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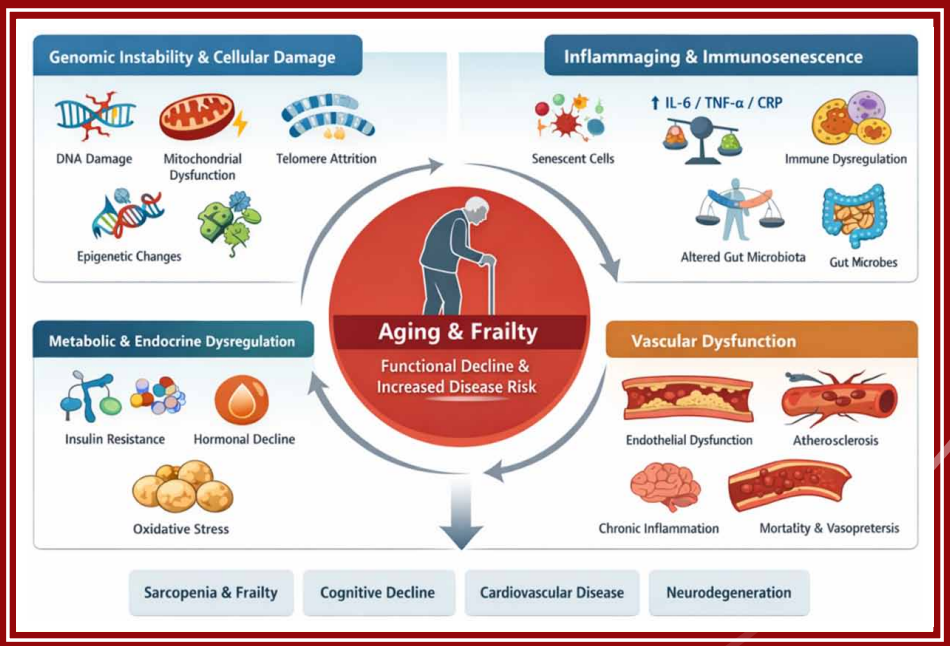

Pathophysiology of biological aging: interplay between inflammaging immunosenescence, metabolic dysregulation, and endothelial dysfunction leading to frailty and age- related disease.

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MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

42 Votsi Street, Patras 26221, Greece
Tel: +30 2610 279579, Fax: +30 2610 220518
email: iede_pel@yahoo.gr

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Editor-in-Chief
Christos Triantos
email: achaiki.iatriki@gmail.com

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Dear colleagues,

In the current issue, the editorial by Bartsokas Chistos explores how authorship inflation distorts bibliometric metrics and emphasizes the need for more transparent and responsible authorship practices in medical research. In addition, the editorial by Kalafateli Maria examines the emerging role of GLP-1 receptor agonists in MASLD and their potential to address both liver disease and the underlying systemic metabolic dysfunction.

The current issue features four review articles. The first review by Eleftherakis et al. provides a comprehensive overview of the pathophysiology, clinical presentation, diagnostic approach, and current treatment strategies of IgG4-related disease, highlighting its multisystem nature and the challenges associated with its diagnosis and management. The second review, authored by Georgiadis et al. systematically synthesizes and critically evaluates current evidence on the epidemiology, pathophysiology, clinical presentation, diagnostic approaches, treatment strategies, and broader psychosocial and economic impact of endometriosis, with the aim of identifying knowledge gaps and highlighting emerging directions for improved diagnosis and personalized management. The third review by Roumelioti et al. presents a practical framework that integrates cross-cultural adaptation procedures with psychometric validation and measurement-equivalence testing to support valid and fair comparisons of public health literacy instruments across linguistic and cultural groups. Finally, the review by Marlafeka et al. outlines the current evidence on established and emerging biomarkers of aging, with a focus on frailty, cardiovascular and thrombotic risk, and infection-related conditions in elderly patients, highlighting their role in diagnosis, risk stratification, and personalized clinical management.

Yours sincerely,

C. Triantos
Professor of Internal Medicine and Gastroenterology
Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

The Illusion of Impact: Rethinking Authorship, Collaboration, and the h-Index in Medical Research

Christos Bartsokas

Abstract

Bibliometric indicators such as publication counts, citation numbers, and the Hirsch index have become central to the evaluation of academic performance in medicine. However, the growing prevalence of honorary and collaborative authorship practices raises significant concerns about the validity of these metrics. When individuals are included as authors without meeting established criteria, the meaning of authorship is diluted, accountability becomes fragmented, and the integrity of the scientific record is compromised. The COVID-19 pandemic highlighted this issue, as large multicenter studies frequently included hundreds or thousands of collaborators whose roles varied widely, yet each accrued academic credit. This editorial examines the ethical, academic, and cultural implications of inflated authorship practices. It argues that restoring the value of authorship requires stricter adherence to international standards, broader use of contributorship models such as the Contributor Roles Taxonomy, and reforms in how institutions and funding bodies evaluate scholarly performance. Ultimately, authorship must remain a marker of intellectual responsibility rather than an academic currency. Without such reforms, bibliometric measures risk becoming increasingly detached from genuine scientific contribution.

Key words: *Authorship ethics; honorary authorship; research integrity; h-index; bibliometrics*

The academic currency of modern medicine is increasingly measured in numbers: publication counts, citation metrics, and above all, the Hirsch index (h-index). These indicators, while easy to quantify, are seductive in their apparent ability to distill a career's worth of scholarship into a single figure. Promotions, grants, and reputations often hinge on them. Yet beneath the surface lies a growing distortion: the proliferation of authorship without contribution, and the inflation of academic metrics through practices that weaken both the meaning of authorship and the credibility of research itself.

Department of Surgery, Nicosia General Hospital, Nicosia, Cyprus
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The phenomenon is not marginal. It has been described for decades as "honorary authorship," "gift authorship," or more recently as the inclusion of "collaborators" en masse in large-scale projects. Surveys consistently reveal that a substantial proportion of medical publications include at least one author who does not meet accepted authorship standards. In one cross-sectional survey of high-impact biomedical journals, nearly one-fifth of articles contained honorary authors, and ghost authorship was also common [2]. These practices are not limited to obscure venues—they permeate leading journals, shaping the bibliometric landscape at the very top of the academic hierarchy.

The International Committee of Medical Journal Editors (ICMJE) attempted to close this loophole by issuing precise authorship criteria: substantial contributions to

the conception or design of the work, or the acquisition, analysis, or interpretation of data; drafting or revising the article critically; final approval of the version to be published; and agreement to be accountable for all aspects of the work. Importantly, all four conditions must be met [1]. Despite this clarity, adherence is uneven, and enforcement is weak. Journals typically accept what is declared, while institutions may have little incentive to question inflated bylines that enhance their perceived productivity.

Nowhere was the scale of this phenomenon more visible than during the COVID-19 pandemic. Large international registries and clinical consortia produced papers with thousands of named contributors. These collaborations unquestionably played a role in rapidly generating evidence, yet it is implausible that every listed name met the ICMJE's rigorous conditions. The byline, once an assurance of intellectual accountability, became a roll call of institutional participation. Each name, however, still counted toward citation databases, generating h-index growth untethered from individual scientific labor.

The implications are profound. For early-career researchers who labor intensively on study design, statistical analysis, and manuscript preparation, the impact of their work may be diluted by hundreds of nominal co-authors. For institutions, hiring and promotion committees face a distorted picture: candidates whose CVs boast dozens of high-profile publications but whose real intellectual contribution may be minimal. For the scientific community at large, the erosion of authorship integrity weakens accountability. If responsibility is distributed so thinly that no individual feels answerable, then errors, misinterpretations, or even misconduct become harder to trace.

Supporters of inclusive authorship models argue that modern science is inherently collaborative. The complexity of clinical trials, the logistics of multicenter data collection, and the sheer scale of "big data" projects necessitate vast teams. Denying authorship, they claim, risks alienating local investigators whose contributions—such as patient recruitment or database management—are essential. Some even suggest that the definition of authorship should evolve, with a more collective understanding of credit in the age of team science [3,4].

This argument, while understandable, conflicts with established authorship standards. There is nothing dishonorable in acknowledging those who facilitate a project without meeting the intellectual and accountability requirements of authorship. The problem arises when acknowledgments are replaced by authorship, thereby diluting the meaning of the latter. If everyone who touches a project is an "author," then the term ceases to distinguish between those who conceived, analyzed, and interpreted the work and those who simply enabled it.

Recognizing this, several initiatives have emerged to clarify roles. The CRediT (Contributor Roles Taxonomy) system, now adopted by many journals, requires explicit attribution of contributions such as conceptualization, methodology, data curation, writing, and supervision [9]. By shifting from the binary of "author" versus "non-author" to a detailed mapping of responsibilities, these frameworks promise greater transparency. Studies suggest that contributorship statements reduce honorary authorship and help clarify accountability [10,12]. Still, uptake is inconsistent, and in many cases contributorship is presented alongside inflated bylines, not instead of them.

The deeper issue is structural. Academic systems that reward numbers above nuance incentivize questionable practices. A scholar with an h-index of 50 achieved through mass collaborations may appear more "productive" than one with an h-index of 20 who has led several original and methodologically rigorous projects. Committees faced with evaluating hundreds of candidates often prefer the simplicity of metrics to the complexity of qualitative judgment. Thus, the system rewards quantity, and individuals adapt their behavior accordingly [14,15].

The risks of continuing down this path are significant. Metrics become increasingly decoupled from true scholarly merit, and bibliometric inflation erodes trust in the system itself. The public, already wary of perceived conflicts of interest and reproducibility crises in science, may see inflated authorship as further evidence that academic medicine prioritizes career advancement over truth. Within the profession, cynicism grows: if authorship is easy to obtain without genuine work, then its value diminishes even for those who deserve it [5,8].

What then should be done? The solutions must operate at multiple levels. Journals must move beyond symbolic adherence to ICMJE criteria and rigorously enforce contributorship declarations. Authorship disputes should not be left to institutions alone, as conflicts of interest may prevent honest adjudication. Editorial boards could consider limiting the number of named authors on multicenter studies, with the remainder acknowledged in consortium listings, though this remains controversial.

Institutions must also recalibrate how they evaluate researchers. Metrics such as the h-index should be contextualized, not used as blunt instruments. Review committees should assess not only the number of papers but also the depth of contribution, the role in study leadership, and the originality of ideas. Granting agencies, too, should resist the temptation to equate high citation counts with excellence, recognizing that inflated bibliometrics can mask mediocrity as easily as they can signal brilliance [13].

Finally, researchers themselves must recommit to the principle that authorship is a responsibility, not a reward. By refusing to lend their names to projects in which they play no intellectual role, they affirm the value of integrity over expedience. This cultural change will be slow, but it begins with individual decisions. As long as there are willing honorary authors, the system will continue to generate them.

The tension between inclusivity and accountability will not vanish. Modern medicine does require collaboration on unprecedented scales. But collaboration does not demand authorship. By distinguishing clearly between those who are truly authors and those who are valuable contributors, the medical community can preserve both fairness and credibility.

The h-index was never meant to be an oracle of scientific worth. It is a rough heuristic, useful only when interpreted with judgment. When inflated through honorary authorship, it becomes worse than meaningless—it becomes misleading. To restore integrity to the metrics we rely on, we must restore integrity to the practices that feed them. Otherwise, we risk living in a world where academic "impact" is abundant, but genuine intellectual contribution is increasingly scarce.

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Corresponding author:

Christos Bartsokas, MD, MSc, PhD, FACS
Department of Surgery, Nicosia General Hospital,
Nicosia, Cyprus, E-mail: bartsokas@gmail.com

Targeting Metabolism in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): The Emerging Role of GLP-1 Receptor Agonists

Maria Kalafateli

The recent evolution from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) reflects more than a change in nomenclature [1]. It acknowledges that MASLD is a multisystemic metabolic disorder that extends far beyond the liver. While progressive liver disease, cirrhosis, and hepatocellular carcinoma (HCC) remain critical concerns, epidemiological data consistently show that these patients are more likely to succumb to cardiovascular disease and non-HCC malignancies than to hepatic complications [2]. Consequently, therapeutic strategies cannot focus exclusively on reducing hepatic steatosis or improving histology; they must simultaneously address the broader cardiometabolic risk profile that ultimately dictates patient survival.

Indeed, MASLD is increasingly recognized as the hepatic manifestation of systemic metabolic dysfunction. Ectopic lipid accumulation in the liver is not an isolated event but rather the downstream consequence of a complex, pathological interplay among obesity, insulin resistance, adipose tissue dysfunction, and chronic low-grade inflammation [3]. Consequently, therapeutic approaches targeting solely liver-specific pathways risk failing to address the upstream metabolic drivers that fuel disease progression and ultimately determine morbidity and mortality.

This paradigm shift has profound implications for drug development. Historically, clinical trial endpoints have focused strictly on hepatic histology, specifically steatohepatitis resolution and fibrosis regression. While these outcomes remain clinically relevant, an ideal therapy for MASLD should also improve obesity, insulin sensitivity, dyslipidemia, type 2 diabetes mellitus (T2DM) and chronic kidney disease. In other words, treatments that target the metabolic roots of the disease may offer greater overall benefit than therapies acting primarily within the liver [3].

Among emerging options, GLP-1 receptor agonists (GLP-1RAs) have attracted considerable attention. Originally developed for the management of T2DM and later for obesity, these agents exert multiple beneficial effects across several organ systems [4]. By inducing substantial weight loss, improving insulin sensitivity, and reducing systemic inflammation, GLP-1RAs target key pathogenic mechanisms driving MASLD [4]. Because human hepatocytes lack functional GLP-1 receptors [5], these benefits are achieved indirectly, mediated through the reversal of lipotoxicity, visceral adiposity, and systemic inflammatory stress [5]. The resulting reduction in hepatic steatosis highlights how targeting extrahepatic, upstream pathways can yield profound downstream liver benefits.

The transition of these agents into the MASLD therapeutic armamentarium was a logical step considering

4th Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece

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Key words: *Metabolic dysfunction-associated steatotic liver disease; GLP 1 receptor agonists; incretins; diabetes mellitus; obesity*

that obesity and T2DM are the principal drivers of disease progression and adverse outcomes [6]. This approach achieved its definitive validation in the phase 3 ESSENCE trial, where semaglutide 2.4 mg demonstrated highly significant rates of steatohepatitis resolution without worsening of fibrosis, alongside a moderate anti-fibrotic effect [7]. These findings ultimately led to accelerated FDA approval of semaglutide 2.4 mg for metabolic dysfunction-associated steatohepatitis (MASH) in August 2025, marking a historic milestone.

Nevertheless, while GLP-1RA monotherapy consistently resolves steatohepatitis, its capacity to improve liver fibrosis has been comparatively modest [6]. This limitation has fueled the rapid development of the next generation of metabolic therapies: dual and triple incretin agonists. Multi-agonists combining GLP-1 with glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG) receptors have achieved unprecedented weight loss and metabolic control [6]. Those incorporating glucagon agonism are particularly compelling; unlike GLP-1, glucagon acts directly on the liver to enhance lipid oxidation and energy expenditure. Emerging phase 2 data suggest that dual and triple agonists may achieve greater fibrosis improvement than first-generation GLP-1RAs, raising the possibility that metabolic therapies capable of inducing profound weight loss and directly modulating hepatic metabolism may ultimately overcome one of the principal limitations of current incretin-based treatment [8].

Most importantly, the clinical value of GLP-1RAs extends beyond the liver. Large-scale cardiovascular outcome trials in patients with obesity and T2DM have consistently demonstrated reductions in major adverse cardiovascular events (MACE), while recent studies have also documented slower chronic kidney disease progression [9, 10]. This holistic protection highlights a significant contrast with purely liver-directed therapies, such as the thyroid hormone receptor-β agonist resmetirom, the only other approved pharmacotherapy for MASH. While resmetirom effectively improves liver outcomes by directly targeting downstream intrahepatic pathways, its cardiorenal effects remain uncertain and appear largely neutral [11].

Therefore, clinicians are moving toward a personalized, risk-stratified treatment model. Many experts currently favor GLP-1RAs for patients with MASLD who have obesity, T2DM, or high cardiometabolic risk [12]. Conversely, resmetirom may be preferred in patients without obesity or diabetes, or in those for whom a more liver-focused therapeutic approach is appropriate [12]. Looking forward, the ultimate solution for MASLD management likely lies in combination therapy. Given the multifactorial nature of the disease, it is unlikely that a single agent will optimally address steatosis, inflammation, fibrosis, obesity, and cardiometabolic risk simultaneously in all patients. Combination regimens that pair metabolism-targeting therapies such as GLP-1 receptor agonists with liver-directed agents such as resmetirom may offer complementary benefits [12]. Ongoing and future studies will determine whether such combinations can achieve additive or even synergistic effects on both hepatic and extrahepatic outcomes.

Despite their promise, GLP-1RAs are not without limitations. Real-world data indicate that approximately 40% of patients discontinue treatment within the first year, primarily due to gastrointestinal intolerance [13]. Furthermore, rapid weight loss introduces the risk of lean muscle mass depletion, a serious concern for sarcopenia in older patients or those with cirrhosis [14]. Most importantly, discontinuation of therapy is frequently followed by substantial weight regain and metabolic relapse [15]. These observations highlight that MASLD, like obesity, is a chronic disease that requires long-term management to sustain clinical benefits.

To conclude, the emergence of GLP-1 receptor agonists has fundamentally altered the therapeutic landscape of MASLD. By treating the metabolic disease rather than the organ in isolation, these agents address the metabolic dysfunction that lies at the core of disease pathogenesis. While important questions remain regarding their mechanisms of action, long-term safety, antifibrotic efficacy, and optimal combination with liver-directed treatments, the overarching message is clear: effective management of MASLD requires targeting metabolism. Future therapies should be judged by their efficacy to reduce cardiovascular events, prevent kidney disease progression, improve quality of life, and ultimately reduce overall mortality.

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Corresponding author:

Maria Kalafateli
4th Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokratio Hospital, Thessaloniki, Greece,
E-mail: mariakalaf@hotmail.com

An overview of pathophysiology, clinical presentation, diagnosis, treatment, and prognosis of IgG4-related disease

Georgios I. Eleftherakis[1], Christodoulos Chatzigrigoriadis[2]

Abstract

Immunoglobulin G4 (IgG4) is a peculiar type of IgG that normally suppresses the immune response. IgG4-related disease (IgG4-RD) is a rare, immune-mediated fibroinflammatory condition characterized by elevated serum IgG4 levels and tissue infiltration by IgG4-positive plasma cells. It can affect multiple organs, such as the liver, bile ducts, pancreas, retroperitoneum, salivary/lacrimal ducts, kidneys, lungs, lacrimal/salivary glands, and lymph nodes. Multisystem involvement occurs, presenting with systemic symptoms, such as fatigue, fever, and weight loss. Thus, the diverse and nonspecific clinical manifestations of IgG4-RD explain why it is often misdiagnosed as other autoimmune disorders, malignancies, and infectious diseases. Although serology, imaging, and flow cytometry are useful tests for diagnosing IgG4-RD, biopsy remains the gold standard. The levels of the eosinophils, immunoglobulins, and complement, combined with imaging studies, are useful for monitoring the disease course. Although corticosteroids are first-line agents, non-steroidal immunosuppressants are available options. Organ-specific interventional treatment is also essential. This narrative review provides an in-depth review of pathophysiology, clinical presentation, diagnostic criteria, and treatment strategies for IgG4-RD.

Key words: *IgG4-related disease; autoimmunity; humoral immunity; B cells; plasma cells*

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a systemic condition that can involve various organs [1]. First recognized in association with autoimmune pancreatitis, IgG4-RD is now understood to be a broader disease entity encompassing multiple organ systems [1]. The condition can present either localized or widespread organ involvement, often leading to misdiagnosis as malignancy, e.g., pancreatic cancer; infectious diseases, e.g., tuberculosis; or other autoimmune diseases, e.g., sarcoidosis and vasculitis [1,2,3].

[1]Department of Internal Medicine, University General Hospital of Patras, 26504 Rio, Greece
[2]School of Medicine, University of Patras, Patras, Greece
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Typical histopathological findings in IgG4-RD are characterized by the classic triad of diffuse lymphoplasmacytic infiltration, obliterative phlebitis, and storiform fibrosis [1-8]. IgG4 is a distinct subclass with unique anti-inflammatory properties that help prevent autoimmunity [1-3]. Thus, its role in the pathogenesis of IgG4-RD remains controversial [4]. Aside from humoral immunity, multiple pathophysiological mechanisms are implicated, including the Th2 pathway, eosinophils, cytotoxic cells, and regulatory cells, but the triggering event remains unknown [1-4].

The clinical presentation of IgG4-RD is highly variable, ranging from incidental imaging abnormalities to end-organ failure [1-3,7,9]. The differential diagnosis is broad because the signs and symptoms are usually nonspecific; thus, cancer, infectious disease, and

infiltrative disorders should be considered during the investigationas as their management differs [1-3,7]. The typical diagnostic workup includes serology, imaging, and histopathology [1-9]. A multidisciplinary approach with proper clinical correlation is necessary for an accurate diagnosis [2,3].

Treatment is necessary for the majority of patients, while regular follow-up is appropriate for patients with indolent, stable, and limited disease [1,7,9]. Corticosteroids are first-line agents, but non-steroidal immunosuppressants are reasonable in high-risk patients or for the management of a flare [1,2,7-9]. The long-term effect of biologic agents, such as rituximab, is promising [1,2,7-9]. Further research on the treatment strategies and novel agents is crucial for better outcomes.

The structure and the function of the IgG4 antibody

Immunoglobulins are protective molecules of humoral immunity, consisting of two heavy and two light chains. The chains of each pair are typically identical. There are two types of light chains (κ, λ) and five types of heavy chains (γ, α, δ, ε, μ) chains that are combined randomly. There are five classes of immunoglobulins; the type of heavy chain determines each class. The presence of the γ chain defines immunoglobulin G (IgG). Immunoglobulin G4 (IgG4) is one of the four subclasses of IgG, representing less than 5% of the total IgG [1]. However, its prevalence is highly variable in the healthy population. It has unique structural and functional properties that differentiate it from other IgG subclasses (Table 1).

IgG4 physiologically suppresses the immune system through multiple mechanisms:

1. The disulfide bonds between the heavy chains of IgG4 are weak, allowing them to dissociate. Moreover, IgG4 half-molecules consisting of a heavy and a light chain are formed and bind to other IgG4 half-molecules randomly. Notably, the Fc portion of IgG4 interacts with other antibodies, especially IgG4, similarly to rheumatoid factor [1,3]. As a result, new antibodies with two different Fab regions are formed, each recognizing a different antigen. These antibodies are functionally monovalent with a restricted ability to cross-link antigens, form immune complexes, and bind complement or Fcγ receptor (FcγR) [1,11]. This process is called fragment antigen binding (Fab)-arm exchange and occurs in the endosomes of endothelial cells in the presence of reducing factors [2, 3].
2. Unlike IgG1 and IgG3, which activate complement via the classical pathway, IgG4 has a lower affinity for C1q and Fcγ receptor (FcγR), explaining its minimal ability to activate complement, phagocytes, and cellular immunity [1,3]. Instead, it plays a role in dampening excessive immune responses and is often considered a marker of immune tolerance.
3. IgG4 is produced in response to chronic antigen exposure, such as allergens or persistent infections [1]. T helper 2 (Th2) cells typically secrete interleukin 4 (IL-4) and IL-13, leading to the production of IgE and IgG4 in the context of the Th2 pathway. How-

Table 1. *Features of IgG subclasses.*

Feature	IgG1	IgG2	IgG3	IgG4
Relative abundance (% of total IgG in serum)	60	32	4	4 (highly variable)
Fc γ receptor binding	+++	+/–	+++	+/–
C1q binding	++	+	+++	+/–
Hinge length (number of aminoacids)	15	12	Up to 62	12
Inter-heavy-chain disulfide bonds	2	4	11 (depending on allotype)	2
Fab-armex change	No	No	No	Yes
Fc glycosylation	Yes	Yes	Yes	Yes
Fab glycosylation	Yes	Yes	Yes	Greater than other subclasses

IgG; Immunoglobulin G, Fab: Fragment antigen-binding, C1q: complement component 1q, Fc: Fragment crystallizable region.

ever, more IgG4 is produced during a modified Th2 response in which T regulatory (Treg) cells secrete inhibitory cytokines, such as IL-10 [1]. Thus, the ratio of IgG4/IgE increases in the presence of IL-10, IL-12, and IL-21 [1].

Pathology and pathophysiology

Despite its general anti-inflammatory properties, IgG4 is implicated in the pathogenesis of IgG4-RD due to the excessive production and tissue infiltration of IgG4-positive plasma cells [3]. It remains unclear whether IgG4 acts as a primary or secondary inducer of inflammation in patients with IgG4-RD; it may also represent an innocent bystander or a decompensatory mechanism of inflammation [1,2,3]. Chronic immune stimulation, cytokine signaling (interleukin-4, interleukin-10, and transforming growth factor-β), and abnormal B and T cell activity seem to play a role [3] (Figure 1). The etiology of IgG4-RD may be multifactorial; genetics, infectious diseases, and autoimmunity may represent the initial stimuli of IgG4-RD [1].

IgG4-RD requires all the following histopathological findings: a) tissue infiltration by IgG4-positive plasma cells and lymphocytes, b) storiform (whorled) fibrosis patterns, and c) obliterative phlebitis, which is defined as inflammation leading to the occlusion of veins [1-7]. The lymphoplasmacytic infiltrate consists of plasma cells and T cells diffusely distributed in the area of inflammation, while B cells and plasma cells tend to form extranodal germinal centers [1,3]. IgG4-positive plasma cells typically predominate over other types of plasma cells, making up more than 50% of total plasma cells [1]. Notably, the cut-off value for IgG4-positive plasma cells in the visual field is organ-specific and ranges from 10 to 200, depending on the affected organ [1,2]. Polyclonality is a typical finding in the population of lymphocytes, but oligoclonal cases have been reported [1-4]. Tissue eosinophilia is a common histopathological finding in the context of a Th2 response; extensive infiltration is observed in eosinophilic angiocentric fibrosis and eosinophilic cholangitis, resembling allergic disorders and eosinophilic granulomatosis with polyangiitis [1-3,6,7]. Neutrophils and granulomas are atypical findings, although neutrophils are observed in lesions of the respiratory and gastrointestinal mucosa [1,6]. Fibrosis exhibits a patchy distribution with a radial arrangement of collagen fibers, a feature highly specific to IgG4-RD [2,3]. It should be noted that in advanced stages of IgG4-RD, fibrosis predominates over lymphoplasmacytic infiltrate, complicating the diagnosis and management [2,8]. Obliterative phlebitis presents as a lymphoplasmacytic infiltrate in the vascular wall, without necrosis, that occludes the lumen of medium-sized veins; a similar pattern sometimes affects the arteries,

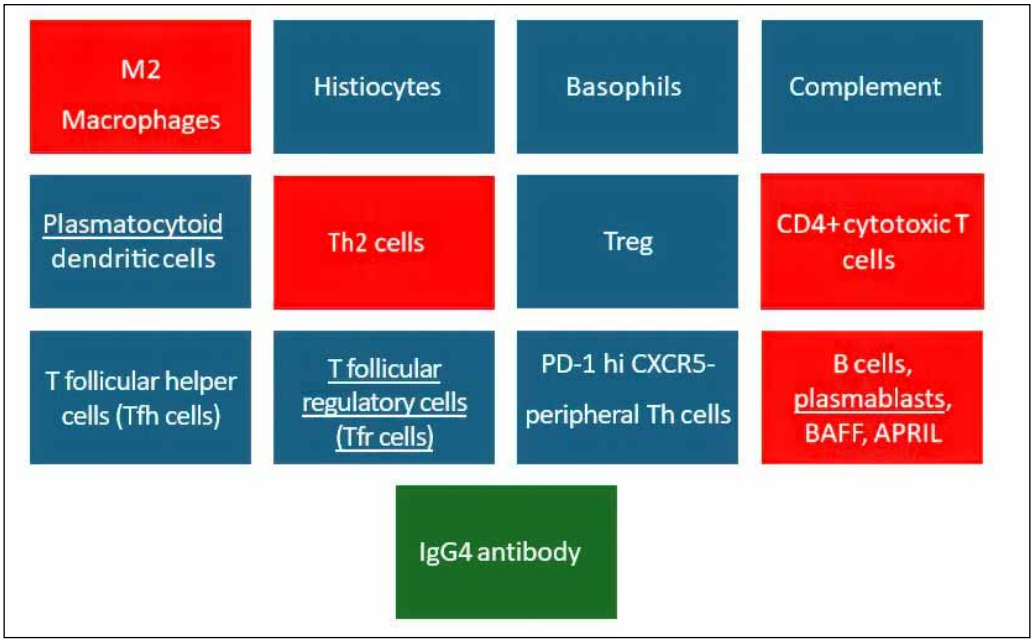

Figure 1. The immune components of the IgG4-related disease.

especially in the lungs and the pancreas [2,6,7]. The degree of obstruction is variable, but phlebitis without obstruction is also commonly observed [3,7].

The role of IgG4 in the pathogenesis of IgG4-RD is a controversial topic. As mentioned earlier, IgG4 normally causes immunosuppression; thus, its involvement in an immune attack against autoantigens is paradoxical [1-3]. The three main theories claim that a) IgG4 causes direct tissue injury, b) IgG4 has a neutral effect on tissue damage, and c) IgG4 protects the tissue from further damage [1-3]. According to the first theory, the initial inflammatory stimulus triggers the production of IgG4, resulting in the formation of toxic immune complexes [1,3]. According to the second theory, the initial inflammatory stimulus induces both the production of IgG4 and the activation of immune cells that release profibrotic cytokines, which means that IgG4 is a byproduct of this disorder [1,3]. According to the third theory, IgG4 is overproduced as a compensatory mechanism to decrease the activity of the immune disorder [2,3]. The underlying cause of this controversy is the lack of knowledge about the initial inflammatory stimulus; hence, its relationship with the production of IgG4 is unknown [8]. Another cause is the lack of evidence regarding the degree of Fab-arm exchange in patients with IgG4-RD; thus, the ability of pathological IgG4 to form immune complexes, leading to tissue deposition and inflammation, is unclear [2].

A key component of IgG4-RD pathophysiology is the role of CD4+ cytotoxic T lymphocytes (CD4+ CTLs), which are believed to drive tissue inflammation and fibrosis [7] (Figure 2). Unlike in typical immune responses, where CD8+ cytotoxic cells play a significant role, IgG4-RD features an unusual expansion of CD4+ CTLs that express cytotoxic molecules, such as granzyme B and perforin, comprising the majority of the CD4+ infiltrate [9,10]. It is important to note that the presence of CD4+ cytotoxic cells is associated with the accumulation of CD8+ CTLs in the inflammatory area, attributed to the release of self-peptides by the cytotoxic activity of CD4+ CTLs and their presentation on the surface of B cells [9,11]. These cells contribute to chronic tissue damage by inducing apoptosis of resident cells. Consequently, tissue repair is activated, promoting the activation of fibroblasts and enhancing collagen deposition, leading to fibrosis. As a result, the presence of CD4+ CTLs correlates with disease activity, and their decline indicates an adequate response to treatment; however, further investigation is necessary to clarify the association between the levels of CD8+ CTLs and disease activity [8,11].

Tregs and activated B cells play a role in disease modulation [8]. Generally, the function of Treg cells is impaired in autoimmune diseases, but this rule does not apply to IgG4-RD [1]. Although this is a controversial

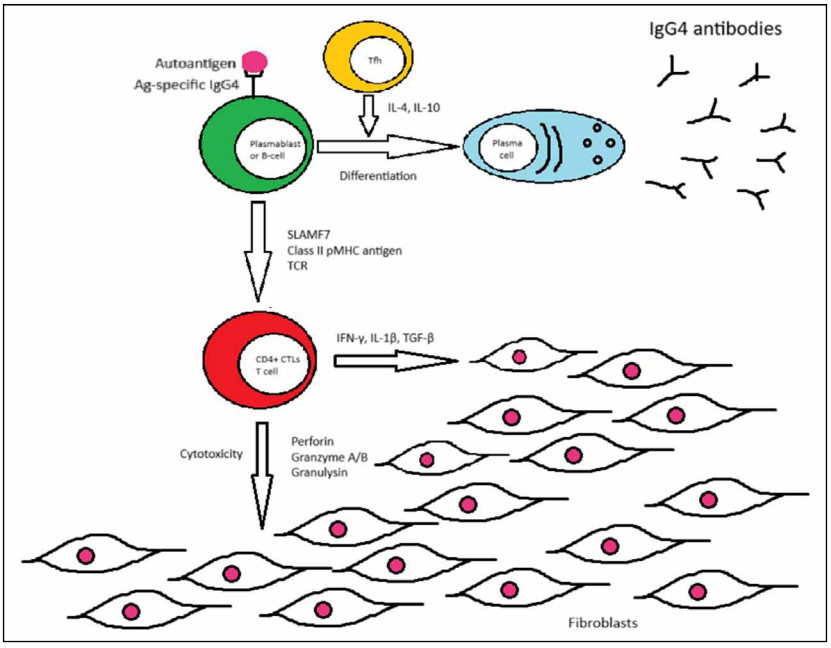

Figure 2. The pathogenesis of IgG4-related disease.

topic, increased numbers of Tregs in the peripheral blood and the area of inflammation have been associated with the release of IL-5, IL-10, IL-13, and tumor growth factor-β (TGF-β), leading to increased production of IgG4 and fibrosis, respectively [1,3,8]. In addition, activated Breg cells may contribute to the elevation of IL-10 and TGF-β, and their presence is associated with pancreatic involvement [1,3,4]. Of course, regulatory immune cells possibly represent a compensatory mechanism to control excessive immune activation against normal tissues. B cells are responsible for antigen presentation to CD4+ and perhaps CD8+ T cells and are precursors of IgG4+ plasma cells [2,8,11].

Although the transition from the inflammatory phase to the fibrotic phase is less clear, emerging research has also implicated the role of macrophage and fibroblast interactions in the development of progressive organ fibrosis [8]. Th2-skewed immune responses involving regulatory cells, along with cytokines such as IL-4, IL-5, IL-10, IL-13, interferon-γ (IFN-γ), and TGF-β, are thought to be essential for the activation of eosinophils, alternatively activated macrophages, myofibroblasts, and fibroblasts [3,7,8]. However, the importance of Th2 cells in the pathogenesis of IgG4-RD has been questioned, as they represent a minority of the inflammatory infiltrate, and their elevation is especially linked with atopic disease, so further research is necessary [3,7,8,11,12]. It seems that innate immune cells, such as M2 macrophages, release cytokines that induce the deposition of fibrous tissue [8]. Interestingly, myofibroblasts and fibroblasts are involved in the active phase of the disease, while persistent activation of fibroblasts in the chronic phase leads to excessive collagen production, eventually leading to structural organ damage [3].

Clinicoradiological manifestations and differential diagnosis

IgG4-RD tends to affect middle-aged or elderly male patients; however, it depends on the affected organ and the nationality [1-3,7,8,13-16]. This observation contradicts the general rule that autoimmunity is more common in young female patients [1-3]. For example, significant male predominance has been reported in pancreatic, renal, and retroperitoneal disease, while head and neck involvement is equally distributed between the sexes [2,13,17,18].

IgG4-RD is typically presented as a subacute or chronic disease with nonspecific complaints or as an incidental finding in imaging or histopathological studies [1-3,7,9,19,20]. The clinical findings are usually related to the organs involved; signs and symptoms of acute illness or systemic inflammation are unlikely to occur [1-3,9]. Interestingly, fever is an exclusion criterion for IgG4-RD in contrast to other rheumatic diseases [9,16,19]. However, weight loss might occur, but this is probably a consequence of malabsorption in patients with long-standing pancreatic or biliary involvement [2,3,7,9,19,21]. The indolent course of the disease explains why most patients (~60%) at the time of diagnosis have already developed fibrosis and loss of function, which is partially irreversible [1,22]. The number of affected organs is variable, and it may change over time [1,3]. Most patients present clinically evident illness of a single site, but further investigation commonly reveals asymptomatic involvement of other organs [1,19]. It should be noted that multisystem involvement can occur simultaneously or metachronously [1,3]. In addition, self-limited disease has been reported in a minority of patients [1,3]. Atopic diseases are commonly observed in patients with IgG4-RD, but their relationship is questionable [1-4,7,19,23,24]. Although IgG4-RD can affect any organ, it is categorized into four main clinical patterns based on the organs involved and their epidemiological and pathological features, but there are many exceptions to this rule [4,8,19, 25] (Table 2).

Regarding the abdominal manifestations, IgG4-RD is associated with type 1 autoimmune pancreatitis (type 1 AIP), IgG4-RD sclerosing cholangitis, liver disease, mesenteric involvement, and gastritis. Type 1 AIP presents with focal or diffuse a pancreatic enlargement, causing biliary obstruction, pancreatic insufficiency, and possible involvement of the portal vein or splenic vein [2,3,15,26]. Painless jaundice, weight loss, and diabetes mellitus are common clinical features, while acute pancreatitis is a rare complication [2,3,7,19,26]. Interestingly, endocrine dysfunction with glucagon hypersecretion leading to hyperglycemia has been noted in patients with IgG4-RD without radiologic evidence of pancreatitis [27]. In addition, type 1 AIP has been linked with pancreatic cancer and other malignancies, but further studies are necessary to confirm this association [4,19,28,29]. Furthermore, the causality remains unclear; chronic inflammation triggers cellular proliferation and the development of mutations, but AIP could also represent a paraneoplastic complication of a pre-existing neoplasm [28,29]. Imaging may reveal a sausage-shaped pancreas, a tumor-like lesion, diffuse stenosis of the pancreatic duct, a peripancreatic halo (due to involvement of the

Table 2. *The immune components of IgG4-related disease.*

Pattern	Pancreatic-Biliary- Liver Disease	Retroperitoneum and Aorta	Head and Neck	Mikulicz's and Systemic Disease
Typical manifestations	Type 1 Autoimmune Pancreatitis (Type 1 AIP) Sclerosing Cholangitis	Retroperitoneal Fibrosis Large Vessel Disease	Enlargement of salivary and/or lacrimal ducts; eye involvement.	Symmetrical enlargement of lacrimal/salivary glands with involvement of the thorax/abdomen
Dominant sex	Male	Male	Female	Male
Average Age (years)	63	58	55	63
Serum IgG4	Elevated	Normal or elevated	Elevated	Markedly elevated
Inflammatory markers (CRP/ESR)	Normal	Elevated	Normal	Normal
Mimickers	Pancreatic cancer Autoimmune Pancreatitis type II (AIP type II) Primary Sclerosing Cholangitis Cholangiocarcinoma	Lymphoma Erdheim-Chester disease Takayasu arteritis Giant cell Arteritis	Connective Tissue Diseases Giant Cell Arteritis Lymphoma	Connective Tissue Disease Giant cell Arteritis Lymphoma
Fibrosis	Absent	Present	Absent	Present

peripancreatic fat), pancreatic stones, and pancreatic atrophy (in long-standing disease) [1,2,3,7,26]. On the contrary, pancreatic cancer causes focal stenosis with upstream dilation of the pancreatic duct, while type 2 AIP is more likely to present with an acute episode of pancreatitis, inflammatory bowel disease, and a neutrophilic infiltrate on biopsy [26]. IgG4-RD sclerosing cholangitis is related to type 1 AIP and shares a similar clinical and radiological presentation with primary sclerosing cholangitis (PSC); both diseases present with obstructive jaundice leading to liver cirrhosis and a combination of biliary strictures and dilations on cholangiography [2,3,9,19,30]. However, IgG4-RD is associated with cholecystitis (typically manifesting as subclinical thickening of the gallbladder wall without cholelithiasis) and can also cause pseudo-tumors resembling cholangiocarcinoma [1,2,7,9,19]. Liver involvement should be differentiated from autoimmune hepatitis and liver malignancy due to the abnormal liver function tests and the development of inflammatory pseudotumors [2,3,31]. Inflammation of the mesenteric fat is associated with immobilization of the visceral organs, leading to intestinal obstruction [3,32]. IgG4-related gastritis might be symptomatic, presenting as atrophic mucosa, erosions, ulcers, thickened wall, and submucosal tumors; thus, atrophic gastritis, Helicobacter pylori infection, Castleman disease, and gastric malignancy should be excluded [3,33,34].

IgG4-RD can cause head and neck disease, especially involving the salivary glands, lacrimal glands, orbits, and thyroid gland. Non-tender or slightly tender and typically bilateral involvement of major (and sometimes minor) salivary glands is common [2,7,16,19,30,35,36]. Enlargement of the submandibular glands, known as Kuttner's tumor, is the most common form of salivary gland involvement and is specific to IgG4-RD [1,3,35]. Mikulicz's disease involves symmetrical enlargement of the lacrimal, parotid, and submandibular glands [1-3,8-10,30]. It is important to note that sialadenitis caused by IgG4-RD is linked to abnormal saliva flow and the development of sialolithiasis [35]. Dacryoadenitis tends to be bilateral, leading to orbital masses, while dacryocystitis more commonly causes xerophthalmia [3,7,16,30]. Sjögren syndrome is the main differential diagnosis, but IgG4-related salivary and lacrimal gland disease tends to cause mild xerophthalmia or xerostomia that resolves after the administration of corticosteroids. Proptosis, diplopia, and blurry vision may result from swelling of the lacrimal glands or orbital myositis, or both [2,3,7,19,30]. Interestingly, some cases report thickening or compression of nearby nerves [2,3]. Scleritis and uveitis are rare eye-related complications of IgG4-RD [7]. Riedel's thyroiditis causes fibrosis and progressive, painless enlargement of the thyroid gland (rocky goiter),

with reduced blood flow and iodine uptake, leading to tracheal compression, laryngeal nerve palsy, cervical lymphadenopathy, thyroid dysfunction (usually hypothyroidism), and rare involvement of the parathyroid glands [1-3,37,38]. Hence, Hashimoto thyroiditis and thyroid cancer should be excluded based on imaging and histopathology.

IgG4-RD affects the retroperitoneal structures, such as the aorta, kidneys, and ureters. It accounts for a significant portion of idiopathic retroperitoneal fibrosis, which involves connective tissue around major vessels, the upper urinary system, and pelvic structures [1-4,7,16,19,30,39-41]. Common but nonspecific symptoms include back pain or abdominal pain, sometimes radiating to the inguinal areas or thighs [2,40]. However, the overall clinical presentation varies depending on organ-specific complications [39-41]. Moreover, chronic periaortitis (CP) involves inflammatory tissue around the aorta, while chronic aortitis primarily affects the vascular wall [39,40]. Their overlap often makes differentiation difficult; aortitis tends to damage the media, particularly in the thoracic aorta, and can lead to aneurysm formation, whereas periaortitis mainly affects the adventitia and the abdominal aorta [40]. Although the aorta—especially its infrarenal segment extending to the iliac arteries—is most frequently involved, medium-sized branches and retroperitoneal veins can also be affected [2,4,39,40]. Consequently, vascular involvement may manifest as a pulsatile mass, chronic limb ischemia, mesenteric ischemia, coronary artery disease, lower extremity edema, deep venous thrombosis, thrombophlebitis, hydrocele, and varicocele [2,4,39]. The rupture of an inflammatory aneurysm is a rare but life-threatening complication. Vascular imaging often reveals wall thickening (diffuse or localized, sometimes mimicking a mass), dissection, or aneurysms rather than stenosis or strictures [1,3,7,19,30,40]. Fibrous tissue deposition in the retroperitoneal space can irritate or obstruct nearby structures, causing nonspecific symptoms like dysuria and urgency, obstructive uropathy, or renovascular hypertension [39,41]. Regarding the differential diagnosis, rheumatic diseases, such as Takayasu arteritis and giant cell arteritis, tend to affect females and present with fever or arthralgia, while atherosclerosis lacks elevated inflammatory markers [40]. In addition, the exclusion of infectious diseases and malignancies as causes of retroperitoneal fibrosis is recommended [39,40]. Chronic kidney disease can also arise from IgG4-related tubulointerstitial nephritis, leading to proteinuria, hematuria, and potentially progressing to end-stage renal disease [1-3,7,19,30,39,41]. Drug-induced interstitial nephritis, lupus nephritis, and vasculitis should be excluded based on biopsy results [19]. A minority of patients develop nephrotic syndrome due to secondary membranous nephropathy, which differs from primary membranous nephropathy caused by antibodies against phospholipase A2 [2,3,7,30,41]. Renal imaging may reveal enlarged kidneys due to inflammation, atrophic kidneys resulting from long-standing disease, or multiple tumor-like lesions with lower contrast enhancement (with solitary masses being rare), which should be differentiated from renal malignancy [2,3,7,30,39,41].

IgG4-RD can sometimes affect other organs, including the lymph nodes, lungs, serous cavities, skin, nervous system, prostate, and mammary glands (Table 3) [2,3,7,19,30,42-58].

Diagnosis

The diagnosis of IgG4-RD is challenging and depends on the combination of clinical, laboratory, radiological, and histopathological findings. The gold standard is the biopsy result, which should be correlated with the clinical presentation and imaging findings [2,3,30,59]. A significant exception to this rule is type 1 AIP; treatment is indicated in the presence of a typical clinical and radiological presentation without a biopsy [2].

Laboratory testing involves measuring antibodies, complement, inflammatory markers, complete blood count, and plasmablasts/plasma cells. Elevated serum IgG4 (>135 mg/dL) is a useful diagnostic marker, but many patients show normal levels at diagnosis [1-3,7-9,59]. Notably, the upper normal value varies depending on the use of new reagents [60]. Elevated cerebrospinal fluid (CSF) IgG4 suggests immune-mediated inflammation. A recent meta-analysis reports the sensitivity and specificity of IgG4 titers as 87.2% and 82.6%, respectively, though these figures depend on race and disease extent [61]. Adjusting the cutoff value to enhance diagnostic accuracy remains controversial and is currently under investigation [5]. The prozone phenomenon explains the false-negative results in some patients with highly abnormal levels of IgG4; thus, proper serum dilution is recommended to prevent misdiagnosis [2,3,5,8,9]. If the IgG4 levels are normal, a ratio of IgG4/IgG > 10% is suggestive of IgG4-RD, but this remains a controversial marker [2,3,5,7-9]. The nonspecific nature of IgG4 elevation is observed in malignant, autoimmune, and infectious

Table 3. *Unusual sites of IgG4-RD with their clinical presentation and the differential diagnosis.*

Organs	Clinical presentation	Differential diagnosis
Lymph nodes [2,3,7,19,42,43]	Localized or generalized, non-tender lymphadenopathy. Their size ranges from 1 to 3 cm and occasionally causes compression of vital structures.	Lymphoproliferative, infectious, and other immunologic diseases
Lungs [2,3,7,19,30,44-46]	Incidental findings on radiographs (~75%) or nonspecific symptoms (cough, sputum production, dyspnea, chest pain, and hemoptysis). Imaging reveals tumefactive lesions, central airway disease, or pneumonitis. Pulmonary fibrosis is a potential complication with traction bronchiectasis and honeycombing. Reactive hilar and mediastinal lymphadenopathy is common.	Lung cancer, vasculitis, sarcoidosis, and other causes of interstitial lung disease
Serosal cavities [2,3,7,30,44,46-52]	Pleural disease appears as effusion, increased vascularity, thickening, nodular lesions, plaques, and adhesions within the pleural cavity. Acute pericarditis, pericardial effusion, constrictive pericarditis, and ascites are other manifestations. A case involving ascites, massive right pleural effusion, pericardial effusion, and elevated tumor markers (cancer antigen 125 and α-fetoprotein) may suggest pleuroperitoneal communication in the context of Meigs or pseudo-Meigs syndrome.	Acute coronary syndrome, infectious diseases, malignancies, rheumatic diseases, and cardiac myxoma
Skin [2,53]	Nodules, plaques, masses, macules, papules, or gangrene mainly distributed in the upper body, especially the head and neck area. Usually accompanied by internal organ involvement.	Lymphoproliferative disorders, psoriasis, cutaneous lupus, and systemic sclerosis
Central nervous system [3,7,19,30,54]	Pachymeningitis, cerebral inflammation, and cavernous sinus thrombosis cause cranial nerve palsy, radiculopathy, headache, sensorimotor abnormalities, visual deficits, sensorineural hearing loss, or dementia. The term "hypertrophic pachymeningitis" describes mass-like lesions in the meninges. Pituitary pathology, such as edema or tumor-like lesions, leads to headache, and visual field defects like bitemporal hemianopsia.	Infectious diseases, malignancies, vasculitis, and infiltrative disorders, e.g. sarcoidosis, histiocytosis.
Peripheral nerves [2,19,54]	Rapid or subacute development of sensorimotor neuropathy or the formation of perineural masses.	Vasculitis, demyelination
Prostate [2,3,19,55]	Urgency, incomplete voiding, and hesitancy.	Benign prostate hyperplasia, prostatitis, prostate cancer
Breast [56-58]	Painless and hard breast mass.	Breast cancer

diseases [4]. Other autoantibodies, such as rheumatoid factor, antinuclear antibodies, anti-carbonic anhydrase II antibodies, and anti-smooth muscle antibodies, may also be present [8,15,60,62]. Positive titers of highly specific antibodies for rheumatic diseases are inconsistent with IgG4-RD [16]. Elevation of IgE often occurs with a Th2 response, even without atopy, but this is nonspecific [1,3,4]. Polyclonal gammopathy and elevation of other IgG subclasses, including IgG1 and IgG3, are common; these subclasses activate the complement cascade in many patients [8,15]. Moreover, hypocomplementemia is especially associated with kidney involvement [7,8]. Mild increases in inflammatory markers like C-reactive protein and erythrocyte sedimentation rate mainly involve the aorta and retroperitoneum [7,8]. Eosinophilia is a frequent abnormality in peripheral blood, but highly

abnormal counts (>3,000/mm^3) as well as leukopenia and thrombocytopenia suggest an alternative diagnosis [8,16]. Plasmablasts, which are intermediate cells between B cells and plasma cells, are released from the bone marrow in response to pathogens, vaccines, and self-antigens. Their elevation has been suggested as a highly sensitive and specific biomarker for IgG4-RD, but further clinical research is needed [2,7,62-65].

Imaging provides crucial diagnostic information after careful assessment of the clinical presentation. The radiological findings are often nonspecific and can be misleading in diagnosing cancer. Different imaging techniques are used based on the involved site. Computed tomography (CT) is the most frequently used test. Magnetic resonance imaging (MRI) is often employed, especially when the biliary tree, the aorta, or the central nervous system is involved [9,40,54]. MRI is an alternative to CT for those with abnormal renal function [41]. Ultrasound is valuable for examining masses in the head and neck region as well as the aorta [40]. Typical findings include organ enlargement, fibrosis, and nodular or mass-like lesions [1,2]. Positron emission tomography (PET) scanning is useful for staging and guiding the site of biopsy due to its higher sensitivity [7,8,66-68]. It should be noted that PET is more likely to recognize arterial, salivary gland, and lymph node pathology, while it lacks sensitivity for renal or brain pathology as well as small, non-active lesions [9,40,68].

Regarding the histopathologic findings, the hallmark of IgG4-RD includes dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis. Although biopsies from the brain, meninges, pancreas, great vessels, and retroperitoneum are demanding, larger tissue samples are associated with a higher diagnostic yield [2,8]. Sampling from multiple sites or repeat biopsies may be necessary [2]. For example, submandibular gland biopsy is more likely to be diagnostic than labial gland biopsy for IgG4-related salivary gland disease [2]. However, histopathological diagnosis of IgG4-RD is often established after a needle biopsy; endoscopic and surgical biopsies are currently preferred when there is clinical suspicion of IgG4-RD [6]. Furthermore, needle biopsies often fail to recognize the pattern of storiform fibrosis or obliterative phlebitis, while the peripheral infiltrate of IgG4-positive plasma cells in neoplasms might be misdiagnosed as IgG4-RD [6]. Organ-specific interpretation of immunohistochemistry is mandatory, given the variable cut-off value of IgG4-positive plasma cells, ranging from 10 to 200 per high-power field [6]. However, tissue infiltration by IgG4-positive plasma cells is also observed in other diseases of inflammatory and neoplastic etiology; diffuse presence of IgG4-positive plasma cells and a ratio of IgG4 to IgG-positive plasma cells of more than 40% may increase specificity [6,30]. Plasma cells secreting IgE, IgG1, IgG2, and IgG3 represent a minority of the inflammatory infiltrate [3].

Recent advances in the diagnostic field have established general criteria for diagnosing IgG4-RD [30]. These guidelines allow proper diagnosis and treatment even in the absence of typical serological and histopathological findings [30]. Exclusion criteria from the clinical presentation, laboratory measurements, imaging, and biopsy results should be examined during the investigation [30]. Notably, a significant portion of IgG4-RD cases is missed by the general diagnostic criteria in clinical practice due to atypical presentation or involvement of atypical sites [30]. Consequently, organ-specific criteria have been developed to maximize the sensitivity for type 1 AIP, Mikulicz's disease, and kidney disease [30]. For example, they enable the diagnosis of type 1 AIP based on imaging, making a biopsy unnecessary. In cases where it is difficult to obtain a biopsy, a successful trial of corticosteroids can indirectly confirm the presumptive diagnosis of IgG4-RD [30]. However, physicians should maximize their efforts to obtain a tissue sample for the exclusion of malignancy, especially when the response to corticosteroids is inadequate [8].

Treatment

Fibrosis is a pathological process characterized by excessive tissue scarring, often resulting in organ dysfunction. Preventing fibrosis is crucial for maintaining organ health and avoiding severe complications. Advancements in early diagnosis and appropriate treatment allow successful outcomes. It is vital to start treating before the establishment of fibrosis [1,8]. However, relapses are common, necessitating long-term follow-up. Evidence is still lacking due to insufficient clinical data [8,9].

Treatment of IgG4-RD is indicated under certain circumstances. All patients with symptomatic disease, subclinical involvement of high-risk organs (pancreas, extrapancreatic biliary tree, meninges, aorta, kidney, retroperitoneum, pericardium), subclinical multi-organ disease, or active progression of pre-existing imaging abnormalities are candidates for immunosuppressive treatment [7,19]. The choice of "watch and wait" is appropriate for patients with asymptomatic and stable disease limited to organs with a low risk of severe complications

and fibrosis [1,7,19]. Medical treatment is divided into two main phases: induction and maintenance, as in rheumatic diseases [7]. Interventional treatment may be necessary for the management of anatomical abnormalities, such as biliary stenting, ureteral stenting, and nephrostomy tubes [7,19]. Radiation therapy is rarely used as a last-line treatment [9].

Pharmacologic agents for managing IgG4-RD include corticosteroids, non-steroidal alternatives, and biologic agents [1,2,9]. Corticosteroids are the first-line therapy for inducing remission, and they are often used for maintenance [1,2,19]. Disease-modifying antirheumatic drugs (DMARDs), such as azathioprine, mycophenolate mofetil, leflunomide, methotrexate, cyclosporine, iguratimod, and cyclophosphamide, are typically used for maintenance, but the evidence remains limited [1,2]. Recently, various biologic agents have been studied, with rituximab being the most common [1]. Although corticosteroids are considered the cornerstone of treatment in IgG4-RD, most patients will eventually receive non-steroidal immunosuppressants to achieve remission and reduce corticosteroid toxicity [9].

Induction of treatment is the first step in IgG4-RD to decrease the disease's activity. The drug regimen typically involves corticosteroids; rituximab or methotrexate are alternatives if corticosteroids are strongly contraindicated [1,2,7]. The recommendations about the dose and the duration of the regimen vary depending on the clinical scenario and the expert's experience. Initially, a medium dose of prednisone, administered orally at 0.4-0.6 mg/kg/day (30-40 mg/day), is administered until resolution, which typically occurs after 2-4 weeks [1,2,7,8,15,19]. Occasionally, a pulse of intravenous methylprednisolone (100-1,000 mg/day for 3 days) is used before the per os regimen for acute complications, such as acute kidney injury or neurological complications [1,7,8]. High doses seem to have similar efficacy to the medium dose of oral corticosteroids [7,8]. Lower doses may be considered when the symptoms are mild. A careful taper should be followed; otherwise, faster withdrawal increases the risk of exacerbation [7,8]. Tapering can be achieved with the following methods: a) reduction of the dose at a rate of 5 mg every two weeks until a final daily dose of 7.5 mg, or b) reduction of the dose at a rate of 10 mg every two weeks until a daily dose of 20 mg, followed a few weeks later with a reduction at a rate of 5 mg every two weeks [1,2]. The total duration of tapering is generally 3-6 months [1,2,7,19].

Maintenance of treatment is achieved with non-steroidal immunosuppressants or low-dose corticosteroids [8]. The addition of nonsteroidal immunosuppressants in the induction phase is indicated in certain patients at increased risk for recurrence (elevated IgE, eosinophilia, elevated IgG4, multiorgan involvement, involvement of high-risk organs, hypocomplementemia) [7,8,9,19]. All patients with a relapse should receive the aforementioned taper of corticosteroids followed by a maintenance plan [7,8]. Japanese experts tend to continue low-dose corticosteroids in the majority of patients for up to three years, but other physicians prefer the combination regimen to discontinue corticosteroids as soon as possible [7]. Rituximab may represent the most effective DMARD, but further research is needed on dosing [1,2,7,8]. Interestingly, the choice of DMARDs varies depending on the organ involved [19].

Regular follow-up, e.g., every six months, with several laboratory tests and imaging techniques, helps assess disease activity and treatment response. However, the management should be guided by these tests after correlation with clinical response. Elevation of serum antibodies (IgG4, IgE, and IgG4/IgG), CSF IgG4, and eosinophils is associated with more active disease [7,8]. It should be noted that changes in the concentration of IgG4 predict relapses in those with elevated IgG4 at baseline [7,8]. Hypocomplementemia occurs during recurrence, implying kidney disease [7,8]. The association of plasmablasts with disease activity is promising, but their use in clinical practice is currently limited [7,8]. Among imaging studies, a PET scan shows active sites of inflammation but cannot differentiate lymphadenopathy from other diseases [7,8].

CONCLUSION

IgG4-related disease is a complex, multisystem disorder that requires a high index of suspicion for diagnosis. Advances in our understanding of its immunopathogenesis and treatment options have significantly improved patient outcomes. Continued research is necessary to further elucidate its mechanisms, refine diagnostic criteria, and optimize management strategies to prevent long-term complications and improve the quality of life for affected individuals.

Future Directions

Ongoing research is focused on identifying novel biomarkers for early detection, understanding the genetic predisposition of IgG4-RD, and developing targeted therapies to improve treatment efficacy while minimiz-

ing treatment-related adverse effects. Large-scale clinical trials are needed to evaluate new therapeutic agents and their long-term impact on disease progression.

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Corresponding author:

Georgios Eleftherakis
Department of Internal Medicine, University General Hospital of Patras, 26504 Rio, Greece,
Tel.: + 30 6945 608345, E-mail: up1045533@upnet.gr

Systematic review of endometriosis

Giannakakis Georgiadis[1], Angelos Daniilidis[2]

Abstract

Endometriosis, a chronic gynecological disorder characterized by the growth of endometrial-like tissue outside the uterus, affects a significant percentage of reproductive-age women and remains a complex condition with multifaceted clinical, biological, and genetic dimensions. This systematic review critically synthesizes the most highly cited research over the last decade to provide a comprehensive, evidence-based overview of the advances in endometriosis, spanning its epidemiology, pathophysiology, diagnostic approaches, and treatment modalities.

By categorizing studies into key themes, this review highlights emerging insights into the etiology and mechanisms of endometriosis, emphasizing the roles of genetic predisposition, immune dysregulation, and environmental factors. Recent developments in diagnostic techniques, particularly those improving non-invasive diagnostics, are examined, reflecting a shift toward early, accessible detection aimed at mitigating the condition's impact on fertility and quality of life. Furthermore, therapeutic strategies are explored, from pharmacological innovations and hormonal treatments to the evolving scope of surgical interventions, including fertility-preserving options. This work underscores the significant progress made in understanding endometriosis, while also identifying enduring challenges in effective long-term management and individualized care. Limitations in current research, such as the variability in diagnostic criteria and the scarcity of longitudinal data, are discussed to underscore areas for future investigation.

Key words: *Endometriosis; pathogenesis; treatment; fertility impact; psychological impact*

INTRODUCTION

Endometriosis is a chronic, inflammatory, estrogen-dependent disease defined by the presence of endometrial-like tissue outside the uterine cavity, predominantly affecting women of reproductive age. It is associated with a broad spectrum of symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility, significantly impacting patients' physical, emotional, and social well-being [1-5]. The global prevalence is currently estimated at 10–15% among women of reproductive age, although the true incidence may be underestimated due to diagnostic delays and variability in clinical presentation [1,6-8].

The burden of endometriosis extends beyond clinical manifestations. It imposes a significant economic cost due to direct medical expenditures and productivity loss and is now widely recognized as a public health issue [9–15]. The average diagnostic delay, reported between 7 and 10 years, highlights systemic deficiencies in early recognition and accurate diagnosis, often attributed to the normalization of menstrual pain, the lack of non-invasive biomarkers, and inconsistent symptomatology [16-20]. Additionally, disparities in access to healthcare services across different populations exacerbate the diagnostic gap, especially in low-resource settings [21-23].

Over the years, substantial progress has been made in understanding the complex pathophysiology of endometriosis, encompassing genetic, immunologic, and hormonal factors. Despite this, challenges remain in its diagnosis and management. Laparoscopy with histological confirmation remains the diagnostic gold standard

[1]Theagenio cancer hospital of Thessaloniki, Gynecological Oncology Department, Thessaloniki, Greece
[2]Papageorgiou General Hospital, Department of Gynaecology - Obstetrics of the Aristotle University of Thessaloniki, A' Obstetrics and Gynaecology Clinic, Thessaloniki, Greece
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[24-28]. Less-invasive imaging modalities and biomarker-based approaches are under active investigation [29-36].

Therapeutic options are diverse, ranging from pharmacological treatments—mainly hormonal suppression—to surgical interventions and assisted reproductive techniques in the case of infertility [28,38-45]. However, there is currently no definitive cure, and recurrence after treatment remains common [24,37,38,46,47]. The management of endometriosis should be individualized, taking into account the severity of symptoms, reproductive goals, patient age, and coexisting medical conditions, thereby emphasizing the importance of a patient-centered approach [13,48-50].

This systematic review synthesizes current evidence regarding the epidemiology, pathogenesis, clinical manifestations, diagnostic methods, therapeutic strategies, and socioeconomic implications of endometriosis. Furthermore, it explores emerging research directions and knowledge gaps that could inform future innovation in diagnostics, personalized treatment, and policy-making [51-54].

1. METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) framework.

A comprehensive electronic search was performed across PubMed, Scopus and the Cochrane Library databases to identify studies published between January 2010 and August 2024.

The following keywords and Boolean operators were applied in various combinations: "endometriosis", "pathogenesis", "diagnosis", "management", "treatment", "fertility", "quality of life", "psychosocial impact" and "economic burden".

Only peer-reviewed original articles, systematic reviews, meta-analyses, and clinical guidelines written in English and involving human subjects were included. Exclusion criteria comprised non-English publications, animal studies, case reports, and non-peer- reviewed materials. Duplicates were removed before screening.

Two independent reviewers performed study selection and data extraction and discrepancies were resolved through consensus. The study selection process is presented in Figure 1.

2. EPIDEMIOLOGY

2.1 Global Prevalence of Endometriosis

The global prevalence of endometriosis is estimated at 10–15% among women of reproductive age, with variations depending on the diagnostic methods and population characteristics [1,6-8]. Underdiagnosis in developing countries may lead to inaccurate global estimates, while higher prevalence is reported in urban areas and is linked to lifestyle factors such as delayed childbearing, stress, and diet [7,55-58].

2.2 High-Risk Populations and Incidence Variability

Incidence rates of endometriosis are higher among women aged 20–40, with ethnic and socioeconomic disparities affecting diagnosis and access to care [14,21-23,59]. Genetic predisposition plays a significant role, with a heritability estimate of around 50% [60-65]. Familial aggregation and twin studies have confirmed this genetic influence, highlighting the importance of early recognition in high-risk populations [63-65].

2.3 Regional and Socioeconomic Influences on Endometriosis

Endometriosis is often underdiagnosed in low-income countries due to limited healthcare resources, while higher prevalence in developed regions may reflect improved diagnostic capabilities [14,21–23]. Environmental and occupational exposures, particularly to endocrine-disrupting chemicals (EDCs), have emerged as potential contributors to the rising incidence of endometriosis [55,56,58].

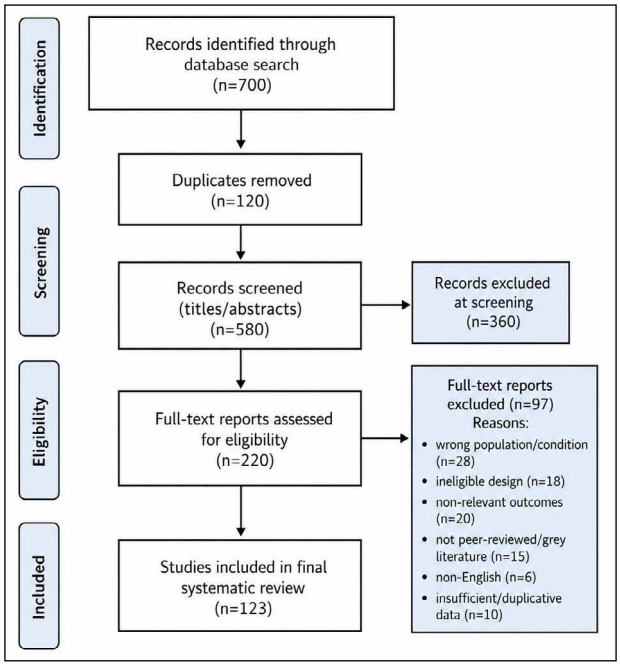

Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility, and inclusion.

Socioeconomic disparities, access to gynecological care, and cultural perceptions of menstrual pain further affect diagnosis and disease management across populations [14,19–23].

Recent epidemiological data indicate that the global burden of endometriosis may be underestimated, especially among underserved groups, emphasizing the need for harmonized diagnostic criteria and the development of international registries [7,66].

3. PATHOGENESIS AND RISK FACTORS

3.1 Retrograde Menstruation and Other Pathophysiological Theories

The theory of retrograde menstruation, originally proposed by Sampson in 1927, remains a central explanation for pathogenesis of endometriosis [67-69]. It posits that menstrual debris containing viable endometrial cells travels backward through the fallopian tubes into the peritoneal cavity, where it adheres and proliferates on ectopic sites. However, this theory alone cannot explain all cases, including such as distant lesions or those occurring in women with obstructed menstrual flow [68,69].

Consequently, alternative mechanisms such as coelomic metaplasia, Müllerian remnant transformation, and stem-cell involvement have been proposed [68,69,70-72]. The coelomic-metaplasia theory suggests that peritoneal cells, under specific stimuli, may transform into endometrial-like cells [68-71]. Müllerianosis and lymphatic or hematogenous dissemination have also been implicated in extrapelvic disease, including thoracic and neural endometriosis [68,69]. More recently, bone-marrow-derived and mesenchymal stem cells have been shown to contribute to lesion initiation and persistence, particularly in deep infiltrating endometriosis and ovarian endometriomas [70-72].

3.2 Genetic and Epigenetic Factors

Familial clustering of endometriosis supports a genetic predisposition [62,63,65]. Twin and genome-wide association studies (GWAS) have identified susceptibility loci on chromosomes 1p36, 7p15.2, 9p21 and 12q22 [60,62,63]. Several single nucleotide polymorphisms (SNPs) near genes involved in estrogen metabolism [estrogen receptor 1 (ESR1)], cell adhesion [cyclin dependent kinase inhibitor 2B antisense RNA 1 (CDKN2BAS)], and immune modulation [wingless-type MMTV integration site family, member 4 (WNT4), vezatin (VEZT)] are consistently linked with increased risk [60,62,63,65,73]. A growing body of evidence supports a unifying genetic-epigenetic model linking heritable susceptibility with acquired molecular alterations in endometriotic tissue [74].

Epigenetic mechanisms — including DNA methylation, histone modifications, and non- coding RNAs — play a pivotal role in aberrant gene expression within endometriotic lesions [69,71,72,75]. Aberrant methylation of genes regulating steroid-hormone signaling, matrix remodeling, and inflammation (e.g. HOXA10, SF-1, CYP19A1) has been demonstrated [69,71,72]. Moreover, dysregulation of microRNAs such as the miR- 200 family and let-7 further contributes to lesion persistence, proliferation, and apoptosis resistance [69,71,72,75].

3.3 Inflammation and Immune Dysfunction

Endometriosis is increasingly recognized as a chronic systemic inflammatory disease [66,69,71]. Peritoneal fluid of affected women contains elevated levels of pro-inflammatory cytokines [interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α)] and growth factors [vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1)], promoting angiogenesis and lesion survival [69,71,72,76].

Macrophages, neutrophils, and activated T cells exhibit impaired phagocytic activity, enabling ectopic endometrial cells to evade immune clearance [69,71,72]. Natural killer cells show reduced cytotoxicity, while regulatory T cells (Tregs) are up-regulated, contributing to immune tolerance [69,71,72]. The detection of autoantibodies further supports a possible autoimmune component [71].

3.4 Hormonal Dysregulation

Endometriosis is an estrogen-dependent and progesterone-resistant disorder [69,72,77]. Ectopic lesions display increased aromatase expression and local estrogen production even without ovarian activity [69,72]. Progesterone-receptor isoform B (PR-B) is down- regulated in ectopic tissue, resulting in impaired responsiveness, persistent inflammation, and unopposed estrogen-driven proliferation [72,77]. Estrogen promotes cellular proliferation, angiogenesis, and neuroinflammation, enhancing lesion persistence [69,71,72]. The imbalance between estradiol and progesterone contributes to apoptosis resistance and chronic disease progression [69,72].

3.5 Environmental and Anatomical Factors

Exposure to endocrine-disrupting chemicals (EDCs) — including dioxins, polychlorinated biphenyls (PCBs) and phthalates — has been linked to increased endometriosis risk in both animal and epidemiologic

studies [55,56,58]. Although mechanisms are not fully elucidated, these agents likely disrupt hormonal signaling and immune surveillance [55,56,58]. Anatomical abnormalities such as Müllerian anomalies enhance retrograde menstruation and are associated with early-onset and severe disease [68,69,71]. Menstrual characteristics — early menarche, short cycles, prolonged bleeding — further modify individual risk [59,78,79].

4. CLINICAL PRESENTATION AND DIAGNOSIS

4.1 Symptomatology

Endometriosis exhibits a broad spectrum of clinical manifestations, ranging from asymptomatic cases to severe, debilitating symptoms. The most commonly reported include dysmenorrhea, non-cyclic pelvic pain, deep dyspareunia, dyschezia, dysuria, and infertility [81-83].

Symptoms are typically chronic and progressive, profoundly affecting quality of life [81,82]. Pain intensity often shows poor correlation with disease extent — women with minimal lesions may experience severe pain, while others with extensive disease can remain asymptomatic [81,82,84].

Infertility affects approximately 30–50% of women with endometriosis and may result from distorted pelvic anatomy, chronic inflammation, altered immune responses [69], or impaired folliculogenesis and endometrial receptivity [41,42,85-87]. Gastrointestinal and urinary manifestations are more common in deep infiltrating endometriosis (DIE), particularly when lesions involve the rectovaginal septum, bowel, or bladder [29,30,31,88].

Psychological distress — notably anxiety, depression, and sexual dysfunction — is highly prevalent, underscoring the need for a holistic, multidisciplinary management approach [89-92].

4.2 Classification and Staging

Multiple systems have been proposed to assess the extent and severity of endometriosis. The revised American Society for Reproductive Medicine (rASRM) classification remains the most widely applied, staging disease from I (minimal) to IV (severe) based on lesion location, depth, and adhesions. However, it correlates poorly with symptom burden and fertility outcomes [26,28,84].

To address these limitations, the #ENZIAN classification was introduced, enabling detailed topographic mapping of DIE and extraperitoneal disease compartments [93]. Comparative analyses suggest that #ENZIAN offers improved prognostic accuracy for fertility outcomes relative to rASRM and the Endometriosis Fertility Index (EFI) [94]. The EFI, in turn, is validated as a predictive tool for spontaneous conception following surgery and is increasingly adopted in reproductive practice [95]. Recent consensus guidelines emphasize the integration of these complementary systems into individualized clinical decision-making [96].

4.3 Diagnostic Modalities

The diagnostic gold standard remains laparoscopy with histological confirmation of endometrial glands and/or stroma in ectopic sites [24,26,28,97,98]. Its invasive nature and variable surgical expertise have, however, prompted a major shift toward non- invasive diagnostic approaches [24,28,30,34-36,99].

Transvaginal ultrasound (TVUS) is considered the first-line imaging tool for suspected endometriomas or DIE when performed by trained sonographers [29,31,100].

Magnetic resonance imaging (MRI) offers superior delineation and pre-surgical mapping, especially in complex or multifocal disease [28-31].

Serum biomarkers, notably CA-125, demonstrate limited sensitivity in early disease; novel candidates such as miRNAs, cytokine panels, and immune-modulatory molecules show promise but remain non-validated for clinical routine [32-35].

Artificial intelligence (AI)–based diagnostic tools are an emerging field, enhancing lesion detection on TVUS and MRI while reducing inter-observer variability. Early trials show high sensitivity but require large-scale validation before clinical adoption [100-103].

Given the absence of a reliable non-invasive test, timely recognition of characteristic symptoms, clinical expertise, and prompt referral remain essential for accurate diagnosis [16-20,24,25,28]. Future diagnostic strategies will increasingly rely on the integration of imaging, molecular, and AI-driven tools within specialized multidisciplinary centers [36,102]. The main diagnostic modalities are summarized in Table 1.

5. TREATMENT OPTIONS

5.1 Pharmacological Management

Medical therapy for endometriosis aims to suppress ovarian function, reduce estrogen- driven inflammation, and relieve pain.

First-line options include nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and combined oral contraceptives (COCs), which suppress ovulation and

Table 1. *Diagnostic Modalities for Endometriosis.*

Diagnostic Modality	Description / Mechanism	Accuracy (Sensitivity/ Specificity)	Key Advantages	Limitations	Reference s
TVUS (transvagin al ultrasound)	First-line imaging for ovarian endometrioma s and DIE; detects lesions in ovaries, rectovaginal septum, bladder.	DIE sensitivity > 90%, specificity > 85% (expert hands).	Widely available, non-invasive, low cost, dynamic.	Operator-dependent; limited for small superficial lesions.	[29,31,100]
MRI (magnetic resonance imaging)	Multiplanar mapping; valuable for complex or pre-surgical cases.	DIE sensitivity > 90%, specificity ≈ 88%.	Excellent soft-tissue contrast, detects extrapelvic disease.	High cost; limited access; specialized interpretation.	[28-31]
Serum biomarkers (CA-125, miRNAs)	Reflect inflammatory/ ectopic activity.	CA-125 sens. 50–70%; miRNAs promising but heterogeneous.	Simple, minimally invasive; adjunct to imaging.	Non-diagnostic alone; no validated biomarker for routine use.	[32-35]
AI-assisted imaging	Algorithm- aided TVUS/MRI for lesion detection/ class ification.	Early studies → high sensitivity (pilot data).	Reduces operator bias; speeds interpretation.	Still experimental; external validation needed.	[100-103]
Diagnostic laparoscopy (gold standard)	Direct visualization ± biopsy confirmation.	Specificity ≈ 100%.	Enables simultaneous diagnosis & treatment.	Invasive; anesthesia/surgical risk; cost.	[24,26,28,97]

induce a pseudo- pregnancy state to reduce menstrual bleeding [24,28,77,96].

Progestins such as dienogest and norethisterone acetate are widely used for their anti- estrogenic and anti-inflammatory effects. Dienogest, in particular, effectively reduces lesion volume and pain with excellent long-term tolerability [37,77].

Gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide, triptorelin) create a reversible hypoestrogenic state akin to medical menopause, reducing pain but often causing vasomotor symptoms, bone loss, and mood changes. Add-back therapy with low- dose estrogen–progestin is recommended for extended use [24,28,96].

GnRH antagonists (e.g., elagolix, relugolix) act directly at the pituitary level, providing dose-dependent estrogen suppression and faster reversibility. Recent phase-3 trials confirm significant improvements in pain and quality of life with manageable side effects [38].

Aromatase inhibitors (e.g., letrozole, anastrozole) can be used as adjuncts in refractory or postmenopausal cases, though their off-label status and bone demineralization risk limit long-term use [105].

Despite symptomatic relief, medical therapies do not eliminate lesions or prevent recurrence after discontinuation, emphasizing the importance of individualized, stepwise management [24,28,53,86]. The principal hormonal treatment options are summarized in Table 2.

5.2 Surgical Approaches

Laparoscopic surgery remains the cornerstone of definitive diagnosis and treatment, especially for cases resistant to medical therapy or associated with endometriomas and DIE [26,46,104,106,107,108].

The surgical goal is complete excision or ablation of visible lesions, adhesiolysis, and restoration of pelvic anatomy [46,104,106,107].

Excision is generally favored over ablation for deep lesions, as it offers lower recurrence and greater pain relief [46,104,106,107].

For ovarian endometriomas, cystectomy is preferred to drainage/coagulation, yielding improved symptom control and lower recurrence - though with possible impact on ovarian reserve [24,41,43,46,108].

Recurrence rates remain 30–50% within five years, depending on disease severity, surgeon experience,

Table 2. *Hormonal Therapies for Endometriosis: Mechanism, Efficacy, and Limitations*

Therapy	Mechanism of Action	Main Benefits	Limitations / Side Effects	Reference s
NSAIDs	Inhibit prostaglandin synthesis	Analgesia, menstrual pain relief	GI irritation, minimal lesion effect	[28,77,80,88,96]
COCs	Suppress ovulation, reduce menstrual flow	Cycle control, pain reduction	Breakthrough bleeding, contraindicated in vascular disease	[28,77,80,88,96]
Progestins (e.g., dienogest)	Endometrial atrophy, anti-inflammatory	Pain reduction, long-term safety	Irregular bleeding, mood changes	[77,37]
GnRH agonists	Pituitary downregulation → hypoestrogenism	Effective for severe pain	Bone loss, hot flushes → add-back therapy	[24, 28,96]
GnRH antagonists	Immediate, reversible suppression	Dose flexibility, rapid effect	Mild hypoestrogenic effects long-term	[38]
Aromatase inhibitors	Inhibit peripheral/local estrogen synthesis	Useful for refractory disease	Bone loss, arthralgia	[105]
SPRMs / SERMs	Modulate progesterone/ estroge n receptors	Promising targeted therapy	Limited clinical data	[28,50,77]

and postoperative hormonal suppression [37,44,46,77, 85,104,106,107]. The main surgical approaches and outcomes are summarized in Table 3.

5.3 Assisted Reproductive Technologies (ART)

For women with endometriosis-associated infertility, assisted reproductive technologies provide an effective route to conception [42,45,85,109].

In mild to moderate disease, intrauterine insemination (IUI) with ovulation induction may be attempted [42,85,109].

In advanced stages or after failed conservative management, in vitro fertilization (IVF) remains the preferred option [42,45,85,110].

Pre-IVF surgical treatment may improve outcomes in selected patients, but unnecessary surgery should be avoided to preserve ovarian reserve [41-44,85,95].

Meta-analyses confirm that fertility outcomes depend heavily on disease stage and prior surgery, underscoring the need for individualized reproductive planning [42,45,85,94,109,110].

5.4 Emerging and Complementary Therapies

Recent studies explore targeted molecular and immunologic therapies, including anti- TNF-α agents, angiogenesis inhibitors, and neuroinflammatory pathway modulators [47,50,102].

Cochrane evidence suggests anti-TNF-α may reduce

Table 3. *Surgical Approaches and Outcomes in Endometriosis.*

Surgical Technique	Indication / Lesion Type	Main Advantages	Risks / Limitations	References
Ablation (thermal/laser)	Superficial disease	Minimally invasive	Incomplete removal → recurrence	[46,106,107]
Excision (laparoscopic/ robotic)	DIE, endometriomas	Lower recurrence, QoL improvement	Technical complexity, potential complications	[46,106,107]
Cystectomy	Ovarian endometriomas >3–4 cm	Pain relief, improved IVF access	Reduced ovarian reserve	[43,46,108]
Bowel shaving/resection	DIE with bowel infiltration	Improved pain and bowel function	Surgical morbidity	[46,104,107]
Multidisciplinary surgery	Urinary + GI involvement	Complete anatomical restoration	Prolonged OR time, ↑ complications	[46,97,104,107]

pelvic pain but requires further validation [47].

The endocannabinoid system and microbiota modulation are new research frontiers, with cannabinoid-based interventions showing potential benefits for pain and inflammation control [111].

Complementary approaches — dietary modification, acupuncture, and pelvic-floor physiotherapy — may improve pain and quality of life, though evidence remains limited and heterogeneous [39,48,49].

5.5 Personalized and Multidisciplinary Management

A multidisciplinary, patient-centered model is essential for long-term disease control. Collaboration between gynecologists, fertility specialists, pain physicians, psychologists, and pelvic physiotherapists ensures comprehensive care [25,28,48,49].

Therapeutic decisions should consider symptom profile, fertility goals, patient age, comorbidities, and personal preferences, promoting optimal quality of life and functional outcomes [25,48,49,88].

6. FERTILITY AND PREGNANCY OUTCOMES

6.1 Impact on Fertility

Endometriosis is a major cause of infertility, affecting up to 50% of women seeking conception [85,112].

The underlying mechanisms are multifactorial. In advanced disease, pelvic adhesions and anatomical distortion compromise oocyte release, tubal patency, and fertilization [42,44,85]. However, even in minimal or mild endometriosis, infertility can result from subclinical inflammation, oxidative stress, immune dysregulation, and defective endometrial receptivity [71,86,87,113].

Endometrial receptivity is reduced due to altered expression of implantation markers such as integrins, Homeobox A10 (HOXA10), and leukemia inhibitory factor (LIF), all critical for embryo implantation [86,87]. Elevated concentrations of cytokines, prostaglandins, and reactive oxygen species (ROS) in the peritoneal and follicular fluid further impair gamete function and embryo development [71,76,114].

Ovarian endometriomas may adversely affect the follicular microenvironment, lower antral follicle count, and diminish ovarian reserve, particularly after repeated surgery or when bilateral [71,85,113].

6.2 Role of Surgery and ART

Laparoscopic excision of endometriotic lesions can improve spontaneous conception rates, especially in stage I–II disease [42,44,85]. However, its benefit in advanced disease is less consistent, as irreversible anatomic damage often limits natural fertility [42,44,85].

Assisted reproductive technologies (ART) — particularly in vitro fertilization (IVF) — remain the cornerstone of fertility management for moderate-to-severe endometriosis [42,44,45,110]. IVF outcomes are generally favorable, though some studies report reduced oocyte yield and implantation rates compared with those associated with other infertility etiologies [42, 45, 85, 109].

Surgical removal of endometriomas prior to IVF remains controversial. While it may enhance follicle accessibility and reduce local inflammation, it can also compromise ovarian reserve. Thus, intervention should be individualized and guided by endometrioma size, ovarian function, and previous surgical history [41-44,85].

The Endometriosis Fertility Index (EFI) is a validated tool integrating surgical and reproductive data to predict natural conception probability and guide the timing of ART [95]. The main fertility and pregnancy outcomes associated with endometriosis are summarized in Table 4.

6.3 Pregnancy Outcomes

Although endometriosis does not preclude pregnancy, affected women exhibit higher obstetric risk profiles. Meta-analyses have demonstrated increased rates of preterm birth, placenta previa, preeclampsia, small-for-gestational-age infants, and cesarean delivery [85,113,115].

In DIE, abnormal placentation and defective decidualization likely contribute to these complications through chronic inflammation and fibrosis at the implantation site [85,113,114].

Additionally, women with endometriosis have higher rates of first-trimester bleeding and spontaneous miscarriage, particularly those with severe pelvic disease or those with extensive adhesions [85,113,115].

Despite these risks, most pregnancies progress favorably with appropriate prenatal surveillance and multidisciplinary obstetric management [85,113,115].

Symptoms of endometriosis often improve during pregnancy due to hormonal suppression, but recurrence is common postpartum, necessitating counseling and long- term follow-up [113].

7. QUALITY OF LIFE AND PSYCHOSOCIAL IMPACT

7.1 Physical and Functional Impairment

Endometriosis profoundly affects physical functioning and daily life, mainly through chronic pelvic pain, fatigue, dysmenorrhea, and dyspareunia [4,90,116].

Table 4. *Fertility and Pregnancy Outcomes in Women with Endometriosis.*

Aspect	Findings / Mechanisms	Clinical Implications	References
Spontaneous fertility	Reduced fecundity even in minimal disease due to inflammation and altered receptivity	Early fertility assessment and individualized strategy	[71,85-87,113,114]
Surgical benefit	Excision improves conception in stage I–II; limited benefit in stage III– IV	Consider surgery before ART only if anatomic correction feasible	[42, 44, 85]
IVF / ART outcomes	Slightly lower oocyte yield and live-birth rate (~10– 15% lower vs. tubal factor infertility)	ART remains primary treatment; optimize stimulation protocol	[42,45,85,107,108]
EFI score	Combines surgical and reproductive factors	Predicts fertility potential; EFI ≥7 → high probability of conception	[95]
Endometriomas	Bilateral/recurrent cysts reduce reserve; surgery may worsen	Avoid repeated cystectomy unless symptomatic	[41-43, 85]

Many women experience reduced occupational productivity, including both presenteeism and absenteeism as well as restrictions in physical or social activities [117].

Pain, often cyclic, may evolve into a chronic state, severely impairing mobility, sleep, and overall well-being [90,116].

Beyond pain, persistent fatigue, gastrointestinal discomfort, and low physical stamina undermine quality of life [90,116].

Endometriosis-associated fatigue is increasingly recognized as a distinct clinical symptom, independent of lesion extent and is associated with inflammatory cytokines and endocrine dysregulation [90,114].

7.2 Psychological Distress and Mental Health

A substantial proportion of patients report anxiety, depression, and emotional distress. Chronic pain, dyspareunia, and infertility contribute to feelings of helplessness, frustration, and social isolation [89,90,118].

Elevated rates of major depressive and generalized anxiety disorders—and even suicidal ideation—have been documented among women with moderate-to-severe disease [51,90,108].

Sleep disturbance and emotional dysregulation frequently persist during asymptomatic phases, underscoring the chronic psychological dimension of endometriosis [51,90]. Dyspareunia further aggravates relationship strain and body-image dissatisfaction, fueling low self-esteem and sexual dysfunction [81,119].

Such psychological sequelae often remain unresolved despite medical or surgical therapy, emphasizing the need for integrated mental-health support within standard care [51,114].

7.3 Social and Relational Challenges

The social consequences of endometriosis extend to intimacy, relationships, and social participation. Fear of pain during intercourse may lead to avoidance, communication breakdown, and emotional withdrawal [81,119].

Among younger women, symptom unpredictability can interfere with education, dating, and career planning [83].

Persistent stigma and under ecognition contribute to delayed diagnosis and psychological suffering.

Many patients describe feeling dismissed or disbelieved by clinicians, relatives, or employers, thereby intensifying distress [19,20,119,120].

This invisibility often drives social isolation and loss of workplace belonging, reinforcing the importance of public awareness and advocacy [13].

7.4 Economic and Occupational Impact

The economic burden of endometriosis is substantial [11,13,15,117].

It includes direct healthcare costs (consultations, imaging, surgeries and medication) and indirect costs from reduced work capacity, disability leave, and productivity loss [11,15,117].

Women with endometriosis miss more workdays and are more likely to change jobs, or reduce working hours [13,117].

On average, 10–12 hours of productivity are lost

weekly per patient, with measurable national economic implications [11,117].

Combined with out-of-pocket medical expenses and limited insurance coverage, these factors highlights the need for earlier diagnosis, effective pain management, and supportive employment policies [13,15,117].

7.5 Importance of Holistic and Multidisciplinary Care

Optimizing quality of life requires a holistic, patient-centered model that extends beyond pharmacologic symptom control.

Comprehensive care should include psychological counseling, sexual therapy, physiotherapy, and social-support services tailored to individual needs [28,49,52]. Multidisciplinary teams—comprising gynecologists, psychologists, pain specialists, and physiotherapists—address the full biopsychosocial burden [28,49,52].

Education, empowerment, and self-management programs improve treatment adherence, coping skills, and emotional resilience, reinforcing their role in long-term management [49,52].

8. FUTURE DIRECTIONS AND RESEARCH PERSPECTIVES

Despite major progress in understanding endometriosis, significant challenges persist in diagnosis, treatment, and long-term management.

The future of research lies in interdisciplinary collaboration, emerging molecular technologies, and personalized medicine, all aiming for earlier detection, targeted therapies, and improved quality of life.

This section outlines the most promising directions shaping the next era of endometriosis research.

8.1 Refining Pathophysiological Models

Traditionally viewed as a gynecologic disorder caused by retrograde menstruation, endometriosis is now recognized as a complex, systemic disease driven by endocrine, immune, genetic, and epigenetic mechanisms [71,114,121].

Contemporary models suggest a multi-hit pathogenesis involving peritoneal inflammation, immune escape, altered stem-cell behavior, and epigenetic reprogramming [40,71,114,121].

Emerging evidence links aberrant Müllerian development and disruption of the endometrial–myometrial interface to DIE, particularly among adolescents and early-onset cases [71,104,123].

Such findings could lead to the identification of molecular subtypes ("phenotypes"), improving diagnostic accuracy, prognostic evaluation, and individualized therapy [27,62,104].

8.2 Biomarkers and Non-Invasive Diagnosis

A key unmet need remains the development of non-invasive diagnostic tools. While laparoscopy is the diagnostic gold standard, its invasive nature, cost, and contribution to diagnostic delay drive the search for reliable biomarkers.

Candidate markers include microRNAs, inflammatory cytokines (IL-6, TNF-α), CA-125, and vascular endothelial growth factor (VEGF); however their sensitivity and specificity remain inconsistent. Recent advances in transcriptomics, metabolomics, and proteomics from blood, urine, or menstrual effluent are promising avenues [96, 102].

Integrating these multi-omic signatures through machine learning and AI may enable high-accuracy diagnostic panels capable of complementing or replacing surgical confirmation [74,96,100,102,103].

AI-assisted imaging—especially MRI and high-resolution transvaginal ultrasound (TVUS)—is evolving toward automated lesion mapping, potentially revolutionizing early and non-invasive diagnosis [29,31,100,103].

8.3 Innovation in Therapeutics

The next generation of endometriosis treatment moves beyond hormonal suppression, targeting molecular pathways that drive inflammation, neuroangiogenesis, and fibrosis [40,72,121].

Current research directions include:

- Anti-angiogenic agents (e.g., bevacizumab, sunitinib) to suppress neovascularization and lesion growth [50,121].
- Immunomodulators (e.g., TNF-α and IL-1β inhibitors) to restore immune homeostasis and improve lesion clearance [122].
- Selective estrogen and progesterone receptor modulators (SERMs, SPRMs) offering tissue-selective hormonal control [28,50,77].
- GnRH antagonists (such as elagolix and relugolix) that allow dose-dependent suppression with fewer hypoestrogenic effects [28,38].
- Cannabinoids and neuromodulators for pain modulation through central and peripheral pathways [51,111].

Experimental frontiers include gene therapy, mesenchymal stem-cell repair, and anti- fibrotic molecules such as pirfenidone or transforming growth factor-β

(TGF-β) inhibitors, though these remain in preclinical stages [50,53].

8.4 Personalized Medicine and Disease Stratification

Endometriosis is a heterogeneous disorder—clinically, histologically, and molecularly. The rise of precision medicine—fueled by genomic and proteomic profiling—promises a transformative approach.

AI-based algorithms integrating clinical, imaging, and molecular data are being developed to predict disease progression, recurrence, and treatment response [96,100,102,103].

Patient stratification by molecular phenotype, hormone-receptor profile, or neurovascular characteristics could enable tailored therapies while minimizing overtreatment [27,62,96,104].

Ongoing and future clinical trials are adopting subgroup-specific designs, enhancing real- world applicability and moving toward truly individualized care [38,53,95].

8.5 Addressing Health Equity and Inclusion in Research

Historically, endometriosis research has underrepresented non-majority populations, creating critical knowledge gaps.

Future efforts must prioritize inclusivity across demographics and gender identities, encompassing:

- Adolescents, in whom disease may be underdiagnosed or misattributed to primary dysmenorrhea [123].
- Transgender and non-binary individuals, who face distinct diagnostic and therapeutic barriers.
- Ethnic and socioeconomic minorities, who disproportionately experience delayed diagnosis and limited care access [13,21-23].

Integrating patient-centered qualitative research and real-world registries from diverse populations is essential to develop equitable global guidelines and ensure that advances reach all affected individuals [14,23,59-61].

8.6 Policy Advocacy and Funding Priorities

Despite its high prevalence and economic burden, endometriosis remains underfunded relative to comparable chronic diseases.

Key policy priorities include:

- Expanding public awareness and menstrual health education to shorten diagnostic delay.
- Increasing investment in basic and translational research.
- Establishing national registries and longitudinal databases to monitor disease course and treatment outcomes.
- Embedding endometriosis management within broader reproductive health and chronic pain frameworks.

Sustained governmental and institutional support is vital to translate scientific progress into accessible, evidence-based care, ensuring measurable improvement in women's health worldwide [11-15,21,114]. Emerging therapeutic strategies are summarized in Table 5.

Table 5. *Emerging and Investigational Therapies in Endometriosis.*

Therapeutic Category	Example Agents / Targets	Proposed Mechanism	Development Stage	References
Anti-angiogenic	Bevacizumab, sunitinib	Inhibit neovascularization and lesion growth	Phase II	[50,121]
Immunomodulator y	TNF-α, IL-1β blockers	Restore immune clearance, reduce inflammation	Preclinical / Early clinical	[123]
Anti-fibrotic	Pirfenidone, anti-TGF-β	Reduce fibrosis and adhesion formation	Preclinical	[50,121]
Hormone receptor modulators	SERMs, SPRMs	Tissue-selective hormonal modulation	Phase II–III	[28,50,77]
Neuro-modulators	Cannabinoids, gabapentinoi ds	Central and peripheral pain modulation	Pilot studies	[51,111]
Regenerative / Gene-based	Mesenchyma l stem cells, CRISPR	Tissue repair and genetic correction	Experimental	[50,53]

9. ECONOMIC BURDEN OF DISEASE

Endometriosis imposes a substantial economic burden on individuals, healthcare systems, and society. Total costs include both direct medical expenses and indirect losses related to productivity, disability, and diminished quality of life [11-15,21,117].

9.1 Direct Costs

Direct healthcare costs encompass physician visits, diagnostic imaging, laboratory testing, medical therapy, and surgical interventions.

Among these, laparoscopy and repeat surgeries, particularly for deep infiltrating endometriosis (DIE), account for the largest proportion [12,117].

Prolonged diagnostic delay—often exceeding 7–10 years—further inflates costs due to repeated consultations, misdiagnoses, and ineffective treatments before definitive management [13,19,20,119].

A 2020 European cost-analysis reported an annual per-patient direct cost between €3,000 and €9,000, depending on disease severity, comorbidities, and treatment modality [12,15,21].

Recent health-economic comparisons indicate that endometriosis-related expenditures rival or surpass those of other chronic disorders such as diabetes or Crohn's disease, underscoring its underappreciated financial impact [11,12,14,15].

9.2 Indirect Costs

Indirect costs often exceed direct medical expenses, primarily through absenteeism, presenteeism, disability leave, and early workforce exit [12,15,117].

Women with endometriosis lose on average 10–12 hours of work productivity weekly, particularly during menses or symptomatic exacerbations [11,15,117].

Younger women may experience career delays or educational interruptions, while others face unreimbursed expenses for complementary therapies, fertility procedures, or travel to specialized centers [13,15,21].

A 2023 systematic review confirmed that productivity loss constitutes nearly two-thirds of the total economic cost in high-income countries [12,15,117].

9.3 Broader Societal Impact

At the population level, endometriosis translates into billions of euros in annual healthcare and productivity losses [11,12,21].

A global estimate (2012) placed the yearly economic cost at approximately $69.4 billion in the United States and €30 billion in Europe, with comparable trends in Asia and Latin America [12,15,117].

Despite this scale, endometriosis remains severely underfunded and insufficiently prioritized in public health frameworks.

Strategic investments in earlier diagnosis, streamlined treatment pathways, and multidisciplinary models of care could markedly reduce long-term costs and improve both clinical and economic outcomes [11,13-15,21,117].

10. CONCLUSIONS

Endometriosis is a multifaceted, chronic, and often progressive disease affecting a significant proportion of women of reproductive age, with wide-ranging repercussions for physical health, fertility, psychological well-being, and socioeconomic stability.

Although described over a century ago, it remains a diagnostic and therapeutic challenge due to its heterogeneity, elusive pathogenesis, and variable treatment response.

This review consolidates current evidence on the clinical, psychosocial, and economic burden of endometriosis.

Diagnostic delay remains a major barrier, leading to years of untreated symptoms and preventable suffering.

The absence of a pathognomonic marker and reliance on surgical confirmation perpetuate this gap, while ongoing advances in imaging and biomarker discovery hold promise for the future.

Pathophysiologically, endometriosis represents a systemic inflammatory and hormonal disorder, shaped by retrograde menstruation, immune dysregulation, genetic susceptibility, and epigenetic reprogramming.

The conventional classification into superficial peritoneal, ovarian, and deep infiltrating forms offers clinical guidance but does not fully capture its biological diversity.

Management must be individualized.

Pharmacologic therapies—COCs, progestins, and GnRH analogs—remain first-line for symptom relief, yet they are palliative rather than curative.

Surgical excision, though effective for diagnosis and pain relief, carries recurrence risk and may impact fertility, underscoring the need for judicious selection.

Assisted reproductive technologies (ART) continue to offer reproductive hope, but success rates vary by disease stage and prior surgery.

An interdisciplinary model, integrating fertility, pain,

and mental-health specialists, yields the most favorable long-term outcomes.

Beyond the physical domain, endometriosis exerts a profound psychosocial toll. Depression, anxiety, sexual dysfunction, and relationship strain are common and demand holistic, empathetic care.

Its economic cost, compounded by healthcare spending and lost productivity, further underscores the urgency for policy attention and resource allocation.

The future of endometriosis management will hinge on precision medicine, molecular phenotyping, artificial intelligence, and multi-omic integration, enabling earlier diagnosis and targeted therapy.

Investment in inclusive research, public education, and policy reform is essential to reduce diagnostic delay and improve equity in care access.

In conclusion, endometriosis must be recognized as a systemic, biopsychosocial condition requiring multidisciplinary collaboration, patient-centered strategies, and sustained scientific innovation.

By uniting research, clinical expertise, and advocacy, the global health community can move toward earlier diagnosis, improved quality of life, and true empowerment for the millions of women affected by this disease worldwide.

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Corresponding author:

Giannakakis Georgiadis
Gynecological Oncology Department, Theagenio Cancer Hospital of Thessaloniki, Thessaloniki, Greece
E-mail: john_geo94@yahoo.com

From Translation to Fair Comparisons: A Practical Framework for Cross-Cultural Adaptation and Measurement Equivalence of Public Health Literacy Instruments

Maria Roumelioti[1], George J. Xydopoulos[2], Georgia Mikrouli[2], Emily Diamantopoulou[2], Eleni Jelastopulu[1]

Abstract

Public health research and education increasingly rely on literacy scales (eHealth, Media/News, and Digital Literacies) to design and evaluate interventions. Instruments are often adapted across languages, yet translation alone is insufficient for valid comparisons unless adapted versions demonstrate measurement equivalence. This narrative article provides an educational, practice-oriented framework that links cross-cultural adaptation workflows with Consensus-based Standards for the selection of Health Measurement Instruments-aligned evidence generation and measurement equivalence concepts, with special attention to objective true/false knowledge scales that are vulnerable to familiarity-related bias. We synthesize established cross-cultural adaptation guidance (preparation, dual forward translation, reconciliation, back-translation, expert review, cognitive debriefing, proofreading, and documentation) with a methodological framework for evidence building and cross-group comparability using multi-group confirmatory factor analysis and differential item functioning. Decision points are illustrated using two contrasting case examples: a self-report eHealth Literacy Scale and a concise 15-item True/False News Literacy Knowledge Scale. Treating cross-cultural adaptation as a validity procedure, and explicitly planning for measurement equivalence, supports fairer group comparisons and stronger evaluation of eHealth and news literacy interventions. The framework emphasizes transparent documentation, student-friendly decision points, and minimum reporting essentials.

Key words: *eHealth literacy; news literacy; public health education; cross-cultural adaptation; measurement invariance*

INTRODUCTION

In the last two decades, accelerated digital transformation has reshaped how individuals access information on health, current affairs and public life [1–3]. eHealth has been defined as an emerging field at the intersection of medical informatics and public health referring to health services and information delivered or enhanced through the internet and related technologies [4]. This shift underscores the growing importance of eHealth literacy in enabling individuals to effectively locate, evaluate and use online health information [1].

Online health information is routinely sought, consumed and distributed via websites, social media platforms, mobile applications and patient portals, while

[1]Department of Public Health, Epidemiology and Quality of Life, School of Medicine, University of Patras, Patras, Greece
[2]Division of Linguistics, Department of Philology, University of Patras, Patras, Greece

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news on politics, science and health disseminated across increasingly fragmented and interactive media environments [5–7]. In this context, a broader set of competencies-beyond basic reading skills- is required to navigate digital information effectively [1,2]. These competencies are often conceptualized as eHealth literacy in the health domain and news literacy in the media domain [1,5].

With the evolution of digital technologies and online environments, the conceptualization of eHealth literacy has also evolved. Subsequent work has introduced the concepts of eHealth literacy 2.0 and 3.0 to capture interactive, participatory and data-driven aspects of digital health, encompassing social media use, mobile health applications, wearables and algorithmically curated content [2,8]. eHealth literacy was defined as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to address or solve a health problem" [2]. This definition is operationalized within the eHealth Literacy Lily Model, which proposes that eHealth literacy is a meta-literacy grounded on six foundational literacies: traditional, health, information, scientific, media and computer literacy [2]. To support measurement in research and practice, the eHealth Literacy Scale (eHEALS) and the revised version, the eHealth Literacy Scale-Revised (eHEALS-R) provide standardized self-report measures of perceived eHealth literacy. In brief, eHEALS assesses individuals' perceived skills and confidence in locating, evaluating, and applying online health information, while eHEALS-R extends this focus to better align with contemporary, interactive digital health contexts and support updated applications in research and practice [9].

In parallel, scholars in communication and media studies have focused on news literacy, a scale that captures individuals' understanding of how news is produced, distributed and consumed, and their ability to critically evaluate news content [5]. Contemporary frameworks conceptualize news literacy in terms of five interrelated domains—the "Five C's": context, creation, content, circulation and consumption—domains that collectively delineate the social, economic and technological conditions under which news is created and accessed [5]. Drawing on this framework, Maksl and colleagues [5] developed a concise, 15-item True/False News Literacy Knowledge Scale, derived from a larger item pool and refined through multiple studies using item response theory (IRT) and differential item functioning (DIF) analyses—approaches used to (a) identify items that most reliably discriminate between individuals with lower versus higher levels of knowledge and (b) assess whether any item performs differently across respondent subgroups despite comparable underlying ability. In broad terms, IRT focuses on how individual items function across levels of the underlying scale, supporting item-level refinement beyond simple total-score approaches. One widely used IRT approach is Rasch modeling, which helps ensure that a set of items forms a coherent scale and that total scores can be interpreted consistently across respondents and groups. DIF analyses, in turn, help evaluate whether items behave equivalently across groups (e.g., demographic subgroups or language versions), which is particularly relevant when instruments are translated and used in new cultural contexts. This combination strengthens the psychometric adequacy and cross-group comparability of the final scale, yielding a psychometrically robust, knowledge-based measure suitable for evaluating news literacy and the impact of educational interventions in diverse populations. In addition to providing a psychometric framework for validation, Maksl et al. [5] underscore item-design choices that facilitate cross-context adaptation (e.g., avoiding overly brand-or ownership-specific content and platform-specific wording) and recommend item-level analyses including IRT/Rasch and DIF to assess comparability after translation. For translated instruments, these item-level checks can help distinguish true differences in the construct from artifacts of wording, familiarity, or culture-specific references.

Both eHealth literacy and news literacy are particularly pertinent in the contemporary information environment, in which health-related misinformation, "fake news" and conspiracy narratives are prevalent. Repeated exposure may increase the perceived veracity of misinformation (the illusory truth effect) even when statements are false [10,11], and familiarity may bias judgments via mere exposure [11,12]. These familiarity-based effects are particularly relevant when instruments rely on objective true/false formats, where recognition can be mistaken for knowledge [11,12]. Individuals with higher eHealth literacy are more likely to navigate online health information effectively, engage in shared decision-making and appropriately use digital health tools, whereas those with higher news literacy are better equipped to distinguish credible news from misleading or deliberately manipulative content. As a result, robust

and culturally transferable measurement instruments are required to support cross-group comparability and evidence generation across cultural and linguistic settings [13–16].

Cross-cultural research has long emphasized that mere linguistic translation is insufficient when adapting instruments for new populations. Differences in language structure, media systems, health care organization and everyday practices may all affect how items are understood and how scales are expressed. Accordingly, several guidelines have been developed to support the translation and cultural adaptation of instruments in health and social research. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Translation and Cultural Adaptation provided a ten-step set of "Principles of Good Practice" for translating patient-reported outcome measures (PROM), measures emphasizing documentation, harmonization across language versions and cognitive debriefing with patients [13]. Alongside, Sousa and Rojjanasrirat proposed a clear seven-step guideline for translation, adaptation and validation of instruments for cross-cultural health care research, emphasizing forward and backward translation, expert committee review, pretesting and psychometric evaluation with particular attention to content validity and psychometric testing in the target context [14]. Complementing these process-focused recommendations, Maksl et al. highlight item-design choices that facilitate cross-context adaptation (e.g., avoiding brand, ownership or platform-specific content) and recommend item-level analyses-such as IRT and DIF- to evaluate comparability after translation [5]. A recent practical guideline for novice researchers reiterates that cross-cultural adaptation must address not only language but also cultural and measurement equivalence, and that documentation of decisions is essential for transparency and replicability [24].

To date, however, there has been limited discussion of how these frameworks can be combined and tailored for literacy-related instruments such as eHEALS-R and news literacy scales, particularly in settings such as Greece, where such measures are still emerging.

While we developed a protocol for the Greek adaptation and planned validation elsewhere, the present article provides a broad, educational framework for public health students and applied researchers. It links cross-cultural adaptation steps to a methodological framework for evidence generation and measurement equivalence, and highlights a key challenge: objective true/false knowledge scales may be biased by familiarity-related effects, representing a threat to validity beyond linguistic translation [10–12]. To appraise methodological quality, we applied the Scale for the Assessment of Narrative Review Articles (SANRA) tool to self-assess key quality domains for narrative reviews and enhance transparency and rigor [17].

MATERIALS AND METHODS

To develop the proposed framework, we conducted a purposive narrative review. We first anchored the framework in widely used guidance for translation and cultural adaptation and for evaluation of measurement properties. We then complemented these sources with targeted searches in PubMed and Scopus using combinations of terms related to cross-cultural adaptation/translation, measurement equivalence (including multigroup confirmatory factor analysis), and item-level approaches (e.g., DIF, IRT), followed by citation tracking to identify additional relevant publications [13–16, 18, 19].

RESULTS OF THE SYNTHESIS

Cross-cultural adaptation as a validity procedure

Cross-cultural adaptation can be understood as a sequence of validity-relevant decisions rather than a purely linguistic task [20]. The central goal is to achieve conceptual and functional equivalence: items should represent the same scale and elicit the same interpretation in the target language and cultural context. Translation and cultural adaptation should be treated as part of construct validation, aiming to preserve semantic, idiomatic, experiential, and conceptual equivalence across languages and contexts [13–15]. Frameworks commonly distinguish multiple forms of equivalence (e.g., conceptual, item, semantic/linguistic, operational, and measurement equivalence), which helps structure committee review and subsequent psychometric testing [20].

The proposed framework is based on a synthesis of three complementary methodological sources. First, the ISPOR Task Force "Principles of Good Practice" offers a more granular ten-step process for translation and cultural adaptation (TCA), i.e., the structured process of translating an instrument and adapting it to the target culture while preserving conceptual equivalence across language versions, supported by transparent documentation. These guidelines emphasize preparation, reconciliation, harmonization across language versions, cognitive debriefing, proofreading, and transparent documentation [13]. Second, Sousa and

Rojjanasrirat provide a clear, user-friendly seven-step guideline that links TCA to content validity assessment and psychometric testing in the target population [14]. Third, because the 15-item News Literacy Knowledge Scale is an objective, knowledge-based true/false scale, we incorporate instrument-specific constraints and validation logic described in Maksl et al. [5], including maintaining coverage of the "Five C's", avoiding ultra-contextual or platform-tied wording, and planning IRT/Rasch and DIF analyses to support comparability.

These sources overlap in core translation steps (forward translation, reconciliation, backward translation, expert review and pretesting), but they differ in emphasis. ISPOR [13] foregrounds standardized operational procedures and reporting, while Sousa and Rojjanasrirat [14] foreground content validity and psychometric evidence in the target context. Maksl et al. [5] add scale-specific requirements that are particularly relevant when adapting objective knowledge items (rather than self-report items), such as ensuring a single defensible correct answer per statement, preserving the intended balance and domain structure, and evaluating item-level behavior (difficulty, fit, DIF) after translation. A comparative overview and implications for the planned pre-test and cross-sectional study are presented in Table 1.

In practice, this third strand provides an instrument-anchored adaptation layer, preserving the five-domain structure and item-level knowledge claims while allowing context-specific adaptations.

By synthesizing overlapping and complementary elements, this approach aims to retain the user-friendly stepwise guidance of major translation frameworks while strengthening documentation and planning for cross-group comparability after translation [13, 14, 16, 18, 19]. Short case examples (eHEALS-R and a 15-item True/False News Literacy Knowledge Scale) highlight how the same logic can apply across different response formats [5, 8, 9, 21]. Maintaining a decision log —an item-level record of translation/adaptation choices and their rationale —strengthens transparency and auditability, supports harmonization across versions, and facilitates downstream psychometric evaluation, consistent with recommendations to systematically document translation and cultural-adaptation decisions throughout the process and in the final report [13–15]. A Greek applied example that illustrates that adaptation extends beyond translation is the cultural adaptation and pilot testing of a Health Literacy Universal Precautions Toolkit for primary care professionals working with older adults. In this case, extensive context-specific modifications were combined with structured training and follow-up implementation, resulting in measurable improvement in communication-related self-efficacy and retained gains over time [22]. A complementary Greek applied example from the digital-caregiving domain is the cultural adaptation and piloting of the WHO iSupport Dementia eLearning platform, where stakeholder feedback during piloting highlighted usability, accessibility and interaction needs (e.g., downloadable content, reduced screen-reading burden, videos/forum support) before wider rollout [23].

A practical workflow for cross-cultural adaptation and validation commonly includes the following elements:

Step 1 – Preparation and permissions

To obtain written permission to translate/adapt the instruments; assemble the translation team and expert committee (including content and measurement specialists); define the target population(s) and mode of administration; prepare a glossary of key terms (e.g., online health resources, algorithms, sponsored content) and a decision log/template to document all translation choices and their rationales [13,14]. When ambiguities arise, consultation with the original instrument developers is recommended; all feedback should be documented in the decision log.

Step 2 – Forward translation

To produce at least two independent forward translations by bilingual translators whose native language is the target language [13,14]. For true/false knowledge items, prioritize renderings that preserve the intended truth value and avoid overly local brand- or platform-specific wording unless essential [5]. WHO guidance additionally recommends that forward translators have the target language as their mother tongue, excellent command of the source language, and familiarity with health/disability concepts; translators should explicitly flag problematic terms/phrases for subsequent linguistic evaluation [24].

Step 3 – Reconciliation

Reconcile the forward translations into a single synthesized version (v1) through structured discussion, documenting alternatives and decisions [13,14]. Verify that each true/false statement remains unambiguous, evidence-consistent, and defensible as true or false in the target language context [5].

Table 1. *Comparison of three complementary methodological sources informing the proposed TCA.*

Topic	ISPOR Task Force (Wild et al.) [13]	Sousa & Rojjanasrirat [14]	Maksl et al. (15-item true/false news literacy knowledge) [5]	Student-oriented public health takeaway
Primary focus	Good-practice workflow for translation and cultural adaptation of patient-reported outcome measures (often used more broadly).	User-friendly stepwise guideline for translation/cultural adaptation followed by psychometric testing in the target population.	Instrument-anchored adaptation/validation constraints for a true/false knowledge test (single correct answer, domain coverage).	Choose a translation workflow, but also plan how evidence will be generated and reported; knowledge tests need extra rules beyond language.
Step structure	Multi-step process: preparation, dual forward translation, reconciliation back-translation, review, cognitive debriefing, finalization, and documentation.	Similar core steps with emphasis on expert committee review, pretesting/cognitive interviews, and subsequent validation.	Not a generic translation framework; emphasizes preserving item meaning and answer key, and evaluating item performance after adaptation.	Use a clear step-by-step flow and produce concrete outputs (versions, decision log, debriefing summary, final report).
Conceptual equivalence	Emphasizes conceptual equivalence through iterative translations, expert review, and documentation.	Highlights 'centering' (symmetrical translation) to optimize conceptual and technical accuracy, not literal word-for-word translation.	Emphasizes that adaptation must not change what counts as correct/incorrect; preserve the construct map (e.g., "Five C's").	Treat adaptation as a validity procedure: preserve meaning first, then test whether items function equivalently across groups.
Roles and actors	Defines project roles (project manager, translators, reconciler, debriefing interviewer, proofreader).	Focuses on translators (informed and uninformed), expert committee, and target-language participants for debriefing.	Requires content experts to verify the answer key and domain mapping; benefits from psychometrics expertise for item-level analyses.	Plan a small but diverse team: translators + domain expert(s) + measurement/psychometrics support, even in student projects.
Cognitive debriefing / pretesting	Core step to evaluate comprehension and cultural relevance in target-language users.	Explicitly recommends pretesting with the target population and using findings to revise items.	Useful but item reuse can create familiarity bias in knowledge tests; consider parallel forms or spacing.	Do debriefing, but avoid training participants on knowledge items; document what changed and why.
Documentation	Stresses transparent reporting and a final translation report.	Encourages clear reporting of each step and psychometric outcomes.	Emphasizes reporting that supports interpretability of item-level results and domain coverage.	Make your work replicable: keep a decision log, version history, and a summary table of changes.
Evidence after translation	Not always detailed; assumes evaluation is needed for intended use.	Explicitly links adaptation to subsequent psychometric validation.	Stresses item-level evaluation and potential DIF/IRT analyses for fairness.	Do not stop at translation: plan structural validity, reliability, and equivalence testing (invariance/DIF) before comparing groups.
Special risks	General translation risks: ambiguity, poor cultural fit, inconsistent terminology.	Same general risks with emphasis on target-user comprehension.	Additional risks: guessing, truth-value drift, and familiarity/illusory truth effects with repeated exposure.	Knowledge tests need safeguards (truth verification, 'I don't know' options if appropriate, avoid repeated exposure, and item diagnostics).

Abbreviations: TCA, translation and cultural adaptation; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; DIF, differential item functioning; IRT, item response theory.

Step 4 – Back-translation

Have an independent translator back-translate v1 into the source language (the instrument's original language), who is a native speaker of the source language and blinded to the original version [13]. Use the back-translation to flag potential conceptual drift, particularly for technical, media-system, and platform-related terms [13,14].

Step 5 – Back-translation review

Compare the back-translation with the source version to identify discrepancies in meaning, tone, and assumed context, and revise v1 accordingly [13]. For the knowledge items, confirm that revisions do not alter the intended truth value, and that each item still supports a single correct answer consistent with the original intent [5].

Step 6 – Harmonization and expert committee review

A multidisciplinary expert committee reviews all items for semantic, idiomatic, experiential, and conceptual equivalence, resolving any remaining issues and confirming cultural fit [13,14]. Additional considerations for true/false knowledge items include: (a) preserving domain coverage, (b) retaining the intended mix of true and false statements, and (c) ensuring the response options (including 'Don't know', if used) function as intended [5]. WHO further describes a structured linguistic evaluation step (bilingual panel, including an editor-in-chief) supported by a standardized linguistic evaluation data sheet to resolve highlighted terms/phrases and document decisions [24]. This step maps closely onto the harmonization/committee phases emphasized in an 8-step adaptation guideline (forward translation, synthesis, back translation, harmonization, pre-testing, field testing, psychometric validation, and analysis of psychometric properties) [20].

Step 7 – Cognitive debriefing / pretesting

Cognitive debriefing is also a key safeguard against cross-cultural bias (method, content, and construct bias) and against systematic response-style differences that can distort comparability (e.g., acquiescence or extreme responding), before proceeding to larger-scale field testing [20]. Conduct cognitive debriefing and, if feasible, a small pilot with members of the target population (ISPOR suggests a small sample, typically 5-8 respondents, for the pre-test) to evaluate comprehension, retrieval, judgment, and response processes, consistent with ISPOR recommendations [13]. In line with Sousa & Rojjanasrirat, consider a pilot of approximately 10–40 participants and structured expert feedback to support content validity (e.g., clarity and relevance) [14]. For true/false knowledge items, verify that respondents interpret each claim as intended and do not encounter ambiguity that could shift the correct answer [5]. For pre-testing, WHO suggests a minimum of 10 respondents per section, with representation across sex and age groups [24].

Step 8 – Review of debriefing results and finalization

Review cognitive debriefing/pilot findings, implement revisions, and re-check conceptual equivalence across items and instructions [13, 14]. Confirm that any changes preserve the intended construct coverage for each instrument and the domain mapping for true/false knowledge items [5].

Step 9 – Proofreading

Proofread the near-final version for language, consistency, formatting, and administration instructions; check numbering, response anchors, and layout for unintended cues, particularly in true/false items [13].

Step 10 – Final report and planned psychometric evaluation

Recommended reporting for the validation phase commonly includes evidence for structural validity, internal consistency, reliability, measurement error, responsiveness, and where relevant measurement invariance/DIF and floor/ceiling effects [24]. Produce the final TCA report and archive all intermediate versions, decisions, and rationales to ensure transparency and reproducibility [13]. Following translation, conduct psychometric evaluation in appropriately powered target language-speaking samples as recommended for cross-cultural instrument use [14]. Planned analyses include reliability and validity testing for each instrument; for the true/false knowledge items, assess item difficulty and fit (e.g., IRT/Rasch where appropriate), differential item functioning across key demographic/educational groups, and convergent/criterion validity via correlations with related constructs [5].

DISCUSSION

Linking adaptation to measurement evidence and equivalence

After an adapted version is finalized, evidence generation should follow a structured plan. COSMIN

methodology frames measurement as a set of properties that must be supported with appropriate analyses and transparent reporting, including content validity, structural validity, internal consistency, reliability, and cross-cultural validity [16,18,19]. Integrating cross-cultural adaptation and COSMIN-based measurement evidence to support the TCA of the instruments, we followed established cross-cultural adaptation procedures—dual forward translation, synthesis, back-translation, expert committee review, and pretesting with cognitive debriefing—to maximize semantic, idiomatic, experiential, and conceptual equivalence between the source and target versions [13,15]. The guideline by Sousa and Rojjanasrirat further links translation decisions to subsequent validation, underscoring that translation is necessary but not sufficient for cross-language comparability [14]. After translation, the adapted versions should be evaluated in line with COSMIN guidance for measurement properties, with particular attention to structural validity, reliability, and cross-cultural validity/measurement invariance [16,18,19]. Cross-cultural validity refers to whether items function equivalently across language versions; this can be examined using multi-group confirmatory factor analysis and/or differential item functioning DIF analyses in IRT/Rasch or regression frameworks, and interpreted using COSMIN criteria for what constitutes important differences [16]. For latent-variable self-report instruments, multi-group confirmatory factor analysis can assess whether the measurement structure holds across groups (e.g., configural, metric, and scalar invariance). For both self-report and knowledge tests, differential item functioning analyses, often within item response theory (IRT)/Rasch frameworks, can identify items that behave differently across groups after controlling for overall trait level. Importantly, adaptation decisions and equivalence testing should inform each other. If cognitive debriefing identifies a term interpreted differently across subgroups, that item becomes a candidate for careful monitoring in subsequent analyses. Conversely, an item that shows substantial differential item functioning (DIF) requires content review and, depending on the purpose, may need rewording, additional clarification, or removal, balanced against domain coverage and interpretability.

In addition to these general equivalence considerations, objective true/false knowledge scales introduce extra adaptation constraints related to truth value, guessing, and familiarity effects.

The special case of true/false knowledge tests: truth value, guessing, and familiarity

Objective true/false knowledge scales impose additional adaptation constraints: each item must preserve its intended truth value in the target context, and correct responses may also occur by guessing [5]. Accordingly, adaptation extends beyond wording to verifying that the underlying factual claim, reference frame, and domain mapping remain stable and meaningful. Knowledge measures are particularly sensitive to context because item statements may embed time-bound, culture-specific, or system-specific assumptions; translation should therefore preserve each item's intended truth value while keeping the statement natural and interpretable in the target language [5].

Beyond translation, familiarity-related effects constitute a distinct threat to validity: repeated exposure can increase processing fluency and perceived accuracy (the illusory truth effect), even when statements are false [10,11], and mere exposure can increase acceptance independently of content quality [12]. To mitigate familiarity-driven bias in cognitive debriefing, piloting, and repeated administrations, we recommend avoiding reuse of the same items between pretesting and the main psychometric study where feasible (or using alternate forms/adequate spacing when repetition is unavoidable), randomizing and counterbalancing item order and condition assignment, and measuring perceived familiarity for analytic adjustment (e.g., covariate or sensitivity checks), to ensure observed differences reflect the intended construct rather than prior exposure [10–12].

A concise reporting checklist: decision points and minimum essentials

For student projects and applied public health studies, it is useful to separate (i) translation outputs, (ii) evidence to be generated, and (iii) documentation for transparent reporting. The aim is to make adaptation decisions traceable and reproducible.

Accordingly, we emphasize documentation of (a) how key terms were negotiated across translators and reviewers, and (b) how the resulting version was checked with the target users to ensure interpretability in the language and cultural context.

Greek applied evidence supports extending TCA reporting beyond linguistic equivalence to include an "implementation layer", documenting context-driven adaptations and whether training-related skills were

sustained in practice [22]. Similarly, the Greek pilot of WHO iSupport Dementia indicates that user-centered adaptation must also address usability and accessibility constraints (e.g., navigation, screen-reading fatigue, and interactive features) to enable successful rollout [23].

The combination of forward translation by both informed and lay translators, back translation and expert committee review offers multiple opportunities to detect conceptual drift and identify areas where simple linguistic translation may not be adequate. Cognitive debriefing with target users is especially important for these instruments, as it can reveal how respondents interpret complex or technical terms, and whether examples drawn from other media systems are meaningful in the language and cultural context.

Minimum reporting essentials:

- Describe permissions, translators' backgrounds, and how reconciliation decisions were made (including a decision log).
- Report cognitive debriefing methods (sample characteristics, interview approach, and the most common issues identified).
- Provide a clear description of the final version and any culturally adapted items (what changed and why).
- Report evidence for structural validity, reliability, and cross-cultural validity (invariance/DIF) before interpreting group differences.

Table 2 summarizes key decision points and common pitfalls, showing how to report these minimum essentials and how to document planned or completed evidence for key measurement properties and cross-group comparability [13–16,18,19].

LIMITATIONS

This narrative review proposes a methodological framework and does not present empirical data; accordingly, the feasibility, acceptability, and measurement performance of the adapted target-language versions should be established in appropriately powered samples. The workflow synthesizes widely used guidance, yet implementation quality may vary across settings and teams, and the framework cannot eliminate all sources of context sensitivity inherent to literacy measures (e.g., time-bound media practices or platform-specific exposure). In addition, the review is not a systematic evidence synthesis and may not capture all relevant methodological discussions; readers should interpret recommendations as a structured, practice-oriented roadmap rather than prescriptive rules.

CONCLUSIONS

By integrating process-oriented translation and cultural adaptation steps with measurement-focused planning for equivalence and item-level diagnostics, the proposed framework provides a transparent and reproducible workflow for adapting literacy-related

Table 2. *Key decision points and common pitfalls for student projects.*

Stage	Minimum deliverable	Common pitfall to avoid
Item content	Truth-value check with justification for the correct answer (evidence/source) and a brief item rationale.	Literal translation that changes the factual claim or makes it time- or culture-bound.
Translation team	Named review group with content and measurement expertise; documented decisions (who reviewed, when, outcomes); Developer feedback log (queries-responses-decisions)	Over-reliance on bilingual translators without construct/measurement expertise; no developer consultation -ambiguous items unsolved.
Pre-testing	Cognitive debriefing report (sample, interview guide, top issues, revisions made + rationale).	No interview guide / no record of changes → pre-test becomes "proofreading" and cannot justify revisions.
Equivalence	Analysis plan + results for measurement invariance (MG-CFA) and/or DIF/IRT with decision rules; or explicit limitation if not feasible.	Reporting between-group comparisons without an equivalence plan (MG-CFA/DIF) or an explicit limitation statement.
Familiarity bias	If reuse is unavoidable: spacing/alternate forms + measure perceived familiarity; run a sensitivity check.	Inflated scores due to prior exposure rather than learning gains.

Note: Table 2 translates the comparative synthesis in Table 1 into minimum deliverables and common pitfalls for student projects.

Abbreviations: MG-CFA, multi-group confirmatory factor analysis; CFA, confirmatory factor analysis; DIF, differential item functioning; IRT, item response theory; TCA, translation and cultural adaptation.

instruments in the target-language context. Applied to eHEALS-R and the 15-item True/False News Literacy Knowledge Scale, the approach emphasizes multidisciplinary collaboration, explicit documentation of translation decisions, and analytic safeguards to strengthen cross-group interpretability. Establishing psychometrically sound target-language versions of these instruments can enable more rigorous evaluation of digital health and media literacy interventions and support meaningful comparisons across populations and settings.

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Corresponding author:

Maria Roumelioti
Department of Public Health, Epidemiology and Quality of Life, School of Medicine, University of Patras, Patras, Greece,
Tel.: +30 2610969873, +30 6981044775,
E-mail: mroum@upatras.gr

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Biomarkers of Aging

Ioanna Marlafeka[1], Dimitris Efthymiou[1], Ioannis Spyridonidis[3], Prokopis Karydis[1], Eirini Adamopoulou[1], Maria Lagadinou[1,2], Markos Marangos[1,2], Dimitris Velissaris[1,2]

Abstract

Population aging represents a major global health challenge, accompanied by increasing heterogeneity in functional status, comorbidity burden, and vulnerability to adverse outcomes among older adults. Biological aging is driven by complex molecular and cellular processes, including chronic low-grade inflammation [inflammaging], immune dysregulation [immunosenescence], endothelial dysfunction, and metabolic alterations, which collectively reduce physiological reserves and impair stress responses. In this context, biomarkers have emerged as valuable tools for assessing biological vulnerability beyond chronological age.

This narrative review summarizes current evidence on established and emerging biomarkers relevant to aging, frailty, cardiovascular and thrombotic risk, and infection-related conditions in older adults, with particular emphasis on sepsis-associated indicators. Frailty, a central geriatric syndrome linking biological aging to adverse clinical outcomes, is closely associated with inflammatory, nutritional, endocrine, and metabolic biomarkers. In addition, infection and sepsis biomarkers—including procalcitonin, presepsin, monocyte distribution width, pancreatic stone protein, soluble urokinase plasminogen activator receptor, and bioactive adrenomedullin—provide important diagnostic and prognostic information, especially in elderly patients with atypical clinical presentations.

Special attention is given to biomarkers reflecting endothelial dysfunction and microcirculatory failure, which appear particularly relevant in the pathophysiology of severe infections and septic shock. Emerging evidence suggests that multimarker approaches integrating biological, clinical, and functional data may enhance risk stratification and support personalized management strategies in geriatric populations.

Overall, biomarkers of aging represent a promising avenue for improving diagnosis, prognostication, and individualized care in older adults. However, further large-scale, elderly-focused studies are required to validate their clinical utility, establish age-specific thresholds, and facilitate integration into routine practice.

Key words: *Biological aging; frailty; biomarkers; inflammaging; immunosenescence; sepsis; endothelial dysfunction; elderly patients; risk stratification; prognosis*

INTRODUCTION

Population aging represents one of the most profound demographic shifts of the 21st century and constitutes a major challenge for modern healthcare systems. World Health Organization [WHO] defines aging not purely in chronological terms, but mainly as the progressive accumulation of molecular and cellular damage that leads to a decline in physiological reserves, increased vulnerability to stressors, and ultimately higher morbidity and mortality. In this context, older adults constitute a heterogeneous population, characterized by multimorbidity, polypharmacy, and highly variable functional status, all of which complicate clinical decision-making and prognostication.

Within this framework lies the emerging hypothesis

[1]Internal Medicine Clinic, University Hospital of Patras, Patras, Greece
[2]Medical School, University of Patras, Patras, Greece
[3]Department of Radiology, University Hospital of Patras, Patras, Greece

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of geriatrics, which proposes that targeting the aging process itself, and not just the individual diseases that accompany it, can prevent or mitigate many related diseases thus enhancing healthy longevity. Central to this approach is the identification of reliable biomarkers that reflect underlying biological processes such as chronic inflammation, immune dysregulation, endothelial dysfunction, and metabolic derangements. Biomarkers are defined as measurable biological characteristics that reflect normal physiological processes, pathological states, or responses to therapeutic interventions, and they play a pivotal role in diagnosis, risk stratification, prognosis, and monitoring of disease progression.

The clinical utility of biomarkers is particularly important in the elderly, mainly because atypical presentations of acute illness, blunted inflammatory responses, and the coexistence of chronic low-grade inflammation often limit the diagnostic accuracy of traditional clinical signs and laboratory parameters. As a result, biomarkers may offer valuable objective information that complements clinical assessment and supports timely and individualized management. However, biomarker interpretation in the elderly requires careful consideration, as age-related physiological changes and comorbid conditions may significantly influence baseline levels and dynamic responses.

Among geriatric syndromes, frailty has emerged as a key concept linking biological aging to adverse clinical outcomes. Frailty reflects a state of reduced biological reserve and increased vulnerability to stress, such as infections, trauma, or surgical interventions, and is strongly associated with hospitalization, disability, and mortality. Growing evidence suggests that frailty is closely related to inflammatory, metabolic, cardiovascular, and immune biomarkers, highlighting the potential role of laboratory indicators in identifying high-risk older individuals.

Beyond chronic conditions, acute illnesses—particularly infections and sepsis—represent a major cause of morbidity and mortality in the elderly population. Sepsis is increasingly recognized as a syndrome driven not only by dysregulated inflammation but also by profound endothelial dysfunction and microcirculatory failure, processes that are amplified in older adults. In this setting, novel biomarkers reflecting immune activation and vascular integrity have gained considerable attention, as they may provide superior prognostic information compared to traditional inflammatory markers.

This narrative review aims to summarize and critically discuss the role of established and emerging biomarkers in the elderly population, with a particular focus on frailty, cardiovascular and thrombotic markers, and infection-related biomarkers, including sepsis-associated indicators. Special emphasis is placed on biomarkers that reflect endothelial dysfunction and disease severity, highlighting their potential contribution to personalized and precision medicine in older patients.

MATERIALS AND METHODS

This study was designed as a narrative review aiming to summarize current evidence on biomarkers of aging, frailty, and sepsis in elderly populations. A comprehensive literature search was conducted using electronic databases, including PubMed and MEDLINE.

The search included studies published from January 2000 to February 2026, in order to capture both foundational and contemporary evidence in the field. Additional emphasis was placed on more recent literature [last 5–10 years] to reflect current advances in biomarker research.

Search terms included combinations of "aging", "frailty", "biomarkers", "inflammaging", "immunosenescence", "sepsis", "endothelial dysfunction," and "elderly patients".

Eligible studies included original research articles, systematic reviews, and meta-analyses published in English. Studies were selected based on their clinical relevance to elderly populations and their contribution to understanding both the biological mechanisms and clinical applications of biomarkers. Particular emphasis was placed on inflammatory, metabolic, cardiovascular, and infection-related biomarkers, including both established and emerging markers such as procalcitonin, presepsin, monocyte distribution width, pancreatic stone protein, soluble urokinase plasminogen activator receptor, and bioactive adrenomedullin.

Screening was performed in two stages, including title and abstract evaluation followed by full-text review. Studies involving general adult populations were also considered when subgroup analyses or findings relevant to elderly patients were available.

Data extraction was performed qualitatively, and findings were synthesized into thematic categories, including biological mechanisms of aging, frailty-associated biomarkers, and infection/sepsis-related biomarkers. Due to heterogeneity in study designs, populations, and outcome measures, no quantitative meta-analysis was performed.

Biological Background of Aging: Inflammaging and Immunosenescence

Aging is a complex biological process characterized

by the progressive decline of physiological integrity, leading to impaired homeostasis and increased vulnerability to disease. At the molecular and cellular level, aging is driven by the accumulation of DNA damage, mitochondrial dysfunction, oxidative stress, telomere attrition, and epigenetic alterations, all of which contribute to reduced cellular resilience and impaired tissue repair mechanisms [1,2]. These changes are not only associated with chronic diseases but also profoundly influence the host response to acute stressors, such as infection or trauma.

One of the hallmarks of biological aging is inflammaging, a state of chronic, low-grade systemic inflammation that develops in the absence of overt infection [3]. Inflammaging is characterized by persistently elevated levels of proinflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). This inflammatory milieu is thought to arise from multiple sources, including cellular senescence, immune cell dysregulation, chronic antigenic stimulation, alterations in gut microbiota, and the accumulation of damage-associated molecular patterns (DAMPs) [3,4]. Importantly, inflammaging has been strongly linked to frailty, sarcopenia, cardiovascular disease, neurodegeneration, and increased mortality in older adults [5].

Closely related to inflammaging is immunosenescence, which refers to age-related qualitative and quantitative changes in both innate and adaptive immunity. Immunosenescence is characterized by reduced naïve T-cell production, expansion of memory and T-cell subsets, impaired B-cell function, and diminished antigen-presenting capacity of innate immune cells [6]. As a result, older patients often exhibit a paradoxical immune profile in which a blunted response to new pathogens is accompanied by an exaggerated or dysregulated inflammatory activation. All the above partly explains why elderly patients may present with atypical or muted clinical signs of infection while simultaneously being at higher risk for severe disease and adverse outcomes.

Additionally, this interaction between inflammaging and immunosenescence has important implications for biomarker interpretation in older patients. Baseline elevations of inflammatory markers may reduce the specificity of traditional biomarkers for acute disease, while impaired immune responsiveness may delay or attenuate biomarker rises during early infection [7]. Consequently, reliance on single inflammatory markers may be insufficient in geriatric populations, underscoring the need for biomarkers that reflect broader pathophysiological processes, such as endothelial dysfunction, microcirculatory failure, and immune–vascular crosstalk.

Endothelial dysfunction represents another critical component of biological aging. Age-related changes in endothelial cells include reduced nitric oxide bioavailability, increased oxidative stress, impaired barrier function, and enhanced expression of adhesion molecules [8]. These alterations predispose older adults to vascular leakage, thrombosis, and organ hypoperfusion, particularly during acute inflammatory states such as sepsis. The aging endothelium therefore constitutes a key interface between chronic low-grade inflammation and acute organ dysfunction, making endothelial-derived biomarkers especially relevant in elderly populations.

Within this biological framework, biomarkers of aging should not be viewed merely as diagnostic tools but as integrative indicators of systemic vulnerability. Ideal biomarkers in older adults should reflect cumulative biological stress, correlate with functional decline and clinical outcomes, and provide prognostic information beyond chronological age alone. Understanding the underlying mechanisms of inflammaging, immunosenescence, and endothelial dysfunction is essential for the rational selection and interpretation of biomarkers in both chronic and acute disease states in the elderly (Figure 1).

Frailty as a Central Geriatric Syndrome: Biomarkers and Clinical Outcomes

Frailty refers to a multidimensional geriatric syndrome that reflects a state of decreased physiological reserve and increased vulnerability to stress, such as infections, falls, or surgical interventions. Unlike chronological aging, frailty captures biological heterogeneity among older adults and has emerged as a powerful predictor of adverse outcomes, including hospitalization, disability, institutionalization, and mortality [9,10]. It is not a single disease entity but rather a dynamic condition resulting from the cumulative decline of multiple organ systems.

Recent data from several observational studies and systematic reviews support a close association between frailty and chronic systemic inflammation. Specifically, it has been demonstrated that frail older individuals exhibit significantly higher circulating levels of proinflammatory cytokines, particularly IL-6, CRP, and TNF-α, compared with robust counterparts [11–13]. These findings reinforce the concept of inflammaging as a biological substrate of frailty, whereby persistent low-

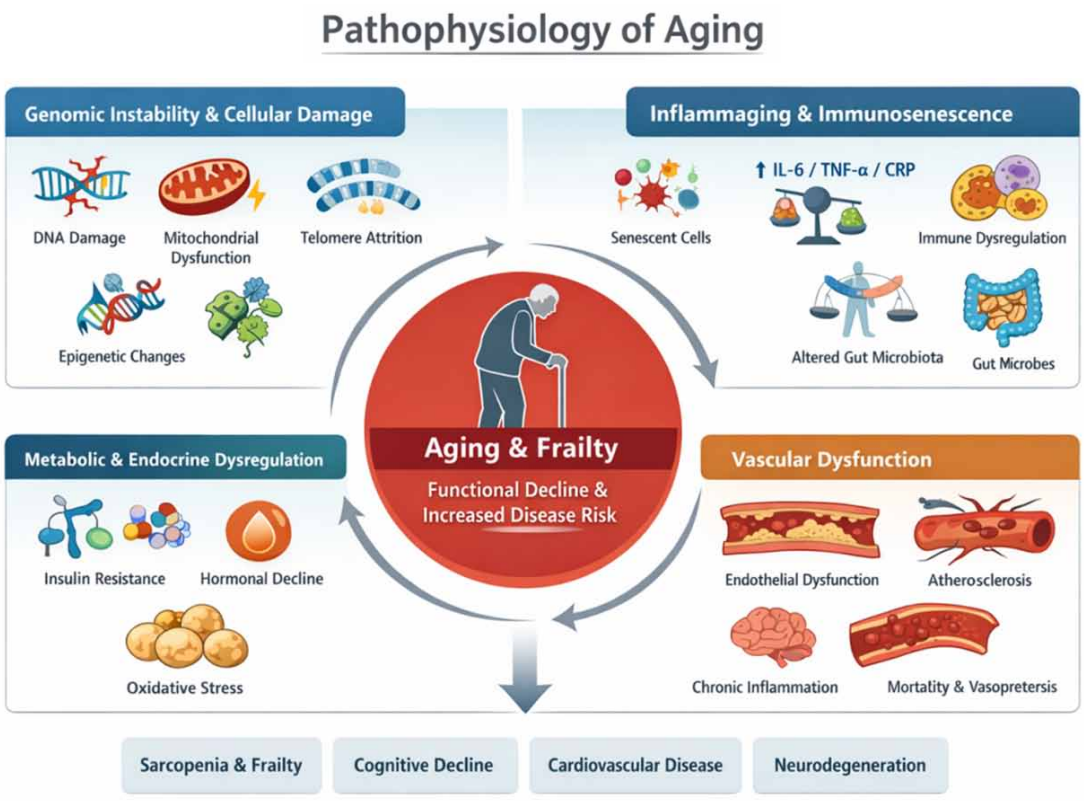

Figure 1. Pathophysiology of biological aging: interplay between inflammaging immunosenescence, metabolic dysregulation, and endothelial dysfunction leading to frailty and age- related disease.

grade inflammation contributes to muscle catabolism, impaired immune function, and reduced stress tolerance. Elevated inflammatory markers have also been independently associated with incident frailty and worsening frailty trajectories over time [14].

In addition, metabolic and nutritional biomarkers play a critical role in the frailty phenotype. Low serum albumin levels, often reflecting chronic inflammation, malnutrition, or underlying disease burden, have been consistently associated with frailty and poor clinical outcomes [15]. Similarly, reduced concentrations of vitamin D and insulin-like growth factor-1 (IGF-1) have been linked to sarcopenia, impaired physical performance, and increased frailty risk, underscoring the interaction between endocrine dysregulation and functional decline in the elderly [16,17].

Alterations in lipid metabolism have also been increasingly recognized as relevant biomarkers in frailty assessment. Contrary to what is commonly believed, several studies have reported lower total cholesterol and low-density lipoprotein (LDL) levels in frail elderly individuals, potentially reflecting underlying catabolic states, chronic inflammation, or malnutrition rather than cardiovascular protection [18]. More recently, attention has shifted toward non–high-density lipoprotein (non-HDL) cholesterol as a more comprehensive marker of atherogenic lipid burden and metabolic health.

In detail, a recent population-based study by Pan et al. demonstrated a U-shaped association between non-HDL cholesterol levels and frailty risk in individuals aged 65 years and older [19]. Specifically, both low (<63 mg/dL) and very high (>259 mg/dL) non-HDL cholesterol concentrations were associated with an increased likelihood of frailty, suggesting that extremes of lipid levels may reflect underlying biological vulnerability. These findings highlight the potential role of lipid parameters as early biomarkers of frailty, while also emphasizing the need for cautious interpretation and further prospective validation.

In summary, biomarkers associated with frailty do not concern isolated changes in laboratory findings but essentially reflect multiple interactions. Although no single biomarker has yet achieved sufficient sensitivity and specificity for routine frailty diagnosis, combinations of biomarkers may enhance risk stratification and prognostication. Importantly, frailty-associated biomarkers

have been shown to predict not only frailty status but also clinically meaningful outcomes, including length of hospital stay, readmission rates, falls, and mortality [20].

From a clinical perspective, the integration of biomarker assessment with established frailty scales may offer a more comprehensive evaluation of older patients, enabling earlier identification of high-risk individuals and more personalized management strategies. However, the lack of standardized cut-off values and the heterogeneity of frailty definitions remain significant challenges, underscoring the need for large, well-designed prospective studies focusing specifically on elderly populations (Table 1).

Infection and Sepsis Biomarkers in the Elderly

Infections and sepsis represent a leading cause of hospitalization and mortality in older adults. Age-related immune dysregulation, multimorbidity, and atypical clinical presentations frequently delay diagnosis and initiation of appropriate therapy, contributing to poor outcomes. In this setting, biomarkers play a critical role in supporting early recognition, risk stratification, and prognostic assessment, complementing clinical judgment and severity scores (Table 2).

Procalcitonin

Procalcitonin (PCT) is one of the most extensively studied biomarkers for the diagnosis of bacterial infection and sepsis. Meta-analyses evaluating elderly populations have demonstrated that PCT retains good diagnostic accuracy, with reported areas under the curve (AUC) approaching 0.89 and pooled sensitivity and specificity of approximately 83% [25]. These findings suggest that PCT can contribute both to the confirmation and exclusion of bacterial infection in older patients.

Table 1. *Key biomarkers of biological aging and frailty: mechanisms and clinical relevance in older adults.*

Biomarker	Main mechanism / biological rationale	Clinical relevance in older adults / frailty	Representative references
IL-6	Pro-inflammatory cytokine involved in chronic low-grade inflammation ("inflammaging")	Associated with frailty, reduced physiological reserve, disability, and adverse outcomes	Franceschi et al., 2018 [3] Soysal et al., 2016 [5] Leng et al., 2007 [11]
CRP	Acute-phase reactant reflecting systemic inflammation	Elevated in frail older adults; non-specific marker of chronic inflammatory burden	Ferrucci & Fabbri, 2018; [4] Walston et al., 2002 [12] Hubbard et al., 2009 [13]
TNF-α	Pro-inflammatory cytokine linked to catabolism and immune dysregulation	Associated with frailty biology and adverse outcomes	Franceschi et al., 2018; [3] Soysal et al., 2016 [5]
Albumin	Reflects nutritional status, inflammation, and disease burden	Low levels associated with frailty, poor functional status, and worse prognosis	Cabrerizo et al., 2015 [15]
Vitamin D	Regulates muscle function and metabolism	Low levels linked to sarcopenia and frailty	Visser et al., 2003 [16]
IGF-1	Marker of anabolic/endocrine function	Reduced levels associated with frailty and impaired performance	Cappola et al., 2003 [17]
Totalcholesterol / LDL-C	Reflect metabolic reserve; low levels may indicate catabolism	Lower levels associated with frailty and vulnerability	Volpatoetal., 2001 [18]
Non-HDL cholesterol	Marker of atherogenic lipid burden	U-shaped association with frailty risk	Pan et al., 2025 [19]
NT-proBNP	Reflects myocardial stress and cardiac dysfunction	Useful in cardiovascular risk assessment in elderly	Januzzi et al., 2018; [21] Hildebrandt et al., 2010 [22]
D-dimer	Marker of coagulationactivation	Useful for thrombotic risk; requires age-adjusted interpretation	Righini et al., 2014 [23] A Penaloza et al., 2012 [24]

Table 2. *Emerging and established biomarkers in sepsis: diagnostic and prognostic tools in the elderly.*

Biomarker	Main mechanism / biological rationale	Main clini caluse	Representative references
Procalcitonin (PCT)	Increases in bacterial infections and systemic inflammation	Diagnosis of bacterial infection and sepsis; guides antibiotic decisions	Wacker et al., 2013; [25] Gómez-Cerquera et al., 2015 [27]
Presepsin	Released during monocyte activation by bacterial components	Early diagnosis and severity assessment; correlates with organ dysfunction	Yaegashi et al., 2015 [28] Lee et al., 2022 [29] Kyriazopoulou et al., 2023 [30]
MDW	Reflects monocyte size variability during inflammation	Early sepsis detection; rapid and low-cost	Crouser et al., 2017 [31] Motawea et al., 2023 [33]
PSP	Stress protein released during infection	Early detection and prognosis of sepsis	Prazak et al., 2021 [34] Pugin et al., 2021 [35]
suPAR	Marker of immune activation and chronic inflammation	Prognostic marker for severity and mortality	Eugen-Olsen, 2011 [36] Zhao et al., 2021 [37]
Bio-ADM	Reflects endothelial dysfunction and vascular leakage	Prognostic marker in septic shock; correlates with mortality and vasopressor need	Caironi et al., 2017 [39] Mebazaa et al., 2018 [40] Kim et al., 2019 [41]

Clinical studies have further shown that a PCT cut-off of 0.5 ng/mL provides acceptable diagnostic performance in elderly cohorts, with high specificity for bacterial infection, although sensitivity may be reduced in early disease stages or in immunocompromised patients [26,27]. Importantly, PCT should not be interpreted in isolation but rather in conjunction with clinical assessment, microbiological data, and other laboratory parameters, particularly in older adults with chronic inflammatory conditions.

Presepsin

Presepsin, the soluble CD14 subtype released into circulation following monocyte activation by bacterial components, has emerged as a promising biomarker for both the diagnosis and prognosis of sepsis. Data from several different studies show that presepsin levels not only increase rapidly in bacterial infections but also correlate with disease severity and organ dysfunction [28].

In a large prospective observational study, presepsin concentrations were significantly higher in patients with sepsis compared with those with non-infectious organ failure and were further elevated in septic shock, supporting its role as a severity marker [29]. More recent data indicate that presepsin levels rise in a severity-dependent manner and are strongly associated with the development of organ failure, including in elderly populations [30]. Compared with CRP and PCT, presepsin has shown comparable or superior diagnostic performance in selected studies, although inter-study heterogeneity and limited standardization remain challenges.

Monocyte Distribution Width

Monocyte distribution width (MDW) is an emerging biomarker derived automatically from complete blood count analysis, reflecting changes in monocyte size heterogeneity during systemic inflammation. MDW has gained attention due to its availability at the point of care, lack of additional cost, and rapid turnaround time.

Clinical studies in emergency department settings have demonstrated that MDW is significantly higher in septic compared with non-septic patients, including older adults with atypical presentations [31]. In a recent study, the use of an MDW cut-off >21.5 units was associated with earlier recognition of sepsis and a significant reduction in time to antimicrobial administration, although no direct impact on mortality was observed [32]. A meta-analysis further confirmed the diagnostic value of MDW, reporting a pooled AUC of 0.79 and performance comparable or slightly superior to that of PCT [33]. These findings support the role of MDW as a practical adjunctive biomarker for early sepsis detection in elderly patients.

Pancreatic Stone Protein and suPAR

Pancreatic stone protein (PSP) is a stress-induced protein secreted by pancreatic and duodenal cells,

with increasing evidence supporting its role in sepsis diagnosis and prognosis. Studies comparing PSP with traditional biomarkers have shown higher AUC values for infection detection and superior prognostic performance for septic shock development [34]. Serial measurements of PSP have further demonstrated value in early sepsis detection in critically ill patients, suggesting a role in dynamic risk assessment [35].

Soluble urokinase plasminogen activator receptor (suPAR) reflects immune system activation and chronic inflammation. Elevated suPAR levels have been consistently associated with disease severity, organ failure, and mortality in sepsis [36]. In elderly septic patients, suPAR concentrations correlate positively with severity scores such as SOFA and APACHE II, as well as with proinflammatory cytokine profiles, highlighting its prognostic rather than diagnostic utility [37].

Bioactive Adrenomedullin as a Sepsis Biomarker

Bioactive adrenomedullin (bio-ADM) has emerged as a key biomarker reflecting endothelial dysfunction, microcirculatory failure, and disease severity in sepsis. Adrenomedullin is a vasoactive peptide with potent vasodilatory, anti-inflammatory, and endothelial-protective properties, playing a central role in maintaining vascular integrity and homeostasis during systemic inflammation [38,39]. In sepsis, excessive production of adrenomedullin is thought to represent a compensatory response to profound endothelial injury and increased vascular permeability.

Early clinical studies demonstrated that circulating adrenomedullin and proadrenomedullin levels are significantly elevated in patients with severe sepsis and septic shock and are strongly associated with disease severity and adverse outcomes [39,40]. Subsequent investigations focusing on the biologically active form of adrenomedullin provided more precise prognostic information. The AdrenOSS-1 study showed that bio-ADM levels were independently associated with organ failure and mortality in septic patients, outperforming several traditional biomarkers [40].

Multiple observational studies have since confirmed that elevated bio-ADM concentrations correlate with the severity of circulatory failure, need for vasopressor support, and short-term mortality in both intensive care and emergency department settings [41–43]. Importantly, bio-ADM has been shown to reflect endothelial barrier dysfunction, a central pathophysiological mechanism in septic shock, linking biomarker elevation directly to microvascular leakage and tissue hypoperfusion [44,45].

Meta-analytical data further support the prognostic value of adrenomedullin-related biomarkers in sepsis, demonstrating significant associations with mortality and organ dysfunction across heterogeneous patient populations [46]. More recent studies have highlighted the potential additive value of bio-ADM when combined with other biomarkers or severity scores, suggesting a role in multimarker strategies for risk stratification [47].

Beyond its role as a biomarker, adrenomedullin has attracted interest as a potential therapeutic target. Experimental and translational studies indicate that modulation of adrenomedullin signaling may promote vascular integrity and improve outcomes in sepsis, further underscoring its central role in disease pathophysiology [48,49]. Although routine clinical implementation of bio-ADM measurement is not yet widespread, current evidence supports its utility as a robust prognostic biomarker, particularly in elderly patients who are prone to endothelial dysfunction and circulatory instability.

Clinical Implications

The expanding body of evidence on biomarkers of aging highlights their potential to enhance clinical decision-making in older adults across a wide range of settings. Given the heterogeneity of the elderly population, biomarkers may assist clinicians in moving beyond chronological age toward a more individualized assessment of biological vulnerability, disease severity, and prognosis.

In daily clinical practice, biomarkers can support early diagnosis, particularly in older patients with atypical or blunted clinical presentations. Infection- and sepsis-related biomarkers such as PCT, presepsin, MDW, and bioactive adrenomedullin may facilitate earlier recognition of high-risk patients, allowing timely initiation of antimicrobial therapy and hemodynamic support [25–33],[40–43].

Beyond diagnosis, biomarkers play a crucial role in risk stratification and prognosis. Frailty-associated biomarkers, endothelial markers, and sepsis-related biomarkers have been consistently associated with adverse outcomes, including organ failure, prolonged hospitalization, and mortality [11–14],[37],[41–46]. In this context, biomarkers may aid in identifying elderly patients who require closer monitoring, higher levels of care, or early escalation of treatment.

Importantly, biomarkers should not be used in iso-

lation. Their greatest clinical value lies in integration with comprehensive geriatric assessment, validated clinical scores, and physician judgment. Multimarker approaches may offer superior prognostic performance compared with single biomarkers, particularly in complex syndromes such as sepsis and frailty [47]. However, standardization of cut-off values and validation in elderly-specific cohorts remain critical prerequisites for widespread implementation.

DISCUSSION

This narrative review highlights the growing role of biomarkers as integrative tools for understanding biological aging, frailty, and acute disease in older adults. Rather than serving solely as diagnostic adjuncts, biomarkers increasingly reflect fundamental pathophysiological mechanisms that underlie vulnerability, disease severity, and adverse outcomes in this population.

One of the central themes emerging from the reviewed evidence is that aging is accompanied by a complex interplay between chronic low-grade inflammation, immune dysregulation, endothelial dysfunction, and metabolic alterations. These processes collectively contribute to reduced physiological reserve and impaired stress responses, rendering older adults particularly susceptible to clinical deterioration during acute illness. Biomarkers associated with inflammaging and immunosenescence, such as IL-6, CRP, and TNF-α, have consistently been linked to frailty and poor outcomes, supporting their role as indicators of biological rather than chronological aging [3–5],[11–14].

Importantly, frailty emerges as a unifying clinical construct that bridges biological aging and adverse outcomes. The association of frailty with inflammatory, nutritional, endocrine, and lipid biomarkers underscores its multifactorial nature and highlights the limitations of relying on single laboratory parameters [9,10],[15–19]. While no individual biomarker has demonstrated sufficient discriminatory power to define frailty in isolation, combined biomarker profiles may enhance risk stratification, particularly when integrated with established frailty scales and comprehensive geriatric assessment.

In the cardiovascular and thrombotic domains, this review reinforces the necessity of age-adapted biomarker interpretation. Natriuretic peptides and D-dimers remain clinically valuable in older adults, provided that age-related physiological changes are acknowledged. The success of age-adjusted D-dimer thresholds in safely excluding venous thromboembolism exemplifies how biomarker interpretation can be optimized for elderly populations without compromising safety [23,24]. These findings highlight an important principle: biomarkers should not be abandoned in older patients, but rather contextualized within the biology of aging.

The most compelling advances, however, are observed in the field of infection and sepsis biomarkers. Sepsis in older adults is frequently characterized by atypical presentations, delayed diagnosis, and disproportionate mortality. Traditional inflammatory markers may be insufficient in this setting due to baseline inflammation and blunted immune responses. Emerging biomarkers such as presepsin, MDW, PSP, and suPAR provide additional prognostic insight by reflecting immune activation, cellular stress, and disease severity [28–37]. Their value lies less in binary diagnosis and more in early risk stratification and trajectory prediction.

Among these biomarkers, bioactive adrenomedullin warrants particular attention. Unlike conventional inflammatory markers, bio-ADM directly reflects endothelial dysfunction and microcirculatory failure—core mechanisms in the pathogenesis of septic shock [39–46]. The consistent association between elevated bio-ADM levels, organ failure, vasopressor requirement, and mortality across multiple cohorts underscores its robustness as a prognostic biomarker [40–43],[46,47]. This is especially relevant in older adults, in whom age-related endothelial vulnerability may amplify the clinical impact of sepsis.

From a translational perspective, bio-ADM represents a paradigm shift in biomarker research, linking molecular signaling pathways to clinically meaningful outcomes. Its potential role as both a prognostic marker and a therapeutic target further distinguishes it from other biomarkers, aligning with emerging concepts of precision medicine in critical care [48,49]. Nevertheless, routine clinical implementation requires standardized assays, validated cut-off values, and clear guidance on how bio-ADM measurement should influence therapeutic decisions.

Despite the growing body of evidence, several limitations must be acknowledged. Most biomarker studies include heterogeneous populations with limited age-specific analyses, and elderly patients—particularly the frailest—are often underrepresented. Additionally, variability in study design, timing of biomarker measurement, and outcome definitions limits direct comparison across studies. These challenges underscore the need for large, prospective, elderly-focused studies designed

specifically to evaluate biomarker-guided strategies.

Finally, the clinical utility of biomarkers should be viewed within a multimodal framework. Biomarkers are most effective when combined with clinical assessment, functional status evaluation, and validated severity scores. Future approaches integrating biomarker panels with frailty indices and artificial intelligence–driven models may further enhance prognostic accuracy and support individualized care pathways for older patients [47].

Future Perspectives

Future advances in the field are likely to focus on multimarker strategies that combine inflammatory, metabolic, cardiovascular, and endothelial biomarkers with clinical and functional assessments. The integration of biomarker panels with frailty indices and severity scores may significantly enhance risk prediction and support personalized management strategies in elderly patients.

Artificial intelligence and machine-learning models represent a promising avenue for synthesizing complex biomarker data with clinical variables to generate individualized prognostic predictions [49]. Additionally, biomarkers such as bioactive adrenomedullin may not only serve as prognostic tools but also emerge as therapeutic targets, reflecting a shift toward pathophysiology-driven interventions in sepsis and critical illness [48,49].

Large, prospective, elderly-focused studies are essential to validate existing biomarkers, establish age-specific thresholds, and determine their impact on clinical outcomes and healthcare resource utilization. Such efforts will be critical to translating biomarker research into routine geriatric practice.

CONCLUSION

Biomarkers represent a rapidly evolving and highly promising tool in the care of older adults. By reflecting key biological processes such as inflammaging, immunosenescence, endothelial dysfunction, and metabolic dysregulation, biomarkers provide valuable information beyond chronological age alone. Their application has the potential to improve diagnosis, prognostication, and individualized management, particularly in high-risk conditions such as frailty, cardiovascular disease, and sepsis.

Among emerging biomarkers, those related to endothelial function—most notably bioactive adrenomedullin—appear particularly relevant in elderly patients, offering robust prognostic information in sepsis and septic shock. However, widespread clinical implementation requires further validation, standardization, and integration into multimodal assessment strategies.

Ultimately, the thoughtful incorporation of biomarkers into geriatric medicine may contribute to earlier recognition of vulnerability, more precise risk stratification, and improved quality of care for the aging population.

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Corresponding author:

Ioanna Marlafeka
E-mail: dr.jomarl@gmail.com

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