S3 and Supplementary Fig. S2).

4. Biomarkers domains

Association between multimorbidity and biomarkers classified according to specific domains is summarized by means of harvest plots reported in Fig. 2 and Supplementary Fig. S3.

4.1. Inflammatory markers

Thirteen articles investigated the relationship between inflammatory markers and multimorbidity. Amongst all inflammatory markers, interleukin-6 (IL-6) showed consistent direct association with multimorbidity in two good to high quality studies, in both longitudinal and cross-sectional analyses (Fabbri et al., 2015; St. Sauver et al., 2022). Among other pro- and anti-inflammatory cytokines only interleukin-1 receptor antagonist (IL-1RA) exhibited a direct cross-sectional association with multimorbidity (Fabbri et al., 2015). C-reactive protein (CRP) was associated with multimorbidity only in one cross-sectional study (St. Sauver et al., 2022), while no association was shown in one study examining both longitudinal and cross-sectional data (Fabbri et al., 2015) and two other cross-sectional studies (Martínez-Velilla et al., 2012; Cheong et al., 2023). One study showed also conflicting results for the soluble Tumor Necrosis Factor-α (TNF-α) receptors 2 (sTNFAR2), that displayed no association in the longitudinal analysis in contrast to a direct association found cross-sectionally. Conversely, sTNFAR1 showed no association both in both longitudinal and cross-sectional analyses

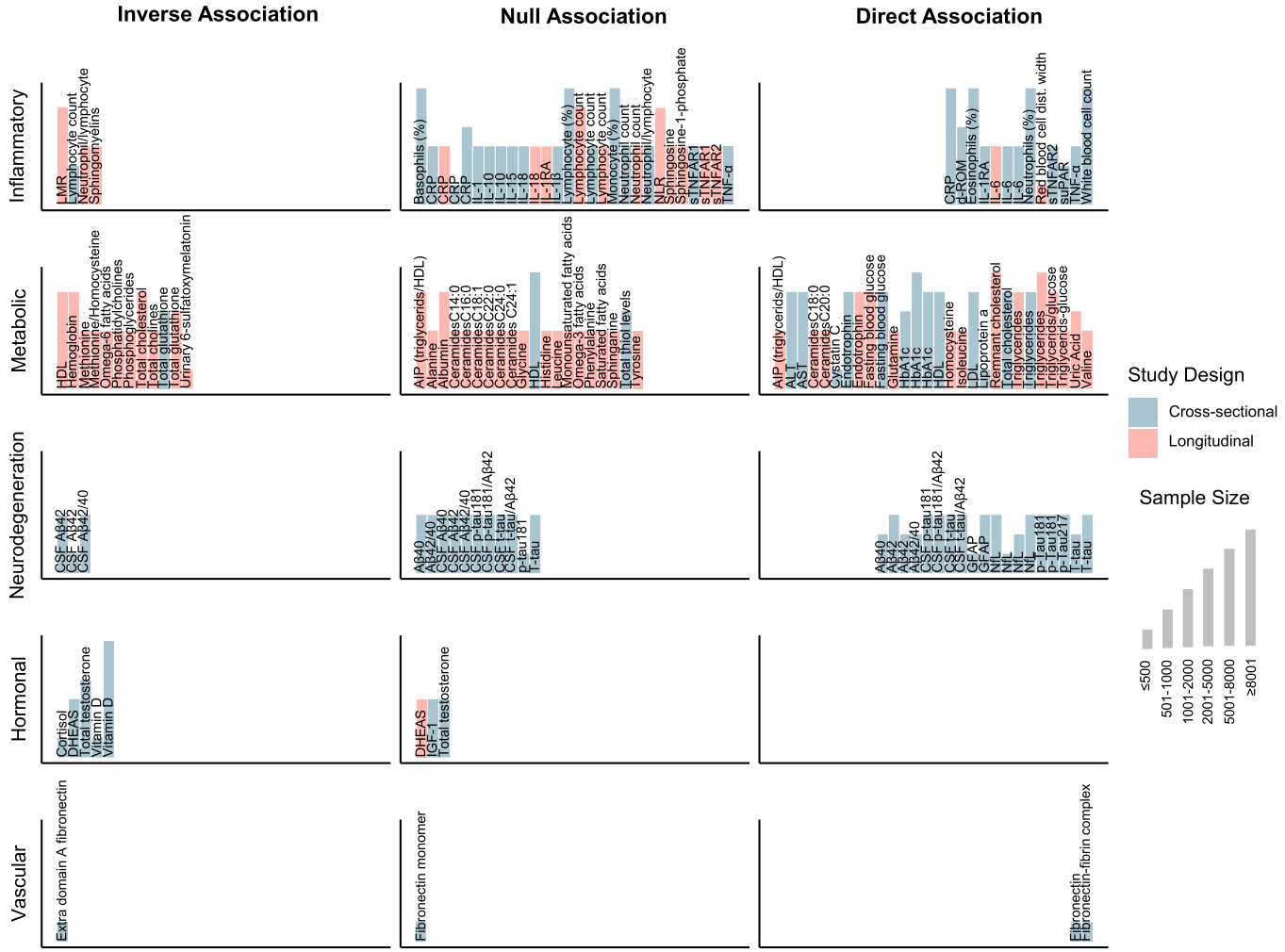

Fig. 2. Harvest plot of different associations of biomarkers to multimorbidity in relation to sample size. Each panel represent a different biomarker domain: inflammatory, metabolic, neurodegenerative, hormonal and vascular biomarkers and each segment represent an inverse, null or direct association, respectively. The height of the bars indicates the sample size. *Derivatives of Reactive Oxygen Metabolites (d-ROM).

(Fabbri et al., 2015). Conflicting data were available from two studies on TNF- α (Fabbri et al., 2015; St. Sauver et al., 2022).

Concerning inflammatory markers derived from the blood count, a cohort study indicated a longitudinal direct association between red blood cell distribution width (RDW) and multimorbidity (Martínez-Velilla et al., 2012). Data on lymphocyte and neutrophil counts provided conflicting results, with two studies showing no association with multimorbidity (Cheong et al., 2023; Pellegrino et al., 2024), one study showing inverse association for lymphocytes (Marengoni et al., 2008) and one a direct association for neutrophils percentage (Stepanova et al., 2015). Longitudinal data from two different good-quality studies about neutrophil-to-lymphocyte ratio (NLR) were also conflicting, with one study showing a direct association (Pellegrino et al., 2024) and the another showing no association (Cheong et al., 2023).

Among the retrieved studies, five investigated genetic and epigenetic inflammatory markers of multimorbidity. Given the exploratory nature of those studies, their results were not summarized in the harvest plot (Supplementary Table S1). One study with a longitudinal design, evaluated the association between epigenetic age acceleration (EAA) and worsening multimorbidity. In summary, the DNA Methylation profiles (DNAm) PhenoAge clock was found to be associated with a higher risk of severe multimorbidity. Specifically, for every standard deviation increase in PhenoAge acceleration (7.0 years), there was a 6 % increase in the rate of acquiring additional chronic conditions and a 7 % increase in the severity-weighted multimorbidity score (Jain et al., 2023). The other four studies retrieved had a cross-sectional design. The first study outlined a direct association of the CRP single-nucleotide polymorphism (SNP) rs1205 CC genotype with increased prevalence of multimorbidity (Liu et al., 2016). The second investigated DNA methylation patterns in peripheral blood mononuclear cells (PBMCs) among older nursing home residents and identified nine Differentially Methylated Regions (DMRs) to be associated with multimorbidity status. In particular, methylation of cg07725579, located near the transcriptional start site for the gene Signal Regulatory Protein Beta 2 (SIRPB2) was directly correlated with higher comorbidity score (Verschoor et al., 2018). The third study found a direct correlation between miR-181a levels, a type of MicroRNAs (miRNAs), and multimorbidity burden, particularly in females (Iannone et al., 2022). Finally, the last study, assessed the effect of several aging biomarkers to estimate biological age and derived an “inflammatory clock” of aging (iAGE), using artificial intelligence and deep learning architectures. This metric correlated with multiple aging phenotypes and predicted multimorbidity. Specifically, CXCL9, within the iAge clock, emerged as a key biomarker and a master regulator of vascular function and cellular senescence and an age-independent significant contributor associated to cardiovascular aging (Sayed et al., 2021).

4.2. Metabolic markers

Fifteen articles explored metabolic markers in relation to multimorbidity. Haemoglobin A1c (HbA1c) consistently emerged as directly associated with multimorbidity (Stepanova et al., 2015; Zhang et al., 2019; Schöttker et al., 2016). Fasting blood glucose showed also a direct association both longitudinally and cross-sectionally (Cheong et al., 2023; Zhang et al., 2019). Triglycerides were found to be consistently associated with multimorbidity in two longitudinal (Cheong et al., 2023; Zhao et al., 2024) and one cross-sectional study (Zhang et al., 2019), along with low-density lipoprotein (LDL) cholesterol that emerged as directly related to multimorbidity. Total cholesterol showed conflicting results emerging as inversely associated with multimorbidity in a longitudinal study (Cheong et al., 2023), while directly associated in a cross-sectional one (Zhang et al., 2019). High-density lipoprotein (HDL) cholesterol also showed conflicting results in both longitudinal and cross-sectional analyses (Cheong et al., 2023; Stepanova et al., 2015; Zhang et al., 2019). Further metabolites related to lipids and glucose levels emerged as related to multimorbidity and cardiometabolic multimorbidity (Xiao et al., 2024). In this context, one longitudinal study found a direct association between multimorbidity and Ceramides 18:0 and C20:0, while showing a null association for the rest of the ceramides addressed (St Sauver et al., 2023). Similarly, Omega-3 fatty acids showed no association while Omega-6 fatty acids emerged as inversely associated with multimorbidity longitudinally (Caballero et al., 2023). Homocysteine showed a direct association with cardiovascular multimorbidity in one longitudinal study (Calderón-Larrañaga et al., 2020). Kidney and liver metabolism markers such as Cystatin C, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were also cross-sectionally directly associated with multimorbidity in two studies (Zhang et al., 2019; Garrafa et al., 2017). Only one longitudinal study evaluated association of kidney and liver markers with 10 different clusters of multimorbidity (data not included in Fig. 2, see Supplementary Table S1 for details), showing that *Cluster 4 - Cardio-Circulatory and Renal* was associated with both abnormal kidney and liver function, while *Cluster 3 - Minority Metabolic Autoimmune-Inflammatory* and *Cluster 8 - Digestive* were respectively characterized by altered kidney and liver function (Villén et al., 2020). Endotrophin was also found to have a direct association with multimorbidity both longitudinally and cross-sectionally (Staunstrup et al., 2021) while total glutathione was inversely associated with multimorbidity in both longitudinal and cross-sectional analyses (Pérez et al., 2020).

Two longitudinal studies and one cross-sectional, investigated metabolomic markers of multimorbidity and their results were not summarized in the harvest plot (Supplementary Table S1). The EPIC-Norfolk cohort study, deemed of high quality, assessed 458 metabolites in relation to major diseases and all-cause mortality and identified pathways and common risk factors for multiple non-communicable diseases and multimorbidity. The study revealing that 65.6 % of these metabolites were shared across multiple diseases, while specific ones, such as γ-glutamylglycine, 7-methylxanthine, and various glycerophospholipids, were uniquely associated with some diseases such as type 2 diabetes, chronic obstructive pulmonary disease (COPD), coronary heart disease, and liver disease. Furthermore, key shared pathways included amino acid metabolism influenced by kidney function, inflammation-related pathways involving N-acetylneuraminate, and microbial-derived metabolites like indole propionate (Pietzner et al., 2021). A second longitudinal study by *Mulugeta et al.* identified six metabolic subgroups using the Self-Organizing Map (SOM) technique. Subgroup I was characterized by higher apolipoprotein B, higher systolic blood pressure, higher rheumatoid factor, adequate glycaemic control, normal kidney biomarkers; Subgroup II presented elevated triglyceride, high body fat score, higher liver enzyme; Subgroup III showed elevated triglycerides, high body fat score, higher C-reactive protein. Subgroups II and III showed the highest cardiometabolic multimorbidity occurrence and Subgroup III also exhibited the highest mortality and chronic morbidity rates. For consistency with the chosen classification of biomarkers, Subgroup IV, V and VI are discussed later in the hormonal markers section (Mulugeta et al., 2022). Finally, one good-quality cross-sectional study identified three main plasma biomarker groups: "lipid metabolism," "HDL cholesterol" and "amino acid/glycolysis/ketogenesis." The first two groups were directly associated with cardiometabolic multimorbidity, while the HDL cholesterol group was inversely linked to both multimorbidity and neuropsychiatric multimorbidity in unadjusted analyses (Vázquez-Fernández et al., 2024).

4.3. Neurodegeneration markers

Seven cross-sectional studies investigated the association between neurodegeneration biomarkers and multimorbidity. Results were conflicting in regard to cerebrospinal fluid (CFS) amyloid β-protein (Aβ) 40, Aβ42, and their ratio CFS Aβ40/Aβ42, with a tendency of showing an inverse association to multimorbidity (Aerqin et al., 2024; Li et al., 2024; Stirland et al., 2019). Conversely, two studies showed a significant

direct association with multimorbidity for plasma levels of Aβ42, Aβ40 and Aβ40/Aβ42 (Ren et al., 2024; Syrjanen et al., 2022). More consistent results were found for plasmatic Neurofilament Light Chain (NfL) that showed significant direct association with multimorbidity in four studies (Ren et al., 2024; Syrjanen et al., 2022; Sarto et al., 2024; Valletta et al., 2024), along with glial fibrillary acidic protein (GFAP) that was directly associated with occurrence of multimorbidity in two good-quality study (Sarto et al., 2024; Valletta et al., 2024). Total tau (T-tau) showed conflicting findings, resulting in null association and a direct association for both CSF (Aerqin et al., 2024; Li et al., 2024) and plasmatic form (Ren et al., 2024; Syrjanen et al., 2022; Valletta et al., 2024), while p − tau 181 showed, irrespectively of the biological source, a direct association in three study (Li et al., 2024; Valletta et al., 2024; Mielke et al., 2022), a null associations in two studies (Aerqin et al., 2024; Sarto et al., 2024). Similarly, CSF p-tau181/Aβ42 and t-tau/Aβ42 tended to show conflicting results (Aerqin et al., 2024; Li et al., 2024). Finally, in one study, plasmatic p-tau 217 emerged as directly associated to multimorbidity (Mielke et al., 2022).

4.4. Hormonal markers

Five studies addressed hormonal biomarkers in relation to multimorbidity. Conflicting results were showed in studies assessing total testosterone and Dehydroepiandrosterone sulfate (DEHAS) (Fabbri et al., 2015; Peterson et al., 2018). One cross-sectional study found cortisol levels to be inversely correlated to multimorbidity (Rotman-Pikielny et al., 2006) while a null association was found for insulin-like growth factor 1 (IGF-1) in another study (Fabbri et al., 2015). Lastly, vitamin D displayed an inverse association with multimorbidity in two studies (Gökçen et al., 2018; Meems et al., 2015). Concerning hormonal-omics markers, the above-mentioned study by *Mulugeta et al.* identified the following marker subgroups: Subgroup IV, composed by high HDL, high vitamin D, High bilirubin, low estradiol; Subgroup V, including high estradiol, high testosterone in men, high sex-hormone binding globulin for both sexes; and Subgroup VI, including high urinary excretion biomarkers without albuminuria and higher IGF. Subgroups IV and V showed the lowest occurrence of multimorbidity (Mulugeta et al., 2022) (Supplementary Table S1).

4.5. Vascular biomarkers

One single cross-sectional study outlined how Extra domain A fibronectin (EDA-FN) had an inverse association with multimorbidity while, fibronectin (FN) and fibronectin−fibrin complex showed a significant direct association (Pupek et al., 2016).

5. Discussion

In this study, we conducted a systematic review of the literature with the aim of providing a comprehensive synthesis of existing evidence regarding biomarkers of multimorbidity, with potential clinical relevance. We retrieved 43 studies published between 2008 and 2024 that reported information on several biomarkers of multimorbidity, providing a richer and more exploitable framework in comparison to a previous work published by Ferreira GD et al. in 2018 (Ferreira et al., 2018).

Our appraisal suggests that routinely assessed inflammatory and metabolic biomarkers, as well as markers of neurodegeneration, might play an active role in detecting and potentially anticipating the occurrence of multimorbidity. Conversely, hormonal and vascular markers were evaluated in only a small number of studies, often with inconsistent findings, reflecting the limited evidence in these domains and emphasizing the need for further research to clarify their potential role in multimorbidity.

Markers of inflammation and low-grade inflammation have been extensively studied in relation to aging and the occurrence of multiple age-related conditions (Franceschi and Campisi, 2014; Franceschi et al., 2018 Oct; Ferrucci and Fabbri, 2018 Sep; Schaap et al., 2009). Chronic low-grade inflammation, or "inflammaging", along with immunosenescence (Hazeldine and Lord, 2015), emerges as a critical factor that increases the susceptibility to the development of age-related diseases (Ferrucci and Fabbri, 2018 Sep; Fulop et al., 2018 Jan; Franceschi et al., 2017, 2000; Baylis et al., 2013). Our review found consistent direct associations between IL-6 and multimorbidity across studies, reinforcing its role in the pathogenesis of chronic inflammation and age-related diseases (Franceschi et al., 2018 Oct; Ershler, 1993). Indeed, IL-6 serum concentration increases with age, reflecting the regulatory imbalance due to immunosenescence (Hazeldine and Lord, 2015; Franceschi et al., 2000) and its association to several chronic diseases and multimorbidity (Ferreira et al., 2018; Ershler, 1993; Maggio et al., 2006; Tanaka et al., 2014; Ershler and Keller, 2000; Aliyu et al., 2022; Choy et al., 2020; Chung et al., 2009). IL-6 levels also influence serum levels of other systemic inflammation markers, such as CRP (Tanaka et al., 2014; Ansar and Ghosh, 2013). However, our review revealed conflicting results regarding CRP's role in multimorbidity, possibly due to its transient nature during acute phases and variability in response to chronic insults, outlining the need for more precise studies to establish its clinical usefulness in this context (Nouvenne et al., 2016). Furthermore, despite the renowned role of TNF signalling pathways in several chronic inflammatory conditions and its potential contribution to multimorbidity (Bradley, 2008; Memon et al., 2021; Holtmann and Neurath, 2005), our review provides conflicting results with respect to TNF-α and its soluble receptors (sTNFAR1 and 2). This may be related to the dual nature of TNF-α that has both pro-inflammatory and anti-inflammatory/immunoregulatory effects mediated by Tumor Necrosis Factor Receptor 1 (TNFR1) and 2 (TNFR2), respectively (Tseng et al., 2018; Yang et al., 2019). This might impact on its role as a multimorbidity marker and its application as potential therapeutical target in this context (Tseng et al., 2018). Despite their recognized role in predicting disease severity, results concerning neutrophil, lymphocyte and their ratio in relation to multimorbidity were inconsistent and warrant further investigation (Hazeldine et al., 2015; Hazeldine and Lord, 2021; Patel et al., 2009; Buonacera et al., 2022). Finally, complex inflammatory markers like epigenetic modulations and circulating miRNAs are emerging as potential contributors to multimorbidity (Franceschi et al., 2018 Oct; Karakas et al., 2017; Sharma-Oates et al., 2024).

Metabolic markers also emerged as significant indicators of multimorbidity. Glycemic and lipid metabolism markers, along with kidney and liver function indicators, were linked to multimorbidity, particularly in cardiometabolic contexts (Ferreira et al., 2018; Jin et al., 2023). These findings corroborate the well-established association between metabolic dysregulation and chronic conditions such as diabetes, cardiovascular diseases, and metabolic syndrome (Thienemann et al., 2020). Notably, hyperglycaemia (Ding et al., 2024), hypertriglyceridemia (Nordestgaard et al., 2007; Ascaso et al., 2011; Murad et al., 2012) and hypercholesterolemia (Han and Kim, 2021; Marzetti et al., 2018; Castelli et al., 1992) are strongly associated to the onset of cardiovascular diseases and the development of complications of diabetes, increasing the risk of overall mortality. However, glycemic control markers might play a more intricated role as suggested by recent evidence implying that hypoglycaemia could also impact on multimorbidity (Chiang et al., 2018; McCoy et al., 2020). Liver and kidney function markers also proved to be important, with cystatin C and markers of hepatic necrosis emerging as strong predictors of multimorbidity and related mortality (Ferreira et al., 2018; Jin et al., 2023; Suksamai et al., 2021; West et al., 2022; Chen et al., 2022; Djakpo et al., 2020). Finally, homocysteine and endotrophin were directly associated with multimorbidity, linking elevated levels of these biomarkers to increased risk of cardiovascular diseases, metabolic dysfunction, and fibrotic processes (Peng et al., 2015; Smith et al., 2018; Alkaissi and McFarlane, 2023; Sun et al., 2014).

Biomarkers for neurodegenerative diseases have been well studied, particularly for their role in diagnosing and managing conditions like Alzheimer's disease (Jack et al., 2013; Shaw et al., 2007; Hansson, 2021). However, their association with multimorbidity remains less explored (Olsson et al., 2016). Mixed findings were observed in the direction of the association of CSF Aβ40, Aβ42, and the Aβ40/Aβ42 ratio and multimorbidity. Conversely, and differently to most evidence that suggests that CSF markers might be more reliable than plasma-based biomarkers in detecting neurodegenerative diseases (Olsson et al., 2016), we found a consistent direct association of plasma levels of Aβ40, Aβ42, and Aβ40/Aβ42 ratio with multimorbidity implying that plasma measurements could be useful indicators of multimorbidity. Conflicting results were found for T-tau irrespectively of the biological form, while its phosphorylated form 181 showed potential direct association. On the other hands, Serum NfL, and GFAP were consistently associated with multimorbidity, aligning with recent findings linking these markers to overall and cardiovascular mortality in aging populations, with potential role in prognostication as well (Halloway et al., 2024; Chen et al., 2023; Nguyen et al., 2022). Finally, p-tau217 has emerged as a reliable biomarkers of pre-clinical Alzheimer disease and might also have a role in early-detection of multimorbidity (Lai et al., 2024), although further research is warranted.

The assessment of hormonal biomarkers in relation to multimorbidity revealed inconsistent associations and showed different correlations depending on study design and quality. For instance, testosterone levels showed an association with multimorbidity in some studies but no association in others, possibly reflecting the complex interplay between hormone levels, metabolic syndrome, and cardiovascular disease (Corona et al., 2011; Cittadini et al., 2021). Other hormonal markers like DHEA-S and IGF-1 also yielded mixed results. Cortisol presented an inverse association with multimorbidity, contradicting previous studies linking higher cortisol levels to various chronic conditions. This discrepancy might be due to cortisol's circadian variation, complicating its use as a biomarker for multimorbidity (Schoorlemmer et al., 2009; Ortiz et al., 2022; Hounkpatin et al., 2024). Vitamin D, however, consistently showed an inverse association with multimorbidity, supporting the hypothesis that deficiency could be a risk factor for multiple diseases, though stronger evidence is still required to confirm its role (de Borst M et al., 2010; Theodoratou et al., 2014).

Evidence concerning vascular biomarkers in relation to multimorbidity was scarce. We retrieve only one study addressing EDA-FN that displayed an inverse association in contrast to FN itself and fibronectin-fibrin complex that showed a direct association with multimorbidity. FN is a multifunctional glycoprotein and its plasmatic levels have been associated with thromboembolism (Pecheniuk et al., 2008), with the formation of atherosclerotic plaques (Holm Nielsen et al., 2020) and with ischemic heart disease (Song et al., 2001). A recently published study revealed that lower plasmatic level of fibronectin predicted the occurrence of coronary heart disease but not severity (Peng et al., 2023) and murine models suggests that mutations in the fibronectin gene could lead to different phenotypes that increased the risk of different disease (White and Muro, 2011), however further research is required to establish its potential involvement in multimorbidity occurrence.

5.1. *Knowledge gaps, challenges and future perspectives*

The search of biomarkers of multimorbidity comprises significant methodological challenges. Table 1 summarizes the knowledge gaps, the challenges and the potential strategies we have identified to address them in future investigations in the field. The definitions and operationalization of multimorbidity differ considerably, leading to inconsistent results that hinder comparability among studies. Furthermore, most studies are characterized by a cross-sectional design, useful for identifying correlations, but inadequate for clarifying causal pathways and progression trends in multimorbidity and when longitudinal design

Table 1
Summary of knowledge gaps and challenges, implications and future perspective.

Knowledge gaps and challenges	Implications	Future perspectives
Heterogeneous definitions & operationalization of multimorbidity	– Limits the ability to accurately correlate specific biomarkers with multimorbidity physiopathology hindering research progress in the field and possible clinical exploitation in the future. – Limits synthesis of findings to inform tools for future clinical use.	– Develop and adopt a standardized, consensus-driven definition of multimorbidity to ensure consistency in biomarker research and assessment of multimorbidity in both clinical and research settings. – Generate practical recommendations for the operationalization of multimorbidity in biomarker studies to enhance comparability and reproducibility to be used in clinical studies and, prospectively, clinical settings.
Lack of longitudinal studies	– Hinders understanding of the temporal relationship – and so causality - between biomarker changes and multimorbidity progression. – Limits the ability to use biomarkers for early detection and long-term monitoring of multimorbidity.	– Conduct more longitudinal studies to track biomarker changes over time and their association with multimorbidity development to reduce the gap in knowledge and eventually provide information for interventional clinical studies. – Develop biomarkers as tools for predicting and monitoring the progression of multimorbidity, enabling earlier intervention and personalized treatment strategies in clinical settings and primary care.
Inconsistent methodology across studies	– Inconsistencies prevent the identification and establishment of reliable biomarkers for predicting multimorbidity development. – Difficulties arise in validating biomarkers for treatment monitoring due to varied study designs and populations.	– Standardize biomarker study methodologies, including consistent use of definitions, populations, and measurement techniques for both research accuracy and future clinical utilization. – Promote collaborative meta-analyses to reconcile differences and identify the most reliable biomarkers across studies.
Reliance on convenience samples and biomarkers	– Biases in biomarker selection may lead to overlooking key pathways involved in multimorbidity. – Results from convenience samples may not be generalizable to diverse populations, limiting the applicability of	– Design studies using population-based cohorts to ensure the representativeness of findings and identify more relevant biomarkers. – Encourage the exploration of understudied biomarkers that may be more directly linked to

(*continued on next page*)

Table 1 (*continued*)

Knowledge gaps and challenges	Implications	Future perspectives
	biomarkers for broad prognostication.	multimorbidity, beyond those chosen for convenience.
Limited exploration of specific biological pathways	– A narrow focus on well-known pathways can lead to an incomplete understanding of multimorbidity's physiopathology. – Potentially important biomarkers from less-explored pathways are not identified, hindering their use in prognostication and treatment monitoring for future clinical implications.	– Expand research to include a broader range of biological pathways, such as neurodegenerative and hormonal pathways, to identify novel biomarkers. – Integrate multi-omics approaches to explore complex interactions between different biological systems in multimorbidity.
Underutilization of Advanced Biomarkers and Omics Technologies	– Limits the discovery of novel biomarkers that could provide deeper insights into the physiopathology of multimorbidity at a research level. – Reduces the potential for identifying new therapeutic targets based on biomarker data and utilization at a clinical level.	– Increase the use of advanced omics technologies (e.g., genomics, proteomics, metabolomics) in multimorbidity research to uncover new biomarkers. – Establish large-scale biobanks and data-sharing networks to facilitate the integration of omics data into biomarker studies and support precision medicine.

is adopted, the variability in the methodology limits the comparability among studies. To address these challenges, longitudinal studies employing standardized definitions of multimorbidity and biomarker measurement protocols are required. Moreover, longitudinal data would allow researchers to investigate the temporal dynamics between biomarkers and disease progression, evaluating the validity of different biomarkers as useful predictors that could forecast multimorbidity trajectories and enhance personalized treatment strategies. To this scope, there is a compelling need for a comprehensive understanding of specific biomarker phenotypes and their relationship to multimorbidity, as well as their connections to other clinical outcomes, such as functional decline or healthcare utilization. Expanding research that encompasses previously unexplored biological pathways, including neurodegenerative and hormonal pathways, may uncover novel biomarkers that more accurately represent the complexity of multimorbidity. In light of the multifactorial nature of multimorbidity, a single biomarker approach might not reflect the complexity of this condition. In this context, employing multi-omics strategies that integrate genomics, proteomics, and metabolomics, may help better disentangle the biological interactions that drive diseases' progression thus fostering a precision medicine approach in the framework of multimorbidity. This could enhance our ability to detect complex biomarker signatures, improve risk stratification, and ultimately inform tailored interventions.

5.2. Strength and limitations

Overall, this systematic review provides a framework and thorough insight into biomarkers of multimorbidity, effectively highlighting an important gap of knowledge in this field and using a rigorous methodology to summarize evidence and highlight the need for further research to validate and standardize biomarker use in multimorbidity. However, this work has some limitations: first, due to heterogeneity of the work retrieved, we were unable to conduct a meta-analysis to established pool effect size in relation to different biomarkers. Furthermore, differences in study design, populations and sample size have hindered a standardized assessment and comparison between studies. The heterogeneity in the definition of multimorbidity, with difference in terms of number of diseases evaluated along and in the assessment of multimorbidity patterns, further limited the comparability of the studies examined. Lastly, our search strategy was restricted to English-language studies. Although this is a common approach, it may have led to a language bias and the exclusion of relevant studies published in other languages.

6. Conclusion

This systematic review of the literature on biomarkers of multimorbidity highlights how some inflammatory (i.e. IL-6), metabolic (i.e. HbA1c, triglycerides, LDL cholesterol, Cystatin C) and neurodegenerative biomarkers (i.e. NfL, GFAP and p-tau217) have been recurrently investigated and may show promise in identifying biological patterns associated with multimorbidity and detecting individuals at high risk of developing multimorbidity. These biomarkers could be reliable and feasible screening tools to be measured in clinical settings during a routine assessment, enabling tailored interventions and care plan, predict health trajectories and ensuring a better allocation of health resources. Nevertheless, given the limited number of heterogeneous studies, current evidence remains preliminary and while some of these biomarkers are already measured in routine clinical practice, their role in predicting or stratifying risk for multimorbidity is not yet well established. As such, their integration into clinical screening protocols would require further validation in large prospective, studies. Furthermore, with this work we underlined the presence of relevant knowledge gaps in the study of biomarkers of multimorbidity that need to be filled to have a more complete view of the biological mechanisms leading to multimorbidity. In this regard, multi-omics approaches that integrate diverse biological domains including genomics, proteomics, and metabolomics, may offer a valuable strategy to capture the complexity of multimorbidity and support the identification of a biological signature for risk assessment in future research.

Author contributions

OG and DLV conceptualized and supervised the study. MBZ, LB, EP and MF carried out the literature search. MBZ and FT carried out data extraction and analysis. MF and EP also contributed to data extraction. LB and EP performed the quality evaluation of the studies. DVL, FT, MBZ, LB and GO worked on the interpretation of results. MBZ wrote the manuscript, with supervision by DVL and GO. All authors critically revised the manuscript and approved the final version.

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Declaration of Competing Interest

None of the authors declare conflicts of interest to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2025.102870.

Data availability

Data will be made available on request.

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